

In Silico Biological Activity Prediction of Bioactive Compounds from *Dumortiera hirsuta* (Sw.) Nees. Using Way2Drug PASS Online

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Abstract

The liverwort *Dumortiera hirsuta* (Sw.) Nees. is recognized as a potential source of pharmacologically active metabolites. Bioactive compounds from *D. hirsuta* have been previously reported through in vitro metabolomic analyses using gas chromatography–mass spectrometry (GC–MS) and liquid chromatography–mass spectrometry (LC–MS). In this study, the biological activities of the GC–MS-identified metabolites were evaluated in silico using the Way2Drug PASS Online platform. The results indicated that ten metabolites from *D. hirsuta* exhibit medicinal potential, with Pa values greater than 0.7, suggesting a high probability of biological activity. Among these compounds, stigmasterol (Pa = 0.970) and lathosterol (Pa = 0.960) demonstrated the strongest antihypercholesterolemic potential, indicating their role as natural agents for reducing cholesterol levels. These findings highlight the pharmacological potential of *D. hirsuta* metabolites and warrant further validation through in vitro cholesterol-lowering assays to confirm their predicted activities.

Keywords: antihypercholesterolemic, *Dumortiera hirsuta*, in silico, PASS Online

Introduction

Dumortiera hirsuta (Sw.) Nees. is a thalloid liverwort commonly found in humid environments such as moist forest floors and shaded riverbanks. The species is widely distributed across tropical and subtropical regions of Asia and America but is rarely reported in Europe (Forrest et al., 2011). Previous phytochemical studies have revealed that *D. hirsuta* contains a wide range of bioactive secondary metabolites, including terpenes, flavonoids, and phenolic compounds, which are known for their pharmacological relevance (Setyati et al., 2021). Moreover, Liu et al. (2018) demonstrated that extracts of *D. hirsuta* exhibited significant anticancer activity against the HT-29 human colon cancer cell line, suggesting that this species holds considerable promise as a source of plant-derived therapeutic agents. However, further optimization involving dosage formulation, toxicity profiling, and pharmacokinetic evaluation is necessary to validate its potential use as a natural drug resource.

The discovery and development of plant-derived bioactive compounds often begin with in silico predictions of biological activity, which serve as an essential preliminary step in identifying pharmacologically relevant targets (Brogi et al., 2020). Computational approaches such as the Way2Drug PASS Online platform enable the prediction of biological activity spectra for

chemical substances based on their structural formulas expressed in SMILES notation. This platform provides Pa (probability of being active) and Pi (probability of being inactive) scores for each compound, allowing researchers to evaluate the likelihood of specific biological activities (Druzhilovski et al., 2017).

Gas chromatography–mass spectrometry (GC–MS) remains one of the most reliable analytical techniques for identifying volatile and semi-volatile metabolites, as it separates compounds based on retention time and mass spectral properties (Setyati et al., 2024). Integrating GC–MS metabolite profiling with in silico activity prediction offers a powerful approach to uncovering the pharmacological potential of unexplored bryophyte taxa.

The present study aimed to identify and predict the biological activities of bioactive compounds detected by GC–MS in *D. hirsuta* using the Way2Drug PASS Online platform. This research provides the first attempt to combine GC–MS based metabolite identification with in silico biological activity prediction in this liverwort species. The study thus contributes novel insights into the pharmacological potential of *D. hirsuta* and establishes a foundation for future in vitro and in vivo investigations of its bioactive compounds.

Materials and Methods

The present study employed an in silico approach using secondary data from previously published literature. The list of bioactive compounds of *D. hirsuta* was obtained from Dogra et al. (2024), who identified metabolites of this species through GC–MS analysis. The corresponding chemical structures of these compounds were retrieved from the PubChem database (pubchem.ncbi.nlm.nih.gov) in the form of SMILES (Simplified Molecular Input Line Entry System) notation.

Each SMILES structure was subsequently uploaded to the Way2Drug PASS Online platform (www.way2drug.com/passonline) to predict the potential biological activities of the identified metabolites. The program calculates two probability scores for each compound: Pa (probability of being active) and Pi (probability of being inactive). Compounds with Pa > 0.7 were interpreted as having strong predicted biological activity, whereas those with Pa < 0.7 were considered to have lower activity potential.

To visualize and verify the structural representations of the identified compounds, chemical structures were constructed using the ASKCOS MIT online tool (askcos.mit.edu). The resulting dataset of predicted biological activities was used to assess the pharmacological potential of *D. hirsuta* metabolites.

Results and Discussion

In Silico Potential

Bioactive compounds of *D. hirsuta* were previously identified using gas chromatography–mass spectrometry (GC–MS) by Dogra et al. (2024), a technique that separates and detects compounds based on their retention time and mass spectral fragmentation patterns. In the present study, these compounds were evaluated in silico using the Way2Drug PASS Online platform to predict their potential biological activities and drug-likeness properties. The prediction results provide Pa (probability of activity) and Pi (probability of inactivity) values for each compound. Compounds with Pa > 0.7 were considered to possess strong potential pharmacological activity. Table 1 summarises the predicted biological activities of the GC–MS–identified bioactive compounds from *D. hirsuta*.

Based on the in silico results, the bioactive compounds exhibiting the highest Pa values were stigmaterol (0.970) and lathosterol (0.960), both predicted to act as antihypercholesterolemic agents. Antihypercholesterolemic activity refers to the

ability of a compound to reduce elevated cholesterol levels in the body, thereby contributing to the prevention of cardiovascular and metabolic disorders (Upadhyay, 2021). Such properties are highly beneficial for human health, as persistently high cholesterol levels are associated with an increased risk of atherosclerosis and coronary heart disease.

Lathosterol (Lat) is one of the bioactive compounds that has a cholesterol-like chemical compound structure. The compound can be further identified in plant samples, including liverwort. Medically, the compound has the potential to be an antihypercholesterolemic, which can lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase (Ullah et al., 2020). Other biological activities of Lat can be modified as antiparasites, namely by inhibiting the activity of lathosterol oxidase (LSO). LSO plays an important role in the synthesis of sterols with C-5–C-6 double bonds that maintain membrane stability and intracellular pH homeostasis. Further research on lathosterol should be carried out to target its health potential (Wang et al., 2018).

Longipinene is one of the terpene compounds that has great potential in the health field (Narayanan et al., 2017). The results of the analysis of In silico Way2drug in *D. hirsuta* samples obtained a value of Pa (0.702) with antileukemic potential. Antileukemic activity refers to the compound's potential to inhibit or prevent leukemia cell proliferation. Leukemia is one of the blood cancers that can affect the functionality of the bone marrow and lymphatic tissue. Utilization of natural bioactive compounds in therapeutic applications is essential in antileukemic treatment, because treatment with chemotherapy and radiotherapy can cause side effects (Cotoraci et al., 2021). Longipinene, in addition to having antileukemic potential, also has several other biological activities, namely as antidiabetic, antidiarrheal effects, antiinflammatory, antioxidant, antitumor, anticancer, antiulcer, and hepatoprotective (Narayanan et al., 2017).

Phytol stearate is one of the compounds of the lipid ester group that is hydrophobic (Costa et al., 2025). The results of the analysis of In silico Way2drug in *D. hirsuta* samples obtained a value of Pa (0.702) with antiulcerative potential. Antiulceratives are one of the biological activities that can prevent injuries to the digestive organs, such as in the stomach, caused by bacterial infections (Sharifi-Rad et al., 2018). One of the mechanisms of antiulcers is to ward off free radicals (antioxidants) that are in the mucosal area and can inhibit the

growth of ulcer-causing bacteria such as *Helicobacter pylori*, *E. coli*, *Campylobacter* spp., and *Streptococcus* spp. (Okolo et al., 2025).

Hexadecanoic acid, methyl ester, has another name, methyl palmitate. The compound is a bioactive compound identified in *D. hirsuta* samples that has a value (Pa 0.758) with potential as an anti-inflammatory or for the prevention of inflammation.

The mechanism of these compounds as anti-inflammatories is by significantly inhibiting the growth of proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6, which can damage tissues. Other biological activities of hexadecanoic acid, methyl ester are as antioxidants, antihyperlipidemic, and antimicrobial (Agarwal et al., 2019).

Table 1. Bioactive Compound identified from *D. hirsuta* using GC-MS (Dogra et al., 2024)

RT (min)	Bioactive Compounds	Area%	BAP Pass Online	Pa	Pi
26.473	Longipinene	8.16	Antileukemic	0.702	0.005
30.722	Phytol stearate	3.68	Antiulcerative	0.804	0.004
32.610	Hexadecanoic acid, methyl ester	0.86	Anti-inflammatory, intestinal	0.758	0.002
36.294	Phytol	5.82	Antiviral (Rhinovirus)	0.710	0.003
43.192	Phthalic acid, bis(2-ethylhexyl) ester	6.45	Antieczematic	0.895	0.005
46.339	Tetracosane	2.94	Phenol O-methyltransferase inhibitor	0.871	0.002
48.025	Squalene	1.17	Anti-inflammatory	0.701	0.016
54.298	Stigmasterol	5.43	Antihypercholesterolemic	0.970	0.002
53.924	Lathosterol	4.68	Antihypercholesterolemic	0.960	0.002
59.707	Tris(2,4-di-tert-butylphenyl) phosphate	6.22	General anesthetic	0.785	0.005

Phytol is one of the secondary metabolites found in *D. hirsuta*. Phytol is a natural terpenoid compound that has antioxidant activity and plays a role in reducing inflammation. This compound inhibits the production of the COX-2 enzyme in the formation of prostaglandins, which are the main mediators of inflammation. This inhibition is effective in relieving inflammatory symptoms because it can reduce leukocyte migration and enzymatic activity that triggers inflammation (Cintya et al., 2024). Tetracosane is an aliphatic hydrocarbon compound with values of Pa (0.871) and Pi (0.002). This compound shows high cytotoxicity to cancer cells, so that it has the potential for apoptosis and necrosis in gastric adenocarcinoma (AGS) cells (Uddin et al., 2012). Previous studies have reported that Tetracosane compounds have the potential to be antibiotics and also have cytotoxic activity against HT-29 colon cancer cells by inducing cell apoptosis (Saputri et al., 2015).

Squalene is a class of linear triterpene compounds synthesized in plants for the synthesis of secondary metabolites such as sterols, hormones, or vitamins. Previous research has shown that squalene can reduce skin damage from UV radiation, LDL levels, and cholesterol in the blood, prevent the onset of cardiovascular disease, and have antitumor and anticancer effects against ovarian, breast, lung, and colon cancers (Lozano-Grande et al., 2018). Squalene is an unsaturated fat found on the surface of the skin to soften the skin and function as an antitumor. Previous research has also stated that squalene can synergize with α -tocopherol and β -sitosterol compounds as antioxidants, with squalene as a competitive compound in the crocin bleaching reaction by lowering oxidation levels (Sogandi & Nilasari, 2019).

Tris(2,4-di-tert-butylphenyl) phosphate compound with the chemical formula C₄₂H₆₃O₄P is an organophosphate compound which is a phosphate ester derived from di-tert-butylphenol. This

compound has previously been widely found in *Camellia sasanqua* Thunb. Flowers, *Chimonanthus* spp. Leaves and *Plukenetia volubilis* L. seeds

(Zahara et al., 2022). These compounds can be used as anti-enterococcal and antioxidant (Alraddadi et al., 2024).

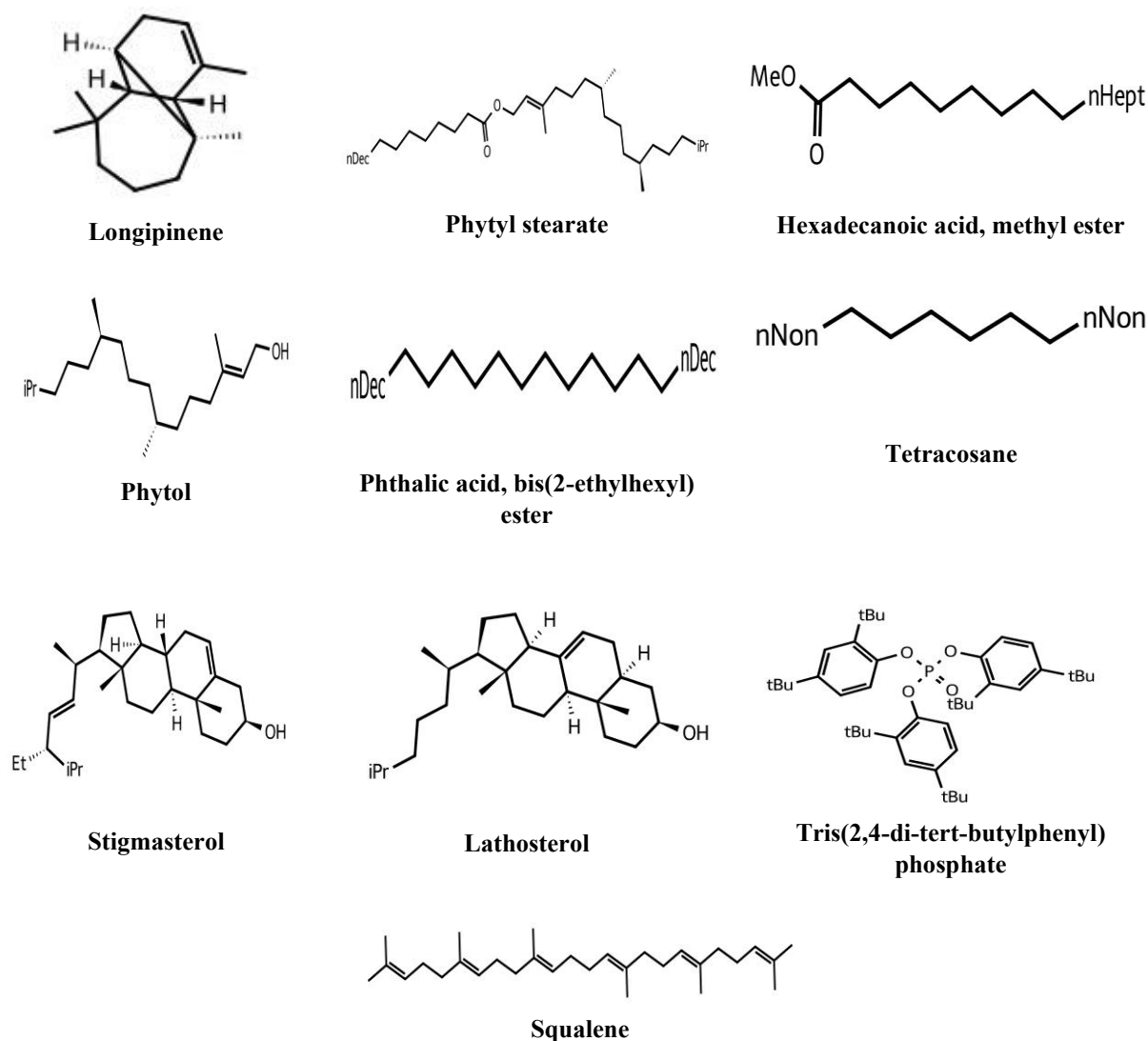


Figure 1. Structures of bioactive compounds from *Dumortiera hirsuta*, illustrated using the ASKCOS MIT platform

Future Potential Development

D. hirsuta is a thalloid liverwort widely distributed across tropical and subtropical regions of Asia, where it typically inhabits shaded and humid environments such as riversides, waterfalls, and moist rock surfaces (Alam et al., 2011). This species is known to contain a variety of secondary metabolites, including triterpenoids, flavonoids, steroids, alkaloids, terpenoids, and saponins, which contribute to its broad pharmacological potential. Ethnobotanical records indicate that *D. hirsuta* has been traditionally utilized in parts of India as an antimalarial and antibiotic agent, reflecting its long-standing medicinal value (Fathoni et al., 2017; Halder & Mitra, 2020).

The pharmacological potential of *D. hirsuta* has been confirmed in several experimental studies. Setyati et al. (2021) reported that the ethyl acetate extract of *D. hirsuta* exhibited antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhi*. The extract produced moderate inhibition zones on culture media, indicating bacteriostatic and bactericidal effects. The mechanism of action was proposed to involve disruption of bacterial cell membrane integrity, leading to apoptosis and cell lysis. Such activity highlights the potential of *D. hirsuta* as a source of natural antimicrobial agents for combating drug-resistant pathogens.

In addition, Liu et al. (2018) demonstrated that *D. hirsuta* extract exhibited anticancer activity in colon cancer models. Using a mouse model with chemically induced colon carcinoma, administration of the extract resulted in a notable reduction in tumor cell proliferation. This effect was attributed to the presence of riccardin, a bis-benzyl compound isolated from *D. hirsuta*, known for its cytotoxic and pro-apoptotic properties. These findings suggest that the liverwort's metabolites could be developed into plant-derived anticancer therapeutics. Further validation using in vitro cell line assays and pharmacokinetic profiling would be essential to elucidate the mechanisms and optimize dosage formulations.

Given its diverse range of metabolites, *D. hirsuta* holds significant promise for future pharmaceutical development. Compounds such as flavonoids, terpenes, and alkaloids, along with unique derivatives like riccardin, could serve as leads for new drug discovery programs (Liu et al., 2018; Sen et al., 2023). Moreover, the increasing global demand for plant-based medicines and the emergence of antibiotic and chemotherapeutic resistance have intensified interest in bryophyte-derived bioactives. The commercialization of *D. hirsuta*-based formulations could provide a sustainable and innovative alternative within the pharmaceutical and nutraceutical industries (Setyati et al., 2021; Mansour et al., 2022).

This study highlights the pharmacological potential of the liverwort *D. hirsuta* through the integration of GC-MS metabolite profiling and in silico biological activity prediction using the Way2Drug PASS Online platform. Ten bioactive compounds previously identified from *D. hirsuta* were evaluated for their predicted pharmacological properties, yielding several metabolites with high Pa values, indicative of strong biological activity. Among them, stigmasterol (Pa = 0.970) and lathosterol (Pa = 0.960) showed the greatest potential as antihypercholesterolemic agents, while other compounds such as longipinene, phytol stearate, hexadecanoic acid methyl ester, phytol, tetracosane, and squalene exhibited diverse biological activities, including antileukemic, antiulcerative, anti-inflammatory, antioxidant, and anticancer effects.

These findings provide scientific evidence that *D. hirsuta* is a promising source of naturally derived metabolites with broad therapeutic relevance. The in silico approach applied here offers a rapid, cost-

effective means of prioritizing candidate compounds for further validation. Nevertheless, in vitro and in vivo investigations are essential to confirm the predicted activities, determine toxicity profiles, and elucidate underlying mechanisms of action.

Acknowledgments

The author gratefully acknowledges the supervising lecturer for their valuable guidance, constructive feedback, and continuous support throughout the preparation of this manuscript.

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