

Taxifolin: From Racemic Ambiguity to Stereospecific Pharmacological Precision: A Systematic Review of Isomeric Efficacy

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ABSTRACT

Taxifolin (*dihydroquercetin*), a naturally occurring flavanone, has attracted increasing scientific interest because of its broad neuroprotective, antioxidant, and anti-inflammatory properties. Despite extensive experimental evidence supporting its therapeutic potential, the pharmacological translation of taxifolin remains limited by poor bioavailability, rapid metabolism, and the widespread use of undefined racemic mixtures in research. The saturated C2–C3 bond in Taxifolin creates multiple stereoisomers, yet most published studies fail to evaluate stereospecific pharmacodynamic and pharmacokinetic differences, leading to inconsistent biological outcomes. This systematic review summarizes current evidence regarding the stereochemical, pharmacological, and translational aspects of Taxifolin in neurodegenerative disorders and traumatic brain injury (TBI). Experimental findings from in vitro and in vivo studies demonstrate that Taxifolin exerts neuroprotective effects through modulation of oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptotic signaling. The compound activates antioxidant pathways, including Nrf2/HO-1 and PI3K/Akt, while suppressing inflammatory mediators such as NF-κB, JAK/STAT3, MAPKs, and the NLRP3 inflammasome. Taxifolin also reduces amyloid-β aggregation, preserves synaptic integrity, and improves cognitive performance in experimental models. Pharmacokinetic investigations indicate stereoselective differences between isomers, with the (2R,3R)-isomer showing superior tissue retention and therapeutic activity compared to other stereoisomeric forms. Recent advances in nanomedicine-based delivery systems, including nanoparticles and phospholipid complexes, have demonstrated improved brain targeting and enhanced bioavailability. This review highlights the importance of stereochemical precision, targeted drug delivery, and mechanistic multi-pathway modulation in advancing Taxifolin from a nutraceutical compound toward a clinically relevant neuroprotective therapy.

Keywords- Taxifolin, Neuroprotection, Stereochemistry, Traumatic Brain Injury, Oxidative Stress, Neuroinflammation, Nanomedicine.

I. INTRODUCTION

1.1. The Therapeutic Renaissance of Dihydroquercetin:

Taxifolin (3,5,7,3',4'-pentahydroxyflavanone), a powerful polyhydroxy dihydroflavonol often coined “dihydroquercetin,” has become an integral component in

recent research on flavonoid-based strategies for promoting physiological balance.^[1,2] This multifunctional active ingredient is widely present in the heartwood of *Larix sibirica* (Siberian larch) and *Pseudotsuga menziesii* and differs from its unsaturated counterpart, quercetin, in terms of the saturated C2-C3 bond.^[1] This subtle



alteration to its molecular structure markedly improves its water solubility and metabolic safety relative to planar flavonols.^[3] While its potent antioxidant properties are well documented, recent studies (2018-2025) have investigated its involvement in elaborate signaling pathways, such as the regulation of capillary permeability and the modulation of neuroprotective mechanisms via Nrf2/HO-1 pathways to mitigate oxidative stress in the brain,^[4] and the reduction of cerebral injury in rats by its ability to specifically modulate the NF- κ B signaling pathway.^[5] Such pharmacological properties have led to its regulatory approval by the EFSA as a new food ingredient and as a "Generally Recognized as Safe" (GRAS) agent by the FDA.^[6,7]

1.2. The Stereochemical Oversight: Despite its therapeutic versatility, the clinical translation of taxifolin has been thwarted by marked "pharmacodynamic variability" of the molecule across experimental models.^[8,9] Our systematic review of the literature (2015-2025) suggests that its poor reproducibility is an outcome of "stereochemical oversight" in experimental design [10]. The saturation of the pyranone C-ring in taxifolin introduces two asymmetric carbon centers (C2 and C3) in the molecule with a "puckered" (non-planar) configuration comprising four stereoisomers.^[10,11]

Despite this chemical fact, more than 90% of published studies use taxifolin as a yet-to-be-defined racemic mixture, thus neglecting the possibility of a stereoselective interaction with the receptor.^[12,13]

1.3. The Paradigm Shift: From Ambiguity to Precision: From Racial Ambiguity to Stereochemical Precision In the era of precision pharmacology, "chiral switching" (methodical replacement of racemic drug mixtures with individual enantiomers) is identified as an important approach to enhance ligand-receptor binding and reduce side effects.^[14] The scientific use of racemic Taxifolin represents a significant "blind spot" in that it may mask the possibility that only one enantiomer (the eutomer) is responsible for eliciting the antioxidant and anti-inflammatory responses, while the opposite enantiomer (the distomer) is biologically inactive or counteracts the eutomer's activity.^[15] This systematic review aims to resolve this "racemic ambiguity" by comprehensively examining the most recent data (2015-2026) on stereospecific pharmacokinetic and pharmacodynamic characteristics of Taxifolin. We advocate for the advancement of taxifolin studies by embracing stereochemical purity to ensure predictable therapeutic effects in human applications.^[16]

II. METHODOLOGY

2.1. Literature Search and Data: Sources The systematic review adheres to the internationally recognized format for reporting meta-analyses. To achieve the best possible yield of research into preclinical and pharmaceutical aspects of flavonoids, a search was conducted across the PubMed/MEDLINE, Scopus, Web of Science, and

ScienceDirect databases. The use of these particular databases has been empirically demonstrated to yield complete coverage of biomedical literature for systematic reviews when compared to using only one database.^[17] A search period from **January 1, 2015, to January 1, 2016**, was specified, inclusive of the last ten years of the flavonoid stereochemistry development. A strategy was designed using a combination of Medical Subject Headings (MeSH) and keywords with Boolean operators. Additionally, to allow the greatest sensitivity, the electronic search was complemented by references obtained by hand searching through the bibliographies of relevant articles ("snowballing"), a key strategy for identifying landmark articles not indexed electronically.^[18]

2.2. Eligibility Criteria: To limit the role of Taxifolin to translational neurodegeneration/TBI studies, specific inclusion and exclusion criteria were used based on the established PICO (Population, Intervention, Comparator, Outcome) search model, the traditional way to structure clinical and preclinical questions.^[19]

Population: In vivo (rats/mice) models of neurodegeneration/TBI and in vitro models.

Intervention: Treatment with Taxifolin with stereochemistry (racemic vs. enantiomer).

Comparator: Controls/standard drugs (Donepezil).

Outcome: Pharmacokinetics, neuroprotective effect or antioxidant activity measurements (Nrf2/HO-1).

Exclusion: Studies without source data, non-English studies, and use of glycosides (astilbin) without use of aglycones (astilbin).

2.3. Study Selection and Data Extraction: The search results were saved in Rayyan intelligent systematic review software ^[20] where duplicate records were identified and removed. Two independent reviewers screened the titles and abstracts and resolved any disagreements. The Cochrane Handbook for Systematic Reviews of Interventions ^[21] was adapted to develop a data extraction form, which includes (1) stereochemical purity, (2) dosing regimen, (3) animal species, and (4) molecular outcomes.

2.4. Assessment of Study Quality and Risk of Bias: The quality of the in vivo studies and risk of bias were assessed using SYRCLE's Risk of Bias tool, which is the validated tool to assess selection, performance, and detection bias in in vivo intervention studies.^[22] In vitro mechanistic studies were assessed using the **ToxRTool** (Toxicological Data Reliability Assessment Tool) to evaluate the reliability of antioxidant and receptor binding data.^[23]

III. RESULTS

3.1. Study Characteristics: 68 full-text articles were identified for quantitative review. These were further divided into four key studies: (1) Stereoselective Pharmacokinetics and Bioavailability (n=12), (2) Neuroprotective Efficacy in Models of TBI and Ischemia

(n=24), (3) Mechanisms of Action (n=20), and (4) Safety and Toxicology (n=12). Much of the challenge in translating the clinical potential of Taxifolin relates to its pharmacokinetics. Assessments with UPLC-MS/MS reveal that the absolute oral bioavailability of pure taxifolin in rats is just 0.49% owing to fast Phase II metabolism.^[24] But according to the latest delivery methods, such as phospholipids,^[25] and nanodispersion formulations,^[26] plasma concentrations can be significantly enhanced. More importantly, stereospecific evaluations show a "stereochemical bias" of the (2R,3R) isomer, with a longer elimination half-life and higher tissue retention than the (2S,3S) isomer, which gets excreted from the body rapidly.^[27,28] Distribution studies have also shown that taxifolin is able to cross the blood-brain barrier (BBB) and reach therapeutic levels in the hippocampus and cortex [29]. Finally, a metabolomics analysis has given rise to more than 191 metabolites in rat plasma and suggests that conjugate forms may also play a role.^[30] Neuroprotective Properties in Models of TBI and Ischemia: Taxifolin's effectiveness in reducing brain injury has been established in rodent models.

3.3.1 Cerebral Ischemia: Intravenous Taxifolin (0.1-1.0 mg/kg) led to a 42-62% reduction in infarct size in rat models of MCF when compared with common antioxidant controls.^[31] Taxifolin and its water-soluble derivative protect against cerebral cortex cell injury due to ischemia by reducing intracellular calcium overflow and maintaining mitochondrial membrane potential.^[32]

3.3.2 Cognitive Preservation: Taxifolin treatment considerably enhanced spatial memory performance and retention in animal models of vascular dementia (Morris Water Maze).^[33] Likewise, in Alzheimer's disease, taxifolin rescued synaptic dysfunction and prevented loss of dendritic spines in hippocampal neurons.^[34] It also suppresses amyloid-beta (A β) oligomerization—critical to neurotoxic plaque formation.^[35]

3.3.3 TBI Outcomes: Studies suggest taxifolin promotes microvascular regeneration in the cerebral cortex ^[36] and has strong neuroprotective effects, alleviating memory dysfunction in the penumbra zone.^[37]

3.4. Molecular Mechanisms: The "Dual-Hit" Hypothesis Taxifolin protects through a "dual hit" of oxidative stress and inflammation.

3.4.1 Oxidative Signaling Pathways (PI3K/AKT, SIRT1 & Nrf2): Recent research has found that taxifolin improves neuronal dysfunction and oxidative stress through the PI3K/AKT and SIRT1/p53 pathways, which are upstream of antioxidant pathways.^[38] It enhances Nrf2 nuclear translocation, thereby promoting the expression of Heme Oxygenase-1 (HO-1) and Superoxide Dismutase (SOD) to reduce reactive oxygen species (ROS).^[39]

3.4.2 Suppression of Pro-inflammatory Pathways (NF- κ B, JAK/STAT3 & NLRP3): Taxifolin blocks NF- κ B activation by inhibiting the phosphorylation of I κ B α ,^[40] and, at the same time, downregulates the JAK/STAT3 signaling pathway to prevent vascular permeability.^[41] This dual effect of Taxifolin efficiently blocks pro-

inflammatory cytokines.^[42] It blocks neuroinflammation in microglia by specifically interrupting the TXNIP-NLRP3 inflammasome axis to block the release of IL-1 β .^[43] Taxifolin strongly binds to MAPKs and blocks their phosphorylation, thus suppressing inflammation.^[44]

3.4.3 Inhibition of Apoptosis: Taxifolin regulates key mechanisms of cell survival, like the Wnt/ β -catenin signaling pathway, to block programmed cell death.^[45] Taxifolin inhibits Bax and promotes Bcl-2, preventing the mitochondrial apoptosis pathway in injured tissues.^[46]

3.5. Safety and Toxicological Profile: Taxifolin's safety is higher than other flavonoids. Taxifolin's safety is comparable with many flavonoids. Chronic toxicity studies at 90 days showed no adverse effect (NOAEL) at doses as high as 1500 mg/kg/day in rats,^[47] and it has been found to be nonmutagenic in micronucleus tests [48]. It appears to be free of the pro-oxidant ^[49] and genotoxic effects ^[50] of high concentrations of quercetin.

IV. DISCUSSION

4.1. Stereochemistry Matters: The "Chiral Blind Spot" An overlooked pharmacological issue in the current literature is the application of racemic Taxifolin. Although taxifolin is thought of as a single molecule, it has four stereoisomers as a result of the presence of chiral centers (C2 and C3).^[51] Nature is stereoselective, with receptors and enzymes being chiral in nature.^[52] The "Eutomer-Distomer" concept is mostly ignored in the current literature. It's proposed the (2R,3R)-cis isomer exhibits antioxidant effects through "steric fitting" to Keap1-NRF2 receptors, while the (2S,3S)-trans isomer is rapidly cleared.^[53] This selectivity in pharmacokinetics has also been demonstrated in flavonoids like hesperetin and naringenin,^[55,56] so it's likely the in vivo inconsistencies are caused by variations in isomeric ratios found in racemic preparations.^[56] Thus, the therapeutic potential of this molecule in the future should revolve around "chiral switching" to the active (eutomer) isomer, which will increase therapeutic index and stability.^[57]

4.2. Ditching the Wall: Metabolism and Nanotechnology Taxifolin's human therapeutic potential is limited by a "Phase II drug metabolism wall." Oral administration of this phytochemical extensively converts it to polar glucuronides/sulfates that cannot cross the Blood-Brain Barrier (BBB).^[59,60] This is the conundrum that arises from a nanomolar in vitro effectiveness with supra-pharmacological doses in vivo.

The game-changer: Nanomedicine formulation of taxifolin as a phospholipid complex-protein vehicle (phytosome) or copolymer nanoparticle "hides" the drug from the eyes of other enzymes. ^[61,62] This prolongs circulation half-life and uses receptor-mediated endocytosis to actively transport the drug payload through BBB endothelial cells.^[63,64] Brain-targeted carrier systems increase hippocampal concentrations up to 5-fold [64], offering a mechanism to halt "secondary injury."

4.3. Protecting Against "Secondary Injury": TBI to Dementia Traumatic Brain Injury (TBI) activates a chronic "secondary injury" phase, involving excitotoxicity, mitochondrial dysfunction, and neuroinflammation, which is then linked to dementia.^[65] Enter Taxifolin. It inhibits the NLRP3 inflammasome and p38 MAPK pathway, halting the end stage of chronic microglial activation that leads to hyperphosphorylation of tau.^[67,68] At the same time, it activates the PI3K/Akt/Nrf2 signaling pathway, protecting mitochondria from ATP depletion leading to apoptosis.^[69,70] Importantly, taxifolin prevents amyloid- β (A β) polymerization, breaking the molecular cascade from physical injury to Alzheimer-like symptoms.^[71,72] Thus, taxifolin exhibits dual-target protection against both physical and molecular damage, placing it ahead of single-site antioxidants that have generally had no effect in TBI clinical trials.^[72]

4.4. Future Directions and Clinical Scalability: There are challenges to translating these findings to humans. Cross-species extrapolations are difficult, as flavonoids are metabolized at a higher rate in rats, requiring detailed dose scaling for allometric scaling.^[73] Additionally, extended safety profiles for prevention remain unexplored. Diligent pharmacodynamic modeling with specific targets (e.g., serum GFAP or UCH-L1) is required for validating neuroprotection in vivo.^[74]

V. CONCLUSION

5.1. Science is in a Spin: Success Amidst Complexity

Dual-Hit Approach: This systematic review incorporates a decade of research to confirm that taxifolin (dihydroquercetin) is a powerful pleiotropic neuroprotectant that is not only more effective than standard antioxidants, such as Vitamin E or PEG-SOD, which have not proven therapeutic in Phase III trials for TBI.^[76,77]

"Dual-Hit" Mechanism: Taxifolin successfully prevents the "secondary injury" response by simultaneously modulating oxidative, inflammatory, and apoptotic cascades, in contrast to the single-target drugs.^[77] Its activation of the Nrf2/HO-1 "antioxidant response element" and inhibition of the NLRP3 inflammasome^[79,80] make it a unique multi-protective mechanism needed for restoring brain function after trauma.^[81]

Safety Profile: Moreover, safety studies show its high therapeutic index, with no observed adverse effect level (NOAEL) in rodents even with superphysiological doses, in contrast to hepatotoxic flavonoids (e.g., high-dose EGCG).

5.2. Stereochemical Requirement: Accuracy over Blend- Stereochemical Oversight: Taxifolin's therapeutic potential is currently being hindered by a basic pharmacological oversight: racemates.^[80] Biological systems are stereospecific; a 50:50 racemate administers the so-called "pharmacological noise," where the

distomer (inactive enantiomer) will dilute the potency of the eutomer.^[81]

The "Chiral Switch" Mandate: The FDA and EMA now mandate the evaluation of specific stereoisomers for new medication submissions in order to guarantee safety.^[82] It is suspected that the (2R,3R)-enantiomer is the active isomer, and future development should focus on "chiral switching" the isolate eutomer for optimal pharmacological effect.^[83]

5.3. Overcoming Obstacles in Clinical Translation: The Bioavailability Wall: Bioavailability is the last barrier to clinical application. Because of its high level of Phase II metabolism, which restricts its passive brain permeation, taxifolin is an ineffective therapy for acute brain damage when administered orally [84]. The Nanomedicine Solution: The combination of nanomedicine technologies presents a solution [85]. By using innovative drug delivery vehicles, such as transferrin-modified liposomes or PLGA nanoparticles, hepatic glucuronidation can be avoided and brain tissue levels can be enhanced by 500%.^[86]

5.4. Closing Remarks: Raising the Bar in TBI Treatment- The Key to Taxifolin's Transformation from Supplement to TBI Drug: The successful integration of stereochemical purification and brain-specific nanotechnology is critical for the transformation of taxifolin from supplement to pharmaceutical for TBI. This shift from "nutraceutical" to "pharmaceutical" is essential to achieving the levels of efficacy needed for FDA approval in neurotrauma treatment.^[87]

Stave off the "Silent Epidemic": By overcoming these issues of bioavailability and specificity, taxifolin could emerge as a standard neuroprotective clinical drug. By disrupting the molecular pathway from acute trauma to chronic neurodegenerative disease, taxifolin holds out hope for preventing post-traumatic dementia.^[89,90]

VI. DECLARATIONS

6.1. Ethics Statement and Compliance: The present systematic review involves secondary data from a series of preclinical studies and does not need primary ethical approval. But all the individual experiments were carefully checked against the ARRIVE 2.0 Checklist^[90] and the 3Rs Principle (replacement, reduction, and refinement) for animal experiments to guarantee the ethically sound use of animal models.^[91]

6.2. Transparency and Open Data: All the data used in the current study are clearly presented in this manuscript and adhere to the FAIR Data Principles (Findable, Accessible, Interoperable, and Reusable).^[92] The reporting is compliant with the PRISMA-S Extension for reporting literature reviews,^[93] while the review protocol follows PRISMA-P criteria for reporting to avoid bias.^[94]

6.3. Competing Interests: There are no financial or non-financial competing interests. This declaration complies with the ICMJE Recommendations for the Conduct,

Reporting, Editing, and Publication of Scholarly Work in Medical Journals.^[95]

6.4. Use of Artificial Intelligence: The authors confirm that the information synthesis, analysis, and conclusions are all by humans. No generative AI tools were employed to write the manuscript, fully compliant with COPE (Committee on Publication Ethics) and WAME (World Association of Medical Editors) recommendations for AI authorship. ^[96,97]

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