

Research Paper

Targeting Neuroinflammation and Apoptosis in Cypermethrin-Induced Neurotoxicity: An *In Silico* Exploration of *Nigella sativa* Phytochemicals

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ABSTRACT

Background:

Cypermethrin, a widely used type II pyrethroid insecticide, has been increasingly implicated in neurotoxicity through the activation of neuroinflammatory and apoptotic pathways, particularly involving nuclear factor-kappa B (NF- κ B) and caspase-3. *Nigella sativa* possesses several bioactive phytochemicals with established antioxidant and neuroprotective properties, yet their target-specific interactions in cypermethrin-induced neurotoxicity remain poorly understood.

Objective:

This study investigated the molecular interactions of selected *Nigella sativa* phytochemicals with NF- κ B and caspase-3 to identify potential neuroprotective candidates against cypermethrin-induced neuroinflammation and apoptosis.

Methods:

An *in silico* molecular docking approach was employed using PyRx. Thymoquinone, thymol, carvacrol, and *p*-cymene were docked against human caspase-3 (PDB: 1GFW) and NF- κ B p65 (PDB: 1VKX), with cypermethrin included as the reference toxicant. Drug-likeness and ADME properties were evaluated using Swiss ADME.

Results:

Cypermethrin exhibited the strongest binding affinities to caspase-3 (-6.2 kcal/mol) and NF- κ B (-7.7 kcal/mol), supporting its direct interaction with proteins implicated in neuronal injury. Among the phytochemicals, carvacrol demonstrated the highest affinity for NF- κ B (-6.3 kcal/mol), while *p*-cymene showed the strongest interaction with caspase-3 (-4.8 kcal/mol). All phytochemicals demonstrated favorable pharmacokinetic properties, including blood-brain barrier permeability and zero Lipinski violations, except *p*-cymene, which showed one violation.

Discussion:

These findings suggest that *Nigella sativa* phytochemicals may exert neuroprotective effects by modulating the inflammatory-apoptotic axis central to cypermethrin neurotoxicity. Carvacrol, in particular, emerged as a promising anti-inflammatory candidate, while thymoquinone's established multi-target activity supports its continued development for mitigating pesticide-induced neuronal damage.

KEYWORDS: *Nigella sativa*; Cypermethrin; Neuroinflammation; Caspase-3; NF- κ B.

INTRODUCTION

Cypermethrin is one of the most extensively used type II synthetic pyrethroid insecticides globally, owing to its effectiveness in agricultural pest control, public health interventions, and domestic applications. Despite its perceived safety profile, increasing evidence indicates that chronic and repeated exposure to cypermethrin poses substantial risks to the central nervous system. Experimental studies have demonstrated that cypermethrin induces oxidative stress, neuroinflammation, synaptic dysfunction, and neuronal loss in several brain regions, including the hippocampus, cerebral cortex, and corpus callosum^{1,2,3,4}.

The neurotoxic effects of cypermethrin are mediated through a complex interplay of inflammatory and apoptotic pathways. Among these, nuclear factor-kappa B (NF- κ B) serves as a master regulator of neuroinflammation by promoting the transcription of pro-inflammatory cytokines such as interleukin-1 β , interleukin-6, and tumor necrosis factor- α . Concurrently, activation of caspase-3, a key executioner caspase, drives programmed neuronal cell death. Persistent activation of this inflammatory–apoptotic axis has been implicated in the progression of numerous neurodegenerative conditions and represents a critical mechanism underlying pesticide-induced neuronal injury^{1,5}.

Natural products continue to attract considerable attention as sources of multi-target therapeutic agents for neurological disorders. *Nigella sativa* (black seed) is a medicinal plant with a long history of ethnopharmacological use and is rich in bioactive constituents including thymoquinone, thymol, carvacrol, and p-cymene. These phytochemicals possess antioxidant, anti-inflammatory, and anti-apoptotic properties and have demonstrated protective effects in both experimental and computational models of neurological disease^{2,6}. Notably, thymoquinone has been reported to ameliorate cypermethrin-induced oxidative stress, preserve GABAergic neuronal integrity, and improve cognitive outcomes in animal models, highlighting the therapeutic promise of *Nigella sativa* against pesticide-induced neurotoxicity.

Although the neuroprotective effects of *Nigella sativa* have been increasingly recognized, the molecular interactions between its phytochemicals and key mediators of cypermethrin-induced neuroinflammation and apoptosis remain insufficiently characterized. Molecular docking provides a rapid and cost-effective approach for elucidating these interactions and prioritizing compounds for subsequent experimental validation.

Therefore, this study employed an *in silico* molecular docking strategy to investigate the binding interactions of selected *Nigella sativa* phytochemicals with NF- κ B p65 and caspase-3, using cypermethrin as a reference toxicant. By integrating docking and pharmacokinetic analyses, this work aims to provide mechanistic insights into the potential of *Nigella sativa*-derived compounds as modulators of the inflammatory–apoptotic axis in cypermethrin-induced neurotoxicity.

METHODS

Study Design

This study employed a structure-based computational (*in silico*) design in which four *Nigella sativa* phytochemicals were docked individually against two apoptosis- and inflammation-related protein targets implicated in cypermethrin neurotoxicity, with cypermethrin itself docked in parallel as an index/reference ligand at both targets to allow direct comparison of binding behaviour between the toxicant and the candidate phytochemicals.

Target Protein Retrieval and Rationale

Two protein targets were selected based on their established mechanistic role in cypermethrin-associated neurotoxicity, namely the executioner phase of apoptosis and the transcriptional control of neuroinflammation, both of which are up-regulated following cypermethrin exposure¹. Structural coordinates for caspase-3 (PDB: 1GFW) and NF- κ B p65 (PDB: 1VKX) were retrieved from the RCSB Protein Data Bank^{7,8}.

Ligand Library Retrieval

Four *Nigella sativa* phytochemicals, selected on the basis of documented antioxidant, anti-inflammatory, and anti-apoptotic bioactivity, were retrieved as reference standards, alongside cypermethrin itself, which was additionally docked at both targets as the index toxicant against which phytochemical performance was benchmarked. Canonical SMILES and three-dimensional structure-data files (SDF) for all six ligands were retrieved from the PubChem Compound database using their respective Compound Identifiers (CID), as summarised in Table 2⁹⁻¹³.

Table 1: Two protein targets used in this study

Target	PDB ID	Structural Description
Caspase-3 (executioner caspase)	1GFW	Human recombinant caspase-3 (apopain/CPP32) resolved at 2.8 Å in complex with an isatin sulfonamide inhibitor bound at the S2 subsite; a widely used template for structure-based caspase-3 inhibitor discovery.
NF-κB p65 (RelA)	1VKX	NF-κB p50/p65 (RelA) heterodimer bound to κB DNA, resolved at 2.9 Å; the standard, literature-precedented docking template for p65-targeted anti-inflammatory phytochemical screening

Table 2: Ligand library retrieved from PubChem, with molecular identity and Canonical SMILES

Ligand	PubChem CID	Molecular Formula	Molecular Weight (g/mol)	SMILES
Thymoquinone	10281	C ₁₀ H ₁₂ O ₂	164.20	<chem>CC1=CC(=O)C(=CC1=O)C(C)C</chem>
Thymol	6989	C ₁₀ H ₁₄ O	150.22	<chem>CC1=CC(=C(C=C1)C(C)C)O</chem>
Carvacrol	10364	C ₁₀ H ₁₄ O	150.22	<chem>CC1=C(C=C(C=C1)C(C)C)O</chem>
p-Cymene	7463	C ₁₀ H ₁₄	134.22	<chem>CC1=CC=C(C=C1)C(C)C</chem>
Cypermethrin (Toxic Agent)	2912	C ₂₂ H ₁₉ Cl ₂ NO ₃	416.30	<chem>CC1(C(C1C(=O)OC(C#N)C2=CC(=CC=C2)OC3=CC=CC=C3)C=C(Cl)Cl)C</chem>

Ligand and Protein Preparation

Ligand structures downloaded from PubChem were energy-minimised using the MMFF94 force field to relax bond lengths, angles, and torsions prior to docking, and were converted to the docking-engine input format (PDBQT), with rotatable bonds assigned and Gasteiger partial charges computed for each atom. For protein preparation, co-crystallised water molecules, native ligands/inhibitors, and, where present, the DNA duplex were removed from each retrieved structure; missing side chains and hydrogen atoms were added, and Kollman united-atom charges were assigned. Each protein was then converted to the PDBQT format required for docking. The docking search space (grid box) for each target was centred on the native ligand-binding pocket identified from the co-crystallised inhibitor coordinates (caspase-3) or the previously reported p65 ligand-binding/DNA-proximal interface (NF-κB p65), with dimensions set generously to encompass the full binding cavity and immediately adjacent surface residues.

Molecular Docking Protocol

Docking of each of the five ligands (four phytochemicals with cypermethrin) against each of the two prepared targets was performed using pyRx, with an exhaustiveness setting sufficient to sample multiple ligand poses and orientations per run. Docking protocol validity was first confirmed by redocking the native co-crystallised ligand of each target (the isatin sulfonamide inhibitor for caspase-3) into its original binding site and confirming acceptable superposition with the experimentally observed pose, in line with standard practice for caspase-3 docking studies¹⁴. For each ligand-target pair, the pose with the most favourable (most negative) predicted binding free energy (kcal/mol) was retained for subsequent analysis.

Post-Docking Interaction Analysis

The best-ranked pose for each ligand-target complex was visualised and analysed for non-covalent interactions, including hydrogen bonds, hydrophobic contacts, and π -stacking, using a molecular visualisation and interaction-mapping tool (Discovery Studio Visualizer/ PyMOL). Residues contacted by each phytochemical were compared against those contacted by cypermethrin at the same target to identify shared or divergent binding-site engagement, and against residues previously reported as functionally important for ligand binding at each target.

Drug-Likeness and Pharmacokinetic Screening

Each phytochemical was additionally evaluated for oral drug-likeness using Lipinski's rule of five (molecular weight ≤ 500 g/mol, hydrogen bond donors ≤ 5 , hydrogen bond acceptors ≤ 10 , calculated log $P \leq 5$) and for predicted absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile, including blood-brain barrier permeability, given the neurological target of interest.

Data Analysis

Binding affinities (kcal/mol) obtained for the four phytochemicals and cypermethrin at each of the two targets were ranked in ascending order using GraphPad Prism 8.0.3 to identify the phytochemical(s) with the strongest predicted affinity relative to cypermethrin at each target. Interaction fingerprints were compared qualitatively across ligands to identify recurring binding-site residues that may underlie shared or differential activity.

RESULTS

Molecular Docking of Cypermethrin and *Nigella sativa* Phytochemicals

Molecular docking analysis revealed that the reference toxicant, cypermethrin, exhibited the strongest binding affinities toward both caspase-3 (-6.2 kcal/mol) and NF- κ B (-7.7 kcal/mol), highlighting its capacity to directly engage proteins associated with apoptotic and neuroinflammatory signaling.

Among the *Nigella sativa* phytochemicals, carvacrol demonstrated the highest affinity for NF- κ B (-6.3 kcal/mol), followed by thymol (-6.1 kcal/mol) and thymoquinone (-6.0 kcal/mol). Conversely, p-cymene exhibited the most favorable interaction with caspase-3 (-4.8 kcal/mol), marginally exceeding thymoquinone (-4.7 kcal/mol), thymol (-4.6 kcal/mol), and carvacrol (-4.6 kcal/mol).

Although the phytochemicals displayed lower binding energies than cypermethrin, their ability to interact with the same molecular targets suggests a potential role in modulating pathways implicated in cypermethrin-induced neurotoxicity.

Table 3: Molecular docking scores of *Cypermethrin* (Toxic agent) and *Nigella sativa* Phytochemicals against Caspase-3 and NF- κ B

S. No.	Ligands	Caspase-3 Binding Affinity (kcal/mol)	NF- κ B Binding Affinity (kcal/mol)
1.	Cypermethrin (Toxic)	-6.2	-7.7
2.	Thymoquinone	-4.7	-6.0
3.	Thymol	-4.6	-6.1
4.	Carvacrol	-4.6	-6.3
5.	p-Cymene	-4.8	-5.8

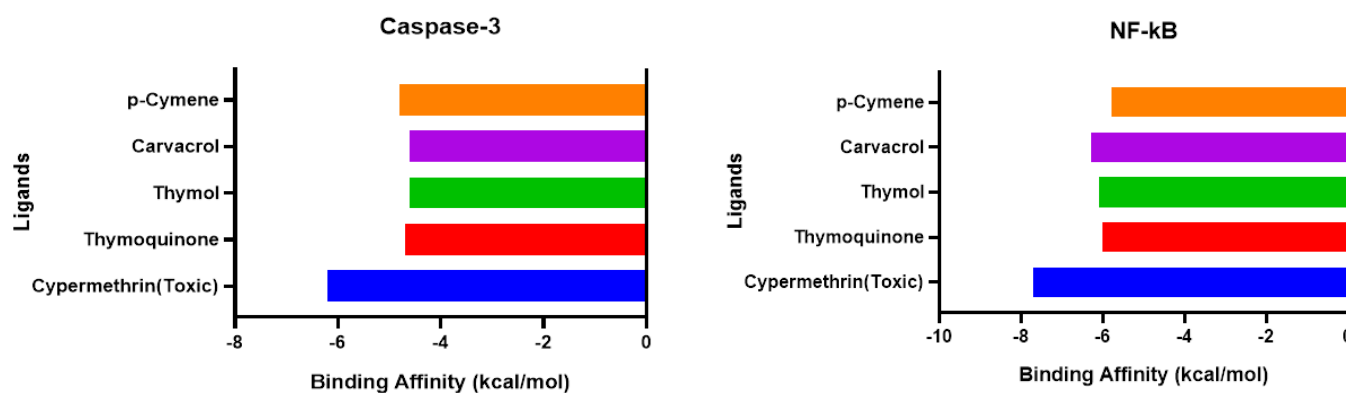


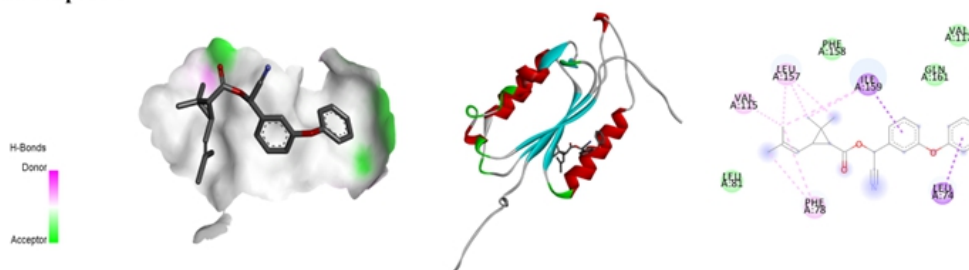
Figure 1: Ranking of Docking Scores for Cypermethrin (Toxic) and *Nigella sativa* Phytochemicals against Caspase-3 and NF-kB

Protein–Ligand Interaction Profiles

Protein–ligand interaction analysis demonstrated that cypermethrin established extensive hydrophobic and stabilizing interactions within the active sites of both proteins, consistent with its strong docking performance.

CYPERMETHRIN AGAINST CASPASE-3 & NF-kB

a. Caspase-3



b. NF-kB

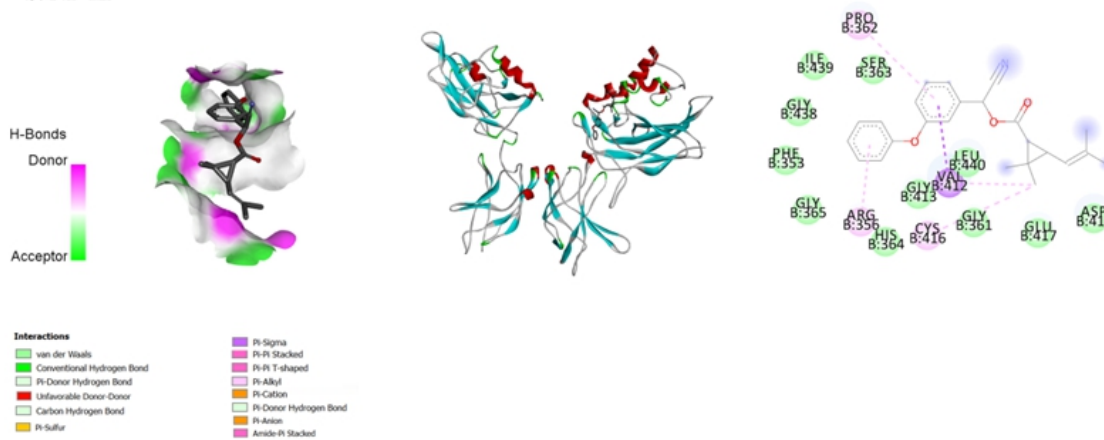


Figure 2: Protein–ligand Interaction Maps of the Cypermethrin Docked against CASPASE-3 & NF-kB
[a. Caspase-3, b. NF-kB]

Similarly, all four *Nigella sativa* phytochemicals occupied the target binding pockets and formed favorable non-covalent interactions. Thymoquinone exhibited additional polar contacts attributable to its quinone moiety, whereas thymol and carvacrol displayed highly comparable interaction patterns owing to their structural resemblance. The predominance of hydrophobic interactions across the monoterpenes suggests that lipophilicity contributes substantially to target engagement.

Importantly, the observed interactions indicate that the phytochemicals possess the structural capability to engage proteins central to the inflammatory–apoptotic axis, supporting their potential as neuroprotective modulators.

N. Sativa Phytochemicals against Caspase-3

a. Thymoquinone



b. Thymol



c. Carvacrol



d. p-Cymene



Figure 3: Protein–ligand Interaction Maps of the *Nigella Sativa* Phytochemicals Docked against CASPASE-3 [a. Thymoquinone, b. Thymol, c. Carvacrol, d. P-Cymene]

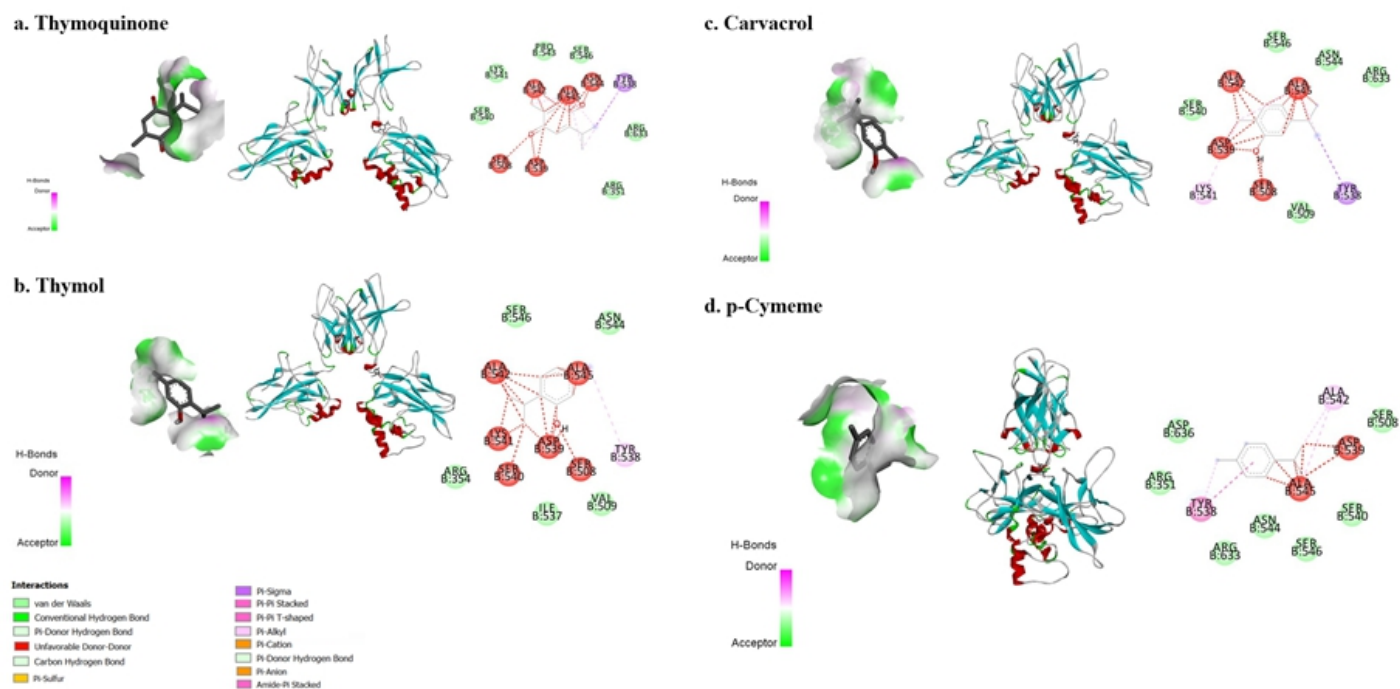
***N. Sativa* Phytochemicals against NF-kB**

Figure 4: Protein–ligand Interaction Maps of the *Nigella Sativa* Phytochemicals Docked against NF-kB
[a. Thymoquinone, b. Thymol, c. Carvacrol, d. P-Cymene]

Drug-Likeness and ADMET Properties

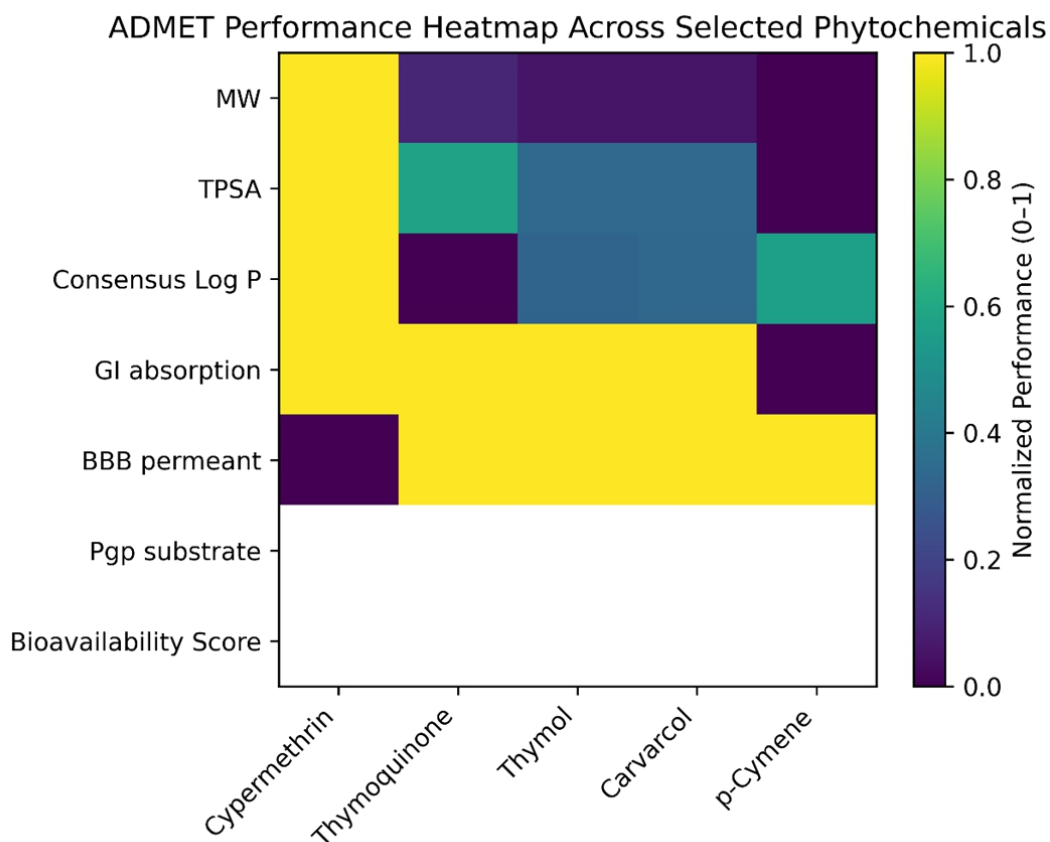
SwissADME analysis demonstrated favorable pharmacokinetic characteristics for the *Nigella sativa* phytochemicals. Thymoquinone, thymol, and carvacrol exhibited high gastrointestinal absorption, predicted blood–brain barrier permeability, and no Lipinski violations, with all compounds achieving a bioavailability score of 0.55.

Table 4: Predicted ADMET and Drug-Likeness Properties of Selected *Nigella sativa* Phytochemicals and Cypermethrin Using Swiss ADME

Ligand	Molecular Weight (g/mol)	TPSA (Å ²)	Consensus LogP	GI Absorption	BBB Permeability	P-gp Substrate	Lipinski Violations	Bio-availability Score
Thymoquinone	164.20	34.14	1.81	High	Yes	No	0	0.55
Thymol	150.22	20.23	2.92	High	Yes	No	0	0.55
Carvacrol	150.22	20.23	2.96	High	Yes	No	0	0.55
<i>p</i> -Cymene	134.22	0.00	3.74	Low	Yes	No	1	0.55
Cypermethrin (Reference Toxicant)	416.30	59.32	5.24	High	No	No	0	0.55

Abbreviations: TPSA, Topological Polar Surface Area; LogP, octanol/water partition coefficient; GI, gastrointestinal; BBB, blood–brain barrier; P-gp, P-glycoprotein.

Thymoquinone demonstrated the lowest consensus LogP (1.81), indicating an advantageous balance between lipophilicity and solubility. Carvacrol (LogP = 2.96) and thymol (LogP = 2.92) similarly displayed desirable pharmacokinetic profiles. Although *p*-cymene exhibited blood–brain barrier permeability, it recorded one Lipinski violation and low gastrointestinal absorption.

**Figure 5:** ADMET Performance Heatmap Across Cypermethrin and *Nigella sativa* Phytochemicals

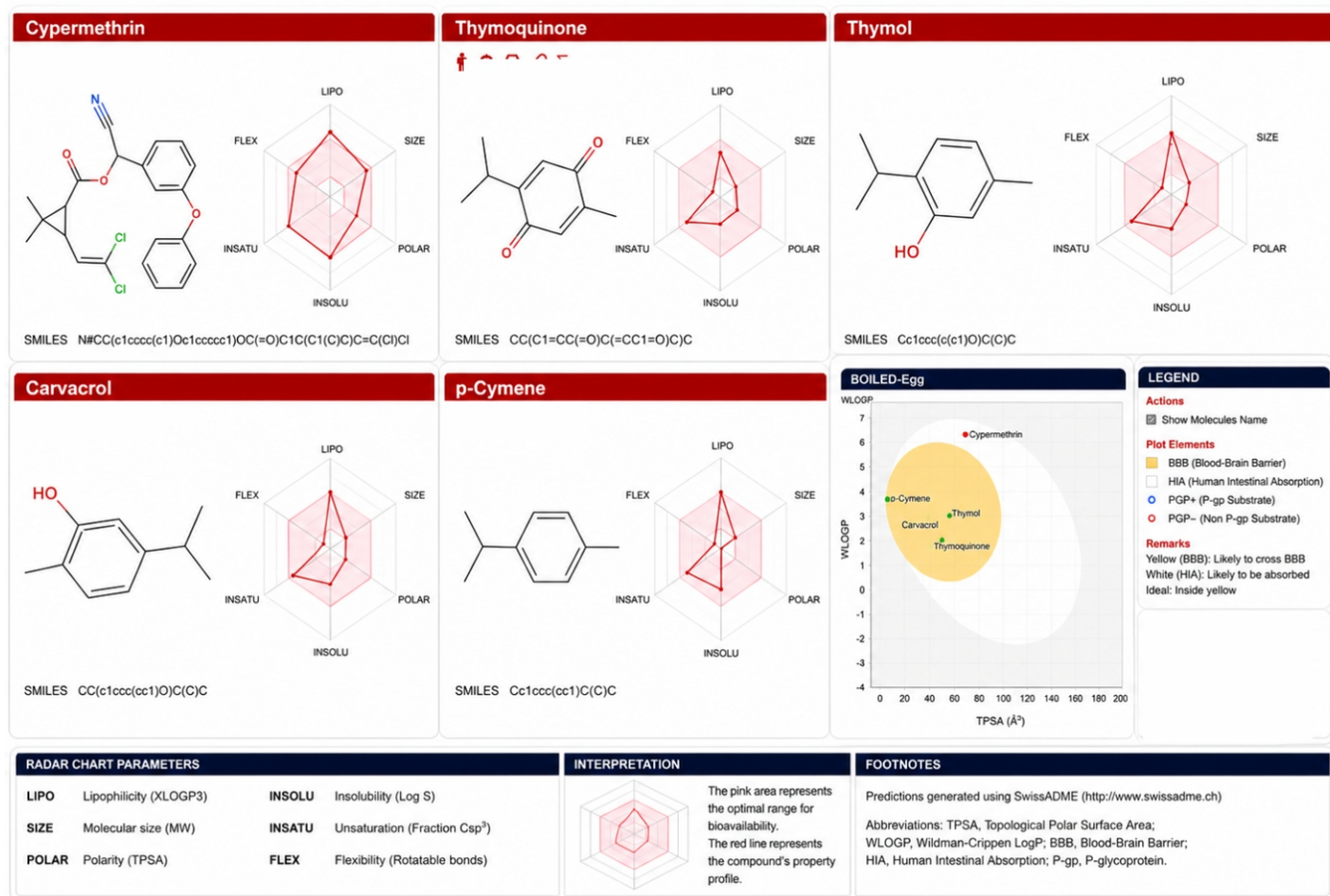


Figure 6: Radar Chart and Boiled Egg Predictions Across Cypermethrin and *Nigella sativa* Phytochemicals

In contrast, cypermethrin exhibited the highest molecular weight (416.30 g/mol) and consensus LogP (5.24), with no predicted blood–brain barrier permeability despite its established neurotoxic effects.

Summary of the Key Findings

Collectively, the findings demonstrate that the selected *Nigella sativa* phytochemicals possess favorable molecular and pharmacokinetic characteristics relevant to neuroprotection. Carvacrol emerged as the strongest NF-κB-interacting phytochemical, while p-cymene exhibited the greatest affinity toward caspase-3 among the plant-derived compounds.

Notably, thymoquinone demonstrated a balanced profile characterized by acceptable target engagement, favorable ADMET properties, and previously documented neuroprotective activity against cypermethrin-induced neuronal injury. These findings support the prioritization of

Nigella sativa phytochemicals for future molecular dynamics simulations and experimental validation as potential modulators of cypermethrin-associated neuroinflammation and apoptosis.

DISCUSSION

The present study employed a structure-based computational approach to investigate the ability of selected *Nigella sativa* phytochemicals to interact with two principal mediators of cypermethrin-induced neurotoxicity, namely NF-κB and caspase-3. Cypermethrin demonstrated the strongest binding affinity toward both targets, exhibiting docking scores of -7.7 kcal/mol against NF-κB and -6.2 kcal/mol against caspase-3. Given that cypermethrin is a well-established neurotoxicant, these findings provide further mechanistic support for its direct involvement in activating the inflammatory and apoptotic pathways implicated in neuronal injury.

Accumulating evidence suggests that cypermethrin exposure initiates oxidative stress, resulting in excessive reactive oxygen species (ROS) generation, mitochondrial dysfunction, and activation of NF- κ B signaling. Activated NF- κ B subsequently promotes the transcription of pro-inflammatory mediators, including IL-1 β , IL-6, TNF- α , inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2), thereby amplifying neuroinflammation. Persistent inflammatory signaling further converges on mitochondrial apoptotic pathways, culminating in caspase-3 activation and neuronal cell death^{1,5}.

Importantly, the objective of the present study was not to identify compounds exhibiting greater affinity than cypermethrin, but rather to determine whether *Nigella sativa* phytochemicals possess the capacity to engage molecular targets central to cypermethrin-induced neurotoxicity. The ability of thymoquinone, thymol, carvacrol, and p-cymene to occupy the binding pockets of both NF- κ B and caspase-3 suggests that these compounds may modulate the inflammatory–apoptotic axis that underlies pesticide-mediated neuronal damage.

Among the phytochemicals, carvacrol demonstrated the greatest affinity toward NF- κ B (-6.3 kcal/mol), indicating a potential role as an anti-inflammatory modulator. Previous investigations have shown that carvacrol suppresses NF- κ B nuclear translocation and attenuates the expression of IL-1 β , IL-6, and TNF- α across several inflammatory models, findings that are consistent with its interaction profile observed in the present study^{15,16}. Likewise, thymol exhibited comparable binding characteristics, reinforcing reports describing its antioxidant and anti-inflammatory activities in neurological disorders⁶.

Although thymoquinone did not exhibit the strongest docking score, it arguably represents the most biologically relevant phytochemical identified in this study. Numerous experimental studies have demonstrated that thymoquinone exerts neuroprotective effects through simultaneous regulation of multiple signaling pathways, including NF- κ B, Nrf2/ARE, PI3K/Akt, AMPK, and SIRT1. Furthermore, thymoquinone has been shown to inhibit the activation of caspases-3, -8, and -9, reduce microglial activation, preserve mitochondrial membrane integrity, and suppress ROS-mediated neuronal injury^{2,17,18}.

Interestingly, p-cymene demonstrated the highest affinity toward caspase-3 (-4.8 kcal/mol) among the *Nigella sativa* phytochemicals. Although comparatively less studied than thymoquinone, p-cymene has been reported to exhibit antioxidant and anti-inflammatory activities, suggesting that it may contribute synergistically to the overall neuroprotective effects of *Nigella sativa*. This observation further supports the concept of phytochemical polypharmacology, whereby multiple constituents collectively modulate interconnected signaling pathways rather than acting through a single molecular target.

The ADMET analysis provides additional support for the translational potential of the investigated phytochemicals. Thymoquinone, thymol, and carvacrol exhibited favorable gastrointestinal absorption, predicted blood–brain barrier permeability, and no violations of Lipinski's Rule of Five. These properties are particularly relevant considering that effective neuroprotective agents must achieve adequate central nervous system bioavailability. In contrast, cypermethrin exhibited poor predicted blood–brain barrier permeability despite its known neurotoxicity, highlighting the limitations of computational pharmacokinetic models when applied to environmental toxicants.

Collectively, the findings support a mechanistic model in which cypermethrin induces neuronal injury through NF- κ B-mediated neuroinflammation and caspase-3-dependent apoptosis, while *Nigella sativa* phytochemicals may mitigate these effects through target engagement and modulation of the inflammatory–apoptotic axis. Notably, thymoquinone appears to function as a multi-target neuroprotective agent, whereas carvacrol emerges as a promising NF- κ B-directed phytochemical. The observed molecular interactions provide a plausible explanation for the previously reported neuroprotective effects of *Nigella sativa* in experimental models of pesticide-induced neurotoxicity.

Nevertheless, this study is limited by the inherent constraints of molecular docking, which provides a static representation of protein–ligand interactions and does not account for protein flexibility, metabolic transformation, or intracellular signaling complexity. Consequently, future studies incorporating molecular dynamics simulations, transcriptomic analyses, and in vivo validation are warranted to confirm the therapeutic relevance of these findings.

In conclusion, the present study demonstrates that *Nigella sativa* phytochemicals possess the molecular capability to interact with critical mediators of cypermethrin-induced neurotoxicity. By targeting NF- κ B and caspase-3, these compounds may represent promising candidates for the development of novel interventions aimed at attenuating pesticide-associated neuroinflammation and apoptosis.

DECLARATIONS

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