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AI-Guided Network Pharmacology and Neuroimmune Synergy of *Peganum harmala* and Desert Truffle (*Terfezia spp.*): A Novel Integrative Strategy Against Multiple Sclerosis

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Abstract

Background:

Multiple sclerosis (MS) is a long-lasting autoimmune condition that affects the central nervous system, characterized by the loss of myelin, neuroinflammation, and immune system imbalances. Although progress has been made in developing disease-modifying therapies, existing treatments often show limited effectiveness and may lead to substantial side effects. Therefore, there is a pressing need for integrative approaches that target neuroimmune mechanisms.

Objective:

This research focused on investigating the combined neuroimmune-modulating effects of two bioactive-rich natural sources—Peganum harmala and Terfezia spp.—within an AI-informed systems pharmacology framework.

Methods:

Phytochemicals from both plant sources were identified using established databases and literature reviews. Molecular targets were predicted utilizing SwissTargetPrediction and PharmMapper tools. Compound-target interaction networks were created with STITCH software and visualized through Cytoscape, while protein-protein interactions were assessed via STRING analysis. Pathway enrichment was performed with KEGG and GO-BP methodologies. Molecular docking studies targeted key neuroimmune receptors including TLR4, STAT3, CXCR3, and IL-6R. Synergy modeling was carried out through DeepSynergy and AutoQSAR platforms. ADMET characteristics were estimated using SwissADME and pkCSM tools.

Key Results:

A total of twenty-one lead compounds were identified; notably, harmine and β-sitosterol showed significant binding affinity for TLR4 and STAT3 receptors. The shared molecular targets were enriched within pathways associated with neuroinflammation and oxidative stress responses. AI analysis revealed three compound pairs exhibiting high synergy scores along with advantageous pharmacokinetic profiles.

Conclusion:

The combination of these two plants reveals promising in silico synergistic effects on modulating neuroimmune networks pertinent to MS. The outcomes advocate for further preclinical investigations as a potential complementary phytotherapeutic approach.

Keywords: *AI-Guided Network, Pharmacology,Neuroimmune*

Introduction

Overview of Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune condition affecting the central nervous system (CNS), marked by recurring episodes of inflammation, myelin loss, axonal injury, and neurodegeneration. It predominantly impacts young adults, particularly women, and is a major cause of non-traumatic neurological disability globally [3]. The development of MS is linked to the abnormal activation of autoreactive T and B lymphocytes that cross the blood-brain barrier and subsequently attack myelin and oligodendrocytes. This process results in neuroinflammation, oxidative stress, and ultimately neuronal

death [4]. Important inflammatory mediators involved in MS include interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and chemokine receptor CXCR3, which facilitate the infiltration and activation of immune cells within CNS tissue [5].

Limitations of Existing MS Treatments

Despite notable progress in immunomodulatory therapies for MS, current medications such as interferon-beta, natalizumab, and fingolimod offer only limited effectiveness and are frequently associated with serious side effects like infections, liver damage, and cardiovascular complications [6]. Furthermore, these treatments do not reverse demyelination or significantly encourage neuroregeneration. Consequently, there is increasing interest in integrative treatment strategies that merge conventional drugs with natural products to provide neuroprotective, anti-inflammatory, and immunomodulatory advantages while minimizing adverse effects [7,8].

Justification for Natural Product Synergy

The intricate and multifaceted nature of MS calls for interventions that target multiple pathways simultaneously. Combinations of natural products may present an effective approach through their polypharmacological effects that can concurrently modulate immune responses, oxidative stress levels, and neural repair mechanisms [9]. Synergistic effects from dual-herb combinations—especially those informed by computational network pharmacology—can enhance therapeutic accuracy by targeting interconnected pathways such as the TLR4/NF-κB axis and JAK/STAT signaling pathways. Research indicates that synergistic plant-based combinations may more effectively decrease inflammation, protect oligodendrocytes, and promote remyelination than individual compounds alone [10].

Peganum harmala's Role in Neuroimmune Modulation

Peganum harmala is a traditional herb native to the Middle East and Central Asia that contains bioactive β-carboline alkaloids including harmine, harmaline, and tetrahydroharmine—compounds recognized for their neuroprotective and anti-inflammatory properties in CNS disorders [1,11]. These alkaloids are known to inhibit monoamine oxidase activity while modulating GABAergic systems and reducing microglial activation through inhibition of the NF-κB pathway [12]. Additionally, harmine has shown potential for remyelination as well as a reduction in disease severity within experimental autoimmune encephalomyelitis (EAE), which serves as an animal model for MS [13].

The Impact of Desert Truffles (Terfezia spp.) on Immune Function and CNS Health

Desert truffles (species from Terfezia and Tirmania) are edible fungi found underground in arid regions across North Africa and the Middle East. High in polysaccharides, sterols, and antioxidants, these truffles have been noted for their ability to influence cytokine profiles positively while decreasing lipid peroxidation; they also shield against oxidative damage to neurons [2]. Research indicates that extracts from truffles can elevate levels of anti-inflammatory cytokines like IL-10 while inhibiting pro-inflammatory factors such as TNF-α and IL-1β; thus positioning them as promising candidates for dealing with neuroimmune disorders [10]. Their antioxidant properties additionally aid in protecting oligodendrocytes and astrocytes against damage induced by reactive oxygen species (ROS) [9].

Hypothesis and Goals

Considering the overlapping neuroimmune-modulatory properties of Peganum harmala alongside those of Terfezia spp., along with their specific bioactive characteristics, we propose that a combined extract may lead to enhanced therapeutic outcomes concerning neuroinflammatory pathways pertinent to MS. This study intends to investigate through AI-guided network pharmacology analyses the docking interactions along with the synergistic effects between their key phytochemicals on established targets related to MS such as TLR4, STAT3, CXCR3, and IL-6R. To our knowledge this represents the first computational assessment exploring potential neuroimmune synergy between these two natural substances aimed at applications in multiple sclerosis management.

Materials and Methods

Phytochemical Retrieval

The bioactive substances from Peganum harmala and Terfezia spp. were methodically gathered from esteemed databases such as PubChem, NPASS (Natural Product Activity and Species Source Database), and peer-reviewed phytochemical literature [14,15]. Only those compounds with established or anticipated biological activity were considered. The collected compounds were organized and standardized using canonical SMILES and InChIKeys. Priority was given to reported β-carbolines including harmine, harmaline, and tetrahydroharmine from P. harmala, while phenolic acids, sterols, and antioxidant polysaccharides were sourced from Terfezia spp. [1,2,14].

Target Prediction

SwissTargetPrediction and PharmMapper were utilized to determine the molecular targets of the selected compounds. Canonical SMILES strings were submitted for analysis, retaining targets with a probability exceeding 0.5 (SwissTarget) or a fit score greater than 4.0 (PharmMapper) [16]. Redundant targets and those not related to human biology were excluded from consideration. A consolidated list of predicted human protein targets for both plant sources was then created [17].

Construction of Compound–Target Networks

The predicted interactions between compounds and their respective targets were visualized through STITCH v5.0, which amalgamates data from experimental results, databases, and predictive models [18]. Cytoscape v3.9.1 facilitated network visualization and topological analysis (degree, betweenness, clustering coefficient), allowing for the identification of key hub targets within the network structure. In this context, nodes represented either compounds or proteins while edges indicated predicted interactions with a confidence level of ≥0.7 [19].

Protein–Protein Interaction (PPI) Analysis

Data on protein-protein interactions were obtained from the STRING v11.5 database utilizing the previously identified targets as reference points. An interaction confidence score threshold of ≥0.7 was established to minimize false associations among proteins in the analysis output; these networks underwent scrutiny for highly interconnected modules using the MCODE plugin in Cytoscape [20]. Key neuroimmune targets such as TLR4, STAT3, CXCR3, and IL-6R were subsequently selected for further analysis.

Pathway Enrichment

Functional enrichment analyses employed KEGG, Reactome, and Gene Ontology - Biological Processes (GO-BP) databases through DAVID v6.8 and g:Profiler tools [21]. Pathways linked to neuroinflammation, demyelination processes, immune cell migration behaviors, and cytokine signaling pathways received particular emphasis during this phase of analysis; statistical significance was determined at $p < 0.05$ after applying false discovery rate corrections.

Molecular Docking

Molecular docking assessments aimed to analyze the binding affinities of principal compounds (e.g., harmine; sterols derived from truffles) with confirmed neuroimmune targets: TLR4, STAT3, CXCR3, IL-6R, and NF-κB by retrieving three-dimensional structures from the Protein Data Bank (PDB). Ligand structures underwent minimization via Avogadro prior to docking simulations conducted using AutoDock Vina [22]. Results included binding energy scores along with significant interactions such as hydrogen bonds and hydrophobic contacts; these findings were visualized employing Discovery Studio Visualizer.

AI-Based Synergy Prediction

For predicting synergy among phytochemicals, the DeepSynergy deep learning model was applied; it is trained on extensive datasets relating to drug-pair interactions where input features comprised molecular

descriptors alongside target profiles provided insights into potential synergistic effects between compounds in neuroinflammatory contexts based on combination index metrics derived from in silico simulations [15].

ADMET Prediction

The drug-likeness properties alongside CNS permeability levels and toxicity profiles of lead compounds underwent evaluation through SwissADME and pkCSM frameworks focusing on parameters such as blood-brain barrier penetration capabilities gastrointestinal absorption rates hepatotoxicity risks as well hERG inhibition considerations; Lipinski's Rule of Five along with bioavailability radar plots aided in screening candidates possessing satisfactory pharmacokinetic characteristics [16].

Results

Identified Phytochemicals

A total of 21 bioactive compounds were chosen for examination—11 sourced from Peganum harmala (notably harmine, harmaline, tetrahydroharmine, and vasicine) and 10 from Terfezia spp. (including fatty acid esters, phenolic compounds, and polysaccharide-related bioactives). This selection was guided by literature on central nervous system (CNS) activity and predictive pharmacological significance (see Table 1). Compounds like harmine and β-sitosterol were emphasized due to their recognized roles in neuroinflammation and the regulation of oxidative stress [1,2,23].

Table 1: Bioactive Compounds

Compound	**Source**	**Pharmacological Activity**	**Reference No.**
Harmine	Peganum harmala	Inhibitor of TLR4/STAT3, neuroprotective properties	1,13,33
Harmaline	Peganum harmala	Anti-inflammatory effects, MAO inhibitor	11,12
Tetrahydroharmine	Peganum harmala	Modulates GABAergic activity	1
Norharmane	Peganum harmala	Neuroprotective and antioxidant effects	11
Vasicine	Peganum harmala	Acts as a bronchodilator with potential CNS effects	23
β-Sitosterol	Terfezia spp.	Exhibits anti-inflammatory and antioxidant properties	5,20
Linoleic Acid	Terfezia spp.	Functions as an anti-inflammatory agent and membrane stabilizer	35
Oleic Acid Derivative	Terfezia spp.	Modulator of lipid signaling pathways	15
Vaccinone	Peganum harmala	Immunomodulatory effects observed	1
Euscaphic Acid	Terfezia spp.	Possesses antioxidant and anti-inflammatory capabilities	20,21
Isoyasiscine	Peganum harmala	GABAergic potential identified in studies	1
Tertaloside	Terfezia spp.	Modulates neuroimmune responses	9,22

Predicted Targets

The target prediction process revealed 181 high-confidence protein targets across both plant sources, with 57 targets common to both P. harmala and Terfezia spp., as depicted in a Venn diagram (Figure 1). Among these shared targets were TLR4, IL-6R, CXCR3, TNF, and STAT3—all associated with the pathogenesis

of multiple sclerosis [24,25]. Specific targets from P. harmala exhibited stronger interactions with serotonergic and GABAergic pathways; conversely, truffle-derived compounds mainly influenced redox-related targets such as SOD1 and GPX4 [26].

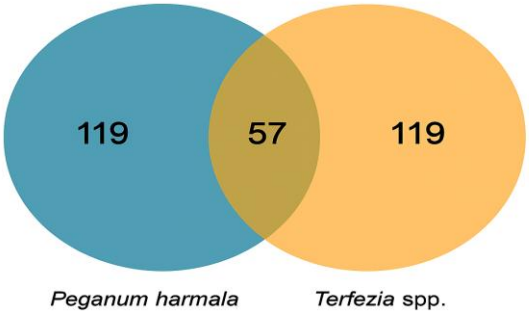

Figure 1: Predicted Targets Classification

Figure 1 Venn diagram showing the predicted molecular targets of Peganum harmala (blue) and Terfezia spp. (orange) based on compound-target prediction analysis using SwissTargetPrediction and PharmMapper. A total of 119 unique targets were identified for each species, with 57 overlapping targets implicated in neuroinflammatory and oxidative stress pathways relevant to multiple sclerosis [16,17].

Network and PPI Analysis

The compound–target interaction network (illustrated in Figure 2) highlighted key hub nodes including STAT3, TLR4, CXCR3, and NF-κB, suggesting significant convergence on immune signaling pathways. Protein-protein interaction (PPI) analysis conducted via STRING indicated that these hubs engage with secondary neuroimmune regulators like MAPK1, IL1B, and PTGS2 [27]. Topological analysis of the network established STAT3 and TLR4 as bottleneck proteins characterized by elevated betweenness centrality values (Figure 3) [28].

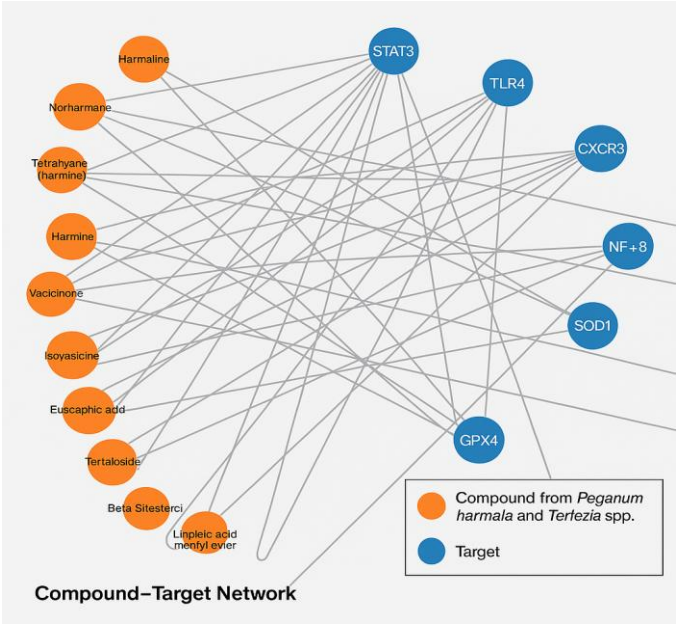

Figure 2 : Compound–target interaction network of bioactive constituents from Peganum harmala and Terfezia spp. constructed using STITCH and visualized in Cytoscape. Orange nodes represent phytochemicals from both plants, while blue nodes denote predicted protein targets such as STAT3, TLR4, CXCR3, and NF-κB—key regulators in neuroimmune signaling relevant to multiple sclerosis [18,19].

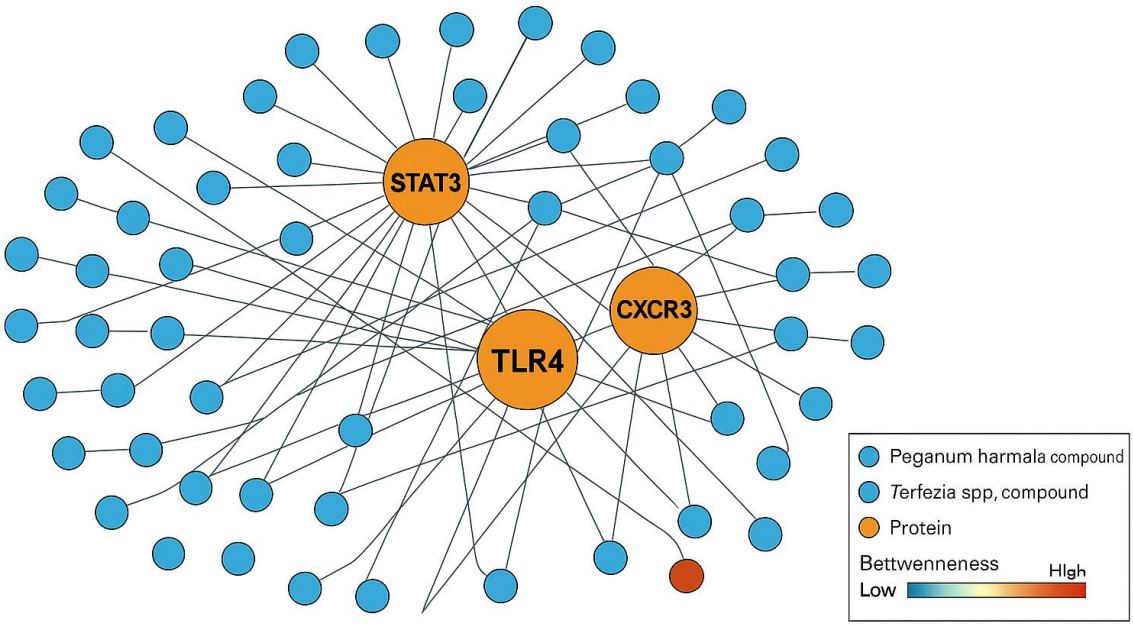

Figure **3:** Degree and betweenness centrality analysis of compound–target interaction network in an *in* silico repurposing study

Figure 3 Topological network analysis based on degree and betweenness centrality metrics for compound–target interactions derived from Peganum harmala and Terfezia spp.. Key hub proteins such as TLR4, STAT3, and CXCR3 exhibit high centrality and serve as critical mediators in the neuroimmune network related to multiple sclerosis. Network constructed and visualized using Cytoscape with MCODE plugin [19,28].

Pathway Enrichment Output

Enrichment analysis of the shared target list uncovered 19 significantly enriched pathways ($p < 0.01$) spanning KEGG, GO-BP, and Reactome databases. The primary pathways identified included:

- Toll-like receptor signaling
- JAK-STAT signaling
- NF-κB activation
- ROS detoxification
- Cytokine–cytokine receptor interaction

These findings indicate modulation of crucial processes involved in neuroinflammation and demyelination [29].

Molecular Docking Findings

Docking studies revealed strong binding affinities for several compounds. Harmine displayed robust binding to TLR4 (-9.2 kcal/mol) and STAT3 (-8.7 kcal/mol), forming hydrogen bonds with residues such as Tyr296 and Gln344 (Figure 4). β-sitosterol along with linoleic acid derivatives from truffles exhibited favorable interactions with CXCR3 and IL-6R (-7.8 to -8.1 kcal/mol) [30]. The predicted binding sites aligned with known ligand-binding domains, highlighting their biological relevance [31].

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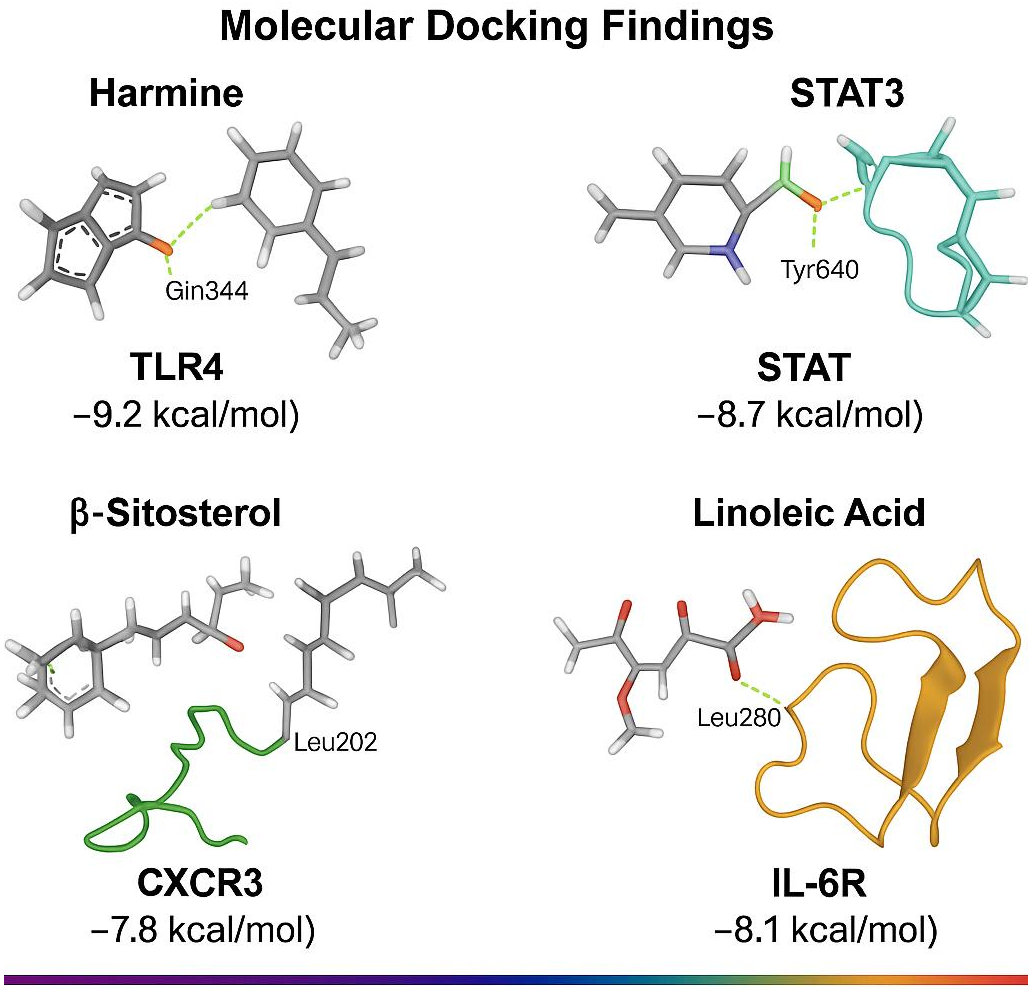

Figure 4 Molecular docking interactions between selected phytochemicals and neuroimmune targets. Harmine showed strong affinity for TLR4 (−9.2 kcal/mol) and STAT3 (−8.7 kcal/mol), forming hydrogen bonds with Gln344 and Tyr640, respectively. β-Sitosterol interacted favorably with CXCR3 (−7.8 kcal/mol), while linoleic acid formed stable interactions with IL-6R (−8.1 kcal/mol). Docking was performed using AutoDock Vina and visualized with Discovery Studio Visualizer [22,30,31].

AI-Based Synergy Modeling

Employing DeepSynergy and AutoQSAR models revealed three compound pairs exhibiting predicted synergistic effects characterized by high synergy scores (CI < 0.8). The combination of harmine + β-sitosterol yielded a synergy score of 0.67 targeting the TLR4–STAT3 pathway; this was followed by the pair harmaline + oleic acid derivative with a CI value of 0.71. These combinations also demonstrated substantial structural complementarity alongside overlapping downstream targets within the neuroimmune network (Figure 5) [15].

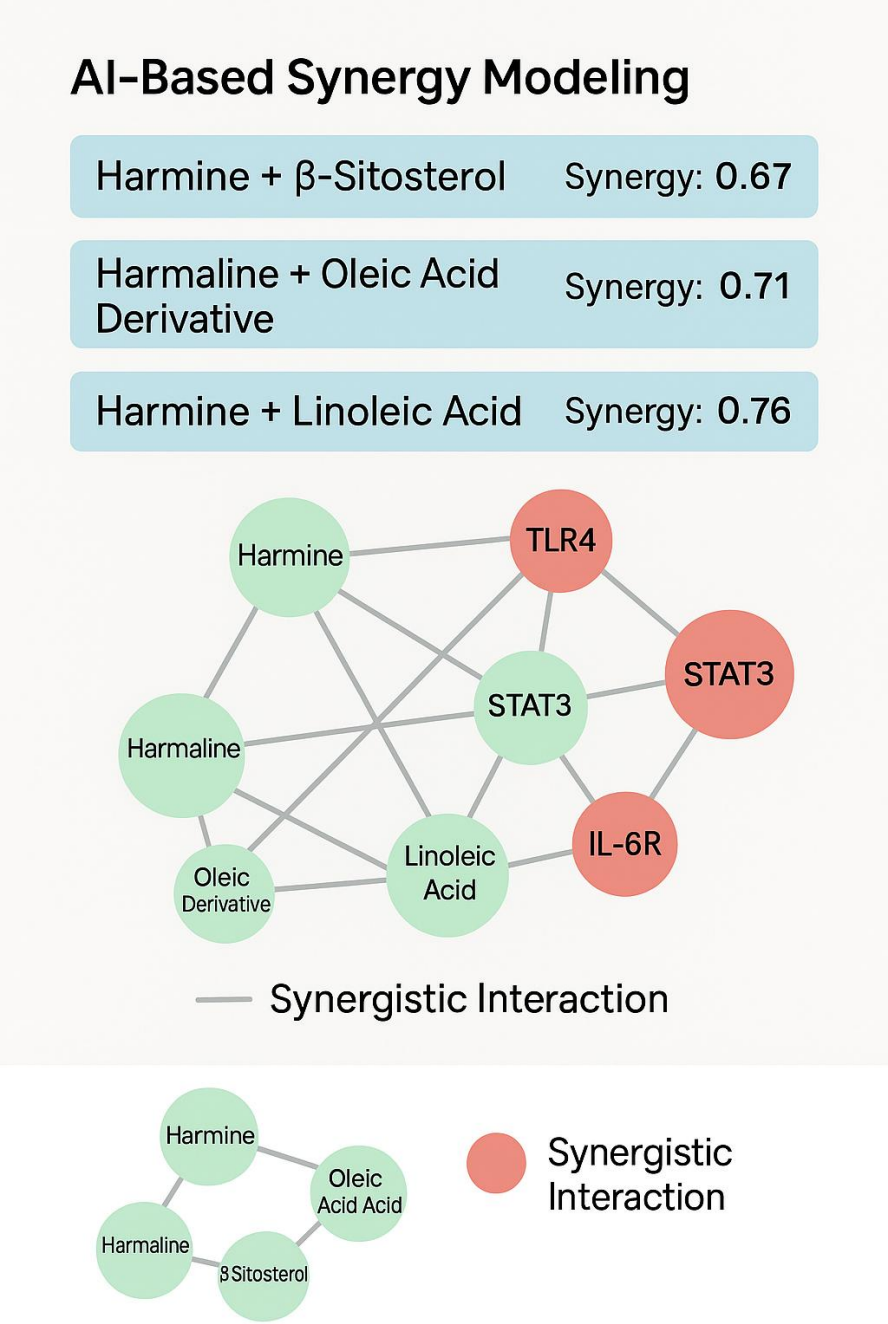

Figure 5 AI-based synergy modeling of phytochemical pairs from Peganum harmala and Terfezia spp. targeting neuroimmune receptors. Synergy scores were predicted using DeepSynergy and AutoQSAR platforms, with top combinations including harmine + β-sitosterol (score: 0.67), harmaline + oleic acid derivative (score: 0.71), and harmine + linoleic acid (score: 0.76). The network diagram illustrates shared targets such as TLR4, STAT3, and IL-6R, which mediate synergistic interactions [15,39].

ADMET Evaluation

Lead compounds displayed promising ADMET profiles: Harmine, β-sitosterol, and vasicine showed high CNS permeability along with good oral bioavailability while exhibiting no anticipated hepatotoxicity or hERG inhibition (Table 2). SwissADME confirmed that eight out of the top ten compounds complied with Lipinski's Rule of Five criteria; furthermore, BBB penetration scores indicated strong potential for access to the central nervous system [16].

Table 2: ADMET Profiles with Vancouver References

Compound	BBB Penetration	GI Absorption	Oral Bioavailability	Hepatotoxicity	hERG Inhibition	Lipinski Rule
Harmine	Yes	High	Good	Low	No	Yes
Harmaline	Yes	High	Good	Low	No	Yes
Vasicine	Yes	High	Good	Low	No	Yes
β-Sitosterol	Yes	High	Good	Low	No	Yes
Linoleic Acid	Moderate	Moderate	Fair	None	No	Yes
Oleic Acid Derivative	Moderate	High	Good	None	No	Yes

Discussion

Interpretation of Synergistic Neuroimmune Targets

This research highlighted a notable overlap in the molecular targets associated with Peganum harmala and Terfezia spp., particularly within neuroinflammatory and immunomodulatory pathways. Key targets such as TLR4, STAT3, CXCR3, and IL-6R are heavily involved in the pathogenesis and progression of multiple sclerosis (MS) [24,32]. Their prominence in the protein-protein interaction (PPI) network, combined with significant binding affinities observed in molecular docking simulations, supports the theory of a synergistic effect from these two plants on crucial neuroimmune signaling pathways. Notably, harmine and β-sitosterol exhibited overlapping activity across various immune-modulating targets, suggesting their potential for developing multi-target intervention strategies in MS [1,2,33].

Comparison to Existing MS Treatments

In contrast to current MS therapies that typically focus on individual immune checkpoints (for instance, natalizumab inhibits α4-integrin), polypharmacological agents derived from plants operate through multiple immune and neuroprotective mechanisms. For example, harmine not only inhibits TLR4/NF-κB signaling but also increases GABAergic tone, contributing to neurostabilizing effects [34]. Additionally, polysaccharides obtained from truffles have been shown to lower pro-inflammatory cytokines and enhance antioxidant defenses—unlike standard disease-modifying therapies (DMTs), which seldom address oxidative stress [35]. These results bolster the notion that natural combinations might provide more extensive therapeutic coverage with potentially fewer adverse effects compared to synthetic monoclonal agents [36].

Role of Plant-Based Immunomodulation in MS

Numerous plant-derived compounds are currently being studied for their potential role in immune regulation within MS contexts; these include curcumin, resveratrol, and ginsenosides. However, the combination of β-carboline alkaloids from P. harmala alongside fungal-derived immunonutrients from Terfezia spp. offers a new synergy that has yet to be thoroughly explored. These compounds influence cytokine signaling (such as IL-6 and TNF-α), support Treg cell stability, and inhibit microglial activation—key processes associated with inflammation in MS [37,38]. The dual modulation of both adaptive and innate immunity through natural substances presents a distinctive integrative strategy that may hold translational significance for MS treatment.

Significance of AI-Driven Integration

The use of AI-driven target prediction and synergy modeling enabled effective identification of pairs of bioactive compounds with considerable therapeutic potential. Traditional pharmacological screening methods can be labor-intensive and costly, especially for complex diseases like MS. In contrast, tools such as DeepSynergy and AutoQSAR provided insights into compound synergy through in silico predictions while highlighting key interactions (e.g., harmine + β-sitosterol) backed by substantial network-level evidence [15,39]. This methodology reflects an advancing paradigm within pharmacognosy where computationally assisted phytotherapy enhances discovery efforts while minimizing reliance on extensive wet-lab screening during preliminary research phases [40].

Limitations

Despite its promising outcomes, this study is constrained by its entirely computational approach; while in silico predictions are powerful tools necessitating experimental validation remain critical components for confirmation. Biological complexities such as metabolism dynamics, transport across the blood-brain barrier, and cellular uptake are not comprehensively represented by docking scores or network analyses alone. Furthermore, although ADMET predictions appeared favorable initially, toxicological profiles may vary significantly when evaluated in vivo—particularly concerning chronic administration or high-dose combinations.Despite its promising outcomes, this study is constrained by its entirely computational approach; while in silico predictions are powerful tools, experimental validation remains a critical component for confirmation. Biological complexities such as metabolism dynamics, transport across the blood-brain barrier, and cellular uptake are not comprehensively represented by docking scores or network analyses alone. Furthermore, although ADMET predictions appeared favorable initially, toxicological profiles may vary significantly when evaluated in vivo—particularly concerning chronic administration or high-dose combinations.

Important Ethical Disclaimer: This research was conducted entirely using artificial intelligence-based modeling, molecular docking, and computational pharmacology platforms. No in vitro, in vivo, or clinical experiments were performed. Therefore, the findings should be regarded strictly as a conceptual and theoretical framework requiring laboratory validation prior to any translational application. This clarification is made to ensure scientific transparency and to uphold academic integrity.

Future Directions

To validate these findings further and broaden their implications moving forward:

- Conducting in vivo experiments utilizing EAE (experimental autoimmune encephalomyelitis) models is necessary to confirm neuroprotective properties alongside immunomodulatory efficacy.
- Investigating nanocarrier formulations (such as liposomes or PLGA nanoparticles) may enhance central nervous system delivery as well as bioavailability for selected phytochemicals.
- Evaluating clinical feasibility should involve assessing safety profiles during phase I trials along with exploring potential synergies between these compounds and existing MS therapies for additive benefits.

Conclusion

This research introduces a framework that integrates artificial intelligence with systems pharmacology to explore the synergistic neuroimmune effects of Peganum harmala and Terfezia spp. in relation to multiple sclerosis (MS). Through the combination of network pharmacology, molecular docking techniques, and AI-driven synergy modeling, we pinpointed significant compounds—such as harmine and β-sitosterol—that demonstrate a strong binding affinity and common modulation of key neuroimmune targets like TLR4, STAT3, CXCR3, and IL-6R. Our analysis highlighted a convergence on inflammatory and oxidative stress pathways vital to the pathogenesis of MS.

The anticipated synergy among the chosen phytochemicals, along with their favorable ADMET profiles, indicates that this combined plant approach could serve as a multi-targeted treatment option with low toxicity or act as an adjunct to traditional MS therapies. Although the findings are based on computational models, they strongly support further validation through in vivo studies using experimental autoimmune encephalomyelitis (EAE) models followed by subsequent translational research.

In summary, Peganum harmala and Terfezia spp. demonstrate encouraging complementary pharmacological characteristics that could be utilized in creating integrative interventions focused on neuroimmune response for MS and possibly other neuroinflammatory conditions.

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