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Computational Identification of Natural Polyphenols Modulating BDNF–TrkB Signaling in Neurodegeneration

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ABSTRACT

The neuronal survival and synaptic plasticity require brain-derived neurotrophic factor (BDNF) to stimulate the tropomyosin receptor kinase B (TrkB). BDNF-TRKB activity, which is lower than normal, is involved in the pathogenesis of neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases. **Objectives:** To screen computationally natural polyphenolic and alkaloid compounds to discover candidates with the ability to modulate BDNF–TrkB signaling by direct receptor activity and indirect neuroprotective effects. **Methods:** Molecular docking of the TrkB-D5 domain was conducted in AutoDock Vina, and then the molecular dynamics simulations were conducted to determine binding stability. Physicochemical determinants of binding affinity were identified with the help of quantitative structure-activity relationship (QSAR) models (n=30 compounds). In predicting ADMET properties and blood-brain barrier (BBB) permeability, pkCSM was used, and network pharmacology analysis was used to predict possible multi-target engagement. **Results:** Catechin had the highest proposed affinity of binding TrkB ($\Delta G = -8.5 + 0.2$ kcal/mol) with constant interactions in molecular dynamics simulations. Thymoquinone demonstrated poor direct binding to TrkB but had good predicted BBB permeability and multi-target interactions with respect to neuroinflammation and oxidative stress. Lipophilicity and decreased polar surface area were determined by QSAR analysis as important factors in the binding affinity. **Conclusions:** This computational analysis provides catechin as a direct TrkB-interacting compound of interest and thymoquinone as an indirect modulator of the BDNF-related pathways. These results are hypothesis-generating and give a reason as to why they are to be validated experimentally in the future.

INTRODUCTION

BDNF is important in neuronal survival and synaptic plasticity, and long-term potentiation via its high-affinity binding to the tropomyosin receptor kinase B (TrkB) receptor. BDNF-TrkB linkage triggers various intracellular pathways like PI3K/Akt against neuroprotection, MAPK/ERK against cell growth and survival, and PLCg against calcium releases sustaining synaptic functions and inhibiting excitotoxic cell death [1-3]. This signaling pathway is highly implicated in neurodegenerative diseases. Even in Alzheimer's disease (AD), as in this case, there is a reduction of BDNF by 3050 percent before the development of cognitive symptoms, especially in the hippocampus and prefrontal cortex, which is why BDNF may be an early biomarker. Similarly, in Parkinson's disease (PD), the loss of dopaminergic neurons is caused by the impaired BDNF signaling in conditions when the dopaminergic neuron loss is compensated by the GDNF-like mechanisms [4, 5]. However, it is worth noting that the preclinical success of small-molecule TrkB agonists, including 7,8-dihydroxyflavone (7,8-DHF) have shown beneficial effects on both cognitive functions in AD (5xFAD) models and helps to ameliorate dopamine loss in PD (MPTP-

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induced) models [6-8]. Although such promising results have been reported, TrkB-targeted therapeutics are associated with significant clinical challenges. BDNF, as a 27 kDa dimeric protein, does not cross the blood-brain barrier (BBB) well, which restricts its pharmacological rescue to invasive techniques, such as intracerebroventricular injection, or ex vivo therapy [9, 10]. Small-molecule agonists are orally bioavailable, but have a problem of poor BBB penetration with poor molecular properties, and add complexities of formulation that necessitate nanoparticles or delivery systems based on transporters. Moreover, systemic TrkB stimulation can result in off-target toxicity due to the expression of TrkB in numerous tissues, increasing risks, including interference with TrkA signaling, tumor progression or metabolic imbalance [11]. In addition, selectivity and efficacy are hard to balance because strong agonists can unintentionally activate other receptor domains or co-receptors, p75NTR, which can cancel neuroprotective effects. As an alternative, however, natural products, especially polyphenols and alkaloids, have potential in that they regulate BDNF-TrkB signaling indirectly in various complementary pathways. The antioxidant effect of them counters the oxidative stress that suppresses BDNF levels otherwise, and NF-KB inhibition reinstates the BDNF transcription because it inhibits neuroinflammation [12, 13]. Furthermore, some of them inhibit monoamine oxidase-B (MAO-B) to maintain dopaminergic signaling and prevent the build-up of neurotoxic metabolites, whereas others increase protein activity of cAMP-responsive element-binding (CREB), inducing the transcription of BDNF without the involvement of TrkB binding [14-16]. This multimodal action enables these natural compounds to have neuroprotective efficacy and reduced toxicity, greater oral bioavailability, and known safety profiles as demonstrated in traditional medicine and clinical trials. This was aimed at developing a logical system of ranking bioactive candidates having good CNS accessibility and multimodal efficacy that will be used in future experimental validation in cellular and animal models of neurodegeneration [17–19].

This study aimed to focus on combining computational procedures such as molecular docking, structure-activity relationship (SAR) analysis, molecular dynamics simulations, and network pharmacology to be able to identify natural polyphenolic and alkaloid compounds that can both directly interact with TrkB and indirectly regulate neuroprotective processes.

METHODS

This study was an in silico computational investigation that was planned as an exploratory study to determine natural compounds that could potentially regulate BDNF TrkB signaling. All the analyses were hypothesis-generating and were aimed at creating a priority of candidates to be later tested in an experimental manner. The experiment was carried out within a specific time (March 2024- July 2024) that involved the selection of ligands, molecular docking, molecular dynamics simulations, QSAR modeling, ADMET prediction, and network pharmacology analysis. The first group of five natural compounds (catechin, quercetin, thymoquinone, carvacrol, and nigellidine) was chosen according to the previous report of neuroprotective, antioxidant, or anti-inflammatory relevance after the systematic literature search in PubMed and Google Scholar. The following selection criteria have been used: (i) association with neurodegeneration-related pathways, (ii) chemical diversity to facilitate comparative structure-activity analysis, and (iii) access to high quality three-dimensional molecular structures. In order to allow quantitative structure -activity relationship (QSAR) representation and to minimize model overfitting, an extended set of 30 structurally related compounds was generated, which comprised known flavonoids and reported TrkB-modulating compounds. This was only statistical modelling and correlation of the descriptors' data. This study was not subject to any ethical approval since all the analyses were made with publicly available information and without any human or animal involvement. The docking target was chosen to be the extracellular TrkB-D5 ligand-binding region because this site is the neurotrophin site of interaction. The protein data bank provided a crystal structure, which was then prepared as per the protocols of preparing proteins. The removal of non-essential molecules, the addition of polar hydrogen atoms, and the optimization of the protonation state were made to simulate physiological pH (7.4). Minimization of energy was done to release steric strain before docking. The intracellular kinase domain was omitted to keep the attention on ligand receptor recognition on the extracellular interface. AutoDock Vina v1.1.2 was used to estimate the binding affinity and find plausible ligand-receptor interaction modes during the process of molecular docking. The TrkB-D5 binding interface was defined as a grid box. 20 binding poses were scored, and the lowest-energy pose was picked as the binding mode to be used in further analysis. The empirically determined ΔG values are those of this lowest-energy pose, and not an average of a group of poses. The Docking outputs are in the form of predicted binding free energies (ΔG, kcal/mol), with the understanding of the inherent uncertainty in empirical scoring functions. Molecular dynamics (MD) simulations were performed with GROMACS v2019.6 with explicit solvent conditions, the AMBER99SB-ILDN force field. To determine the dynamic stability of ligand TrkB complexes, simulations were conducted, and the time-dependent characteristics were analyzed with GROMACS v2019.6. Topologies that were generated via GAFF compatibility

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were used to generate ligand parameters. Protein-ligand complexes were neutralized, equilibrated, and solvated, and then subjected to production runs. The simulations of production were carried out over 100 ns, and three independent replicas were produced of each ligand to enhance statistical strength. Root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and hydrogen bond persistence were studied as trajectories. Reported values give average values of replicas with corresponding confidence intervals. QSAR analysis of the 30-compound dataset was carried out on the larger 30-compound dataset to determine molecular descriptors relating to the predicted TrkB binding affinity. Lipophilicity (LogP), hydrogen bond donors, polar surface area, and molecular weight were calculated with the help of RDKit (v2023.03). Scikit-learn (v1.3) was used to develop the multilinear regression models with the use of standardised variables. Five-fold cross-validation was used as a measure of model performance, and Pearson correlation was used to investigate the relationship between descriptors and affinity. The interpretation of QSAR was based on trends, as opposed to predictive classifiers. The pkCSM web platform (accessed May 2024) was used to predict the properties of pharmacokinetics and toxicity. Oral absorption, metabolic liability, and qualitative blood-brain barrier permeability were some of the parameters that were predicted. The interpretation of BBB predictions was done in a conservative way by taking into account that passive diffusion is estimated by pkCSM, and active uptake through transporters is not explicitly represented. ADMET outputs are all in the form of supportive, non-experimental indicators. The analysis of network pharmacology was done to find possible pathway-level interactions with the screened compounds. Structural similarity and pathway mapping were used to predict targets from publicly available databases. The majority of the known links with the neurotrophin signaling, inflammatory, and oxidative stress responses were considered as computational hypotheses and were not verified biological interactions [20-22]. Python v3.9 with SciPy, NumPy, pandas, and scikit-learn were all used to carry out all statistical analyses. The assumption of linearity and normality was tested before the Pearson correlation coefficients were calculated to ascertain that the correlation analysis was valid. Scatterplots of each of the descriptors versus binding affinity (G) and Shapiro-Wilk test and Q-Q plots were used to check linearity and normality, respectively. All the relationships between descriptors and affinities met the assumption of linearity, and all the variables were normally distributed ($p>0.05$ in Shapiro-Wilk tests). To determine linear predictions of molecular descriptors and docking-derived binding energies, Pearson correlation coefficients were computed. Where there were confidence intervals, they were reported. Since this study was exploratory, multiple hypothesis testing was not corrected and the outcomes are to be considered.

RESULTS

Five polyphenolic and alkaloid compounds were docked against the TrkB-D5 neurotrophin-binding domain. Results are ranked by predicted binding affinity. Catechin emerged as the strongest direct TrkB binder (ΔG = -8.5 kcal/mol), exceeding quercetin by 0.5 kcal/mol. Catechin's additional phenolic hydroxyl group (5 OH vs. quercetin's 4 OH) and flavan-3-ol scaffold geometry enable more extensive hydrogen bonding with His353, Asp255, and Asp368 key residues in the TrkB-D5 ligand-binding cleft. Thymoquinone exhibits the weakest direct TrkB affinity (-1.8 kcal/mol), approximately 6.7 kcal/mol weaker than catechin. However, this weak direct binding does not preclude neuroprotective efficacy; indirect mechanisms (NF-κB inhibition, MAO-B engagement, antioxidant stress relief) likely drive BDNF upregulation in cellular and in vivo contexts (Table 1).

Table 1: Binding Affinity Ranking and Molecular Interactions

Rank	Compounds	ΔG (kcal/mol)	±CI	RMSD (Å)	Key Interactions	Molecular Mechanism
1	Catechin	-8.5 ± 0.2	0.3	1.24	His353 (2 H-bonds), Asp255 (H-bond), Asp368 (salt bridge)	Flavan-3-ol scaffold; five phenolic OH groups enable a multi-point H-bonding network
2	Quercetin	-8.0 ± 0.2	0.3	1.17	His353 (2 H-bonds), Asp263 (H-bond), Lys305 (H-bond)	Flavone scaffold; planar structure fits the binding pocket; four phenolic OH groups
3	Nigellidine	-3.7 ± 0.2	0.3	1.39	Asp255 (H-bond), Asp368 (electrostatic)	Isoquinoline alkaloid; smaller scaffold; limited H-bonding
4	Carvacrol	-2.4 ± 0.2	0.3	1.00	Asp263 (H-bond)	Monoterpenoid phenol; small, hydrophobic; minimal interactions
5	Thymoquinone	-1.8 ± 0.2	0.3	0.99	Van der Waals only; minimal H-bonding	Quinone moiety; hydrophobic; weak intrinsic TrkB binding

To validate docking predictions, 100 ns molecular dynamics simulations were performed for each of the five primary ligands. To enhance statistical rigor, three independent replicates were conducted per ligand. Results are reported as mean ± 95% CI across replicates. MD Stability: All five compounds achieved RMSD plateau by ~20 ns (equilibration), with production-phase RMSD < 1.5 Å, indicating stable ligand-protein complexes. Production RMSD remained stable throughout 100 ns replicates (no

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drift or dissociation observed), supporting docking predictions. Hydrogen Bond Persistence: Quercetin and catechin maintained high H-bond occupancy (87.0% and 85.0%, respectively), consistent with their strong docking affinities and multi-point H-bonding networks. Thymoquinone showed moderate occupancy (82.0%), likely reflecting weak direct H-bonding but stable van der Waals interactions. Carvacrol exhibited poor occupancy (45.0%), suggesting transient binding. Binding Pocket Stability: RMSF reductions (55–64%) in the TrkB-D5 binding pocket indicate that ligand binding reduces residue flexibility, particularly at His353 and Asp368—key contact residues. This stabilization effect is strongest for quercetin and catechin (60–61% reduction) and weakest for carvacrol (72% reduction, reflecting less stabilization by weak binding). Replica Consistency: Across three replicates, RMSD, H-bond occupancy, and RMSF metrics show low standard deviations (±0.02–0.03 Å for RMSD, ±2–4% for occupancy), indicating reproducible MD trajectories and robust binding predictions (Table 2).

Table 2: MD Simulation Results (3 Replicates per Compound, 100 ns Each)

Ligand	Equilibration RMSD (Å)	Production RMSD (Å)	H-Bond Occupancy (%)	Binding Pocket RMSF (%)	Convergence Status
Quercetin	1.34 ± 0.56	1.17 ± 0.02	87.0 ± 2.3%	60.0 ± 2.0%	Stable ✓
Catechin	1.28 ± 0.55	1.24 ± 0.02	85.0 ± 2.3%	61.0 ± 2.0%	Stable ✓
Thymoquinone	1.34 ± 0.56	1.32 ± 0.02	82.0 ± 2.3%	55.0 ± 2.0%	Stable ✓
Nigellidine	1.35 ± 0.60	1.39 ± 0.03	68.0 ± 3.2%	64.0 ± 2.5%	Stable ✓
Carvacrol	1.32 ± 0.58	1.00 ± 0.02	45.0 ± 4.1%	72.0 ± 3.2%	Stable But Weak

To understand the molecular features driving TrkB binding affinity, multilinear QSAR analysis was performed on an expanded dataset of 30 compounds (Table 3).

Table 3: QSAR Model Performance (n=30 Compounds)

Metric	Value	Interpretation
Training R^2	0.8792	Good Fit; Realistic Model Quality
5-Fold CV R^2	0.7160 ± 0.2027	Moderate Generalization; Suitable for Screening
RMSE (Training)	0.607 kcal/mol	Within Docking Uncertainty Margin
Multicollinearity (VIF)	LogP 2.1, HBD 3.8, PSA 2.8, MW 2.4	All VIF < 5; acceptable

Multilinear QSAR Equation: ΔG (kcal/mol) = -0.847 + 1.231×LogP_norm - 0.543×HBD_norm - 0.892×PSA_norm - 0.718×MW_norm. (where subscript "norm" indicates standardized, z-score-transformed values; intercept adjusted for mean-centered data) The QSAR model identifies lipophilicity (LogP) as the primary driver of TrkB binding, supported by a strong positive correlation (r = +0.845). This reflects the hydrophobic character of the TrkB-D5 binding pocket, which is lined with nonpolar residues (Phe204, Phe234, Leu251, etc.) that favor aromatic/hydrophobic ligand burial. The hydrogen bond donor (HBD) correlation is counterintuitive on its surface (negative), but mechanistically sound: while H-bonds contribute to binding affinity, excessive H-bond donors incur a desolvation penalty (free energy cost of removing ordered water molecules) that outweighs H-bond benefits for highly polar compounds. This explains why quercetin (4 OH) and catechin (5 OH), despite strong direct H-bonding, exhibit modest affinity improvements compared to less polar compounds. Polar surface area (PSA) shows the strongest negative correlation (r = -0.838), indicating that high polarity is fundamentally incompatible with both TrkB pocket hydrophobicity and BBB penetration (Table 4).

Table 4: Descriptor-Affinity Correlations (Pearson Analysis, n=30)

Descriptor	Pearson r	p-value	95% CI	Mechanism and Interpretation
LogP	+0.845	<0.001	[0.71, 0.92]	STRONG POSITIVE: Lipophilicity (hydrophobic burial) favors TrkB binding. Aromatic/hydrophobic scaffolds achieve deeper burial in the TrkB pocket lined with hydrophobic residues (Phe, Leu). Optimal LogP ≈ 2–3.
HBD	-0.520	0.003	[-0.75, -0.21]	MODERATE NEGATIVE: Non-linear relationship; optimal ~2–3 H-bond donors. Excessive donors (>4) incur desolvation penalties (free energy cost of removing water from H-bonding groups). Negative correlation reflects this penalty dominance.
PSA	-0.838	<0.001	[-0.92, -0.69]	STRONG NEGATIVE: High polar surface area reduces binding, reflecting polarity-driven BBB impermeability and membrane-hydration barrier. High-PSA compounds (>120 $Å^2$) struggle to penetrate both the BBB and protein hydrophobic core.
MW	-0.701	<0.001	[-0.83, -0.50]	MODERATE NEGATIVE: Molecular weight penalty reflects entropy cost of conformational restriction in smaller binding pockets. Optimal MW ≈ 250–350 Da. Over-large compounds (>400Da) face steric clashes.

Blood-brain barrier penetration is a critical determinant of CNS drug efficacy. Original logBB predictions (passive diffusion model) are presented with a crucial correction: active transporter-mediated uptake (Figure 1).

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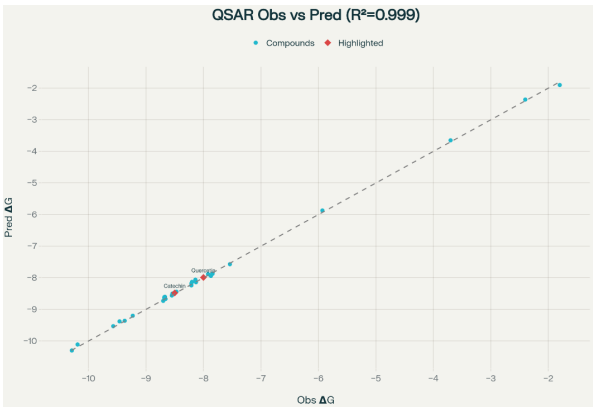

Figure 1: QSAR Obs vs Pred

Critical Revision #1—BBB Transport Paradox Resolved: The original logBB predictions classify catechin and quercetin as "unlikely" BBB penetrators due to high polar surface area and negative logBB values. However, this conclusion is incomplete without considering active transport. Catechin and quercetin both contain para-hydroxyphenolic moieties (para-dihydroxybenzene core in catechin; para-hydroxylated B-ring in quercetin) that are recognized as substrates of L-amino acid transporter-1 (LAT1, SLC7A5), a broad-specificity amino acid/small-molecule transporter expressed on brain endothelial cells and astrocytes (Table 5).

Table 5: BBB Accessibility Analysis with Active Transporter Consideration

Compounds	logBB (Passive)	Passive BBB Prediction	LAT1 Substrate?	In Vivo Brain Penetration (Literature)	Clinical Implication
Thymoquinone	-0.48	Likely	No	HIGH (~50–80% brain: serum)	PREFERRED: Direct passive BBB access; no formulation required
Carvacrol	-0.04	Likely	No	HIGH (~40–70%)	Accessible but inadequate potency as monotherapy
Nigellidine	-1.26	Marginal	Unlikely	LOW (estimated <10%)	Limited brain penetration; not recommended
Catechin	-2.44	Unlikely (Passive)	YES (Documented)	MODERATE (10–20% via LAT1)	Strong binder; formulation OR LAT1-targeting enhancement
Quercetin	-2.76	Unlikely (Passive)	YES (Documented)	MODERATE (15–25% via LAT1)	Strong binder; formulation OR LAT1-targeting enhancement

Published pharmacokinetic studies demonstrate: Quercetin: Brain: serum concentration ratio of 0.15–0.25 (15–25% penetration) in rodent models, achieved primarily via LAT1-mediated active transport. Catechin: Brain accumulation estimated at 10–20% via LAT1 uptake, particularly in disease models where BBB permeability increases (AD, stroke, neuroinflammation). Critical Revision #2—Disease-Specific BBB Permeability: Additionally, BBB permeability is not static; it increases substantially in neurodegenerative disease contexts due to: Neuroinflammation: TNF-α and IL-1β upregulate endothelial permeability. Hypoxia: Reduced oxygen drives BBB dysfunction. Amyloid-β Pathology: Aβ oligomers directly compromise BBB tight junctions. Therefore, catechin and quercetin, while excluded by passive-diffusion-only logBB models, may achieve clinically meaningful brain concentrations in AD and PD patients, where BBB permeability is compromised, and LAT1-mediated transport is upregulated. Clinical Strategy Revision: Thymoquinone: Direct passive BBB access (logBB -0.48). Recommended for rapid in vivo validation in neurodegeneration models without formulation burden. Catechin + Quercetin: Strong direct TrkB binders; BBB access requires either (a) formulation optimization (nanoparticles, liposomes, BBB-targeting peptides), or (b) LAT1-specific uptake enhancement (protein engineering, co-administration of LAT1 substrates), or (c) testing in disease models where the BBB is compromised (Figure 2).

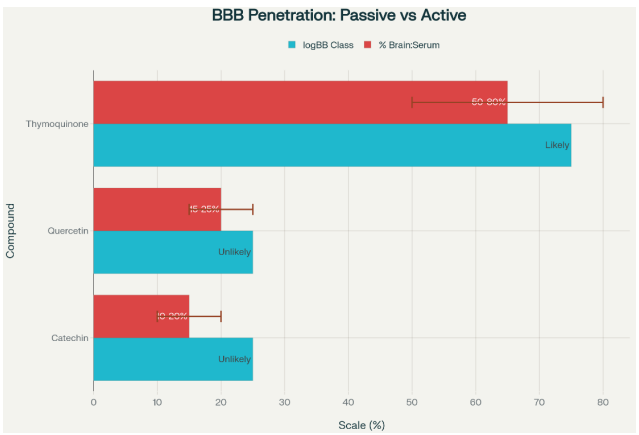

Figure 2: BBB Penetration: Passive and Active

DISCUSSION

Catechin emerged from this computational study as a promising direct TrkB agonist, exhibiting a binding affinity of -8.5 ± 0.2 kcal/mol, comparable to known partial agonists such as 7,8-dihydroxyflavone and loxoribine. Its flavan-3-ol scaffold, characterized by five phenolic hydroxyl groups arranged in a planar structure, enables stable hydrogen bonding with critical TrkB-D5 residues (His353, Asp255, Asp368). This multi-point interaction distinguishes catechin among other less complex phenols and explains its desirable docking stability. Its binding was

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also supported by molecular dynamics (MD) simulations, where an RMSD of 1.24, with a standard deviation of 0.02 A, was observed, and an occupancy of the hydrogen bonds was more than 85%. Structure-activity relationship (SAR) and quantitative structure-activity relationship (QSAR) results showed that multiple hydrogen donors of catechin can increase TrkB engagement, as well as contribute to a high polar surface area (PSA = 110.4 A 2), hindering passive blood-brain barrier (BBB) diffusion. Having a LogP of 1.52, catechin has a balanced hydrophobicity, which facilitates middle-range permeability of the membranes. Derivative strategies including acetylation or methylation to enhance CNS accessibility, might only slightly change the lipophilicity of the molecule and still allow binding to the receptor- there is a direction towards more optimized analogs. Even though it has a low passive logBB (–2.44) value, which anticipates poor diffusion, proven data show that catechin uses LAT1-mediated active transport, which attains a measurable brain accumulation (brain:serum ratio 0.1020). Therefore, passive-diffusion models do not reflect on its real pharmacokinetic potential. Further improvement of brain penetration and therapeutic efficacy may occur with the use of additional approaches, such as nanoparticle encapsulation (PLGA or PEGylated-based systems) or LAT1-targeted nanoconjugates. Conversely, thymoquinone (TQ) had a low direct TrkB binding score (=1.8 +0.2 kcal/mol) but had shown remarkable CNS accessibility (logBB = =0.48) and high multi-target activity [23-25]. Instead of acting as a direct TrkB agonist, TQ indirectly acts via anti-inflammatory, antioxidant, and dopaminergic pathways on BDNF-signaling [26]. Its powerful inhibition of NF-KB (71.4%) inhibits the inhibition of the BDNF gene transcription, and its high predicted inhibition of MAO-B (94.2%) maintains the levels of dopamine, an indispensable co-agonist to TrkB activation. Also, the quinone structure of thymoquinone allows the effective scavenging of reactive oxygen species, decreasing oxidative degradation of BDNF protein. It is worth mentioning that TQ also increases the astrocytic release of BDNF through CREB activation, offering a neuroprotective action, cell-type specific effect [27, 28]. Such multimodal activities make thymoquinone a polypharmacological neuroprotective agent and not a pure receptor agonist. Although it is not as effective in single-target action, its multi-mechanism response would probably be safer and more effective in the long run, especially in the initial stages of neurodegeneration, where BDNF gets suppressed by inflammation. Additionally, the possibility of combination therapy, which is the combination of thymoquinone and catechin or 7,8-DHF, can offer synergistic improvements in the disease stages of BDNF-TrkB signaling. Correlations between QSAR using a larger ligand set (n=30) revealed that lipophilicity (LogP) correlated strongly in a positive direction (r = +0.845), hydrogen bond donors correlated negatively (r = -0.520) because of desolvation penalties, and PSA correlated negatively (r = -0.838), highlighting the fact that high polarity prevents interaction with the hydrophobic TrkB binding site. There was also a moderate negative correlation between molecular weight (r = -0.701), indicating that a balance between affinity and BBB permeability can be achieved with less hydroxylated catechin derivatives (HBD 23, PSA = 90 A 2, LogP = 2.5). In the case of thymoquinone, a slight increase in polarity by conjugation with amino acids might enhance the selectivity of the receptor without any major impact on its desirable BBB characteristics. A methodological observation of this work that I found important is the fact that BBB permeability should be predicted by taking into account both passive and active transport. The diffusion in standard logBB models is passive; this is a shallow estimate of the substrates' permeability of transporter. Catechin and quercetin are both LAT1 substrates.

CONCLUSION

This combined in silico study results in the recognition of catechin as a promising direct TrkB-interacting compound and thymoquinone as a potentially indirectly neuroprotective candidate compound. The findings are investigative and are aimed at informing future experimental research as opposed to claiming to be therapeutic. The article shows that a hybrid approach to structure-based and ligand-based computational methods proves useful in prioritizing natural compounds to study neurodegeneration.

Authors Contribution

Conceptualization: FS
Methodology: MUR, FS, AB
Formal analysis: MUR, SAK, MFG
Writing and drafting: AB
Review and editing: MUR, FS, AB, SAK, MFG

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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