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Phytochemical Profiling and In Silico Analyses Reveal Drug-like Characteristics in the Moss *Brachythecium salebrosum* (Bryophyta, Brachytheciaceae)

El perfil fitoquímico y los análisis in silico revelan características similares a las de los fármacos en el musgo *Brachythecium salebrosum* (Bryophyta, Brachytheciaceae)

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Abstract

Bryophytes have long been used as traditional medicine in many Asian countries, particularly China and India. They are known to possess a variety of phytochemicals with known medicinal properties. While bryophytes are broadly recognized for their medicinal potential, the moss *Brachythecium salebrosum* was selected for this study due to its ecological adaptability and the lack of detailed phytochemical and pharmacological investigations on this species. For the present study, Gas Chromatography-Mass Spectrometry (GC-MS) coupled with a bioinformatics approach was employed to investigate the phytochemical constituents and their drug-like affinities in this moss. A total of 55 phytochemical compounds were identified, with four major compounds—phenol, phytol, 2,4-di-tert-butylphenol, and n-hexadecanoic acid, comprising 48.11% of the total compounds. Interestingly, we also reported odd-numbered fatty acids, which are rare in plants. Molecular

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docking analysis and pharmacokinetic studies of these four compounds revealed robust drug-like properties. The study explored the involvement of certain genes in various metabolic pathways and their associations with different diseases. The findings suggest that *B. salebrosum* contains a reservoir of medicinally important compounds with drug-like characteristics. This study represents the first comprehensive examination of the phytochemical profiling linked to drug kinetic studies of this taxon. The presence of new binding sites as reported in this study will further pave the way for drug discovery and development.

Keywords: Bryophytes; docking; ligand; methanolic extract; phytochemistry; therapeutics.

Resumen

Las briofitas se han utilizado desde hace mucho tiempo como medicina tradicional en muchos países asiáticos, en particular en China e India. Se sabe que poseen una variedad de fitoquímicos con reconocidas propiedades medicinales. Si bien las briofitas son ampliamente reconocidas por su potencial medicinal, el musgo *Brachythecium salebrosum* se seleccionó para este estudio debido a su adaptabilidad ecológica y a la ausencia de investigaciones fitoquímicas y farmacológicas detalladas en esta especie. Por lo tanto, en el presente estudio se empleó cromatografía de gases-espectrometría de masas (GC-MS) junto con un enfoque bioinformático para investigar los componentes fitoquímicos y sus afinidades farmacológicas en este musgo. Se identificaron 55 compuestos fitoquímicos, de los cuales cuatro compuestos principales —fenol, fitol, 2,4-di-terc-butilfenol y ácido n-hexadecanoico— representan el 48,11 % del total. Cabe destacar que también se reportan ácidos grasos de número impar, poco frecuentes en plantas. El análisis de acoplamiento molecular y los estudios farmacocinéticos de estos cuatro compuestos revelaron sólidas propiedades farmacológicas. El estudio exploró la participación de varios genes en diversas vías metabólicas y su asociación con diferentes enfermedades. Los hallazgos sugieren que *B. salebrosum* contiene un reservorio de compuestos de importancia medicinal con características farmacológicas. Hasta donde sabemos, este estudio constituye el primer análisis exhaustivo del perfil fitoquímico vinculado con estudios farmacocinéticos de este taxón. La presencia de nuevos sitios de unión como los informados en este estudio allanará aún más el camino para el descubrimiento y desarrollo de fármacos.

Palabras clave: Briofitas; acoplamiento; ligando; extracto metanólico; fitoquímica; terapéutica.

INTRODUCTION

Bryophytes are well-known for producing a diverse array of chemical compounds that enable them to withstand biotic and abiotic stresses (Dziwak *et al*., 2022). They also have a long history of traditional medicinal use, particularly in China, where they have been used to treat various ailments such as cuts, wounds, pulmonary tuberculosis, bacteriosis, pneumonia, and convulsions (Asakawa *et al*., 2013). The secondary metabolites found in bryophytes hold significant potential in economic, pharmacological, and biotechnological applications (Dziwak *et al*., 2022).

In India, there is a rich tradition of utilizing bryophytes for medicinal purposes (Chandra *et al*., 2017). Various Indigenous communities have employed bryophytes for specific treatments. For instance, tribes in South India have used *Frullania ericoides* to improve hair health, while the Irular tribe from Attappady Valley has applied *Targionia hypophylla* to treat skin disorders (Dziwak *et al*., 2022). Similarly, the Gaddi tribe of North India has utilised *Plagiochasma appendiculatum* for managing skin conditions (Chandra *et al*., 2017).

Mosses are particularly noteworthy due to their high content of secondary metabolites such as phenols, terpenoids, flavonoids, fatty acids, polysaccharides, and amino acids (Greeshma *et al*., 2017; Martínez-Abaigar *et al*., 2021). These compounds are recognised for their potent biological activities and have been used in traditional medicine in Siberia (Klavina *et al*., 2015). Mosses have demonstrated therapeutic potential in treating a variety of conditions, including burns, eczema, and other skin diseases (Petkova *et al*., 2023). As a result, the study of phytochemicals in mosses has emerged as a valuable field of research, given their ethnopharmacological and pharmacological relevance.

The integration of computational tools has revolutionized biomedical research, particularly in the identification and screening of drug candidates (Kingsbury, 1997). Bioinformatics plays a critical role in predicting biologically active compounds, characterizing side effects, and assessing drug resistance (Xia, 2017). The field of drug discovery increasingly depends on identifying appropriate target proteins for potential therapeutic compounds (Katara, 2013).

The moss *Brachythecium salebrosum* is characterized by the plants with silky, robust, yellow-green in colour, brown at base, dense- mat forming moss; main stem creeping with sub-pinnate, erect to ascending branches; leaves dense imbricate, terete, plicate, not squarrose, lanceolate in shape; leaf apex apiculate, margins dentate throughout; Costa single, covering almost 2/3rd of leaf length; leaf cells elongate-rhomboid, *ca*. 77 × 8 μm at tip and 57 × 11 μm at the base with shorter rectangular at extreme base, all basal cells are lax and show cytoplasmic development which is obscure in appearance. Perichaetial leaves longer than vegetative cells, sheathing with erect flexuose and outwardly turn tips; seta long, erect, and smooth;

capsule horizontal, oblong-ovate in shape, arcuate; operculum conical in shape with beak somewhat longer; peristome normal hypnoid; spores ±15 μm in diameter and fine papillose in appearance.

This particular moss species stands out from other *Brachythecium* species in India due to its distinct morphological features, such as larger, plicate leaves with a constricted leaf base, narrow leaf apex, and distinctly dentate margins. These unique characteristics have allowed *B. salebrosum* to adapt to a variety of environmental conditions, contributing to its distribution in regions such as India, China, and Bhutan (Gangulee, 1980; Koponen & Li, 1992). Alongside its ecological resilience, the species is also known to produce a diverse range of secondary metabolites, many of which are believed to play a role in its defence against environmental stressors. The species is further known to possess arsenal of secondary metabolites that have antibacterial effects against *Escherichia coli* (Semerjyan *et al*., 2020). However, the actual metabolite profile and their therapeutic potential in terms of human effects has never been assessed.

Given the richness of its phytochemical profile, *B. salebrosum* presents a promising candidate for further investigation into its bioactive compounds. Recent advancements in bioinformatics tools have enabled researchers to efficiently analyze these phytochemicals, assessing their drug-like properties and therapeutic potential. In this study, we employ bioinformatics approaches to explore the pharmacological prospects of the metabolites found in *B. salebrosum*, providing new insights into its possible applications in drug discovery and design.

MATERIALS AND METHODS

Plant Specimen Collection and Identification

We collected the moss specimen from the remote regions of North-Western Himalaya, the Pangi Valley, Himachal Pradesh, India (32°54'48.13" N, 76°27'43" E) which lies at an average elevation of 2250 masl. The sample was cleaned for any debris and soil, separated from the mixture of other moss taxa, and dried. The sample was then identified based on their micromorphological characters using standard literature (Chopra, 1975; Gangulee, 1980; Bansal & Nath, 2013) (Fig. 1). The voucher specimen has been submitted to the Delhi University Herbarium (DUH15359).

Fig. 1. Habit of moss *Brachythecium salebrosum.*
Fig. 1. Hábito del musgo *Brachythecium salebrosum.*

Preparation of Extract

The moss extract was prepared following Joshi *et al*. (2023) with slight modifications. The sample was pulverised using pestle and mortar. We used 80% methanol for extraction for two main reasons: (1) The study focused on medicinally important bioactive compounds, which are predominantly polar or semi-polar in nature. Methanol is well-recognized for its ability to extract a wide range of compounds effectively, (2) Preliminary extractions using hexane and acetone yielded an insufficient number of compounds, which suggest that methanol was the most suitable solvent for our target phytochemicals. For extraction, two grams of pulverised sample was then mixed with 20 ml of 80 % methanol (v/v) and incubated for a period of 72 hours with recurrent mixing in an orbital shaker at 50°C. The mixture was subsequently filtered via Whatman filter paper 1. The filtrate was dried at room temperature (25°C) and then resuspended in 100 μl methanol. From this resuspension, 1μl of solution is taken for analysis.

Gas Chromatography – Mass Spectrometry (GC-MS) Analysis

The extract was injected into PerkinElmer Auto System XL with Turbo mass system. The column Elite- 5MS used for the analysis has dimensions 30 m × 0.250 mm × 0.250 μm. The gas used as the carrier was Helium. The oven temperature ranges from 75°C for five minutes to 280°C hold for ten minutes with an increasing temperature rate of 10°C per minute. The temperature of the used injector was 260°C complemented with the flow rate of 1 ml/min. The temperature of Electron Ionization (EI) was 220°C powered with a scan range of 20 to 610 amu. The final injector volume was 2 μl. The data obtained in the form of chromatograms and the recorded compounds were recognised by assessing the mass spectra of our samples studied with the mass spectra of already known compounds using the National Institute of Standard and Technology (NIST) 14 library.

Pharmacokinetics and Drug-Like Characteristics Assessment

The top four compounds with the highest relative abundance were further selected to study the drug-like characteristics and pharmacokinetic analysis. The canonical SMILES of shortlisted compounds were retrieved from PubChem (Kim *et al.*, 2021) and their physical, chemical, and biological properties were then examined using SwissADME (Daina *et al.*, 2017). These properties include the hydrogen bond donor atoms, molecular weight of compounds, hydrogen bond acceptor atoms, the number of rotatable bonds and the topological polar surface area. We also assessed the lipophilicity and water solubility of compounds in terms of Log P and Log S.

Factors such as gastrointestinal (GI) absorption, skin permeability (Log K_p), inhibitors of some cytochromes P450 (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), blood-brain barrier (BBB), and P-glycoprotein (P-gp) substrate were examined for Pharmacokinetics and medicinal chemistry. The compounds' drug potential was evaluated by assessing their adherence to various filters such as the Lipinski filter, Veber filter, Egan filter, Ghose filter, Muegge filter, and their bioavailability scores using the Abbott Bioavailability score.

Prediction of Target Proteins

The potential target proteins of the shortlisted compounds were predicted using the Swiss Target Prediction Programme (Daina *et al.*, 2019). This was done to ensure their affinity towards our compound of interest, which was further used to analyze their therapeutic potential. The statistically significant targets with the highest probability scores existed were identified and used for successive analysis.

Metabolic Pathways and Disease-Associated Genes of Target Proteins Evaluation

We examined the metabolic pathways and genes associated with diseases by utilising the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (Kanehisa *et al*., 2023) and the DisGenNet database (Piñero-González *et al*., 2015). Both databases were used along with GeneCodis4 (Garcia-Moreno *et al*., 2022). The genes for the top 100 predicted targets of each of the four selected compounds were used for the analysis. The statistically significant associations against the -log (p-value adjusted) were selected and analyzed.

Molecular Docking Analysis

We conducted molecular docking analysis to confirm the accuracy of the predicted targets for each compound. The topmost predicted target with the highest probability score was selected for each compound. We retrieved the three-dimensional (3-D) structures of the predicted targets using protein data bank, i.e., the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) (Burley *et al*., 2021). The 3D conformer assemblies of our compounds were retrieved using PubChem (Kim *et al*., 2021). The pre-requisite for molecular docking analysis is the preparation of receptor (targets) and ligand (compounds) molecules. For this, receptors were prepared by removing water molecules and all the non-standard atoms as they may interfere with the docking analysis, followed by adding polar hydrogen atoms and Kollman charge using UCSF Chimera (Pettersen *et al*., 2004) and AutoDock tool version 1.5.7 (Morris *et al*., 2009). Likewise, the ligands were also prepared. After preparation, we performed site-specific docking for all the ligands and receptors except dual specificity phosphatase CDC25A and phytol, where we performed blind docking. The reason for this is the unavailability of a complete three-dimensional structure of CDC25A. Using Alphafold in RCSB PDB, the predicted complete three-dimensional structure of CDC25A was retrieved, prepared, and blind docking was performed for the predicted structure. We used AutoDock Vina (Trott & Olsson, 2010) to perform both site-specific and blind docking analyses. The thermodynamically favourable Gibbs free binding energies (ΔG) of interaction between the ligand and receptor were produced in a log file. The two- dimensional ligand-receptor poses were observed utilising Discovery Studio Visualiser.

RESULTS

Phytochemical Composition in *B. salebrosum*

The analysis revealed a total of 55 phytochemicals (Table 1). The major phytochemicals identified based on highest relative abundance and percentage peak area are- phenol, *n*-hexadecanoic acid, 2,4- di-tertiary butylphenol, and phytol which comprise a total of 48.11% of all the compounds present in the sample.

Pharmacokinetics and Drug-Likeness Analysis

All four shortlisted compounds were found to have high synthetic accessibility. The compounds phytol and *n*-hexadecanoic acid are found to possess one violation each because their MLOGP values are greater than 4.15. The solubility of all these compounds ranges from very soluble to moderately soluble (Table S1). The pharmacokinetic analysis revealed that these compounds except phytol have high GI absorption and other characteristics such as Skin permeation value ($LogK_p$) have good scores (Table S2). Furthermore, all these compounds followed Lipinski's rule and hence they possess drug-like characteristics (Table S3).

Target Protein Predictions, metabolic pathways, and disease-associates genes

The target prediction revealed the top 100 statistically significant targets of our compounds out of which only the top 15 are taken for further analysis. The predicted topmost targets for our compounds are Carbonic anhydrase II (CA2), Fatty Acid Binding Protein adipocytes 4 (FABP4), and dual-specificity phosphatase CDC25A. (Table 2). Analysis of the genes of the top 15 predicted proteins for each compound revealed the maximum percentage of genes belonging to the Lyase class of enzymes in the case of phenol, fatty acid binding protein and nuclear receptor in the case of *n*-hexadecanoic acid. For 2,4-di-tert-butylphenol and phytol, the maximum percentage of genes belong to the class of nuclear receptors and kinase (Fig. 2A-D). The targeted genes participate in several critical metabolic pathways and diseases. The genes for phenol engage in nitrogen metabolism but a greater number of genes are associated with other metabolic pathways with low significance (Fig. S1A). These genes are also associated with several mental disorders and carcinomas (Fig. S1B). Likewise, the targeted genes for *n*- hexadecanoic acid are associated with the PPAR signaling pathway (Fig. S2A). They are known to be associated with hypertensive diseases and endometrioma (Fig. S2B) with high significant values; genes targeted for 2,4-di-tert-butylphenol are linked to mental illness and Neuroactive ligand-receptor interaction (Fig. S3A, S3B).

Table 1. List of phytochemicals identified from moss methanolic extract.

Tabla 1. Lista de fitoquímicos identificados a partir del extracto metanólico de musgo.

S. N°	Compounds	RT	Formula	MW	m/z
1.	(R)-(-)-Methyl 3-hydroxybutyrate	3.68	C5H10O3	118	0.75
2.	Butanoic acid, 3-hydroxy-, methyl ester, (S)-	3.819	C5H10O3	118	1.47
3.	Butanoic acid, 3-hydroxy-, methyl ester	3.958	C5H10O3	118	3.61
4.	1,2-Propanediol, 1-acetate	4.097	C5H10O3	118	0.18
5.	Butanamide, 3, n-dihydroxy-	4.236	C4H9O3N	119	0.19
6.	Butanoic acid, methyl ester	4.375	C5H10O2	102	0.98
7.	2,4-Diacetoxypentane	4.514	C9H16O4	188	0.35
8.	3-Methoxymethoxybutyric acid	4.653	C6H12O4	148	7.43
9.	Butanoic acid, methyl ester	4.792	C5H10O2	102	1.68
10.	Hexanoic acid, 3-hydroxy-, methyl ester	4.931	C7H14O3	146	9.92
11.	3-Hydroxy-3-methyl-hexanoic acid	5.07	C7H14O3	146	0.52
12.	Heptanoic acid, 3-hydroxy-, methyl ester	5.209	C8H16O3	160	0.88
13.	Ethanol, 1-methoxy-, acetate	5.348	C5H10O3	118	0.43
14.	2- Hydroxymethylcyclopropane car boxylic acid methyl ester	5.487	C6H10O3	130	0.62
15.	Methyl isobutyrate	5.626	C5H10O2	102	1.45
16.	Phenol	5.935	C6H6O	94	6.49
17.	2-Vinylfuran	6.553	C6H6O	94	0.41
18.	3-Methylpyridazine	6.62	C5H6N2	94	0.41
19.	4-Methylpyridazine	8.65	C5H6N2	94	1.99
20.	Formic acid phenyl ester	9.72	C7H6O2	122	0.59
21.	cis-1,2-dihydrocatechol	10.87	C6H8O2	112	3.52
22.	Benzene, ethoxy-	11.35	C8H10O	122	1.07
23.	Phenyl. beta. -chloropropionate	12.84	C9H9O2Cl	184	3.65
24.	3-Oxabicyclo [3.2.0] hept-6-ene-2,4- dione, 1-methyl-	13.798	C7H6O3	138	8.55
25.	Acetic acid, phenyl ester	13.86	C8H8O2	136	0.23
26.	5-Vinylpyrazole	14.84	C5H6N2	94	0.27
27.	2,4-di-tert-butylphenol	15.158	C14H22O	206	0.57
28.	Phenol, 2,6-bis (1,1- dimethyl ethyl)-	19.09	C14H22O	206	2.28
29.	Ethyl 4-t-butylbenzoate	19.355	C13H18O2	206	1.01
30.	Pentanoic acid, 5-hydroxy-, 2,4- di-t-butylphenyl esters	19.56	C19H30O3	306	2.04
31.	Phenol, 2,5-bis (1,1- dimethyl ethyl)-	19.865	C14H22O	206	0.21
32.	Benzaldehyde, 4-hydroxy-3,5- bis(1-methylethyl)-	19.925	C13H18O2	206	1.61
33.	Pentanedioic acid, (2,4-di-t- butylphenyl) monoester	20.035	C19H28O4	320	0.24
34.	Oxirane, [[4-(1,1- dimethyl ethyl) phenoxy] methyl]-	20.365	C13H18O2	206	0.17
35.	n-hexadecanoic acid	20.445	C16H32O2	256	0.44
36.	Eicosanoic acid	20.505	C20H40O2	312	0.95
37.	Tetradecanoic acid	20.535	C14H28O2	228	0.79
38.	Octadecanoic acid	20.565	C18H36O2	284	0.7
39.	Tridecanoic acid	20.595	C13H26O2	214	0.29
40.	Nonadecanoic acid	21.821	C19H38O2	298	0.21
41.	Dodecanoic acid	21.86	C12H24O2	200	0.63
42.	Neophytadiene	22.216	C20H38	278	0.32
43.	Phytol	21.941	C20H40O	296	0.29
44.	3,7,11,15-Tetramethyl-2- hexadecen-1-ol	22.451	C20H40O	296	0.95
45.	Phytol, acetate	22.686	C22H42O2	338	0.35
46.	Oxirane, hexadecyl-	22.921	C18H36O	268	0.28
47.	3,7,11,15-Tetramethylhexadec-2- en-1-yl acetate	23.026	C22H42O2	338	0.19
48.	Oxirane, heptadecyl	23.131	C19H38O	282	2.16
49.	Heptadecanal	23.236	C17H34O	254	0.26
50.	Tetracosanal	23.341	C24H48O	352	0.44
51.	Oxirane, tetradecyl	23.446	C16H32O	240	0.74
52.	Octadecanal	23.551	C18H36O	268	0.65
53.	Pentadecanal	23.656	C15H30O	226	0.6
54.	Hexadecanal	23.761	C16H32O	240	0.24
55.	Eicosanal	23.866	C20H40O	296	0.72

Table 2. Binding affinities of the compounds with their target proteins. Values denoting the binding energies involved in the association of receptors with their ligand

Tabla 2. Afinidades de unión de los compuestos con sus proteínas diana. Valores que indican las energías de enlace implicadas en la asociación de los receptores con su ligando

S. N°	Compounds	Target protein	Binding affinity (ΔG) Kcal/mol
1.	Phenol	Carbonic anhydrase II (CA2)	-4.9
2.	n-Hexadecenoic acid	Fatty acid binding protein adipocyte (FABP4)	-6.7
3.	Phytol	Dual specificity Phosphatase CDC25A	-4.5
4.	2,4-ditertiary butylphenol	Carbonic anhydrase II (CA2)	-6.2

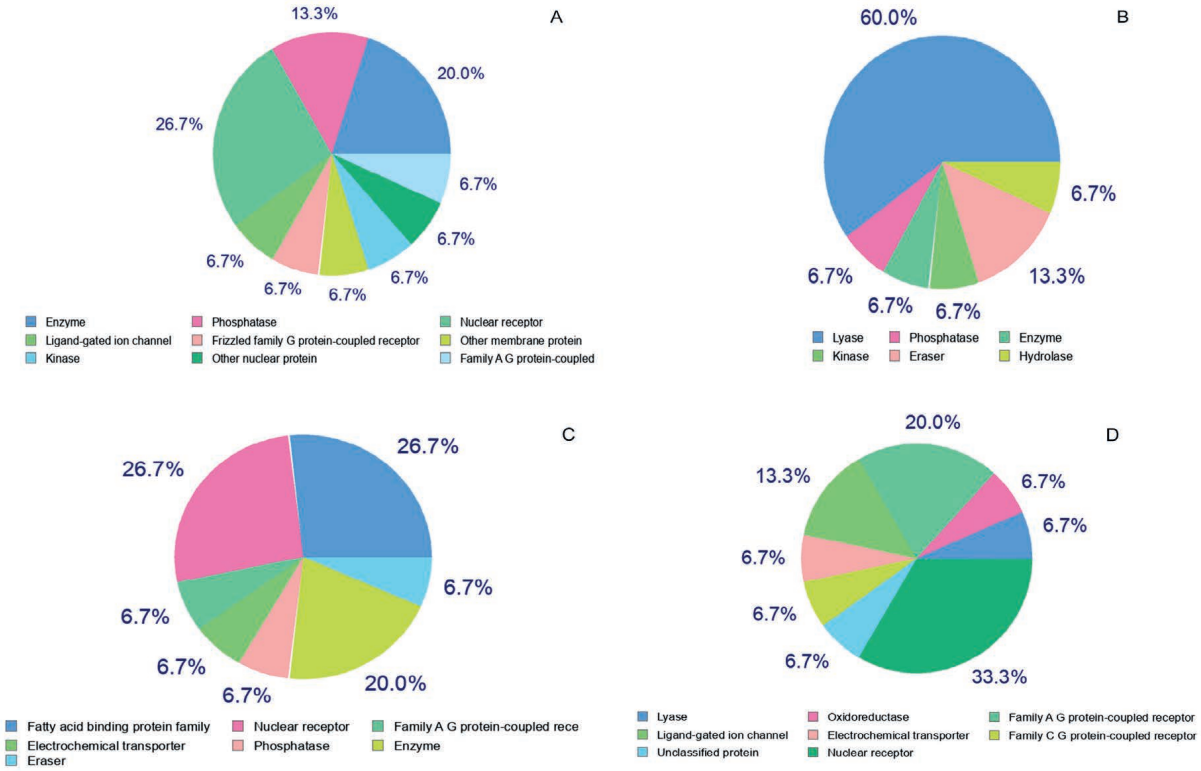

Fig. 2. Pie charts showing the class of genes for top 15 percent of the target proteins. (A) phytol, (B) phenol, (C) *n*-hexadecanoic acid, (D) 2,4-di-tert-butylphenol.

Fig. 2. Gráficos circulares que muestran la clase de genes del 15 % superior de las proteínas diana. (A) fitol, (B) fenol, (C) ácido n-hexadecanoico, (D) 2,4-di-terc-butilfenol.

For phytol, targeted genes are associated with mental illness, carcinomas, etc. and insulin resistance and cancer pathways with high statistical values (Fig. S4A, S4B).

Interactions Between Receptors and Ligands Using Molecular Docking

The analysis of site-specific as well as blind docking generated nine poses each for all the studied compounds. Among all the compounds studied, the most favorable interaction was found between *n*- hexadecanoic acid and FABP4. The Gibbs free binding energies values for studied compounds are presented in Table 2. The interaction between phenol and its target protein, i.e., CA2 was facilitated by 2 hydrogen bonds, 3 pi-alkyl bonds, 3 van der Waals interactions, and 1 pi-cation bond. (Fig. 3A). The interaction between *n*- hexadecanoic acid and FABP4 was facilitated by conventional hydrogen bonds, van der Waals, alkyl bonds, and pi- alkyl bonds (Fig. 3B). Correspondingly, hydrogen bonds, van der Waals, alkyl bonds, and pi-alkyl bonds were involved in the interaction of phytol with CDC25A (Fig. 3C). However, no conventional hydrogen bonding was observed between 2,4-di-tert-butylphenol and phytol (Fig. 3D). All these interactions encompass the previously known binding sites except CDC25A-phytol interaction.

DISCUSSION

Phytochemicals reported and their significance

The present study highlights the therapeutic potential of moss *B. salebrosum*. We identified a total of 55 phytochemicals. Among them, certain compounds such as *cis*-1,2-dihydro catechol, although found with a less significant abundance, are known to be involved in the production of biologically active natural products (Taher *et al*., 2018). Additionally, neophytadiene can be used as a potential anti-cancer drug (Selmy *et al*., 2023). We found the highest relative percentage of phenol in our sample because bryophytes are known to possess a diverse range of chemical compounds including phenols to counter the biotic and abiotic stress (Asakawa & Ludwiczuk, 2017; Cianciullo *et al*., 2021). The occurrence of phytol and *n*-hexadecanoic acid was also expected as many bryophytes contain a good amount of saturated fatty acids (Lu *et al*., 2019), and phytol is known to be the most widespread photosynthetic pigment in plants which results from chlorophyll degradation (Gutbrod *et al*., 2021). Phytol is also known to provide promising results against Schistosomiasis, a devastating parasitic disease worldwide (de Moraes *et al*., 2014). The compound 2,4-di-tert-butylphenol is known to be present in ca. 169 distinct species of living organisms (Zhao *et al*., 2020). It has anti-inflammatory, anti-cancer, insecticidal, antimicrobial, and antifungal properties (Chen & Dai, 2015; Nair *et al*., 2020; Zhao *et al*., 2020).

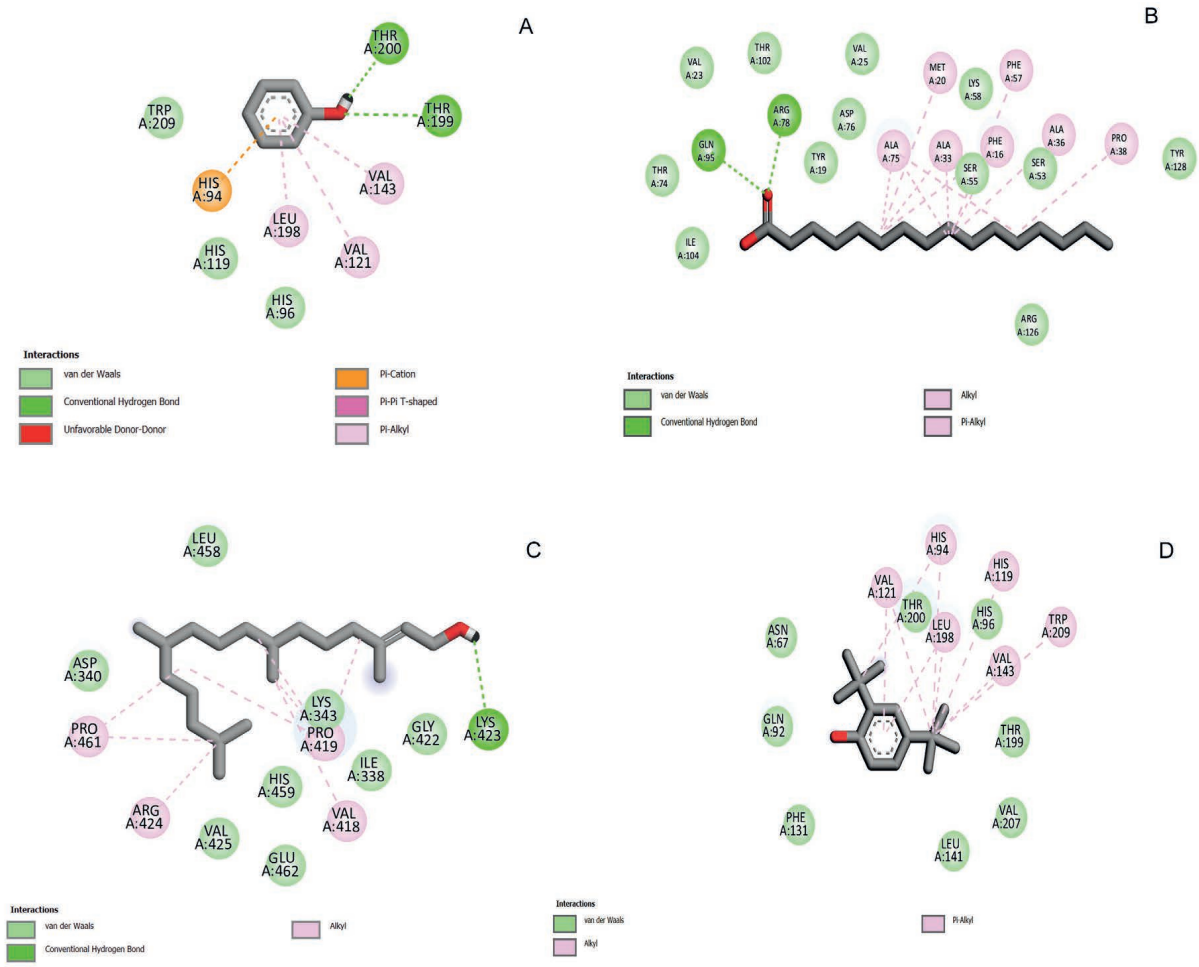

Fig. 3. Interaction between compounds and their target proteins. Different colours showing different types of interactions. A) Phenol interaction with its target. B) n-hexadecanoic acid interaction with its target. C) Phytol interaction with its target. D) 2,4-di-tert-butylphenol interaction with its target.

Fig. 3. Interacción entre los compuestos y sus dianas proteicas. Los diferentes colores indican diferentes tipos de interacción. A) Interacción del fenol con su diana molecular. B) Interacción del ácido n-hexadecanoico con su diana molecular. C) Interacción del fitol con su diana molecular. D) Interacción del 2,4-di-terc-butilfenol con su diana molecular.

Pharmacokinetics, target proteins prediction, and metabolic roles

The physicochemical analyses of these compounds exhibit promising attributes that align with Lipinski's rule of five, suggesting their potential suitability as drug candidate. Furthermore, these compounds exhibited significant binding affinities towards a diverse array of proteins, and computational predictions regarding their putative target proteins unveiled their participation in multiple biological pathways and pathological conditions.

The top two targets of phenols were CA2 and CA3. These carbonic anhydrase enzymes are actively involved in different physiological roles in the human body. CA2 is found in various tissues such as the gastrointestinal tract, erythrocytes, lung, eye, bone osteoclasts, brain, kidney, testis, etc. and is known to be linked with many diseases such as glaucoma, edema, renal tubular acidosis, osteoporosis, etc. (Jakubowski *et al*., 2018). CA3 is localized in cytosol and is known to have an antioxidant effect that protects cells from oxidative damage (Furuhashi *et al*., 2014). The two statistically significant targets of *n*-hexadecanoic acid were FABP4 and Peroxisome Proliferator-Activated Receptor Alpha (PPARA). FABP4 is primarily found in macrophages and adipocytes and is active in developing atherosclerosis and insulin resistance with respect to metaflammation (di Fiore *et al*., 2018). It has also been identified as a critical determinant of the likelihood of ovarian cancer spreading to other parts of the body (Gharpure *et al*., 2018) and promotes obesity-linked breast cancer (Zeng *et al*., 2020). PPARA resides in the liver and is primarily involved in lipid metabolism and its agonists are found to be promising candidates in non-fatty liver diseases (Kersten & Stienstra, 2017). The two topmost targets of phytol were CDC25A and the Androgen Receptor (AR). CDC25A is linked to apoptotic cell cycle pathways (Biswas *et al*., 2017). It also controls tumorigenesis and cell cycle proliferation by controlling the expression of target proteins involved with G1/S cell cycle transition and cyclin D1. The AR is a nuclear factor with significant relevance to prostate cancer, which stands as the second-most frequent cancer among men and currently is the second principal- cause of mortality in men (Ouellette *et al*., 2019; Yu *et al*., 2019; Jia & Han, 2023). The two potential targets of 2,4-di-tert-butylphenol were CA2 and Prostaglandin- Endoperoxide Synthase 1 (PTGS1). PTGS1 is involved in the regulation of osteogenesis of Adipose-derived Stem Cells (ASCs) (Wang *et al*., 2019). The identification of these potential targets, coupled with their associations with diseases that can be fatal in certain instances, underscores the utmost significance of the present study.

Binding sites between ligands and receptor

Molecular docking analysis demonstrates that nearly all the shortlisted compounds formed interactions with the active sites of the target proteins. Some of the active binding sites for FABP4 encompass Phe16, Tyr19, Met20, Val23, Val25, Thr29, Ala33, Phe57, Ile104, Val115, Arg126, and Tyr128 (González & Fischer, 2015). The present docking between *n*-hexadecanoic acid and FABP4 involves all these binding sites except Thr29 and Val115 which reflects the strong affinity of these compounds. Furthermore, our docking analysis revealed the emergence of several new active sites. Specifically, in docking between phenol and CA2, binding occurs at Thr199, and Thr200 with pose one which further reflects the high binding affinity between these two compounds.

Similarly, the interaction between 2,4-di-tert-butylphenol and CA2 unveiled the involvement of multiple new binding sites. The binding event between phytol and CDC25A proved particularly intriguing. The comprehensive Alphafold structure prediction uncovered fresh active pocket regions within the proteins, representing valuable insights that can significantly contribute to drug design and discovery.

CONCLUSION

The present study identifies the moss *B. salebrosum* as a promising source of bioactive phytochemicals with potential therapeutic applications. Through *in silico* analyses, several structurally and functionally diverse compounds were characterized, providing insight into their molecular interactions with key human proteins. The identification of novel potential binding sites for phenol and 2,4-di-tert-butylphenol suggests previously unrecognized modes of protein-ligand interaction, that may hold significance in the development of new drug candidates. Molecular docking results align with target prediction data, reinforcing the reliability of computational approaches in preliminary drug screening. Also, the target proteins associated with the selected compounds are implicated in various physiological and pathological pathways which indicates that these natural molecules may influence multiple biological processes. These findings emphasize the potential of moss-derived compounds in contributing to drug discovery pipelines, particularly in the context of multi-target therapeutics. Although the present investigation relies on computational predictions, it establishes a strong foundation for future experimental validation. *In vitro* and *in vivo* assays will be required to confirm biological activity, assess toxicity, and elucidate pharmacokinetic profiles. The integration of such data can facilitate the transition of these compounds from theoretical models to practical drug development frameworks. This work contributes to the expanding field of natural product research by highlighting mosses as underexplored yet valuable reservoirs of medicinally relevant metabolites, especially in the context of drug discovery aimed at complex and multifactorial human diseases.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPLEMENTARY MATERIAL

Table S1. Different physico-chemical characteristics of shortlisted compounds.

Tabla S1. Diferentes características fisicoquímicas de los compuestos preseleccionados.

Physicochemical properties, lipophilicity, and water solubility of studied compounds				
Parameters	**Phenol**	**n-Hexadecenoic acid**	**Phytol**	**2,4-di-tert-butyl-phenol**
Molecular weight	94.11 g/mol	256.42 g/mol	296.53 g/mol	206.32 g/mol
Num. heavy atoms	7	18	21	15
Num. arom. heavy atoms	6	0	0	6
Fraction Csp3	0	0.94	0.90	0.57
Num. rotatable bonds	0	14	13	2
Num. H-bond acceptors	1	2	1	1
Num. H-bond donors	1	1	1	1
Molar Refractivity	28.46	80.80	98.94	67.01
TPSA	20.23 Å²	37.30 Å²	20.23 Å²	20.23 Å²
Log Po/w (iLOGP)	1.24	3.85	4.71	3.08
Log Po/w (XLOGP3)	1.46	7.17	8.19	5.19
Log Po/w (WLOGP)	1.39	5.55	6.36	3.99
Log Po/w (MLOGP)	1.45	4.19	5.25	3.87
Log Po/w (SILICOS-IT)	1.50	5.25	6.57	3.81
Consensus Log Po/w	1.41	5.20	6.22	3.99
Log S (ESOL)	-1.98	-5.02	-5.98	-4.55
Solubility	9.91e-01 mg/ml; 1.05e-02 mol/l	2.43e-03 mg/ml; 9.49e-06 mol/l	3.10e-04 mg/ml; 1.05e-06 mol/l	5.78e-03 mg/ml; 2.80e-05 mol/l
Class	Very soluble	Moderately soluble	Moderately soluble	Moderately soluble
Log S (Ali)	-1.49	-7.77	-8.47	-5.36
Solubility	3.04e+00 mg/ml; 3.23e-02 mol/l	4.31e-06 mg/ml; 1.68e-08 mol/l	9.94e-07 mg/ml; 3.35e-09 mol/l	8.97e-04 mg/ml; 4.35e-06 mol/l
Class	Very soluble	Poorly soluble	Poorly soluble	Moderately soluble
Log S (SILICOS-IT)	-1.73	-5.31	-5.51	-4.25
Solubility	1.74e+00 mg/ml; 1.85e-02 mol/l	1.25e-03 mg/ml; 4.88e-06 mol/l	9.06e-04 mg/ml; 3.05e-06 mol/l	1.16e-02 mg/ml; 5.64e-05 mol/l
Class	Soluble	Moderately soluble	Moderately soluble	Moderately soluble

Table S2. Pharmacokinetic parameters of the compounds.

Tabla S2. Parámetros farmacocinéticos de los compuestos.

Pharmacokinetics of studied compounds				
Parameters	**Phenol**	**n-Hexadecenoic acid**	**Phytol**	**2,4-di-tert-butyl-phenol**
GI absorption	High	High	Low	High
BBB permeant	Yes	Yes	No	Yes
P-gp substrate	No	No	Yes	No
CYP1A2 inhibitor	Yes	Yes	No	No
CYP2C19 inhibitor	No	No	No	No
CYP2C9 inhibitor	No	Yes	Yes	No
CYP2D6 inhibitor	No	No	No	Yes
CYP3A4 inhibitor	No	No	No	No
Log KP (Skin permeation)	-5.84 cm/s	-2.77 cm/s	-2.29 cm/s	-3.87 cm/s

Table S3. Drug-likeness and medicinal characteristics of the compound.

Tabla S3. Características farmacológicas y medicinales del compuesto.

Druglikeness and medicinal chemistry of studies compounds				
Parameters	**Phenol**	**n-Hexadecenoic acid**	**Phytol**	**2,4-di-tert-butyl-phenol**
Lipinski	Yes; 0 violation	Yes; 1 violation: MLOGP>4.15	Yes; 1 violation: MLOGP>4.15	Yes, 0 violations
Ghose	No; 3 violations: MW<160, MR<40, #atoms<20	Yes	No; 1 violation: WLOGP>5.6	Yes
Veber	Yes	No; 1 violation: Rotors>10	No; 1 violation: Rotors>10	Yes
Egan	Yes	Yes	No; 1 violation: WLOGP>5.88	Yes
Muegge	No; 2 violations: MW<200, Heteroatoms<2	No; 1 violation: XLOGP3>5	No; 2 violations: XLOGP3>5, Heteroatoms<2	Yes
Bioavailability Score	0.55	0.85	0.55	0.55
PAINS	0 alert	0 alert	0 alert	0 alert
Brenk	0 alert	0 alert	1 alert: isolated alkene	0 alert
Leadlikeness	No; 1 violation: MW<250	No; 2 violations: Rotors>7, XLOGP3>3.5	No; 2 violations: Rotors>7, XLOGP3>3.5	No; 2 violations: MW<250, XLOGP3>3.5
Synthetic accessibility	1.00	2.31	4.30	1.43

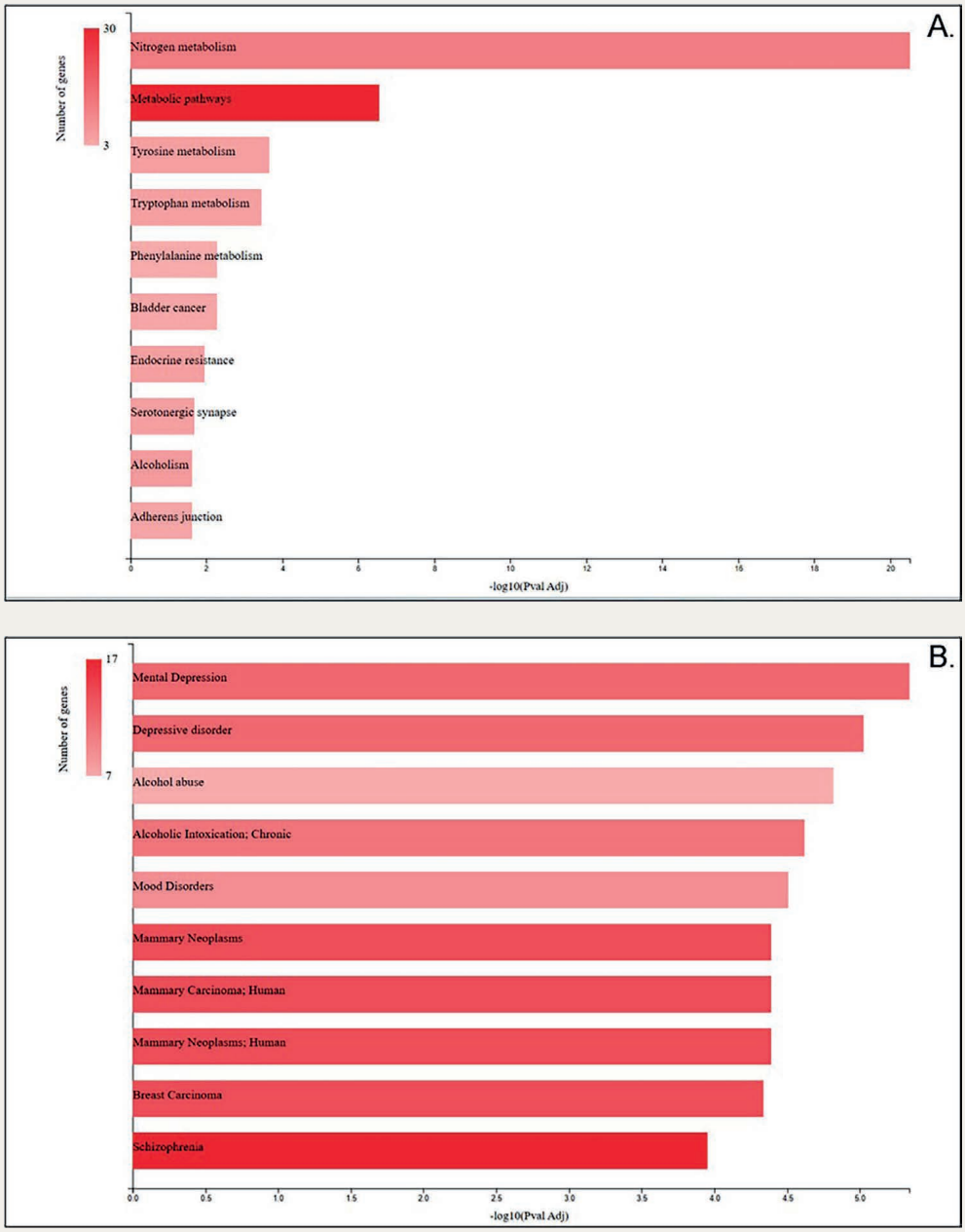


Fig. S1A and S1B. Genes associated with metabolic pathways and disease caused by phenol.

Fig. S1A y S1B. Genes asociados con las vías metabólicas y enfermedades causadas por el fenol.

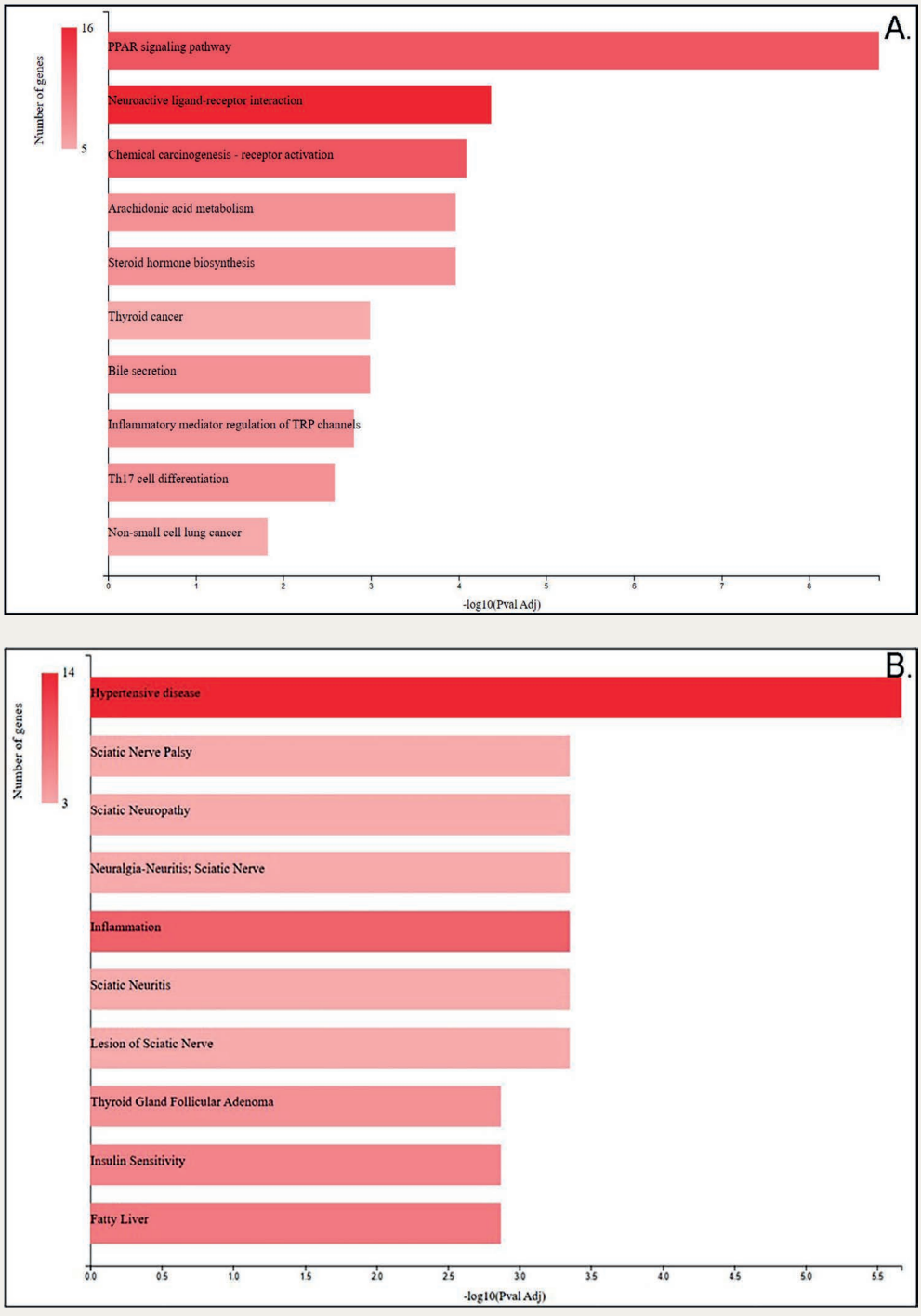
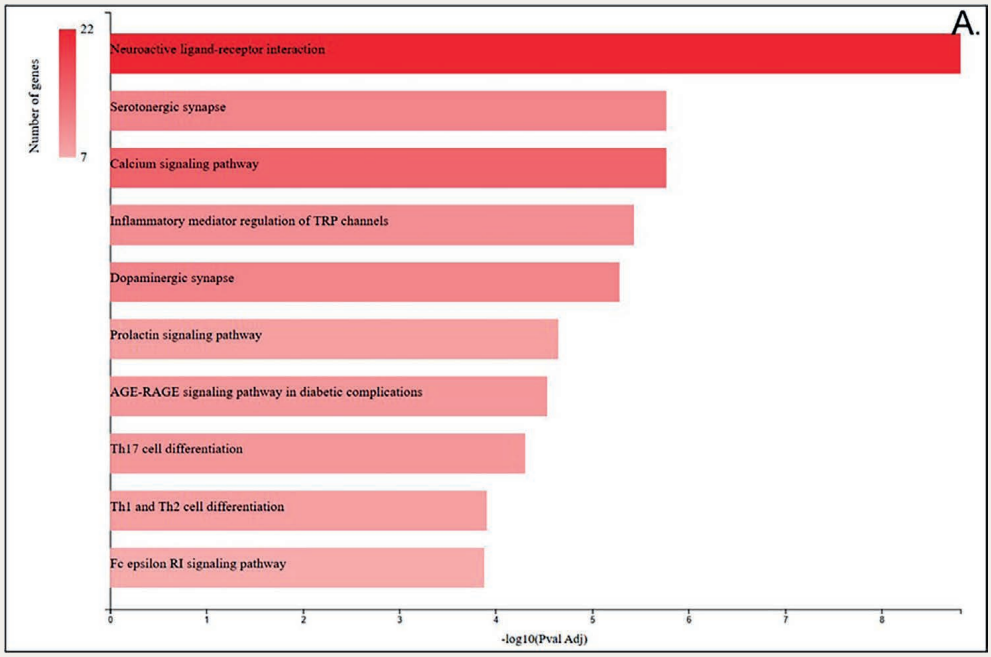


Fig. S2A and S2B. Genes associated with metabolic pathways and disease caused for n-hexadecanoic acid.

Fig. S2A y S2B. Genes asociados con las vías metabólicas y la enfermedad del ácido n-hexadecanoico.



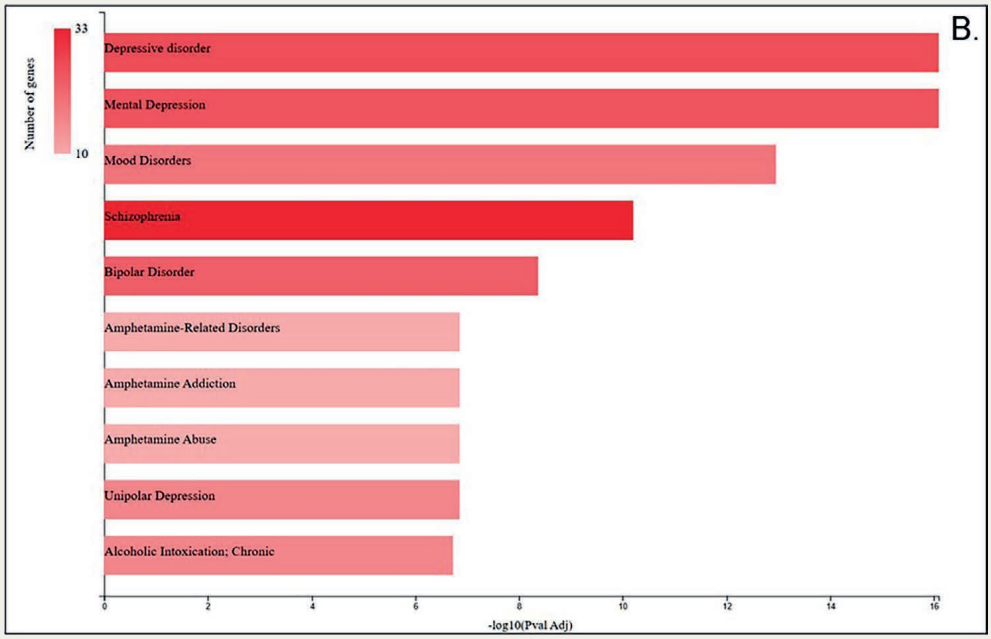
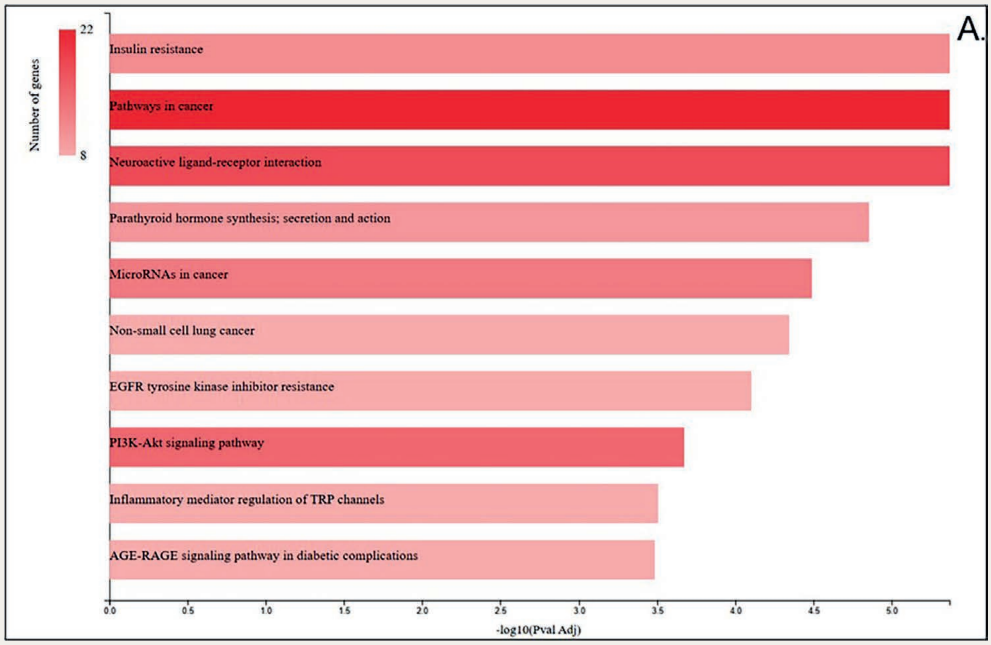


Fig. S3A and S3B. Genes associated with metabolic pathways and disease caused for 2,4-di-tert-butylphenol.

Fig. S3A y S3B. Genes asociados con las vías metabólicas y enfermedades causadaspor 2,4-di-terc-butilfenol.



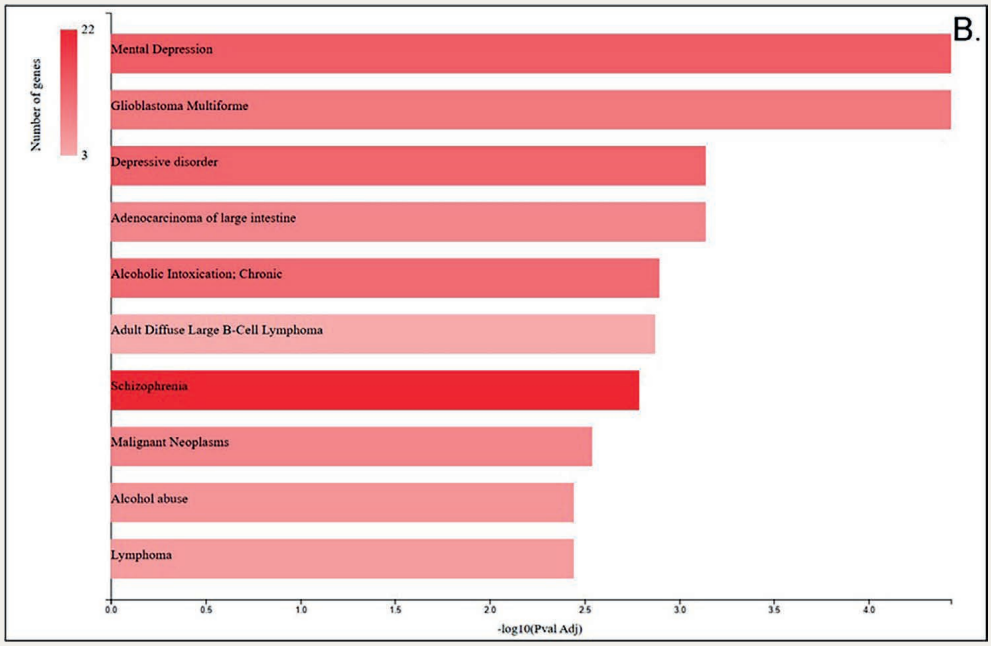


Fig. S4A and S4B. Genes associated with metabolic pathways and disease caused for phytol.

Fig. S4A y S4B. Genes asociados con las vías metabólicas y enfermedades causadas por el fitol.