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Bioactive plant compounds with activity against *Treponema pallidum*

Compostos bioativos de plantas com atividade contra *Treponema pallidum*

Compuestos vegetales bioactivos con actividad contra *Treponema pallidum*

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ABSTRACT

Objective: To analyze the therapeutic potential of bioactive natural products with activity against *Treponema pallidum* as potential sources for future complementary therapeutic strategies. **Methods:** An exploratory literature review was performed in the PubMed, ScienceDirect, and Scopus databases using the search terms "*Treponema pallidum*" AND ("bioactive natural products" OR "natural compounds" OR "plant extracts"), including both *in vitro* and *in silico* studies published between January 2005 and January 2025. After duplicates were removed and titles, abstracts, and full texts were screened, four studies met the inclusion criteria. Phthalic acid (1,2-benzenedicarboxylic acid) was the only isolated compound. Its pharmacokinetic and toxicological properties were evaluated using ADMETlab 2.0 and PreADMET, while oral bioavailability was assessed with SwissADME, producing a bioavailability radar and BOILED-Egg model. **Results:** Phthalic acid, obtained from *Hibiscus rosa-sinensis flowers*, showed a 24 mm inhibition zone at 10 µg/mL using the agar-well diffusion method**.** Among plant extracts, the acetone extract of *Odina wodier* exhibited the highest antimicrobial activity (MIC 0.78 µg/mL; MBC 1.52 µg/mL), followed by extracts from *Moringa oleifera* and *Curculigo orchioides* (MIC 3.12 µg/mL). **Final considerations:** Natural products show promise against *T. pallidum*; however, the predominance of crude extracts limits clinical application, and further isolation and safety studies are needed.

Keywords: *Treponema pallidum*, Natural products, Bioactive compounds, Antimicrobial activity.

RESUMO

Objetivo: Analisar o potencial terapêutico de produtos naturais bioativos com atividade contra *Treponema pallidum* como potenciais fontes para futuras estratégias terapêuticas complementares. **Métodos:** Revisão exploratória nas bases PubMed, ScienceDirect e Scopus, usando os descritores "*Treponema pallidum*" AND ("bioactive natural products" OR "natural compounds" OR "plant extracts"), incluindo estudos tanto *in vitro* quanto *in silico* publicados entre janeiro de 2005 e janeiro de 2025. Após triagem, quatro estudos atenderam aos critérios de inclusão. O ácido ftálico (ácido 1,2-benzenodicarboxílico) foi o único composto isolado. Suas propriedades farmacocinéticas e toxicológicas foram avaliadas com ADMETlab 2.0 e PreADMET, enquanto a biodisponibilidade oral foi estimada com SwissADME, gerando radar de biodisponibilidade e modelo BOILED-Egg. **Resultados:** O ácido ftálico, obtido das flores de *Hibiscus rosa-sinensis*, apresentou zona de inibição de 24 mm na concentração de 10 µg/mL pelo método de difusão em poço em ágar. Entre os extratos vegetais,

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o acetônico de *Odina wodier* mostrou maior atividade antimicrobiana (MIC 0,78 µg/mL; MBC 1,52 µg/mL), seguido pelos extratos de *Moringa oleifera* e *Curculigo orchioides* (MIC 3,12 µg/mL). **Considerações finais:** Produtos naturais mostram potencial contra *T. pallidum*, mas a predominância de extratos brutos limita a aplicação clínica, sendo necessários estudos adicionais de isolamento e segurança.

Palavras-chave: *Treponema pallidum*, Produtos naturais, Compostos vegetais, Atividade antimicrobiana.

RESUMEN

Objetivo: Analizar el potencial terapéutico de productos naturales bioactivos con actividad frente a *Treponema pallidum* como posibles fuentes para futuras estrategias terapéuticas complementarias. **Métodos:** Revisión exploratoria en PubMed, ScienceDirect y Scopus, usando los descriptores "*Treponema pallidum*" AND ("bioactive natural products" OR "natural compounds" OR "plant extracts"), incluyendo tanto estudios *in vitro* como *in silico* publicados entre enero de 2005 y enero de 2025. El ácido ftálico (ácido 1,2-bencenodicarboxílico) fue el único compuesto aislado. Sus propiedades farmacocinéticas y toxicológicas se evaluaron con ADMETlab 2.0 y PreADMET, y la biodisponibilidad oral se estimó con SwissADME, generando radar de biodisponibilidad y modelo BOILED-Egg. **Resultados:** El ácido ftálico, de las flores de *Hibiscus rosa-sinensis*, presentó zona de inhibición de 24 mm a 10 µg/mL mediante difusión en pozo en agar. Entre los extractos vegetales, el acetónico de *Odina wodier* mostró mayor actividad antimicrobiana (MIC 0,78 µg/mL; MBC 1,52 µg/mL), seguido por *Moringa oleifera* y *Curculigo orchioides* (MIC 3,12 µg/mL). **Consideraciones finales:** Los productos naturales muestran potencial frente a *T. pallidum*, pero la predominancia de extractos crudos limita su aplicación clínica, requiriéndose estudios adicionales de aislamiento y seguridad.

Palabras clave: *Treponema pallidum*, Productos naturales, Compuestos bioactivos, Actividad antimicrobiana.

INTRODUCTION

Syphilis is a chronic and highly contagious sexually transmitted infection (STI) caused by the bacterium *Treponema pallidum*, a spirochete that exclusively infects humans (SADOGHI B, et al., 2023). Although it is treatable, its rising prevalence highlights its importance as a growing global public health issue. It affects over 50 million people worldwide and leads to approximately 8 million new cases each year among individuals aged 15 to 49 (JAISWAL AK, et al., 2025).

In Brazil, data from the Syphilis Epidemiological Bulletin (2025) show that, between 2020 and 2024, the detection rate of acquired syphilis per 100,000 inhabitants rose from 61.0 to 120.8 cases. This represents an increase of nearly 98% over this period. Several factors have contributed to this rise, including reduced STI testing and screening during the COVID-19 pandemic, the limited implementation of effective public policies for surveillance, prevention, and sexual health promotion, inconsistent condom use, sociocultural barriers related to stigma and misinformation, unequal access to healthcare services, and ongoing underreporting and delayed diagnosis. Together, these factors contribute to sustaining the spread of the infection (MEHTA P, et al., 2024; ROSSET F, et al., 2025).

Historically, various treatment strategies have been used to control *T. pallidum* infection (MERCURI SR, et al., 2022). However, it was not until 1943, when penicillin was introduced and produced on a large scale, that the disease began to be effectively treated. Penicillin is still the main treatment for syphilis and remains the first-line therapy globally (SILVA RV, et al., 2024).

Nevertheless, limitations associated with alternative antimicrobials, along with reports of treatment failures and concerns regarding potential antimicrobial resistance, have increased scientific interest in new treatment strategies (MOLINI BJ, et al., 2016). In this context, naturally occurring bioactive compounds have gained attention as promising candidates that may complement traditional treatment regimens and expand available therapeutic options (DWIVEDI UN, et al., 2015).

Natural products are now among the most significant sources for discovering new antimicrobial agents. They play a key role in pharmacological innovation and in combating bacterial resistance (ÁLVAREZ-MARTÍNEZ FJ, et al., 2020).

This potential arises mainly from phytochemicals' ability to target multiple molecular sites in bacteria, unlike conventional antibiotics, which usually focus on a single target and may create stronger selective pressure for resistance (GUEDES BN, et al., 2024).

Plant extracts and secondary metabolites, such as alkaloids, flavonoids, and terpenes, show broad chemical diversity and a wide range of pharmacological effects. Moreover, these compounds often exhibit better biocompatibility, lower toxicity, and greater sustainability, making them suitable candidates for the development of new therapeutic approaches (GAJIC I, et al., 2025; ATANASOV AG, 2021).

In this context, this study aims to identify and analyze plant extracts and isolated natural compounds with reported *in vitro* or *in silico* activity against *T. pallidum*, discussing their preliminary pharmacological potential and the limitations associated with their future therapeutic development.

METHODS

This study is characterized as an integrative review with an exploratory and descriptive approach, aimed at investigating plant extracts and bioactive natural compounds with antitreponemal activity against *T. pallidum*. *In vitro* experimental studies and *in silico* computational studies published from January 2005 to January 2025 and written in English were considered eligible.

The literature search was performed in the PubMed, ScienceDirect, and Scopus databases using combinations of the following search terms: "*Treponema pallidum*" AND ("bioactive natural products" OR "natural compounds" OR "plant extracts").

Studies reporting antimicrobial or antitreponemal activity of plant extracts or isolated natural compounds against *T. pallidum* were included. Articles that did not address this pathogen, did not evaluate substances of natural origin, did not specify the plant part used, exclusively evaluated commercially available compounds, or were not published in peer-reviewed scientific journals, such as monographs, dissertations, and theses, were excluded.

The selection process involved the removal of duplicate records, followed by screening based on titles and abstracts, and full-text assessment according to predefined eligibility criteria. Data extracted from the eligible studies were organized and systematized in a table, including information on the scientific name of the plant and botanical family, plant part used, extraction method, observed antimicrobial activity, proposed mechanisms of action, and corresponding bibliographic references.

In addition, *in silico* analyses of the pharmacokinetic and toxicological properties of the identified compounds were performed.

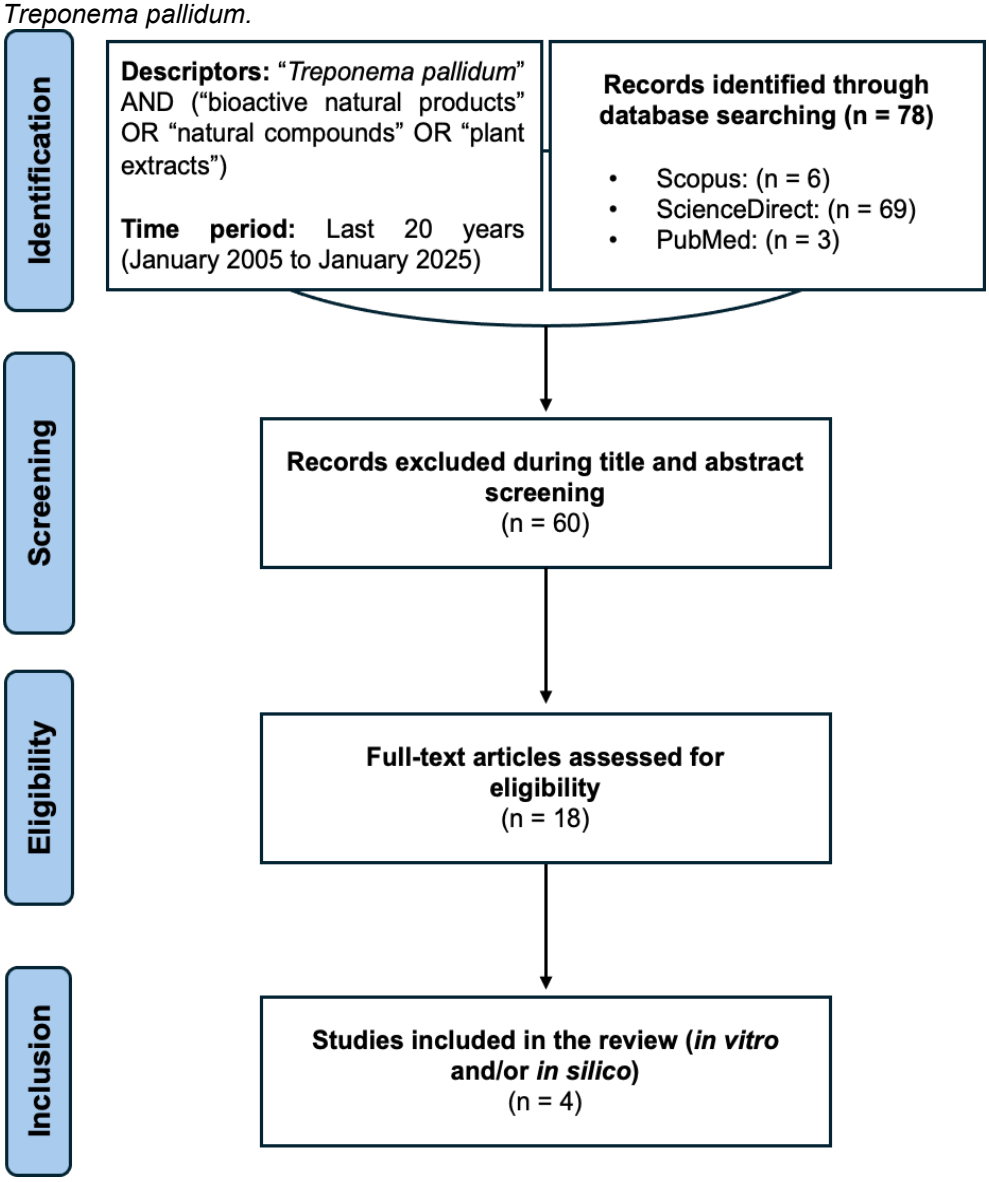
Parameters related to absorption, distribution, metabolism, excretion, and toxicity (ADMET) were evaluated using the ADMETlab 2.0 and PreADMET platforms, according to previously described methodologies. Predicted oral bioavailability parameters were assessed using the SwissADME platform, from which the bioavailability radar and the BOILED-Egg model were generated (DAINA A, et al., 2017).

RESULTS AND DISCUSSION

The literature search conducted in the PubMed, ScienceDirect, and Scopus databases identified a total of 78 records, comprising 6 from Scopus, 69 from ScienceDirect, and 3 from PubMed. After title and abstract screening, 60 records were excluded.

The remaining 18 full-text articles were assessed for eligibility. Of these, 4 studies fully met the inclusion criteria and were included in the final analysis of this review (**Figure 1**).

Figure 1 - Flowchart of the identification, screening, eligibility, and inclusion process of studies in the exploratory review of bioactive natural products with activity against *Treponema pallidum.*



Source: Santos GHB, et al., 2026.

As shown in **Table 1**, crude plant extracts demonstrated considerable chemical diversity and relevant antimicrobial potential against *T. pallidum*, highlighting their importance as promising sources of bioactive compounds for the development of new therapeutic approaches.

The studies investigated different plant organs, including leaves, flowers, seeds, fruits, roots, and latex, from multiple botanical families, such as Anacardiaceae, Malvaceae, Moringaceae, Amaryllidaceae, Apocynaceae, Lamiaceae, and Asphodelaceae. This taxonomic heterogeneity, combined with the antimicrobial activity observed in phylogenetically distinct groups, suggests that the antitreponemal potential is not restricted to a single evolutionary lineage and may reflect the convergent evolution of biosynthetic pathways responsible for the production of structurally and functionally similar secondary metabolites in distant botanical families (HAO DC, XIAO PG, 2020; ZOUINE N, et al., 2024). In addition, the predominance of studies based on crude plant extracts rather than isolated compounds is consistent with the initial stages of bioprospecting pipelines, in which broad screening approaches are commonly employed to identify promising biological activities before compound isolation and structural characterization (BEZERRA WAS, et al., 2024).

Table 1 - Antimicrobial activity (MIC and MBC values) of plant extracts against *Treponema pallidum*.

Species / Family	Extraction Type	*In vitro* Activity	Mechanism of action	References
Odina wodier Roxb. Anacardiaceae	Acetonic extract of the leaves	MIC: 0.78 µg/mL MBC: 1.52 µg/mL Zone of Inhibition (mm): 18 ± 1.61	Possibly through destabilization of membrane proteins	Yabesh JEM, et al., 2019
Moringa oleifera Lam. Moringaceae	Methanolic extract of the flowers	MIC: 3.12 µg/mL MBC: 6.24 µg/mL Zone of Inhibition (mm): 18 ± 1.74		
Curculigo orchioides S.Gaerth. Amaryllidaceae	Chloroformic extract of the roots	MIC: 3.12 µg/mL MBC: 6.24 µg/mL Zone of Inhibition (mm): 18 ± 0.89		
Anacardium occidentale L. Anacardiaceae	Acetonic extract of the seeds	MIC: 6.24 µg/mL MBC: 12.5 µg/mL Zone of Inhibition (mm): 15 ± 0.93		
Ananas comosus (L.) Merr. Bromeliaceae	Acetonic extract of the fruit	MIC: 6.24 µg/mL MBC: 12.50 µg/mL Zone of Inhibition (mm): 16 ± 1.04		
Carissa indica (L.) voigt Apocynaceae	Methanolic extract of the fruit	MIC: 6.24 µg/mL MBC: 12.50 µg/mL Zone of Inhibition (mm): 18 ± 1.91		
Ficus racemosa Willd. Moraceae	Aqueous extract of the latex	MIC: 6.24 µg/mL MBC: 12.50 µg/mL Zone of Inhibition (mm): 17 ± 1.31		
Hibiscus rosa-sinensis L. Malvaceae	Methanolic extract of the flower	MIC: 6.24 µg/mL MBC: 12.50 µg/mL Zone of Inhibition (mm): 19 ± 1.94		
Tribulus terrestris L. Zygophyllaceae	Methanolic extract of the root	MIC: 6.24 µg/mL MBC: 12.50 µg/mL Zone of Inhibition (mm): 16 ± 1.21		
Pedalium murex L. Pedaliaceae	Acetonic extract of the seeds	MIC: 12.50 µg/mL Zone of Inhibition (mm): 17 ± 1.16		
Ricinus communis L. Euphorbiaceae	Methanolic extract of the leaves	MIC: 12.50 µg/mL MBC: 25.0 µg/mL Zone of Inhibition (mm): 18 ± 1.69		
Allium sativum L. Amaryllidaceae	Ethanolic extract of the bulb	Zone of Inhibition (mm): 17.53 at 100 mg/mL	Partial inhibition of RNA and protein synthesis	Farva K, et al., 2023
Azadirachta indica A.Juss. Meliaceae	Ethanolic extract of the seeds	Zone of Inhibition (mm): 17.02 at 100 mg/mL		

Species / Family	Extraction Type	*In vitro* Activity	Mechanism of action	References
Ocimum tenuiflorum L. Lamiaceae	Methanolic extract of the leaves	Zone of Inhibition (mm): 15.87 at 100 mg/mL		
Allium sativum L. Amaryllidaceae	Methanolic extract of the bulb	Zone of Inhibition (mm): 14.91 at 100 mg/mL		
Allium sativum L. Amaryllidaceae	Aqueous extract of the bulb	Zone of Inhibition (mm): 14.89 at 100 mg/mL		
Aloe vera (L.) Burm.f. Asphodelaceae	Methanolic extract of the leaves	Zone of Inhibition (mm): 13.74 at 100 mg/mL		
Zingiber officinale Roscoe Zingiberaceae	Aqueous extract of the dry rhizome	Zone of Inhibition (mm): 13.97 at 100 mg/mL		
Psiadia punctulata Vatke Asteraceae	Ethanolic extract of the leaves	MIC: 9.045 ± 0.198 µg/mL	Inhibition of cell wall synthesis	Alzandi AA, et al., 2023
Teucrium yemense Deflers Lamiaceae		MIC: 9.176 ± 0.311 µg/mL		
Cissus quadrangularis L. Vitaceae		MIC: 12.671 ± 0.191 µg/mL		
Aloe castellorum J.R.I.Wood Asphodelaceae		MIC: 18.009 ± 0.098 µg/mL		
Aloe pseudorubroviolacea Lavranos & Collen. Asphodelaceae		MIC: 21.621 ± 0.189 µg/mL		
Barbeya oleoides Schweinf. Barbeyaceae		MIC: 27.164 ± 0.189 µg/mL		
Hibiscus rosa-sinensis L. Malvaceae	Methanolic extract of the flower	Zone of Inhibition (mm): 18 ± 1.94 at 100 µg/mL	Possible inhibition of acetyltransferase Protein glycosylation locus B (PglB)	Vijayakumar S, et al., 2018

Legend: MIC – Minimum Inhibitory Concentration; MBC – Minimum Bactericidal Concentration.
Source: Santos GHB, et al., 2026.

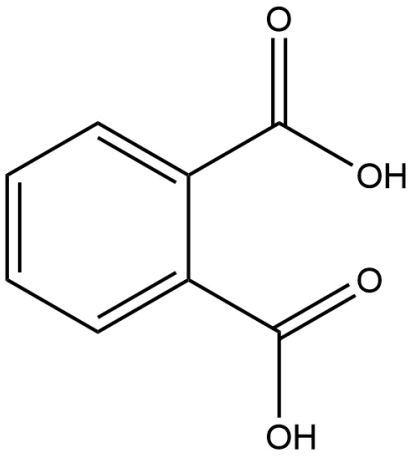
The antimicrobial activity varied according to the plant species, the plant part used, and the extraction solvent. Importantly, all reported activities were obtained from crude plant extracts rather than isolated compounds, preventing the identification of the specific metabolites responsible for the observed effects. Extracts obtained using organic solvents with intermediate polarity, such as acetone and methanol, exhibited superior antimicrobial performance, suggesting greater efficiency in extracting lipophilic or semipolar bioactive metabolites (PILON AC, et al., 2020). Among the evaluated extracts, the acetone leaf extract of *Odina wodier* exhibited the greatest antimicrobial potency (MIC = 0.78 µg/mL; MBC = 1.52 µg/mL), followed by the methanolic flower extract of *Moringa oleifera* and the chloroform root extract of *Curculigo orchioides*, both presenting MIC and MBC values of 3.12 and 6.24 µg/mL, respectively (YABESH JEM, et al., 2019). These findings indicate that both the extraction solvent and the plant tissue may influence the antimicrobial activity of crude plant extracts.

Although the active metabolites responsible for these effects have not yet been identified, the diversity of the proposed mechanisms of action supports the therapeutic potential of these crude extracts. Several extracts have demonstrated the ability to interfere with essential cellular processes, including protein and RNA synthesis, as reported for *Allium sativum*, *Azadirachta indica, Ocimum tenuiflorum, Aloe vera*, and *Zingiber officinale* (FARVA K, et al., 2023). These findings suggest that crude plant extracts may target bacterial pathways distinct from those affected by conventional antibiotics, supporting further investigation into their antimicrobial potential.

Other extracts appear to act through the inhibition of specific enzymes, such as the acetyltransferase PglB, which is involved in protein glycosylation and whose modulation has been suggested for *Hibiscus rosa-sinensis* (VIJAYAKUMAR S, et al., 2018). These findings are particularly relevant because they point to mechanisms distinct from those of penicillin, which primarily inhibits bacterial cell wall synthesis and compromises cell integrity (HALAWA EM, et al., 2024). The identification of alternative molecular targets therefore expands the therapeutic landscape, especially considering the limitations associated with conventional treatments.

Analysis of the selected studies showed that research involving natural products with potential activity against *T. pallidum* is still in its infancy, although preliminary results are encouraging. Although the initial objective of the review was to identify isolated natural compounds with antitreponemal activity, only one of the included studies fully met this criterion. This study reported the antimicrobial activity of phthalic acid (1,2-benzenedicarboxylic acid), isolated from *Hibiscus rosa-sinensis* flowers (**Figure 2**). The compound showed significant inhibitory activity against *T. pallidum*, producing a 24 mm inhibition zone at 10 µg/mL using the agar-well diffusion assay (VIJAYAKUMAR S, et al., 2018). Additional evidence from *Brassica rapa* subsp. *pekinensis* also demonstrated antimicrobial activity and a strong predicted interaction with UDP-3-O-(acyl)-*N*-acetylglucosamine deacetylase (LpxC), although the relevance of this molecular target to *T. pallidum* remains uncertain (RUBAB M, et al., 2018). Therefore, while these findings support the antimicrobial potential of phthalic acid, they should still be considered preliminary.

Figure 2 - Chemical structure of phthalic acid (1,2-benzenedicarboxylic acid).



Source: Santos GHB, et al., 2026. PubChem (CID: 1017).

Structurally, phthalic acid consists of an aromatic ring substituted with two carboxyl groups, which confer both hydrophobic and polar characteristics. This structural arrangement enables multiple modes of interaction with biological targets, including hydrogen bonding, electrostatic interactions, and hydrophobic contacts.

Such properties suggest the ability of phthalic acid to interact with bacterial membrane components as well as essential enzymes such as LpxC.

Previous studies have demonstrated that effective LpxC inhibitors commonly possess ionizable functional groups associated with aromatic moieties, a structural pattern consistent with phthalic acid (LEE CJ, et al., 2011; MIELNICZUK, S et al., 2024; JI P, et al., 2025).

To further investigate its pharmacological potential, the physicochemical, pharmacokinetic, and toxicological properties of phthalic acid were evaluated using *in silico* predictive models (**Table 2**). The compound exhibited a molecular weight of 166.03 g/mol, low lipophilicity (LogP = 0.709), and high aqueous solubility, indicating a predominantly hydrophilic profile. Although high solubility may favor dissolution, low lipophilicity may limit passive diffusion across biological membranes (SHEKHAWAT B; POKHARKAR VB, 2017).

Despite this hydrophilic profile, phthalic acid demonstrated favorable predicted intestinal absorption, including high human intestinal absorption (81.58%), favorable Caco-2 permeability, moderate MDCK permeability, and no predicted inhibition of P-glycoprotein.

These findings suggest a favorable predicted intestinal absorption profile and potential oral bioavailability; however, these predictions do not confirm actual bioavailability and require experimental validation (HUBATSCH I, et al., 2007; MIYAKE T, et al., 2021).

Regarding distribution, phthalic acid exhibited moderate plasma protein binding (PPB = 49.20%), indicating that approximately half of the compound may remain unbound in systemic circulation and therefore available to reach target tissues.

The predicted blood–brain barrier permeability value (BBB = 0.52) suggests a low probability of penetration into the central nervous system, which is consistent with its polar and hydrophilic profile (LAMBRINIDIS G, et al., 2015; KADRY H, et al., 2020).

In terms of metabolism, phthalic acid was predicted to inhibit the cytochrome P450 isoforms CYP2C19 and CYP2C9, while showing neither inhibitory activity nor substrate behavior toward CYP2D6 and CYP3A4. Since cytochrome P450 enzymes play a central role in xenobiotic metabolism and detoxification, inhibition of these isoforms may affect compound clearance and increase the risk of metabolic interactions, toxic accumulation, or adverse effects.

Therefore, these predictions require experimental confirmation before any conclusion regarding its pharmacokinetic safety can be established (GUTTMAN Y; KEREM Z, 2022).

With respect to genetic toxicity, phthalic acid was predicted to be mutagenic in the Ames test, indicating a potential genotoxic risk that warrants careful interpretation. Carcinogenicity predictions were negative in mice but positive in rats, suggesting species-dependent differences in the computational models.

Although these results are based on *in silico* toxicological predictions and require experimental validation, they raise important safety concerns that should be considered before proposing phthalic acid as a potential therapeutic candidate (XU C et al., 2012).

Additionally, phthalic acid showed a low predicted risk of hERG channel inhibition, suggesting a reduced potential for cardiotoxicity, as blockade of this channel is associated with QT interval prolongation and cardiac arrhythmias (SANGUINETTI MC and MITCHESON JS, 2005).

Therefore, despite its demonstrated antimicrobial activity and favorable predicted intestinal absorption profile, the currently available evidence is insufficient to support the therapeutic safety of phthalic acid, and further *in vitro* and *in vivo* toxicological studies are essential before considering its potential clinical application.

Table 2 - In silico predicted physicochemical, pharmacokinetic (ADMET), and toxicological parameters of phthalic acid.

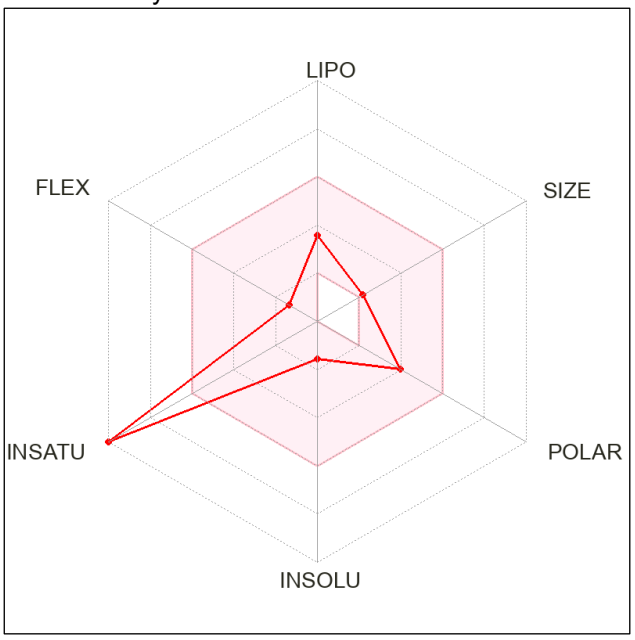
Parameter	Phthalic acid
Molecular weight (g/mol)	166.03
Hydrogen-bond acceptors	4.0
Hydrogen-bond donors	2.0
LogP	0.709
Caco2	-4.718
HIA	81.584
MDCK	29.022
Pgp_inhibition	Non
PPB	49.198
PWS (mg/L)	4718.74
Skin_permeability	-2.108
BBB	0.519
CYP_2C19_inh	Inhibitor
CYP_2C9_inh	Inhibitor
CYP_2D6_inh	Non
CYP_2D6_sub	Non
CYP_3A4_inh	Non
CYP_3A4_sub	Non
Algae_at (mg/L)	0.128
Ames_test	mutagen
Carcino_Mo	negative
Carcino_Rat	positive
daphnia_at	0.627
hERG_inh	low_risk
Medaka_at	0.478
Minnow_at	0.177

Legend: LogP – octanol/water partition coefficient; Caco-2 – intestinal permeability predicted by the Caco-2 cell model; HIA – human intestinal absorption (%); MDCK – permeability predicted using the Madin–Darby canine kidney cell model (nm/sec); Pgp_inhibition – P-glycoprotein inhibition; PPB – plasma protein binding (%); PWS – pure water solubility (mg/L); Skin_permeability – skin permeability; BBB – blood–brain barrier penetration; CYP – cytochrome P450; Algae_at – algal toxicity (mg/L); Ames_test – Salmonella mutagenicity; Carcino_Mo – carcinogenicity in mouse; Carcino_Rat – carcinogenicity in rat; Daphnia_at – toxicity in Daphnia; hERG_inh – hERG potassium channel inhibition; Medaka_at – toxicity in medaka fish; Minnow_at – toxicity in freshwater minnow.
Source: Santos GHB, et al., 2026; data obtained from ADMETlab 2.0 and PreADMET.

The Bioavailability Radar analysis (**Figure 3**) further supports the predicted pharmacokinetic profile of phthalic acid by showing that several physicochemical parameters associated with oral drug-likeness fall within or close to the optimal ranges. Lipophilicity (LIPO), molecular size (SIZE), and polarity (POLAR) were compatible with favorable oral absorption, reflecting the compound's low molecular weight and predominantly hydrophilic nature. The INSOLU parameter indicated high aqueous solubility, consistent with the predicted logS values. However, the INSATU parameter fell outside the optimal range, indicating a low degree of molecular saturation, while the FLEX parameter reflected limited molecular flexibility due to the small number of rotatable bonds. Together, these characteristics suggest that, although phthalic acid presents favorable physicochemical properties for intestinal absorption, some structural features may limit its overall oral bioavailability (DAINA A, et al., 2017).

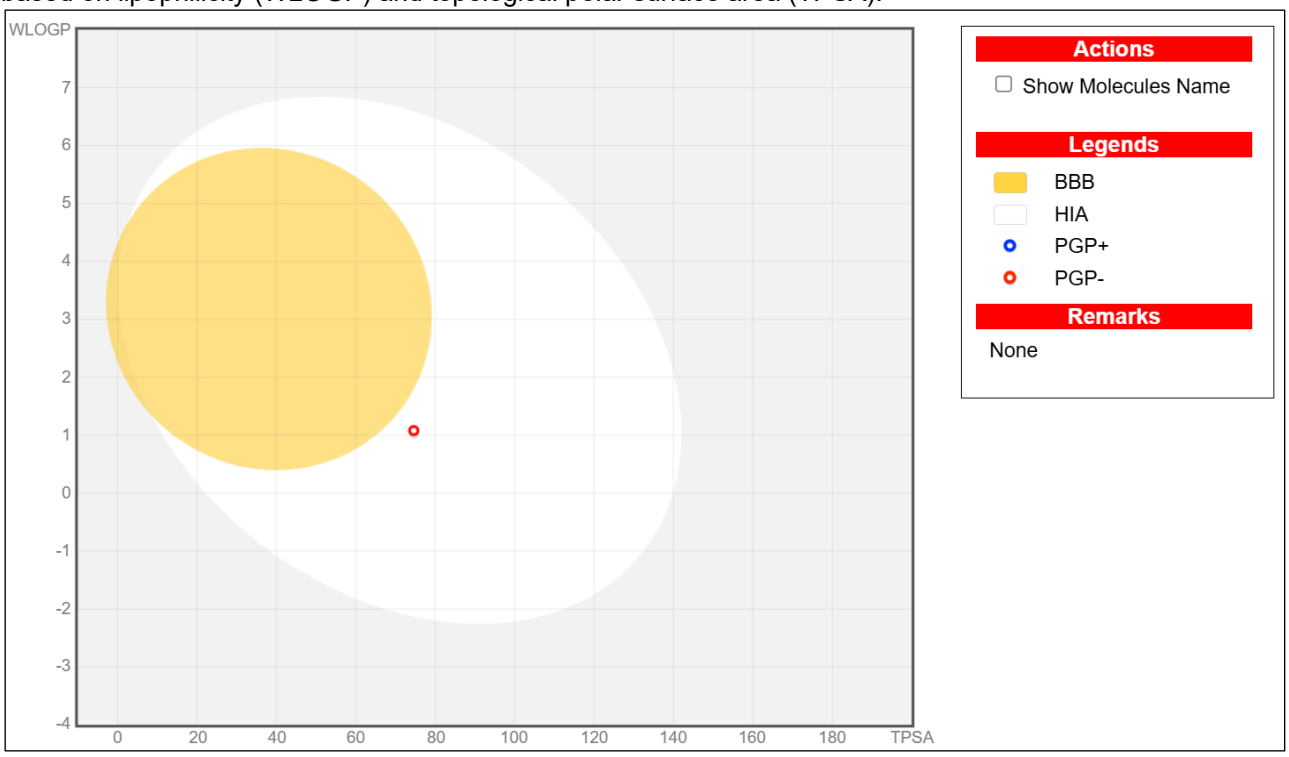
Complementary analysis using the BOILED-Egg model (**Figure 4**) corroborated the ADMET predictions by placing phthalic acid within the region associated with high human intestinal absorption (HIA) while outside the blood–brain barrier (BBB) permeation zone. This distribution pattern reinforces the prediction that the compound may be efficiently absorbed through the gastrointestinal tract but is unlikely to penetrate the central nervous system because of its polar character and low lipophilicity (DAINA A; ZOETE V, 2016). These computational findings are consistent with the predicted pharmacokinetic profile; however, they should be interpreted cautiously, as favorable intestinal absorption does not necessarily translate into adequate oral bioavailability or therapeutic efficacy, both of which require experimental validation.

Figure 3 - Bioavailability radar of phthalic acid, illustrating the relationship between lipophilicity (LIPO), molecular size (SIZE), polarity (POLAR), solubility (INSOLU), degree of unsaturation (INSATU), and molecular flexibility (FLEX), in comparison with the optimal ranges for oral bioavailability.



Source: Santos GHB, et al., 2026. Predictive data obtained using SwissADME.

Figure 4 - BOILED-Egg model of phthalic acid, indicating its localization within the region associated with gastrointestinal absorption (HIA) and outside the area corresponding to blood–brain barrier (BBB) permeation, based on lipophilicity (WLOGP) and topological polar surface area (TPSA).



Source: Santos GHB, et al., 2026. Predictive data obtained using SwissADME.

A key limitation of this review is the small number of eligible studies, with only four meeting the inclusion criteria, reflecting the scarcity of evidence on natural compounds against *T. pallidum*. Moreover, most studies evaluated crude plant extracts rather than isolated compounds, preventing the identification of the specific metabolites responsible for the observed antimicrobial activity. Notably, phthalic acid was the only isolated compound investigated, limiting broader conclusions regarding the therapeutic potential of natural bioactive compounds. The lack of *in vivo* studies further restricts the assessment of efficacy and safety.

Despite these promising findings, research on natural compounds against *T. pallidum* remains at an early stage. Although phthalic acid demonstrated antimicrobial activity, its predicted mutagenic (Ames test) and carcinogenic potential in rats warrants cautious interpretation and further experimental validation. Future studies should prioritize the isolation and characterization of bioactive metabolites, together with comprehensive *in vivo* safety and efficacy evaluations to support their therapeutic potential.

FINAL CONSIDERATIONS

The findings indicate preliminary antitreponemal potential among plant-derived natural products, particularly crude extracts and phthalic acid isolated from *Hibiscus rosa-sinensis*. However, the evidence remains limited, based mainly on *in vitro* assays and computational predictions, with scarce data on isolated compounds, mechanisms of action, selectivity, toxicity, and *in vivo* efficacy. The predicted mutagenic and carcinogenic alerts for phthalic acid reinforce the need for cautious interpretation. Future studies should prioritize compound isolation, structural characterization, standardized antitreponemal assays, cytotoxicity evaluation, *in vivo* validation, and comparison with conventional treatments before any clinical applicability can be proposed.

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DECLARATION OF ARTIFICIAL INTELLIGENCE (AI) AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT to enhance the cohesion of an initial version of the manuscript. After using this tool/service, the authors reviewed and edited the text as needed and take full responsibility for the content of the publication.

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