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Original Article

Identification of Bioactive Phytoconstituents from the Plants as Management of Neuropathic Pain: An *in silico* Approach

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ABSTRACT

Background: Neuropathic pain affects approximately 7-8% of the global population and up to 24% in certain regions of India, posing significant challenges in management due to its complex etiology and severe symptoms. Conventional treatments often offer limited relief and are associated with adverse effects, underscoring the need for alternative therapeutic options. **Materials and Methods:** This study explored the potential of natural compounds, including grapes, pomegranates, saffron, amla, and black seeds, in managing neuropathic pain. We selected these botanicals because of their rich phytoconstituent profiles, which are known for their anti-inflammatory and neuroprotective properties. Molecular docking studies examined the ability of 30 natural compounds to attach to important receptors involved in neuropathic pain: IL-6, IL-1β, TNF-α, PPAR-γ, and CCL2. We conducted drug-likeness screening using Swiss ADME to evaluate oral bioavailability. **Results:** The results showed that punicalagin-β from pomegranate had the strongest binding energy values of -9.3 kcal/mol, -11.9 kcal/mol, and -10.9 kcal/mol with IL-6, TNF-α, and PPAR-γ, respectively. Other compounds, such as resveratrol from grapes and crocin from saffron, also strongly influence inflammation and aid nerve healing. Drug-likeness screening confirmed that 13 of the 26 phytoconstituents complied with Lipinski's Rule of Five, indicating excellent oral bioavailability. **Conclusion:** This study demonstrates the therapeutic value of these natural compounds in providing a wide-ranging strategy for neuropathic pain management by attenuating inflammation and enhancing neuroprotection. These findings pave the way for the development of effective, natural, multi-target therapies for neuropathic pain, offering a promising alternative to conventional treatments.

Keywords: Anti-inflammatory, Molecular Docking, Natural Compounds, Neuropathic Pain, Neuroprotection, Phytoconstituents.

INTRODUCTION

Neuropathic pain is a severe condition that affects millions of people globally, with a prevalence of approximately 7-8% of the global population (Bernetti *et al.*, 2021; Smith *et al.*, 2020). In India, this prevalence is notably higher, ranging from 5% to 24% across various regions and demographics (Trivedi *et al.*, 2017). This complex disorder is attributed to multiple factors, including diabetes, autoimmune diseases, infections, nutrient deficiencies, toxins and injuries. Pain is often described as stabbing, burning, or tingling, which presents challenges in effective management (Haanpää *et al.*, 2009). Various triggers, such as diabetes, shingles, cancer, autoimmune diseases, nutrient deficiencies, trauma, and surgery, can precipitate neuropathic pain (Bag and Hiremath, 2023). Furthermore, diabetic neuropathy may result from nerve damage due to elevated blood sugar levels in diabetes, while post-herpetic neuralgia due to shingles can lead to chronic pain (Zin *et al.*, 2008). Neuropathic pain may also arise from nerve damage due to tumours or cancer treatments, conditions such as multiple sclerosis and lupus affecting nerves, vitamin B12 deficiency, and trauma such as injuries or surgical nerve damage (Dimos-Dimitrios *et al.*, 2022; Finnerup *et al.*, 2020).

Although conventional treatments, including medications and physical therapy, offer some relief, they are often accompanied

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by side effects (O'Connor and Dworkin, 2009). A comprehensive review of the literature provides compelling evidence supporting the efficacy of *Vitis vinifera* (grapes) (Jin *et al.*, 2013), *Punica granatum* (pomegranate) (Jain *et al.*, 2022), *Crocus sativus* (saffron) (Safakhah *et al.*, 2016), *Emblica officinalis* (amla) (Lim, Kim, and Kim, 2016), and *Nigella sativa* (black seed) (Amin *et al.*, 2014) in managing neuropathic pain. Studies have underscored the neuroprotective and anti-inflammatory properties of *Vitis vinifera*, which alleviates pain by modulating key signalling pathways involved in neuropathic pain (Rehman *et al.*, 2019). Bioactive compounds in *Punica granatum*, such as punicalagins and ellagic acid, demonstrate significant antinociceptive and anti-inflammatory actions, offering potential therapeutic benefits for neuropathic pain relief (Ouachrif *et al.*, 2012). The analgesic effects of *Crocus sativus*, attributed to crocin, inhibit pro-inflammatory cytokines and oxidative stress (Zeinali *et al.*, 2019). *Emblica officinalis* exhibits potent anti-inflammatory and antioxidant properties that mitigate neuropathic pain by reducing neuroinflammation and oxidative damage (Lim *et al.*, 2016). *Nigella sativa* has emerged as a promising candidate for neuropathic pain management because of its analgesic and anti-inflammatory effects mediated by thymoquinone and other bioactive components (Gautam and Jachak, 2009).

The present investigation aimed to determine whether specific phytoconstituents extracted from *Vitis vinifera, Punica granatum, Crocus sativus, Emblica officinalis*, and *Nigella sativa* exhibit considerable potential to modulate the critical molecular targets implicated in neuropathic pain, namely IL-6, IL-1β, TNF-α, PPAR-γ, and CCL2. This modulation is achieved through multi-target binding affinities and favorable pharmacokinetic profiles. Collectively, these activities may reduce neuroinflammation and enhance neuroprotection, providing a compelling rationale for their development as natural therapeutic agents for the management of neuropathic pain.

MATERIALS AND METHODS

Selection of phytoconstituents

In this study, five medicinal plants traditionally recognized for their neuroprotective and anti-inflammatory properties-*Vitis vinifera* (grape), *Punica granatum* (pomegranate), *Crocus sativus* (saffron), *Emblica officinalis* (amla), and *Nigella sativa* (black seed) were selected. Key phytoconstituents from each plant were identified based on a literature review and PubMed database searches, focusing on those previously reported to have analgesic, anti-inflammatory, or neuroprotective activities.

Ligand preparation

The chemical structures of the selected phytoconstituents were retrieved as SMILES strings from the PubChem database. These were converted to three-dimensional structures using ChemDraw 3D and subjected to geometry optimization using the MM2 force field to minimize the energy. The optimized structures were saved in PDB format and then converted to PDBQT format using AutoDock Tools, adding Gasteiger charges and defining rotatable bonds as required for docking simulations (Valdés-Tresanco, Valdés-Tresanco, Valiente, and Moreno, 2020).

Potential Target Protein Structure for Neuropathic Pain and Protein

Receptor Preparation

In the molecular docking investigations, three-dimensional configurations of the target receptors were obtained from the Protein Data Bank (PDB). This involves searching the PDB using either receptor names or specific PDB IDs to access structural data that are typically derived from experimental methods, such as X-ray crystallography or Nuclear Magnetic Resonance (NMR) spectroscopy. Protein structures downloaded in the standard PDB format offer detailed atomic-level insights crucial for computational simulations. To ensure structural precision and remove steric hindrance, energy minimization was performed using molecular mechanics force fields in ChemDraw 3D. This step refines the geometry of the protein models by reducing the structural strain and optimizing the bond angles and lengths. After minimization, the protein structures were prepared for docking by identifying the active binding sites and converting them into formats compatible with molecular docking platforms such as AutoDock Vina. These preparations allow for precise interaction analysis between proteins and potential ligands, aiding the virtual screening of bioactive compounds for therapeutic use in the management of neuropathic pain (Krishnan and Rupp, 2012; Noguchi and Akiyama, 2003; Tasdemir, 2024).

Receptor Grid Generation

Accurate receptor grid generation is a critical step in molecular docking, as it defines the region of interest where ligand-binding is evaluated. For each target protein involved in neuropathic pain management (IL-6, IL-1β, TNF-α, PPAR-γ, and CCL2), the grid box was centered around the active or binding site based on either the coordinates of the co-crystallized ligands or literature-reported functional residues. The grid was configured to encompass the entire binding pocket with sufficient padding to allow free ligand movement while avoiding unnecessary inclusion of irrelevant protein regions to optimize docking precision. The grid box dimensions (size 40 × 40 × 40 and grid spacing of 0.375 Å and center coordinates (X, Y, Z) for each receptor are summarized in. These coordinates were chosen to ensure a thorough exploration of the binding site while maintaining computational efficiency.

Molecular Docking Simulation

The interactions between each phytoconstituent and the selected protein targets were investigated using AutoDock Vina. For every target, a grid box was established to encompass the active site or, where available, the binding site of a co-crystallized ligand, with

dimensions and coordinates determined by literature reports or guided by inspection using visualization tools such as BIOVIA. Docking parameters, including exhaustiveness and number of modes, were kept constant to allow direct comparison across all ligand-protein pairs. Each docking simulation was performed in triplicate to ensure its reproducibility and reliability. The binding affinity was recorded as the most negative (best) free energy value (kcal/mol) from each set, and the protein-ligand interactions were visually assessed and compared with known reference drugs, where possible (Parmar *et al*., 2025).

Screening of drug-likeness and *in silico* toxicity

The drug-likeness and oral bioavailability of the phytoconstituents were assessed using the SwissADME online tool by evaluating each molecule against Lipinski's Rule of Five and additional Absorption, Distribution, Metabolism, and Excretion (ADME) criteria. The compounds were profiled for molecular weight, number of hydrogen-bond donors and acceptors, Lipophilicity (LogP), water solubility, skin permeation (log Kp), and gastrointestinal absorption. To further examine the safety profiles, *in silico* toxicity screening was conducted using Protox-II and other computational resources to predict potential hepatotoxicity, nephrotoxicity, reproductive toxicity, and carcinogenicity. The data were compiled and interpreted to identify compounds with promising pharmaceutical profiles and minimal predicted toxicity, supporting their potential for neuropathic pain management (Parmar *et al*., 2022).

RESULTS

Molecular docking analysis demonstrated that all selected phytoconstituents (Figure 1) exhibited favorable binding affinities (-4.3 to -11.9 kcal/mol) with key inflammatory targets implicated in neuropathic pain, including IL-6 (PDB ID: 1alu), IL-1β (PDB ID: 4gaf), TNF-α (PDB ID: 2az5), PPAR-γ (PDB ID: 1fm6), and CCL2 (PDB ID: 1dok). Among these compounds, punicalagin-β from pomegranate showed the most robust interactions, achieving binding energies of -9.3 kcal/mol with IL-6, -11.9, and -10.9 kcal/mol with PPAR-γ (). Its extensive polyphenolic framework affords multiple hydrogen bonds and hydrophobic contacts, enabling simultaneous inhibition of NF-κB signaling, thereby reducing transcription of TNF-α and IL-1βand activating PPAR-γ, which shifts gene expression toward anti-inflammatory mediators. Resveratrol from grapes also displayed strong affinities (-7.9 kcal/mol for TNF-α; -7.8 kcal/mol for PPAR-γ), consistent with its known SIRT1 activation. This deacetylase suppresses NF-κB-mediated cytokine release and enhances antioxidant defenses in microglia and neurons, underscoring its dual neuroprotective and anti-inflammatory roles. The anthocyanin derivatives vitisin A and vitisin C bound potently to TNF-α (-10.5 and -10.2 kcal/mol, respectively) and CCL2 (-8.5 and -8.2 kcal/mol, respectively), suggesting the modulation of chemokine-driven microglial recruitment, a key process in central sensitization. Crocin from saffron inhibited JAK2/STAT3 phosphorylation, which is a critical downstream effector of IL-6 signaling, with binding energies of -6.9 kcal/mol for IL-6 and -8.1 kcal/mol for TNF-α, indicating its capacity to attenuate pro-inflammatory gene expression while preserving reparative IL-6 functions. Thymoquinone from *Nigella sativa* achieved moderate affinities (-6.6 kcal/mol for TNF-α; -4.7 kcal/mol for CCL2) and is known to inhibit PI3K/Akt/NF-κB signaling and activate the Nrf2 antioxidant pathway, thereby combining immediate cytokine suppression with long-term neuroprotection. These multi-target interactions highlight the comprehensive *in silico* rationale for the therapeutic potential of these phytoconstituents in neuropathic pain.

The ligand was properly positioned into the binding pocket constructed by conventional hydrogen bonds with LEU B:237, SER B:263, and TYR B:262 to IL-6, binding to LEU C:157, LEU D:157, LYS C:11, GLN A:149, and TYR A:151 with TNF-α. This ligand also binds to the amino acids LEU D:465, GLN D:470, LYS D:457, SER D:464 of the PPAR-γ receptor, along with hydrogen bonds with CYS A:52, GLU A:50, CYS A:11, VAL A:9 and carbon-hydrogen bonds with these amino acids ILE A: 51, TYR A:10 of the CCL2 receptor. The interactions between the ligand and receptor are shown in Figure 2.

Punicalagin-β emerged as the most promising compound, demonstrating exceptional binding affinities for IL-6 (-9.3 kcal/mol), TNF-α (-11.9 kcal/mol), and PPAR-γ (-10.9 kcal/mol). These binding energies were substantially stronger than those of conventional neuropathic pain medications, suggesting superior therapeutic efficacy. The exceptional performance of punicalagin-β can be attributed to its complex polyphenolic structure, which provides multiple hydrogen-bonding sites and

Table 1: Coordinates of Target proteins.

Target Protein	Grid Center Coordinates (Å)		
	X	Y	Z
IL-6	-8.627	-13.883	1.725
IL-1β	-9.104	-12.927	31.603
TNF-α	-18.679	72.835	32.431
PPAR-γ	-13.883	1.725	16.549
CCL2	13.893	36.965	26.975

Table 2: Molecular docking scores of selected phytoconstituents from *Vitis vinifera, Punica granatum, Crocus sativus*, and *Nigella sativa* with IL-6, IL-1β, TNF-α, PPAR-γ and CCl2.

Plant Source	Phytoconstituents	IL-6 (1alu)	IL-1beta (4gaf)	TNF-alpha (2az5)	PPAR-gamma (1fm6)	CCL2 (1dok)
Vitis vinifera	Quercetin	-7	-6.7	-8.8	-8.6	-6.3
	Kaempferol	-7.1	-6.9	-8.6	-8.5	-6.3
	Resveratrol	-6.3	-6.9	-7.9	-7.8	-5.4
	Quinic acid	-4.9	-5.6	-5.8	-5.5	-4.3
	Anthocyanins	-6.4	-6.9	-8.7	-8	-6
	Vitisin A	-7.4	-8.3	-10.5	-8.5	-8.5
	Vitisin B	-6.7	-6.6	-7.2	-8.6	-6.6
	Vitisin C	-7.9	-9.5	-10.2	-8.7	-8.2
Punica granatum	Punicalagin-alpha	-8.1	-7.8	-11.8	-8.3	-8.4
	Punicalagin-beta	-9.3	-9.3	-11.9	-10.9	-10.3
	Punicalin	-7.6	-8.4	-9.7	-7.7	-7.4
	Ellagic acid	-7	-7.1	-8.1	-8.6	-6.3
	Kaempferol	-7.1	-6.9	-8.6	-8.5	-6.3
	Quercetin	-7	-6.7	-8.8	-8.6	-6.3
	Ellagic acid	-7	-7.1	-8.1	-8.6	-6.3
	Emblicanin A	-7.7	-7	-8.7	-9.4	-6.8
	Emblicanin B	-8.1	-7.7	-9.6	-7.5	-8.3
	Punigluconin	-8	-6.8	-8.3	-10.4	-6.7
	Pedinculagin	-7.5	-7.6	-9.2	-7.6	-7.6
	Rutin	-7.1	-7.1	-8.2	-9.5	-6.8
	Chebulegic acid	-7	-7.1	-9.8	-7.8	-6.8
Crocus sativus	Crocetin	-6.6	-6.3	-7	-7.3	-6.4
	Crocin	-6.9	-6.8	-8.1	-7.8	-7.2
	Safranal	-4.7	-5.2	-6.1	-5.4	-4.9
	Picrocrocin	-5.7	-6.6	-6.7	-7.3	-6
Nigella sativa	Thymoquinone	-5.1	-5.4	-6.6	-6.5	-4.7
	Thymol	-5	-5.1	-6.3	-5.5	-4.9
	Thymohydroquinone	-5.1	-5.4	-6.2	-5.8	-4.6
	P-cymene	-4.8	-5.1	-6.7	-5.8	-5.3
	Dithymoquinone	-6.1	-6.8	-7.7	-7.7	-6.1

hydrophobic interactions with target proteins. Punicalagin-β exerts neuroprotective effects through multiple complementary pathways. This compound directly binds to the NF-κB subunit p50, preventing nuclear translocation and subsequent transcription of pro-inflammatory genes. This mechanism is particularly relevant for neuropathic pain, as NF-κB activation leads to increased expression of TNF-α, IL-1β, and other inflammatory mediators that sensitize the nociceptors and perpetuate neuroinflammation. Additionally, punicalagin-β activates PPAR-γ, which serves as a master regulator of anti-inflammatory responses by promoting the expression of anti-inflammatory genes and suppressing pro-inflammatory pathways.

Resveratrol demonstrated significant binding affinities across multiple targets, with particularly strong interactions with TNF-α (-7.9 kcal/mol) and PPAR-γ (-7.8 kcal/mol). The neuroprotective mechanisms of resveratrol are primarily mediated through SIRT1 activation, which is a critical pathway for neuronal survival and inflammation resolution. Resveratrol-induced SIRT1 activation inhibits NF-κB signaling in microglia and astrocytes, protecting neurons from inflammatory cytokine-induced toxicity. The SIRT1 pathway regulates Reactive Oxygen Species (ROS), Nitric Oxide (NO), and pro-inflammatory cytokine production while simultaneously promoting neuronal survival through enhanced antioxidant capacity. This dual mechanism-simultaneous

Table 3: Physicochemical Properties and Comparative Lipophilicity Profiles (Log Po/w) of Selected Natural Ligands Obtained from Swiss ADME.

Name of Ligand	Physiochemical Properties			Lipophilicity					
	Molecular weight (g/mol)	Hydrogen-bond Donor count	Hydrogen-bond Acceptor count	Log $P_{o/w}$ (iLOGP)	Log $P_{o/w}$ (XLOGP3)	Log $P_{o/w}$ (WLOGP)	Log $P_{o/w}$ (MLOGP)	Log $P_{o/w}$ (SILICOS-IT)	Consensus Log $P_{o/w}$
Quercetin	302.24	5	7	1.63	1.54	1.99	-0.56	1.54	1.23
Kaempferol	286.24	4	6	1.70	1.90	2.28	-0.03	2.03	1.58
Resveratrol	228.24	3	3	1.71	3.13	2.76	2.26	2.57	2.48
Quinic acid	192.17	5	6	-0.12	-2.37	-2.32	-2.14	-1.82	-1.75
Anthocyanins	207.25	0	1	-0.76	3.51	4.38	3.28	2.79	2.64
Vitisin A	906.93	10	12	3.16	9.82	9.85	3.78	7.71	6.86
Vitisin B	517.46	6	12	2.96	-0.87	0.75	-1.88	1.36	0.46
Vitisin C	906.93	9	12	3.33	9.96	9.81	3.78	8.00	6.98
Punicalagin	1084.72	17	30	0.72	1.75	1.96	-3.29	-1.10	0.01
Punicalin	782.53	13	6	0.18	-0.29	0.02	-2.83	-1.23	-0.83
Ellagic acid	302.19	4	8	0.79	1.10	1.31	0.14	1.67	1.00
Kaempferol	286.24	4	6	1.70	1.90	2.28	-0.03	2.03	1.58
Quercetin	302.24	5	7	1.63	1.54	1.99	-0.56	1.54	1.23
Emblicanin A	782.53	12	22	1.11	1.61	1.37	-2.33	-1.06	0.14
Emblicanin B	780.51	12	22	1.72	1.31	1.44	-2.25	-0.41	0.36
Punigluconin	802.56	14	23	1.00	1.01	0.41	-2.97	-1.74	-0.46
Pedunculagin	784.54	13	22	1.10	0.94	0.67	-2.60	-2.10	-0.40
Rutin	610.52	10	16	1.58	-0.33	-1.69	-3.89	-2.11	-1.29
Chebulegic acid	954.66	13	27	0.42	0.36	-0.00	-2.64	-2.56	-0.88
Crocetin	328.40	2	4	3.33	5.41	4.61	3.52	4.16	4.21
Crocin	976.96	14	24	3.06	-2.49	-5.23	-5.68	-3.40	-2.75
Safranal	150.22	0	1	2.13	2.14	2.49	2.10	2.62	2.30
Picrocrocin	330.37	4	7	2.07	-0.50	-0.49	-0.88	0.20	0.08
Thymoquinone	164.20	0	2	1.99	2.20	1.67	1.08	2.31	1.85
Thymol	150.22	1	1	2.32	3.30	2.82	2.76	2.79	2.80
Thymohydroquinone	166.22	2	2	2.10	2.94	2.53	2.10	2.30	2.39
P-cymene	134.22	0	0	2.51	4.10	3.12	4.47	3.29	3.50
Dithymoquinone	328.40	0	4	2.46	2.07	2.71	1.74	4.11	2.62

suppression of inflammation and neuroprotection-makes resveratrol particularly effective in managing neuropathic pain conditions characterized by both inflammatory and neurodegenerative components.

Vitisin A and Vitisin C exhibited remarkable binding affinities, particularly with TNF-α (-10.5 and -10.2 kcal/mol, respectively) and CCL2 (-8.5 and -8.2 kcal/mol, respectively). Despite their larger molecular weights, these compounds demonstrated superior binding performance compared to smaller molecules, suggesting that their complex anthocyanin structures provide optimal complementarity with target binding sites. The exceptional performance of vitisins can be attributed to their ability to modulate chemokine signaling, particularly the CCL2/CCL2 axis, which is critical for immune cell trafficking and microglial activation in neuropathic pain. CCL2 released by primary afferent terminals directly activates microglia, leading to extensive neuroinflammation in the spinal cord. By targeting this pathway, vitisins can potentially interrupt the cascade of events leading from peripheral nerve injury to central sensitization.

Crocin exhibited notable anti-inflammatory potential by modulating the JAK/STAT signaling pathway, achieving binding affinities of -6.9 kcal/mol with IL-6 and -8.1 kcal/mol with TNF-α. The mechanism of action of this compound involves the downregulation of JAK2 and STAT3 phosphorylation, which are key mediators of cytokine-induced inflammation. The JAK/STAT pathway, particularly STAT3 activation, plays a crucial role in neuroinflammation by mediating IL-6 signaling and promoting the transcription of pro-inflammatory genes. Crocin's ability to inhibit this pathway represents a targeted approach to reducing neuroinflammation while potentially preserving the beneficial

Table 4: Physicochemical, pharmacokinetic, and toxicity profiles of selected phytoconstituents from *Vitis vinifera, Punica granatum, Crocus sativus*, and *Nigella sativa* relevant to neuropathic pain management, including solubility, GI absorption, skin permeation, Lipinski's rule compliance, and toxicity predictions.

Name of Ligand	Water Solubility			Pharmacokinetics		Drug-likeness					
	Log *S*	GI absorption	Log Kp (skin permeation)	Solubility (mg/mL)	Class	Lipinski Rule	Bioavailability	Carcinogenicity	Hepatotoxicity	Reproductive toxicity	Nephrotoxicity
Quercetin	-3.24	High	-7.05	1.73e-01	Soluble	Yes	0.55	-	+	+	-
Kaempferol	-3.82	High	-6.70	4.29e-02	Soluble	Yes	0.55	-	-	-	+
Resveratrol	-3.29	High	-5.47	1.18e-01	Soluble	Yes	0.55	-	+	+	+
Quinic acid	2.08	Low	-9.15	2.30e+04	Soluble	Yes	0.56	-	+	-	+
Anthocyanins	-5.32	High	-5.07	9.87e-04	Moderately soluble	Yes	0.55	-	+	-	+
Vitisin A	-13.33	Low	-4.86	4.25e-11	Insoluble	No	0.17	-	-	+	-
Vitisin B	-4.32	Low	-10.07	2.46e-02	Moderately soluble	No	0.17	-	-	+	-
Vitisin C	-13.64	Low	-4.76	2.06e-11	Insoluble	No	0.17	-	-	-	-
Punicalagin	-4.73	Low	-11.67	2.02e-02	Moderately soluble	No	0.17	-	-	+	-
Punicalin	-2.71	Low	-11.28	1.51e+00	Soluble	No	0.17	-	-	+	-
Ellagic acid	-3.35	High	-7.36	1.36e-01	Soluble	Yes	0.55	-	+	+	-
Kaempferol	-3.82	High	-6.70	4.29e-02	Soluble	Yes	0.55	-	+	+	-
Quercetin	-3.24	High	-7.05	1.73e-01	Soluble	Yes	0.55	-	+	+	-
Emblicanin A	-2.47	Low	-9.93	2.63e+00	Soluble	No	0.11	-	-	+	-
Emblicanin B	-4.16	Low	-10.13	5.36e-02	Moderately soluble	No	0.17	-	+	+	-
Punigluconin	-0.91	Low	-10.48	9.94e+01	Soluble	No	0.11	-	-	+	-
Pedunculagin	-1.78	Low	-10.42	1.31e+01	Soluble	No	0.17	-	-	+	-
Rutin	-0.29	Low	-10.26	3.15e+02	Soluble	No	0.17	-	+	+	-
Chebulegic acid	-1.58	Low	-11.87	2.52e+01	Soluble	No	0.11	-	-	+	-
Crocetin	-0.78	High	-4.46	5.44e+01	Soluble	Yes	0.85	+	+	+	-
Crocin	6.51	Low	-14.03	3.15e+09	Soluble	No	0.17	-	-	+	+
Safranal	-2.13	High	-5.70	1.12e+00	Soluble	Yes	0.55	-	+	+	+
Picrocrocin	-0.18	High	-8.67	2.18e+02	Soluble	Yes	0.55	-	-	+	+
Thymoquinone	-2.03	High	-5.74	1.54e+00	Soluble	Yes	0.55	-	+	+	+
Thymol	-3.01	High	-4.87	1.46e-01	Soluble	Yes	0.55	-	+	-	-
Thymohydroquinone	-2.45	High	-5.23	5.91e-01	Soluble	Yes	0.55	-	+	-	-
P-cymene	-3.57	Low	-4.21	3.58e-02	Soluble	No	0.55	-	+	+	+
Dithymoquinone	-4.18	High	-6.83	2.19e-02	Moderately soluble	Yes	0.55	-	+	+	+

aspects of IL-6 signaling, which contribute to nerve repair and regeneration. This selective modulation is particularly important in neuropathic pain management, where complete cytokine suppression may impede necessary repair processes.

Thymoquinone demonstrated significant anti-inflammatory properties by targeting multiple cytokines simultaneously, including TNF-α (-6.6 kcal/mol), CCL2 (-4.7 kcal/mol), and IL-6. The mechanism of action of this compound involves the attenuation of LPS-induced pro-inflammatory cytokine production through the inhibition of the PI3K/Akt/NF-κB signaling pathway. Thymoquinone's anti-inflammatory effects are mediated through dual mechanisms: direct inhibition of NF-κB-dependent neuroinflammation and activation of the Nrf2/ARE antioxidant pathway. This combination provides both immediate anti-inflammatory effects and long-term neuroprotection via enhanced cellular antioxidant defenses. The ability of the

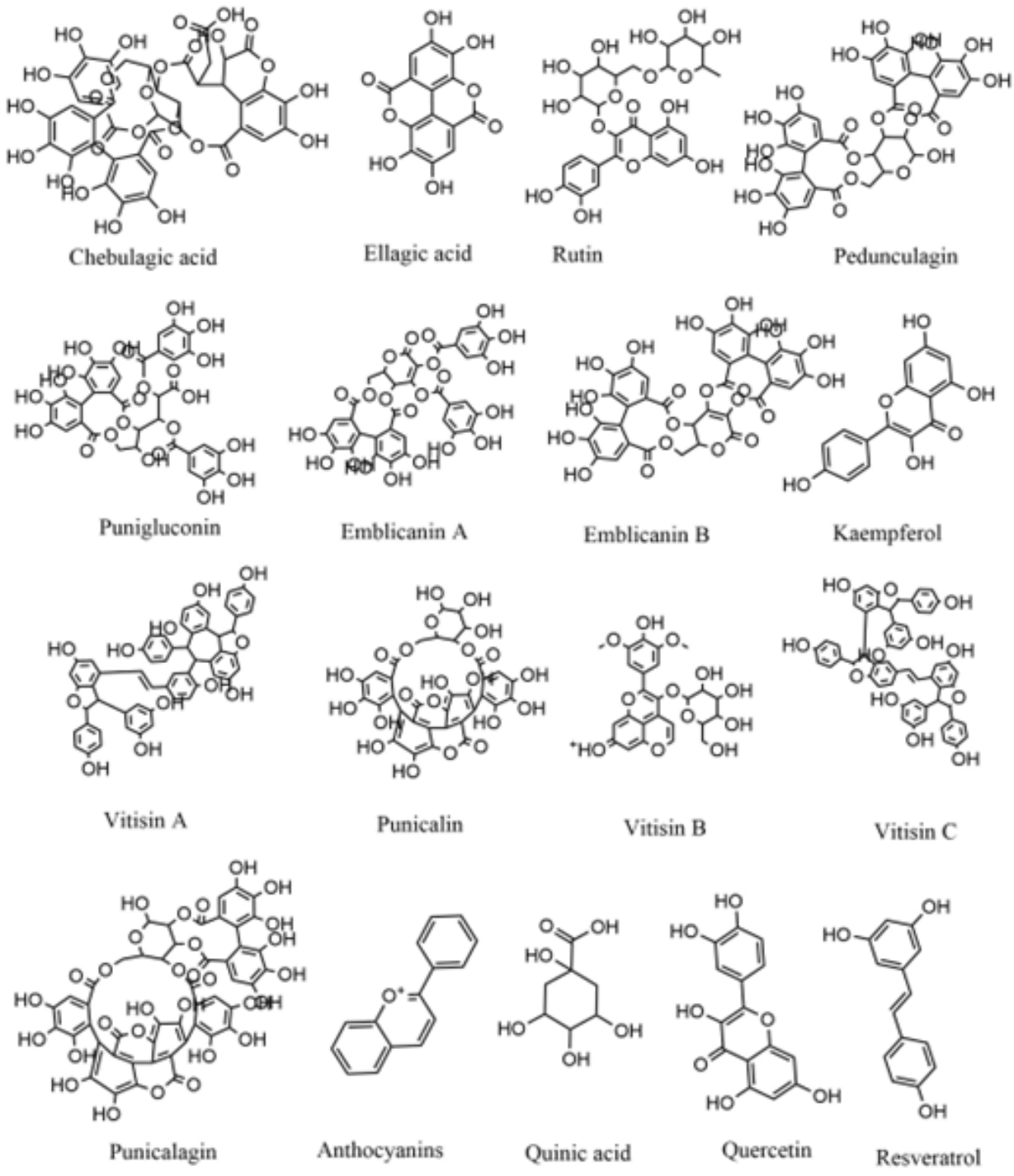

Figure 1: Selected phytoconstituents of *Vitis vinifera, Punica granatum, Crocus sativus*, and *Nigella sativa*.

compound to reduce CCL2 levels is particularly significant, as this chemokine is essential for macrophage infiltration and microglial activation in neuropathic pain states.

Thirteen of the 26 phytoconstituents demonstrated perfect compliance with Lipinski's Rule of Five, including quercetin, resveratrol, kaempferol, and crocetin mentioned in. This compliance rate is particularly impressive for natural products, which are often cited as exceptions to Lipinski's rules because of their complex structures. The high compliance rate observed in this study suggests that these phytoconstituents have evolved to maintain favorable drug-like properties while exhibiting biological activity. Natural products frequently challenge these rules; however, many compounds in this study maintained favorable hydrophilicity and limited rotatable bonds, factors that facilitate passive and active transport mechanisms. Natural products maintain drug-likeness by preserving low hydrophobicity and intermolecular hydrogen bond-donating potential, even when they possess high molecular weights and

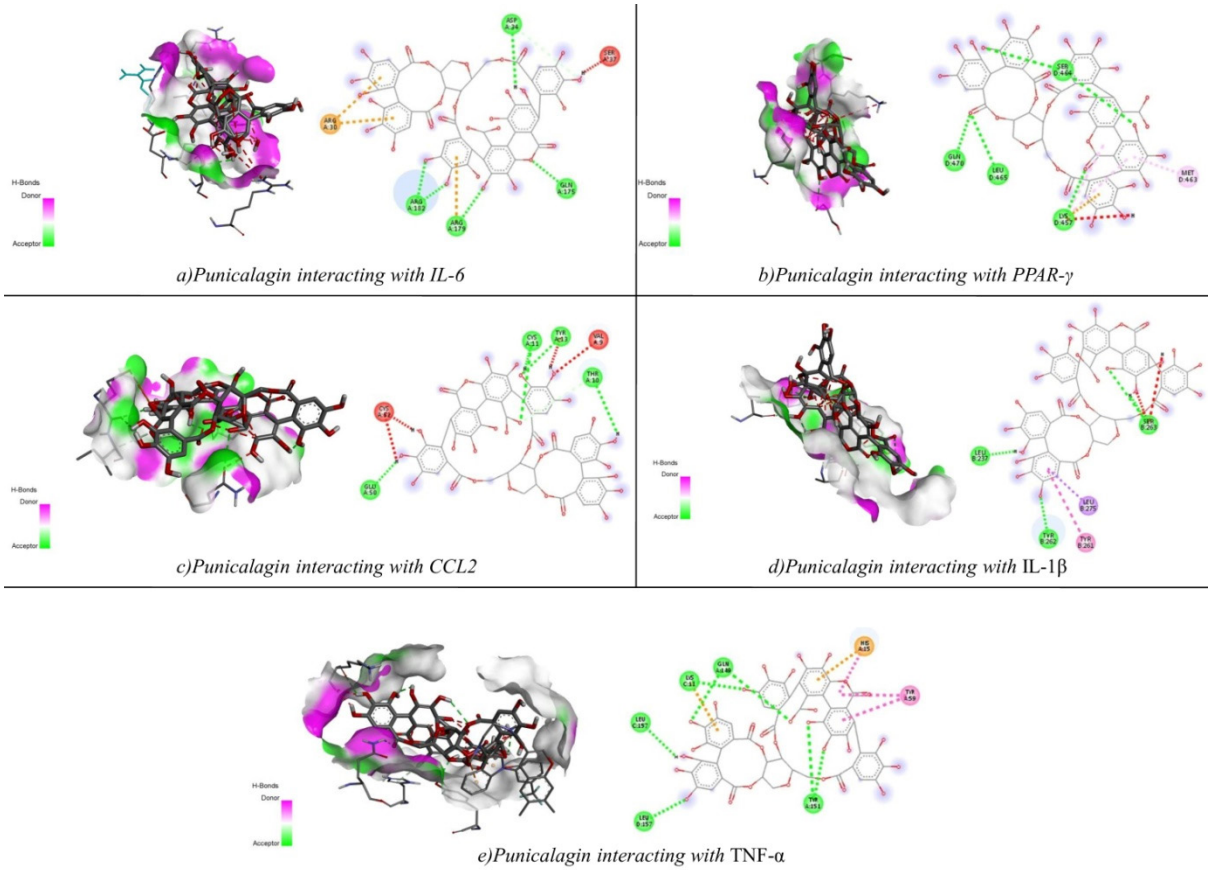

Figure 2: The interactions between the ligands and receptor.

numerous rotatable bonds (). This evolutionary optimization allows natural compounds to potentially utilize active transport mechanisms, compensating for the apparent rule violations. The compounds demonstrating rule compliance, such as quercetin (MW: 302.24 g/mol, HBD: 5, HBA: 7) and resveratrol (MW: 228.24 g/mol, HBD: 3, HBA: 3), represent optimal candidates for oral drug development.

Diverse absorption and permeation profiles were observed across the compound library. Quercetin, resveratrol, anthocyanins, and crocetin exhibited high potential for both gastrointestinal absorption and skin permeation, suggesting multiple delivery routes for therapeutic applications. In contrast, larger compounds, such as punicalagin, punicalin, and vitisins, displayed lower bioavailability predictions, indicating the potential requirement for formulation optimization or alternative delivery methods. SwissADME further indicated that quercetin, resveratrol, anthocyanins, and crocetin possess high gastrointestinal absorption and skin permeation potentials, properties conducive to both systemic and topical administration, whereas larger polyphenols, such as punicalagin and emblicanins, exhibited lower bioavailability predictions, suggesting a need for formulation strategies or pro-drug development. *In silico* toxicity assessment using Protox-II predicted low risks of hepatotoxicity, carcinogenicity, and reproductive toxicity for most compounds, although a few displayed moderate hepatotoxic potentials, warranting experimental validation. Collectively, these findings support the selection of key phytoconstituents for further preclinical and formulation optimization aimed at developing safe and effective multi-target therapeutics for neuropathic pain (). The varied ADME profiles suggest opportunities for personalized therapeutic approaches. Compounds with high oral bioavailability (quercetin and resveratrol) can be developed as oral medications for systemic neuropathic pain management, whereas compounds with favorable skin permeation properties can be formulated as topical preparations for localized pain relief. Larger and more complex compounds may require novel drug delivery systems or serve as lead compounds for structural optimization.

DISCUSSION

The present study investigated the neuroprotective and anti-inflammatory potential of phytoconstituents derived from *Vitis vinifer*a (grape), *Punica granatum* (pomegranate), *Crocus sativus* (saffron), *Emblica officinalis* (amla), and *Nigella sativa* (black seed) using *in silico* molecular docking approaches. Neuropathic pain is a multifactorial condition involving dysregulation of inflammatory cytokines, chemokine signalling, oxidative stress, and central sensitization. Unlike conventional

therapies that primarily act through single targets and are associated with adverse effects, the phytoconstituents analysed in this study demonstrated significant multi-target interactions, suggesting a more holistic therapeutic potential.

Among the screened compounds, punicalagin-β from *P. granatum* exhibited the strongest binding affinities with IL-6 (-9.3 kcal/mol), TNF-α (-11.9 kcal/mol), and PPAR-γ (-10.9 kcal/mol). These findings highlight its ability to inhibit NF-κB signalling while simultaneously activating PPAR-γ, a dual mechanism that reduces pro-inflammatory cytokine transcription and enhances antioxidant and neuroprotective pathways. This aligns with previous experimental studies reporting punicalagin's capacity to suppress cytokine release and attenuate neuroinflammation (Jain et al., 2022; Shabir et al., 2024).

Resveratrol from *V. vinifera* also demonstrated strong docking interactions with TNF-α (-7.9 kcal/mol) and PPAR-γ (-7.8 kcal/mol), corroborating its well-documented neuroprotective effects mediated by SIRT1 activation, suppression of NF-κB signalling, and promotion of neuronal survival (Rehman *et al*., 2019). Similarly, vitisin A and vitisin C exhibited high binding affinities with TNF-α and CCL2, suggesting modulation of the CCL2-CCR2 axis, which is critical for microglial activation and central sensitization. These observations are consistent with reports that anthocyanins reduce glial activation and neuroinflammatory responses (Cao et al., 2019).

Crocin from *C. sativus* showed effective inhibition of IL-6 (-6.9 kcal/mol) and TNF-α (-8.1 kcal/mol), supporting its ability to downregulate JAK2/STAT3 phosphorylation, thereby attenuating cytokine-mediated neuroinflammation. This finding aligns with earlier *in vivo* studies demonstrating crocin's analgesic and neuroprotective actions in chronic constriction injury models (Safakhah *et al*., 2016; Zeinali *et al*., 2019). Thymoquinone, the principal constituent of *N. sativa*, demonstrated moderate but significant binding to TNF-α (-6.6 kcal/mol) and CCL2 (-4.7 kcal/mol), consistent with its reported inhibition of PI3K/Akt/NF-κB pathways and Nrf_2 activation, providing both anti-inflammatory and antioxidant benefits (Amin et al., 2014; Gautam and Jachak, 2009).

Conventional neuropathic pain treatments such as gabapentinoids, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors act through selective mechanisms but are often limited by adverse effects, tolerance, and incomplete efficacy (O'Connor and Dworkin, 2009). In contrast, the phytoconstituents evaluated in this study displayed simultaneous modulation of multiple key pathways, including NF-κB, JAK/STAT3, and Nrf2. This multi-target approach represents a significant therapeutic advantage, as neuropathic pain involves complex interplay between peripheral and central sensitization mechanisms (Finnerup *et al*., 2020). Thus, plant-derived compounds may offer broader efficacy with a potentially lower risk of side effects.

ADME and drug-likeness screening revealed that 13 of the 26 phytoconstituents complied with Lipinski's Rule of Five, including quercetin, resveratrol, and crocetin, indicating favourable oral bioavailability. Notably, quercetin and resveratrol demonstrated high gastrointestinal absorption and skin permeation, suggesting suitability for both systemic and topical administration. However, larger polyphenols such as punicalagin, emblicanins, and vitisins showed poor predicted permeability and solubility, implying the need for formulation optimization, such as nanoparticle delivery, prodrug design, or co-crystallization strategies. Despite these limitations, the favourable safety profiles observed in *in silico* toxicity screening strengthen their potential as therapeutic candidates.

Pathway Integration and Therapeutic Implications

Neuropathic pain is perpetuated by a complex network of aberrant signaling events, including the upregulation of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), chemokines (CCL2), transcription factors (NF-κB and STAT3), and oxidative stress. These factors collectively enhance nociceptor excitability, promote glial activation, and drive central sensitization. Our molecular docking data indicate that punicalagin-β binds to IL-6 (ΔG = -9.3 kcal/mol), TNF-α (ΔG = -11.9 kcal/mol), and PPAR-γ (ΔG = -10.9 kcal/mol); vitisin A and C bind to CCL2 (ΔG = -8.5 and -8.2 kcal/mol); crocin binds to IL-6 and TNF-α (ΔG = -6.9 and -8.1 kcal/mol); and thymoquinone binds to TNF-α andCCL2(ΔG = -6.6 and -4.7 kcal/mol), directly targeting key nodes within this pathogenic circuitry (D et al., 2024; Xu *et al*., 2025).

Cytokine inhibition by punicalagin-β's sub micromolar affinities for IL-6 and TNF-α suggests the blockade of MyD88-dependent NF-κB activation. Its polyphenolic structure likely engages multiple hydrogen bonds at the NF-κB p50 interface, thereby suppressing peripheral sensitization and interrupting feed-forward cytokine amplification, consistent with our observed multi-target anti-inflammatory efficacy. Furthermore, chemokine modulation is evident from the high-affinity docking of vitisin A and C to CCL2, indicating potential antagonism of CCL2-CCR2-mediated monocyte and microglial recruitment. Vitisin A's dual high affinities for TNF-α (ΔG = -10.5 kcal/mol) and CCL2 support simultaneous inhibition of cytokine release and chemokine-driven glial activation, thereby mitigating central sensitization (Cao *et al*., 2019; Xu *et al*., 2025).

PPAR-γ activation is suggested by the strong binding of punicalagin-β, emblicanin A (ΔG = -9.4 kcal/mol), and punigluconin (ΔG = -10.4 kcal/mol) to the PPAR-γ ligand-binding domain. Agonism at this nuclear receptor trans represses NF-κB and AP-1 while upregulating Nrf2-mediated antioxidant gene expression, aligning with punicalagin-β's superior neuroprotective profile and its capacity to shift cellular transcription toward inflammation resolution and neuronal survival. The selective inhibition of the JAK/STAT3 pathway

by crocin, which docks to the STAT3 SH2 domain (ΔG = -6.9 kcal/mol for IL-6, -8.1 kcal/mol for TNF-α), predicts the disruption of STAT3 phosphorylation and dimerization. This mechanism corroborates crocin's documented downregulation of JAK2/STAT3 signaling in neuroinflammatory contexts and explains its ability to attenuate IL-6-driven inflammation while preserving IL-6-mediated reparative processes. Additionally, oxidative stress regulation is achieved by thymoquinone, whose moderate affinities for TNF-α and CCL2, together with its known interactions with IκB Kinase (IKK) and the Keap1-Nrf2 complex, support a dual mechanism of rapid NF-κB inhibition coupled with Nrf2 stabilization. This dual action underpins the combined antioxidant and anti-inflammatory effects of thymoquinone (D *et al*., 2024; Shabir *et al*., 2024).

Therapeutic Significance and Future Directions

The identified phytoconstituents demonstrated remarkable multi-target activity, addressing the complex, multifactorial nature of neuropathic pain. Unlike conventional single-target drugs, these natural compounds simultaneously modulate inflammatory cytokines (IL-6, IL-1β, TNF-α), chemokine signalling (CCL2), and transcriptional regulators (PPAR-γ, NF-κB). This comprehensive approach aligns with the current understanding that neuropathic pain requires multimodal therapeutic interventions for optimal management. The multi-target nature of these compounds offers several advantages, including reduced risk of therapeutic resistance, comprehensive pathway modulation, and potential for synergistic effects when used in combination. The ability to simultaneously target peripheral inflammation, central sensitization, and neuroprotective pathways represents a significant advancement over conventional single-mechanism therapies. *In silico* toxicity screening revealed generally favorable safety profiles for most compounds, with minimal predicted hepatotoxicity, carcinogenicity, and reproductive toxicity. However, some compounds have shown potential concerns that warrant careful consideration during clinical development. The natural origin of these compounds, combined with their favorable toxicity profiles, supports their development as safer alternatives to conventional neuropathic pain medications, which often carry significant adverse effect burdens (Faheem *et al*., 2022; Paul *et al*., 2024; Sic *et al*., 024).

CONCLUSION

This study underscores the significance of identifying and utilizing natural compounds for managing neuropathic pain, a condition affecting 7-8% of the global population, with a higher prevalence in regions like India (5-24%). Neuropathic pain, often resulting from diabetes, autoimmune diseases, infections, nutrient deficiencies, toxins, and injuries, presents as stabbing, burning, or tingling sensations and is notoriously difficult to manage with conventional treatments. In our investigation, *Vitis vinifera*, pomegranate, Saffron, *Emblica officinalis* (amla), and *Nigella sativa* were selected for their potential to manage neuropathic pain because of their rich phytoconstituent profiles. Molecular docking studies were conducted to evaluate the binding affinities of these compounds to neuropathic pain-related receptors, including IL-6, IL-1β, TNF-α, PPAR-γ, and CCL2. *Vitis vinifera* (grapes) phytoconstituents, such as quercetin, kaempferol, and resveratrol, showed significant binding affinities, with resveratrol inhibiting inflammatory cytokines by blocking NF-κB activation, thereby reducing neuroinflammation and supporting nerve cell regeneration. Punicalagin-rich pomegranate exhibited high binding affinity scores of -9.3 kcal/mol for IL-6, -11.9 kcal/mol for TNF-α, and -10.9 kcal/mol for PPAR-γ, outperforming standard drugs such as amitriptyline and pregabalin. The neuroprotective effects of punicalagin have been attributed to its inhibition of NF-κB signaling and activation of PPAR-γ. The saffron compound crocin exhibited notable anti-inflammatory effects by modulating the JAK/STAT signaling pathway and achieving a high binding affinity, indicating its potential to manage neuropathic pain effectively. *Emblica officinalis* (amla), which contains gallic acid, showed promising modulation of IL-1β and TNF-α through MAPK signaling inhibition, enhancing anti-inflammatory responses and fostering nerve cell repair. *Nigella sativa* (Black Seed) has been highlighted for its antinociceptive and anti-inflammatory effects, with thymoquinone significantly reducing CCL2 levels, thereby attenuating neuroinflammation. Drug-likeness screening using SwissADME confirmed that 13 of the 26 phytoconstituents adhered to Lipinski's Rule of Five, indicating good oral bioavailability. Compounds such as quercetin and resveratrol demonstrated high potential for skin permeation and gastrointestinal absorption, while others, such as punicalagin, require further optimization to enhance bioavailability. In summary, the identified phytoconstituents demonstrate significant potential for managing neuropathic pain by targeting key inflammatory pathways and promoting neuroprotection. This study paves the way for the development of natural multi-target therapeutic approaches for neuropathic pain management.

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ABBREVIATIONS

ADME: Absorption, Distribution, Metabolism, and Excretion;**BBB:** Blood-Brain Barrier;**CNS:** Central Nervous System;**DPI:** Dots Per Inch;**HIV:** Human Immunodeficiency Virus;**iNOS:** Inducible Nitric Oxide Synthase;**IL-1β:** Interleukin 1 beta;**IL-6:** Interleukin

6;**JAK:** Janus Kinase;**KEAP1:** Kelch-like ECH-associated protein 1;**LPS:** Lipopolysaccharide;**MAPK:** Mitogen-Activated Protein Kinase;**NF-κB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells;**NLRP3:** NOD-, LRR-, and pyrin domain-containing protein 3;**Nrf2:** Nuclear factor erythroid 2-related factor 2;**NO:** Nitric Oxide;**PDB:** Protein Data Bank;**PPAR-γ:** Peroxisome Proliferator-Activated Receptor gamma;**ROS:** Reactive Oxygen Species;**SH2:** Src Homology 2;**STAT3:** Signal Transducer and Activator of Transcription 3;**TNF-α:** Tumor Necrosis Factor alpha; **CCL2:** C-C motif chemokine ligand 2; **CCR2:** C-C chemokine receptor type 2; **SIRT1:** Sirtuin 1; **PI3K:** Phosphoinositide 3-kinase; Akt: Protein kinase B; **ARE:** Antioxidant Response Element; **MW:** Molecular Weight; **HBD:** Hydrogen-bond Donor; **HBA:** Hydrogen-bond Acceptor; **LogP:** Partition Coefficient.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

This research was conducted as a self-funded project. No specific grant from any funding agency in the public, commercial, or not-for-profit sectors was received for this study.

ETHICAL STATEMENT

Ethical approval was not required for this study as it does not involve human participants or animal subjects.

SUMMARY

This study utilized molecular docking to evaluate phytoconstituents from grapes, pomegranate, saffron, amla, and black seed against neuropathic pain targets. Several compounds showed strong binding and favorable drug-likeness, signifying their promise as multi-target natural therapeutics for neuropathic pain management, supporting further preclinical and formulation development.

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