



Identification of Natural TGF- β 1 Inhibitors Using Molecular Docking and ADMET Analysis

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Abstract

Transforming Growth Factor- β 1 (TGF- β 1) is an important cytokine involved in the regulation of cellular processes such as proliferation, differentiation, immune response, and extracellular matrix production. However, abnormal activation of TGF- β 1 has been associated with fibrosis, cancer progression, and chronic inflammatory diseases, making it an important therapeutic target. This study aimed to identify potential natural inhibitors of TGF- β 1 from phytochemicals derived from *Hyptis verticillata* using molecular docking analysis. Phytochemical compounds reported in *Hyptis verticillata* were retrieved from PubChem database and prepared for docking studies. The crystal structure of TGF- β 1 was obtained from the Protein Data Bank and molecular docking was performed using AutoDock Vina. Binding affinities and molecular interactions between the ligands and receptor were analysed. The docking results revealed binding scores ranging from -4.0 to -7.4 kcal/mol. Among the screened compounds, Oleanolic acid exhibited the strongest binding affinity (-7.4 kcal/mol), followed by Aromadendr-1(10)-en-9-one (-6.3 kcal/mol) and Dehydropodophyllotoxin (-6.1 kcal/mol). These compounds demonstrated favourable interactions within the receptor binding site, suggesting potential inhibitory activity against TGF- β 1 signalling. The findings indicate that phytochemicals from *Hyptis verticillata*, particularly Oleanolic acid, may serve as promising lead compounds for the development of antifibrotic and anticancer therapies. Further experimental studies are recommended to validate their biological activity and therapeutic potential.

Keywords: TGF- β 1; *Hyptis verticillata*; Natural inhibitors; Phytochemicals; Oleanolic acid; Drug discovery

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Introduction

Transforming Growth Factor- β 1 (TGF- β 1) is a multifunctional cytokine and a member of the TGF- β superfamily that plays critical roles in regulating cellular processes such as proliferation, differentiation, apoptosis, immune responses, and extracellular matrix production (Ren *et al.*, 2006; Rahman *et al.*, 2023;). TGF- β 1 signaling is essential for normal physiological functions. Its aberrant activation is implicated in the pathology of numerous diseases, including fibrosis, cancer progression, and chronic inflammatory conditions (W. Wang *et al.*, 2025). In fibrotic diseases and cancer, elevated TGF- β 1 levels contribute to excessive extracellular matrix deposition and promote epithelial-to-mesenchymal transition (EMT), which facilitates tumour invasion and metastasis (Jing *et al.*, 2025).

Targeting the TGF- β 1 signaling pathway has emerged as a promising therapeutic strategy to modulate pathological fibrosis and tumour progression. Approaches to inhibit TGF- β 1 include down-regulating ligand expression, blocking receptor kinase activity, and disrupting downstream SMAD (Suppressor of Mothers against Decapentaplegic) signaling (Wang *et al.*, 2020). While several synthetic small molecule inhibitors have demonstrated activity against TGF- β receptors (e.g., ALK5 inhibitors), their clinical use has been limited by toxicity and off-target effects. As an alternative, natural products have attracted significant interest due to their structural diversity, multitarget potential, and generally favourable safety profiles. Numerous phytoconstituents - including flavonoids, phenolic acids, and terpenoids - have been reported to modulate TGF- β signaling in silico, in vitro, or in vivo, suggesting that plant-derived compounds represent a rich source of potential TGF- β 1 inhibitors (Yu *et al.*, 2025).

Hyptis verticillata Jacq. (family Lamiaceae) is a medicinal plant traditionally used for its anti-inflammatory, antimicrobial, and cytotoxic activities (Kuhnt *et al.*, 1995; Picking *et al.*, 2013). Phytochemical investigations of *H. verticillata* have

identified lignans, terpenoids, flavonoids, phenols, and other bioactive secondary metabolites, many of which exhibit antioxidant and anti-inflammatory properties (Picking *et al.*, 2013; Egbung *et al.*, 2017;). Although the bioactive compounds of *H. verticillata* have not been extensively studied as TGF- β pathway modulators, flavonoids and phenolic compounds - reported constituents of the plant - are known in other systems to interact with signaling proteins and exert inhibitory effects on profibrotic pathways (Egbung *et al.*, 2017; Yu *et al.*, 2025).

Computational methods such as molecular docking is routinely used in early-stage drug discovery to identify and evaluate potential inhibitors against target proteins. Molecular docking predicts the binding orientation and affinity of small molecules within the active site of a receptor. Utilizing this in-silico technique allows efficient screening of multiple phytochemical ligands derived from *H. verticillata* against TGF- β 1, thereby identifying promising candidates for further biological studies.

Therefore, this study aimed to identify potential natural inhibitors of TGF- β 1 from *Hyptis verticillata* through molecular docking. This approach will facilitate the discovery of bioactive plant-derived compounds that may modulate pathological TGF- β 1 signaling and serve as leads for therapeutic development.

Materials and Methods

Preparation of Phytochemical Compounds

Phytochemical constituents of *Hyptis verticillata* were identified from literature and databases, focusing on flavonoids, terpenoids, phenolics, and lignans reported in the plant (Picking *et al.*, 2013; Egbung *et al.*, 2017). The 3D structures of these compounds (Table 1) were retrieved from PubChem (Kim *et al.*, 2021) in SDF format and converted to PDBQT using OpenBabel for docking studies (O'Boyle *et al.*, 2011).

Table 1: Library of phytochemicals derived from *hyptis verticillata*

S/N	Compound Name
1	Aromadendr-1(10)-en-9-one
2	Cadina-4,10(15)-dien-3-one
3	Dehydropodophyllotoxin
4	Oleanolic Acid
5	Thymol
6	3a,4,5,6,7,7a-hexahydro-4,7-methanoindene
7	4,7- methanon-1H-indene
8	R-R, R-E- trans-Phytol
9	Squalene
10	9,12,15-octadecatrien-1-ol
11	1-octadecyne
12	1-fluorodecane

The crystal structure of human TGF- β 1 (Figure 1) was obtained from the Protein Data Bank (PDB ID: 1TGK) (De Crescenzo *et al.*, 2003). The protein structure was prepared using AutoDock Tools, where water molecules were removed, polar hydrogens were added, and Kollman charges were assigned. The

binding site was defined based on the co-crystallized ligand and key residues reported in literature as critical for TGF- β 1 activity.

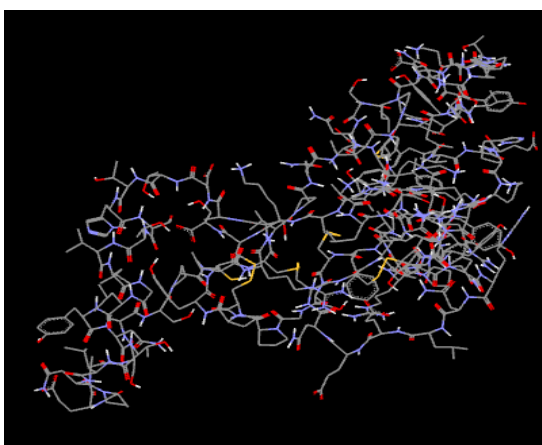
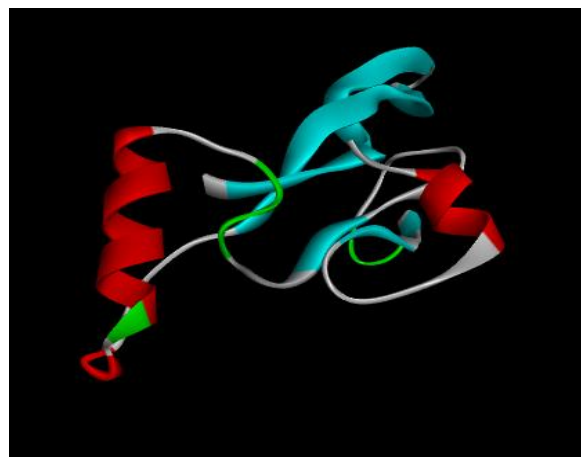


Figure 1: 2D and 3D structure of target protein

Protein Preparation

Protein Target

The target protein used was: Transforming Growth Factor- β 1 (TGK1)

Molecular Docking

Molecular docking was performed using AutoDock Vina (Trott and Olson, 2010). The grid box was

centered on the active site of TGF- β 1 with dimensions sufficient to accommodate all ligands. Docking

parameters included an exhaustiveness of 8, and 9 binding modes per ligand were generated. The best pose for each ligand was selected based on binding affinity scores and interactions with key residues.

Molecular Interaction Analysis

The interactions between ligands and TGF- β 1 were analyzed using Discovery Studio Visualizer and PyMOL software, focusing on hydrogen bonds, hydrophobic contacts, π - π stacking, and salt bridges. Ligands exhibiting strong docking scores.

Despite its claimed pharmacological potential, the safety profile of *L. lanceolata* remains incompletely characterised and, in certain respects, inconsistent. Although oral administration has been reported to be relatively well tolerated at doses up to 5000 mg/kg (Collins *et al.*, 2014), intraperitoneal administration has yielded markedly lower LD₅₀ values, with some reports indicating values as low as 375 mg/kg (Koffi *et al.*, 2025). This disparity suggests the route-dependent nature of toxicity of herbal products and emphasise the necessity for systematic, route-specific safety data prior to the responsible progression of this agent towards safe therapeutic usage.

Results

Molecular docking results

Binding affinity values ranged from -4.0 to -7.4 kcal/mol, indicating varying degrees of ligand–receptor interaction. Oleanolic acid demonstrated the strongest binding affinity (-7.4 kcal/mol), suggesting the highest predicted stability within the receptor binding pocket and potential inhibitory activity against TGF- β 1 signalling. Aromadendr-1(10)-en-9-one (-6.3 kcal/mol) and Dehydropodophyllotoxin (-6.1 kcal/mol) also exhibited notable binding performance, indicating favourable interaction with the target protein. Compounds including Squalene (-5.8 kcal/mol), R-R-R-E-trans-Phytol (-5.7 kcal/mol), and Cadina-4,10(15)-dien-3-one (-5.6 kcal/mol) showed moderate receptor affinity, while compounds such as 1-fluorodecane (-4.0 kcal/mol), 1-octadecyne (-4.3 kcal/mol), and Thymol (-4.8 kcal/mol) displayed comparatively weaker interactions (Table 3).

Table 3: Docking score of phytochemicals from *Hyptis Verticillata* with receptor

Ligand	Binding score
1-fluorodecane	-4.0
1-octadecyne	-4.3
3a,4,5,6,7,7a-hexahydro-4,7-methanoindene	-5.1
4,7, methanon-1H-indene	-5.0
9,12,15-octadecatrien-1-ol,	-5.4
Aromadendr-1(10)-en-9-one	-6.3
Cadina-4,10(15)-dien-3-one	-5.6
Dehydropodophyllotoxin	-6.1
Oleanolic Acid	-7.4
R-R-R-E-trans-Phytol	-5.7
Squalene	-5.8
Thymol	-4.8

Binding structure with target protein

Figure 2 illustrates the molecular interaction of Aromadendr-1(10)-en-9-one within the binding pocket of TGF- β 1 in both two-dimensional (2D) and

three-dimensional (3D) formats. The compound demonstrated favourable accommodation within the active site region and achieved a docking score of -6.3 kcal/mol. The interaction profile suggests stable ligand positioning supported by molecular contacts that may contribute to receptor binding and potential inhibition of TGF- β 1 activity.

The binding orientation and interaction pattern of Dehydropodophyllotoxin with TGF- β 1 is shown in Figure 3. The ligand occupied the receptor binding region with a docking score of -6.1 kcal/mol, indicating strong binding affinity. The molecular interaction pattern observed suggests effective receptor accommodation and supports its potential as a bioactive inhibitor candidate against TGF- β 1 signalling.

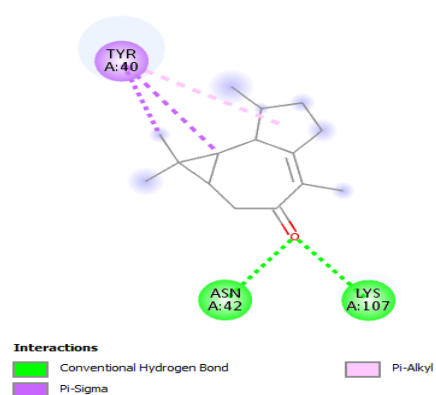


Figure 2: 2D / 3D structure of Aromadendr-1(10)-en-9-one with target protein.

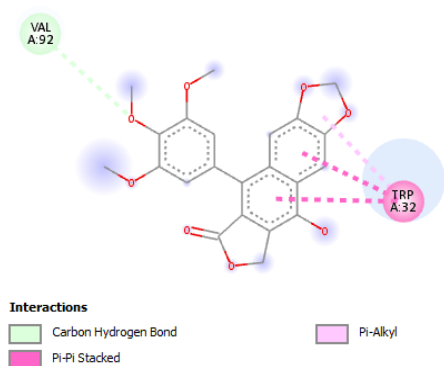
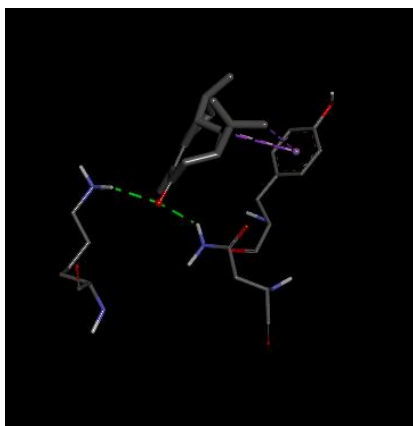


Figure 3: 2D / 3D structure of Dehydropodophyllotoxin with target protein.

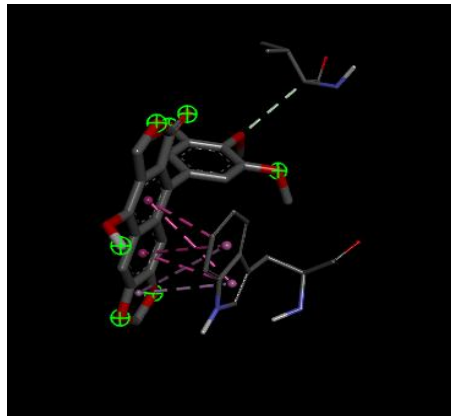


Figure 4 shows the 2D and 3D molecular interaction of Oleanolic acid with TGF- β 1. Among all screened phytocompounds, Oleanolic acid demonstrated the strongest binding affinity with a docking score of -7.4 kcal/mol. The compound exhibited stable orientation within the receptor binding site, indicating favourable ligand–protein interaction and suggesting a high potential for inhibitory activity against TGF- β 1.

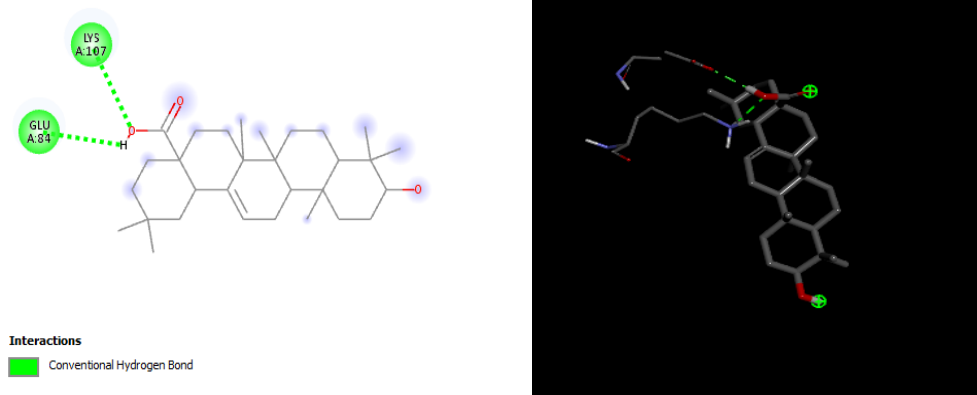


Figure 4: 2D / 3D structure of Oleanolic Acid with target protein

ADMET Results

These compounds exhibited predicted ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile.

The radar plot of Aromadendr-1(10)-en-9-one (Figure 5) indicates that the compound demonstrated favourable non-toxicity characteristics and moderate oral bioavailability, suggesting potential suitability for systemic administration.

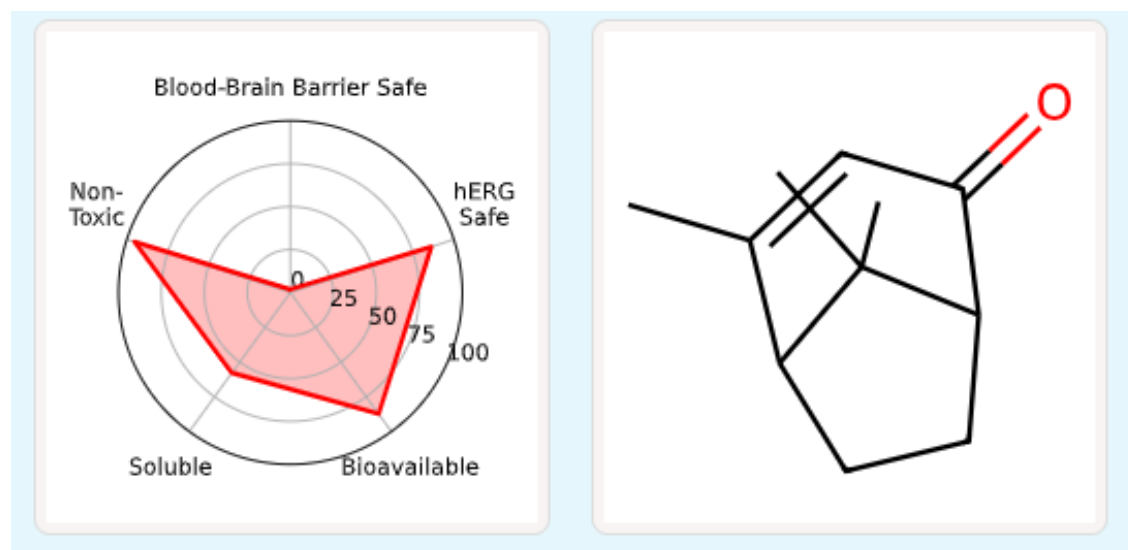


Figure 5: ADMET result of Aromadendr-1(10)-en-9-one.

Dehydropodophyllotoxin demonstrated a relatively balanced pharmacokinetic profile with favourable

predictions for hERG safety, non-toxicity, oral bioavailability, and solubility (Figure 6).

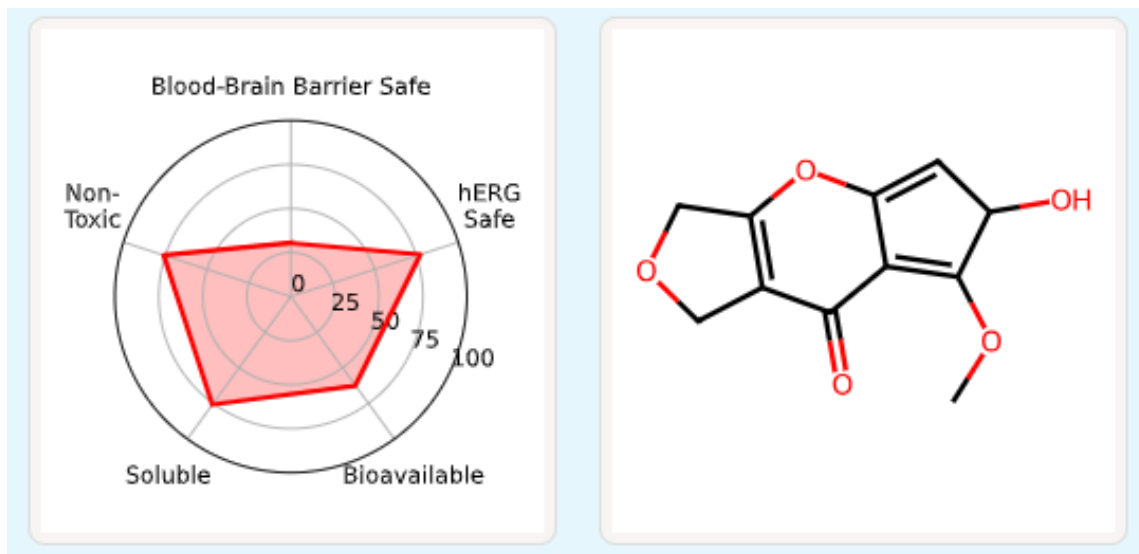


Figure 6: ADMET result of Dehydropodophyllotoxin.

The radar plot of Oleanolic acid demonstrated favourable non-toxicity, good oral bioavailability, and a satisfactory hERG safety profile, indicating an

acceptable preliminary safety prediction (Figure 7). Moderate solubility and lower blood–brain barrier permeability was observed, which may influence systemic distribution and bioavailability.

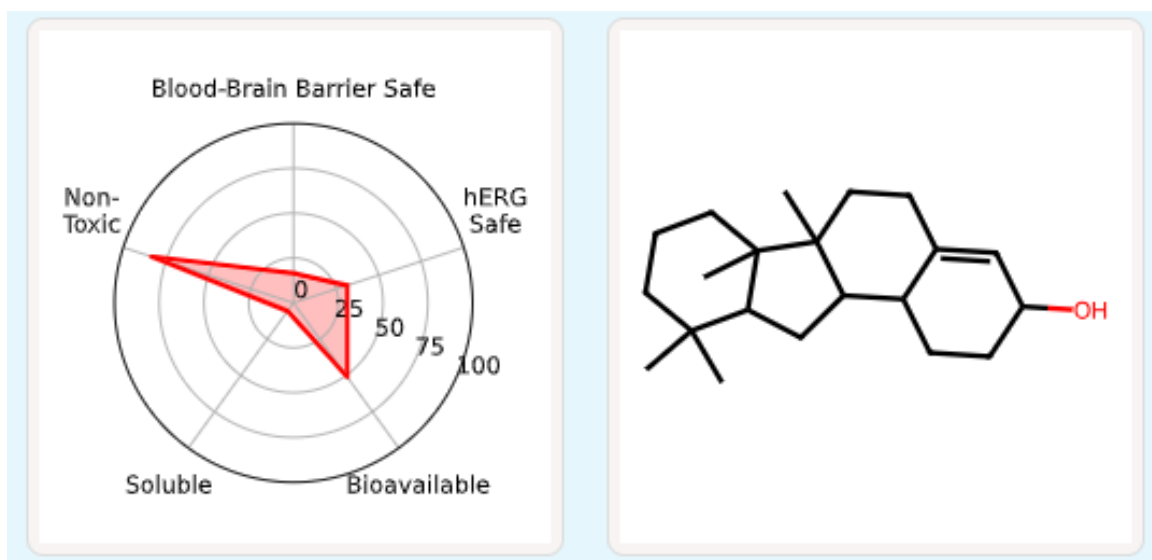


Figure 7: ADMET result of Oleanolic Acid.

Discussion

The present study investigated the potential inhibitory activity of phytochemical constituents of *Hyptis verticillata* against Transforming Growth Factor- β 1

(TGF- β 1) using molecular docking analysis. TGF- β 1 is a multifunctional cytokine implicated in several pathological conditions, particularly fibrosis, tumour progression, and chronic inflammatory diseases due to its role in extracellular matrix deposition and epithelial-mesenchymal transition (EMT) (Deng *et al.*, 2024). Identification of natural compounds capable of modulating this pathway is therefore of considerable therapeutic importance.

The docking results obtained in this study demonstrated varying binding affinities of the phytochemicals toward the TGF- β 1 receptor, with docking scores ranging from -4.0 to -7.4 kcal/mol. Among the investigated compounds, Oleanolic acid exhibited the strongest binding affinity, suggesting a potentially stable interaction with the receptor binding pocket. This result indicates that Oleanolic acid may possess significant inhibitory activity against TGF- β 1 signalling compared to the other screened compounds. Previous studies have reported that oleanolic acid exhibits anti-inflammatory, antifibrotic, hepatoprotective, and anticancer properties through modulation of signalling pathways, including TGF- β /Smad signalling, thereby supporting the findings of this study (Günther and Bednarczyk-Cwynar, 2025).

The strong interaction by Oleanolic acid may be attributed to its pentacyclic triterpenoid structure, which facilitates hydrophobic interactions and stabilises ligand-receptor binding within the active site. Hydrophobic contacts are important determinants of binding stability in protein-ligand interactions, especially in signalling proteins such as TGF- β receptors. The relatively low binding energy suggests spontaneous interaction and favourable molecular recognition between the ligand and receptor (Trott and Olson, 2010).

Dehydropodophyllotoxin also demonstrated strong binding affinity. This compound belongs to the lignan class of phytochemicals, which are known for their cytotoxic and anticancer activities (Imbert, 1998; Gordaliza *et al.*, 2004). Previous reports have shown that podophyllotoxin derivatives interfere with cellular proliferation and may modulate pathways associated with fibrosis and tumour growth (Imbert, 1998). The interaction of Dehydropodophyllotoxin with TGF- β 1, suggests a possible additional mechanism through which this compound may exert therapeutic effects.

Similarly, Aromadendr-1(10)-en-9-one exhibited notable binding affinity while Squalene and R-R-R-E-trans-Phytol showed moderate interactions. These compounds are terpenoid derivatives known for

antioxidant and anti-inflammatory activities (Ferreira *et al.*, 2015; Pagadala *et al.*, 2017). Their moderate docking performance may indicate partial inhibition of TGF- β 1 signalling or supportive synergistic effects when present alongside stronger inhibitors. Terpenoids have previously been reported to suppress profibrotic signalling pathways and reduce oxidative stress associated with chronic inflammatory disorders (Jing *et al.*, 2025; W. Wang *et al.*, 2025).

Compounds such as 1-fluorodecane, Thymol, and 1-octadecyne demonstrated weaker binding affinities. Lower docking scores generally indicate fewer stable interactions within the receptor active site and may suggest limited inhibitory activity against TGF- β 1. Nevertheless, these compounds may still contribute to the overall pharmacological properties of *Hyptis verticillata* through alternative biological mechanisms such as antioxidant or antimicrobial activity (Picking *et al.*, 2013).

The differences in docking scores among the phytochemicals may be related to variations in molecular size, polarity, hydrogen bond donor/acceptor capacity, and structural flexibility (Imbert, 1998; Gordaliza *et al.*, 2004; Kamal *et al.*, 2014). Compounds with larger hydrophobic surfaces and multiple interaction sites generally exhibited better receptor affinity (Kitchen *et al.*, 2004; Pagadala *et al.*, 2017). Molecular docking predicts the preferred orientation of ligands within receptor active sites and provides insight into possible molecular interactions responsible for biological activity (Trott and Olson, 2010). However, docking studies alone cannot fully establish pharmacological efficacy because biological activity also depends on pharmacokinetics, bioavailability, metabolism, and toxicity profiles.

The findings of this study support previous reports that natural products are promising sources of TGF- β pathway inhibitors. Natural compounds possess structural diversity and multitarget properties that make them attractive candidates in drug discovery. Several flavonoids, phenolic compounds, and terpenoids have previously been shown to inhibit TGF- β /Smad signalling and attenuate fibrosis in experimental studies (Jing *et al.*, 2025). The results obtained from *Hyptis verticillata* phytochemicals further reinforce the therapeutic relevance of medicinal plants in the development of novel antifibrotic and anticancer agents. Despite the promising findings, this study has certain limitations. Molecular docking is an in-silico predictive approach and does not fully replicate biological systems. Experimental validation through in-vitro enzyme

inhibition assays, cell culture studies, and in-vivo investigations is necessary to confirm the inhibitory potential of the identified compounds against TGF- β 1 signalling. The study also highlights the usefulness of molecular docking as a rapid and cost-effective tool for screening bioactive phytochemicals in early drug discovery.

Conclusion

This study identified potential natural inhibitors of TGF- β 1 from *Hyptis verticillata* using molecular docking analysis. Among the screened phytochemicals, Oleanolic acid showed the strongest binding affinity, followed by Dehydropodophyllotoxin and Aromadendrol-1(10)-en-9-one, indicating their possible inhibitory activity against TGF- β 1 signaling. These findings suggest that compounds from *Hyptis verticillata* may possess antifibrotic and anticancer potential through modulation of the TGF- β 1 pathway. Although the docking results are promising, further in-vitro and in-vivo studies are necessary to validate their biological activity, safety, and therapeutic effectiveness. Overall, this study highlights the potential of medicinal plant-derived compounds as promising candidates for the development of novel TGF- β 1-targeted therapies.

Disclosure

The authors report no conflicts of interest in this work.

References

Deng Z, Fan T, Xiao C et al. (2024). TGF- β signaling in health, disease and therapeutics. *Signal Transduction and Targeted Therapy* 9(1): 61-.

Egbung GE, Anosike C, Utu-Baku AB et al (2017). Phytochemical evaluation and GC-MS analysis of *Hyptis verticillata* cultivated in Calabar Cross River State, Nigeria. *International Journal of Biological and Chemical Sciences* 11(5): 2548–2559.

Gordaliza, M., Castro, M. A., del Corral, J. M. M., & Feliciano, A. S. (2004). Antitumor properties of podophyllotoxin and related compounds. *Current Pharmaceutical Design*, 10(4), 441–459.

Günther A, Bednarczyk-Cwynar B (2025). Oleanolic acid: A promising antioxidant—sources, mechanisms of action, Therapeutic Potential, and Enhancement of Bioactivity. *Antioxidants* 14(5): 598.

Imbert TF (1998). Discovery of podophyllotoxins. *Biochimie* 80(3): 207–222.

Jing H, Gao Y, Jing L et al (2025). Recent advances in therapeutic use of transforming growth factor-beta inhibitors in cancer and fibrosis. *Frontiers in Oncology* 15: 1489701.

Kamal, A., Kumar, G. B., Nayak, V. L., Reddy, V. S., & Rao, M. V. B. (2014). Synthesis and biological evaluation of podophyllotoxin analogues as anticancer agents. *European Journal of Medicinal Chemistry*, 87, 398–411.

Kim S, Chen J, Cheng T et al. (2021). PubChem in 2021: new data content and improved web interfaces. *Nucleic Acids Research* 49(D1), D1388–D1395.

Kitchen, D. B., Decornez, H., Furr, J. R., & Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: Methods and applications. *Nature Reviews Drug Discovery*, 3(11), 935–949.

Kuhnt M, Probstle A, Rimpler H et al (1995). Biological and pharmacological activities and further constituents of *Hyptis verticillata*. *Planta Medica* 61(3): 227–232.

O’Boyle NM, Banck M, James CA et al. (2011). Open Babel: An open chemical toolbox. *Journal of Cheminformatics*, 3(10).

Picking D, Delgoda R, Boulogne I, Mitchell, S (2013). *Hyptis verticillata* Jacq: a review of its traditional uses, phytochemistry, pharmacology and toxicology. *Journal of Ethnopharmacology* 147(1): 16–41.

Rahman T, Das A, Abir MH et al. (2023). Cytokines and their role as immunotherapeutics and vaccine Adjuvants: The emerging concepts. *Cytokine* 169.

Ren B, Yee KO, Lawler J Khosravi-Far R (2006). Regulation of tumor angiogenesis by thrombospondin-1. *Biochimica et Biophysica Acta - Reviews on Cancer* 1765(2): 178–188.

Trott O, Olson AJ (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry* 31(2): 455–461.

Wang H, Chen M, Sang X et al. (2020). Development of small molecule inhibitors targeting TGF- β ligand and receptor: Structures, mechanism, preclinical studies and clinical usage. *European Journal of Medicinal Chemistry* 191: 112154

Wang W, Gao Y, Chen Y et al. (2025). TGF- β inhibitors: the future for prevention and treatment of liver fibrosis? *Frontiers in Immunology* 16: 1583616.
Yu, X., Shi, Y., Xie, M., & Zhang, J. (2025). Natural compound inhibitors of TGF- β signalling pathway: A

bibliometric analysis and literature review. *Natural Product Research*, 1–16.
<https://doi.org/10.1080/14786419.2025.2545973>

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