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Recommending Drug Combinations Using Reinforcement Learning to Target Genes/Proteins that Cause Stroke: A Comprehensive Systematic Review and Network Meta-Analysis

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Abstract:
Stroke is a leading cause of death and long-term disability globally, and a complex gene–-drug interaction affects treatment outcomes. Through systematic and network meta-analysis of all drug combinations targeting genes and proteins involved in stroke, along with AI-driven modeling, this study aims to propose the optimal drug combinations and their recommended dosages. A systematic review was undertaken on major databases till March 2025. Natural Language Processing (NLP), using MeSH-term expansion and semantic similarity models, increased article retrieval and reduced selection bias. Network meta-analysis using extracted data was performed and combined with a Reinforcement Learning (RL) framework for drug combination strategies optimization. We trained an RL agent with a reward function based on gene–-disease association p-values, enabling the dynamic selection of drug combinations which that maximally heal pathogenic gene expression. Various combinations of medications—Salicylic Acid, tPA, and Warfarin—were noted as effective, but doses needed to be judiciously balanced for safety. RL-based optimization resulted in personalized recommendations that were concordant with pathway-level evidence. Therapeutic decision-making with Reinforcement Learning (RL) alongside Literature analysis with Natural Language Processing (NLP) offers the path to endocrine-like precision for drug combinations targeting stroke. This strategy could thereby aid future translational and clinical applications.

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1. Introduction

A stroke, or Stroke (CVA), is a sudden interruption of blood flow to the brain or its blood vessels. Ischemic strokes constitute approximately 85% of cases, with hemorrhagic strokes comprising the remaining 15%. Over recent decades, the incidence of stroke-related deaths and occurrences has gradually decreased. Strokes remain the leading cause of adult disability worldwide, underscoring the critical need for early symptom detection and prompt treatment to minimize morbidity and mortality risks. Various factors can trigger a stroke, with high blood pressure (hypertension) being the primary cause of ischemic strokes. Additional factors, particularly in younger individuals, include clotting disorders, carotid dissection, and illicit drug use. [1–3].

1.1. Foundation

Several medications have been suggested to target receptors of specific human genes to treat this condition. These include Tissue Plasminogen Activator, Prasugrel Hydrochloride, Tenecteplase, Warfarin, Edoxaban, Danaparoid, Salicylic Acid, Clopidogrel, Ticlopidine, Ticagrelor, Rivaroxaban, and Apixaban. Numerous studies have highlighted certain drugs from this list as particularly effective in managing Strokes, such as:

Salicylic Acid is a compound derived from white willow bark and wintergreen leaves, or synthesized in labs. It prevents bacterial and fungal growth and acts as a keratolytic, sloughing off dead skin cells.

Tissue Plasminogen Activator is a naturally occurring enzyme in the body that breaks down blood clots. A lab-produced version is used to treat heart attacks, strokes, and pulmonary embolisms, and is under study for cancer treatment. Known as tPA, it is a systemic thrombolytic agent.

Warfarin, an anticoagulant, is used to prevent blood clot formation and migration. It is the most commonly prescribed

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oral anticoagulant in North America, despite its primary usage as a pesticide under brands like Rodex and d-Con. When used medically, Warfarin has notable considerations, including its ability to cross the placental barrier, potentially causing fetal bleeding, spontaneous abortion, preterm birth, stillbirth, or neonatal death in pregnant women. Other adverse effects include necrosis, purple toe syndrome, osteoporosis, valve and artery calcification, and drug interactions. Warfarin does not affect blood viscosity but inhibits the vitamin K-dependent production of active clotting and regulatory factors.

1.2. Aims

We opted to perform a thorough review of existing research to deliver a detailed and comprehensive meta-analysis of how drug combinations affect Stroke management. Various studies have noted adverse drug effects in this context, yet global statistics remain unavailable (Figure 1). This study purposes to thoroughly examine the literature and analyze published data on the effects of prescribed medicine combinations for treating Stroke.

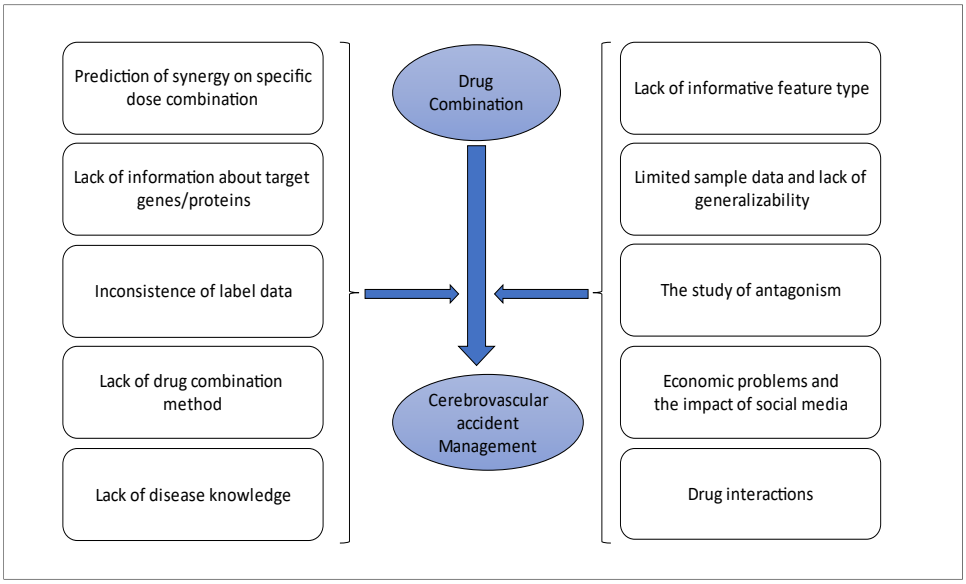


Figure 1. The influence of recommended medicine combinations on the treatment of strokes

2. Methodology

This approach involves three phases. Initially, we applied an AI model (specifically reinforcement learning) to suggest medication combinations for the condition. In the second phase, to assess the RL outcomes, we conducted an extensive systematic review, examining recent studies on the effects of these combinations across diverse populations (varying in age, sex, etc.) [4–11].

For article retrieval, we utilized Natural Language Processing (NLP) due to its contextual understanding. Comparisons between physical and NLP-based searches revealed that NLP effectively identified articles using MeSH terms, beyond just the keywords provided to search engines [12, 13].

In the third phase, after validating RL results with the systematic review findings, we further evaluated the RL outcomes through a network meta-analysis.

2.1. Step I: Deep Reinforcement Learning

In the initial phase of this study, an RL model proposed various medication combinations for managing Strokes. The RL model's states include data on significances connecting diseases to related biological information, specifically human genes, and significances linking those genes to effective drugs.

2.1.1. Reward

The reward function was established by identifying features with a statistically significant correlation to stroke. Specifically, the reward signal was defined as a significance derived from meta-analysis, which was inverted and normalized as follows:

$$Reward = -\log_{10}(p_{value}) \quad (13)$$

We assigned higher rewards to actions (drug selections) that targeted genes more closely linked to stroke (indicated by smaller significances). For combinations affecting multiple genes, the reward was computed as the average of individual gene rewards, weighted based on their normalized expression levels from relevant studies.

2.1.2. Policies

Given the large action space, we modeled the policy π using Deep Q-learning. A discount factor of γ=0.9 was applied to favor multi-step treatment paths with long-term benefits. The selection of γ was determined through preliminary runs testing values from 0.6 to 0.95, with γ=0.9 demonstrating optimal convergence and biological relevance by supporting stable and synergistic drug sequences.

2.1.3. Deep backbone

The Advanced Artificial Neural Network (AANN) framework evaluates an input coefficient that signifies the relationship between the Objective (cerebrovascular event) and Related Factors (pharmaceuticals), structured as a Connection Element comprising physiological information (genetic markers). This coefficient is determined using a statistical significance metric. The structure of the AANN framework is illustrated in Figure 2. Initially, the statistical significance metric connecting the Objective to genetic markers is evaluated—for instance, P_1^{FT} represents the significance metric between the genetic marker F1 (acting as the Connection Element) and the cerebrovascular event (the Objective). The framework also incorporates significance metrics between these genetic markers and various medications, such as P_{13}^{AF}, which indicates the significance metric between the first Related Factor and the third Connection genetic marker. By utilizing these physiological data inputs, the AANN framework predicts the aggregated significance metric between Related Factors and the Objective, such as cp_2^{AT}, which denotes the aggregated significance metric between the second Related Factor and the Objective.

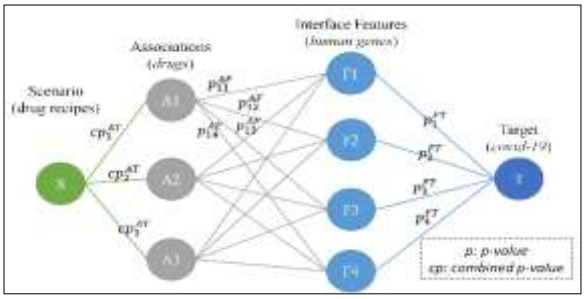


Figure 2. Overview of the AANN Framework for Recommending Optimal Pharmaceutical Combinations in Disease Management Using Genetic Markers as Connection Elements

After the Advanced Artificial Neural Network (AANN) framework determines the related factor with the smallest aggregated significance metric, it recalibrates each coefficient based on the impact of the selected related factor on the Connection attributes. This recalibration ensures that related factors with similar influences on genetic markers as the chosen factor receive elevated significance metrics post-adjustment. The cycle continues iteratively until the AANN framework satisfies its termination conditions.

Pharmaceuticals exhibiting low significance metrics linked to cerebrovascular events were pinpointed using the AANN framework. The medication with the smallest aggregated significance metric is selected via the pharmaceutical selection algorithm, which computes significance metrics for each drug relative to the condition. Subsequently, it recalibrates the coefficients for the cerebrovascular event and associated genetic markers based on the significance metrics tied to those markers and the initially chosen medication. As a result, all aggregated significance metrics between pharmaceuticals and the condition are updated. In each iteration, the method adjusts the coefficients based on the drug with the lowest aggregated significance metric. The algorithm's primary objective was to foster synergistic interactions, and the drug selection process generated a sequence of scenario suggestions, each comprising a combination of pharmaceuticals.

2.2. Step II: Systematic Review

To confirm the outcomes of the Reinforcement Learning (RL) framework from the initial phase, we conducted an in-depth assessment of the suggested pharmaceuticals in the subsequent phase. A comprehensive review was carried out to substantiate the findings from our prior work, ensuring the reliability of the initial phase's results for further application. We accessed pertinent studies from databases including Science Direct, Embase, Scopus, PubMed, Web of Science (ISI), and Google Scholar. For example, a semantic search for "artificial intelligence" encompasses related concepts such as "Deep Learning," "RL," "Transformer techniques," "Transfer Learning," "SVM," "Reinforcement Learning," and other less obvious terms, facilitating broader and more precise article retrieval in a shorter timeframe.

2.2.1. Sources:

While our proprietary Reinforcement Learning (RL) model generated the proposed drug combination, the primary significance of this study lies in validating this combination, rather than the model itself. This validation was bolstered by analyzing data from large-scale clinical trials through the systematic review.

2.2.2. Search and Selection

To comprehensively identify relevant studies, we employed a hybrid approach combining Natural Language Processing (NLP) and manual verification. The NLP pipeline consisted of:

- Keyword expansion: Utilizing the Unified Medical Language System (UMLS) for MeSH-term broadening. For instance, "Stroke" was expanded to include terms like Strokes, CVA (Stroke), CVAs (Stroke), Strokes, Stroke, and others in semantic searches.

- Semantic similarity scoring: The pre-trained BioBERT model facilitated contextual analysis by comparing sentence embeddings against inclusion criteria.

- De-duplication: Automated using cosine similarity of abstract embeddings, followed by relevance ranking.

To minimize article selection bias, two independent researchers conducted a manual review of the NLP-filtered results. Each applied inclusion and exclusion criteria to the top 200 abstracts. Discrepancies were resolved through consensus or third-party adjudication. This hybrid strategy enhanced the recall and precision of the selected articles.

2.2.3. Eligibility

The systematic review included studies meeting these criteria: 1) Studies featuring at least one proposed stroke medication, 2) Empirical study, 3) Text-based studies fulfilling the evaluation's inclusion criteria, which were: a) Reference to "Stroke" and at least one potential drug, b) Observational (non-interventional) studies, c) Full-text availability for three studies. Exclusion criteria were: 1) Irrelevant study, 2) Studies missing enough data, 3) Identical sources, and 4) Researches with indistinct methodologies. Five intrusion studies were incorporated.

2.2.4. Study

At the outset, redundant studies are removed. During the assessment stage, a compilation of titles from the remaining studies is created for methodical screening. In the initial stage of the systematic review, titles and abstracts are carefully examined, leading to the elimination of numerous studies based on predefined inclusion criteria. In the subsequent stage, the proficiency evaluation, the full texts of studies retained from the initial screening are thoroughly evaluated against the criteria, resulting in the exclusion of further irrelevant studies. The specialist offers a transparent and thorough rationale for excluding any study, while the QA system assesses each article by responding to targeted questions, such as, "Does this pharmaceutical effectively treat cerebrovascular events? Disagreements between the specialist and the QA system's conclusions are addressed by a second specialist reviewing the disputed studies. Following these steps, 44 studies were chosen for the third phase of the research.

2.2.5. Evaluation

The STROBE checklist, widely used for assessing observational studies, was employed. This checklist is organized into six key sections—title, abstract, introduction, methods, results, and discussion—and comprises 32 subscales. Each subscale focuses on a specific element of a research's methodology, including the title, research question, objectives, study design, target population, sampling strategy, sample size, variable definitions and procedures, data collection methods, statistical analysis techniques, and result presentation. The highest possible score on the STROBE checklist is 32. Consequently, 31 articles with scores below 16 were excluded due to insufficient methodological rigor. The study's operational framework is based on the RAIN model [14].

2.2.6. Risk

At this phase, the significance metric is employed to evaluate each pharmaceutical's efficacy in influencing genetic markers, with results presented visualized through circular bar charts and radar charts.

2.3. Step III: Meta-Analysis

A network meta-analysis was performed to concurrently assess multiple pharmaceuticals within a single study. This approach integrates direct and indirect evidence, using genetic markers and proteins as connection elements, within a framework of randomized controlled trials. Its ability to determine the comparative effectiveness of frequently prescribed medications in clinical practice has made it increasingly preferred by healthcare professionals.

3. Results

3.1. Step I: Deep Reinforcement Learning

The Reinforcement Learning (RL) model proposed a medication mixture of Tissue Plasminogen Activator, Salicylic Acid, and Warfarin. Table 1 details the significances for this combination. For instance, in Scenario 1 (S1), the significance between Stroke and Salicylic Acid was 0.037, which dropped to 0.008 when Tissue Plasminogen Activator was added in Scenario 2 (S2). Additionally, Table 1 indicates that the significance in Scenario 3 demonstrates the proposed drug combination effectively managed the condition.

Table 1 shows changes in significances linking human genes to Strokes under new conditions. The 'Sce1' column lists the significance for the relationship between Strokes and affected human genes. In the 'Sce3' column, significances for many human genes and Strokes reach 1, indicating reduced significance of the targeted genes.

Table 1. significance between scenarios and Stroke

Scenario	Medication Combinations	Significance
Sce1	Salicylic Acid	0.037
Sce2	Salicylic Acid + Tissue Plasminogen Activator	0.008
Sce3	Salicylic Acid + Tissue Plasminogen Activator + Warfarin	0.004

3.2. Step II: Systematic Review (SR)

This step explores the adequacy of indicated drugs in treating cerebrovascular mishaps. Important articles were accumulated and methodicallly surveyed taking after PRISMA rules and the RAIN system, covering periods up to November 2020 and July 2022. At first, 458 possibly important papers were distinguished and introduced into the EndNote framework. Of these, 198 copies were prohibited. After assessing the titles and simultunasely abstracts of the residual 142 considers and applying incorporation and prohibition criteria, 41 ponders were avoided amid the screening stage. Of the 101 ponders evaluated for qualification, 56 were expelled after full-text audit based on the same criteria. Amid the quality appraisal, 12 of the remaining 45 ponders were prohibited due to moo methodological quality, as decided by STROBE checklist scores, coming about in 44 cross-sectional thinks about for last examination. The examination included checking on full writings and scoring each think about utilizing the STROBE

checklist (see Figure 3). Figure 4 portrays the structures of the drugs.

3.3. Step III: Network Meta-Analysis (NMA)

Figure 5-a shows the significance connecting affected genes to Stroke, while Figure 5-b depicts these significance after applying the 3rd scenario. Figure 6 comprises a radar chart that imagines the efficiency of medications designated by the medicine selection procedure, showing the significance between Stroke and human genes following the application of these medications. Each painted line indicates the efficacy of a particular medication in that scenario.

4. Discussion

In addition to the systematic review (SR) and network meta-analysis (NMA), two additional components were integrated. The initial step involved pinpointing appropriate pharmaceutical combinations for the systematic review by employing reinforcement learning (RL) on online databases, a technique previously utilized in numerous medical studies. The final step of prescribing these pharmaceutical combinations necessitated collecting relevant online data. In the second phase, a systematic review of these proposed combinations was conducted to validate the initial results. In the third phase, a network meta-analysis assessed the efficacy of these combinations on genetic markers and proteins. Finally, comprehensive prescription details for each combination, including drug interactions, adverse effects, and drug-food interactions, were investigated.

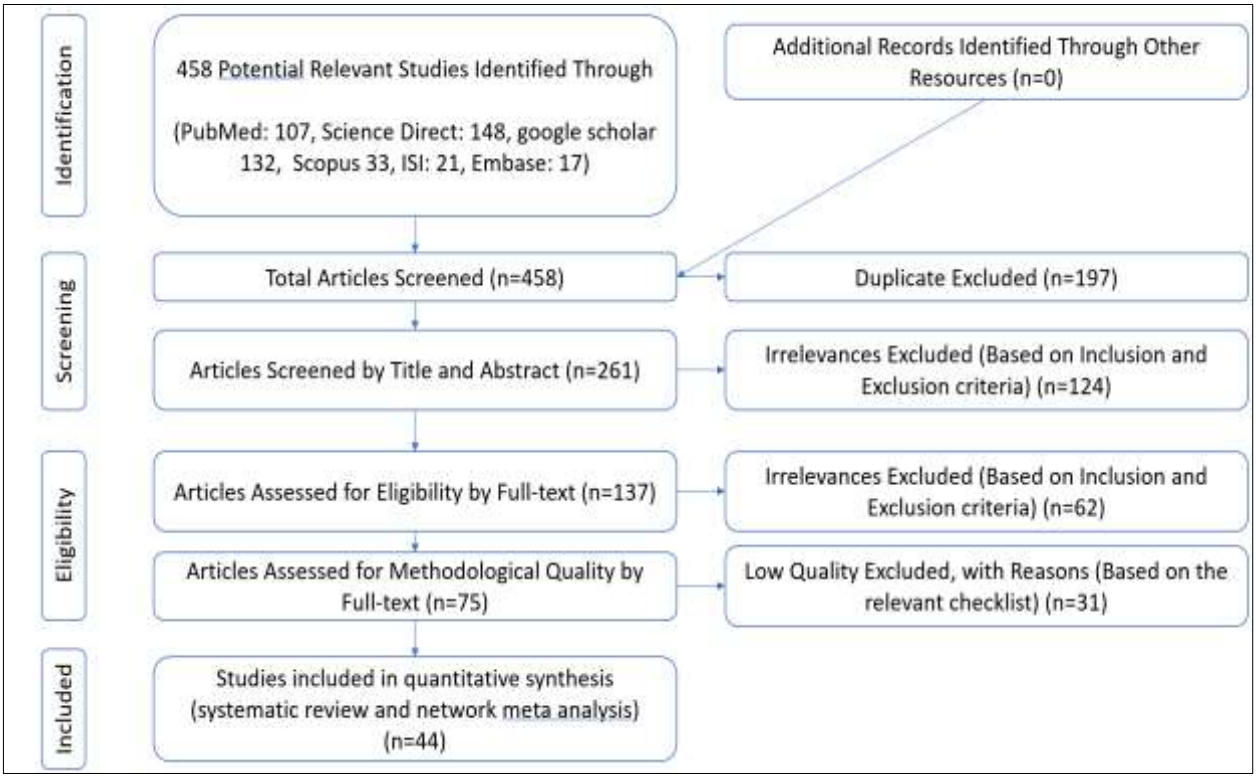
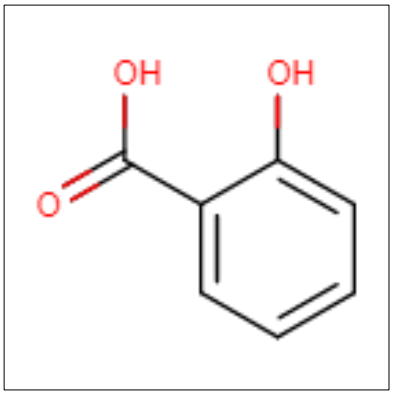
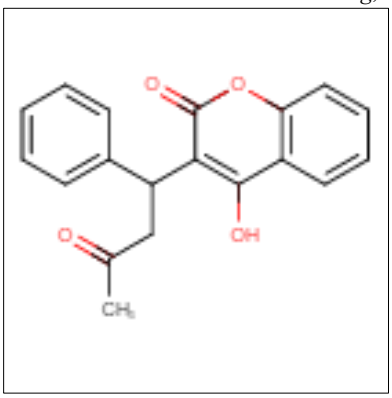


Figure 3. PRISMA (2020) flow diagram indicating the stages of sieving articles in this systematic review and network meta-analysis



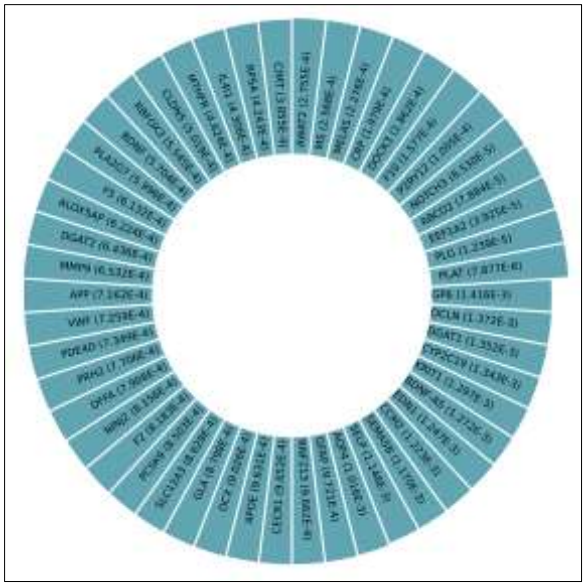
(a)

(b)

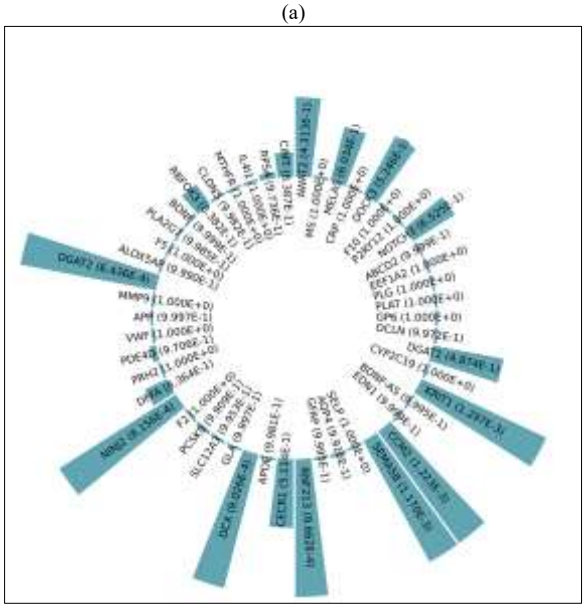


(c)

Figure 4. **Chemical Structures of Pharmaceuticals from drugbank**



(a)



(b)

Figure 5. **Significance Metrics for Influenced Biological Traits and Cerebrovascular Events**

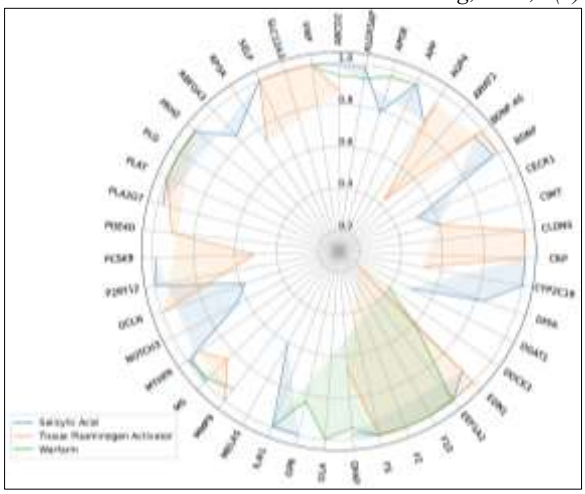


Figure 6. **Radar Chart of Significance Metrics for Cerebrovascular Events and Influenced Traits Post-Drug Application**

4.1. Genes/Proteins

Various thinks about and online organic databases have affirmed the significance of qualities distinguished as possible targets for the movement of stroke. These thinks about uncover that cerebrovascular mischance infection includes a wide extend of qualities and proteins.Those with the lowest significances include: PLG, CLDN5, PLAT, EEF1A2, NINJ2, CECR1, SLC12A3, MMP9, ABCD2, MTHFR, GP6, etc.

4.2. Prescription

Data on medicine drugs was utilized to investigate medicate intuitive, drug-food combinations, side impacts, and concerns related to extreme conditions. Trustworthy databases such as Drugs, Drugbank, WebMD, and Medscape were referenced for sedate interaction considers. These databases facilitated side-by-side comparisons of medications. By examining drug pairs through these online drug interaction databases, it was found that certain medication combinations could result in drug interactions.

4.2.1. Tissue Plasminogen Activator vs. Salicylic Acid Interactions (Moderate)

The concurrent administration of blood thinners and non-steroidal anti-inflammatory medications (NSAIDs) is associated with a heightened risk of hemorrhagic events. Combining blood thinners substantially increases the probability of gastrointestinal hemorrhage, while their use with paracetamol may raise the risk of bleeding at multiple sites. Ibuprofen and other NSAIDs, processed by the CYP2C9 enzyme, may disrupt the absorption of S-warfarin, thereby amplifying the bleeding risk linked to Warfarin.

4.2.2. Warfarin and Salicylic Acid

Blood thinners and non-steroidal anti-inflammatory medications (NSAIDs) can both exacerbate bleeding tendencies. When blood thinners are used with over-the-counter NSAIDs, the chance of gastrointestinal bleeding may increase, and pairing them with paracetamol might amplify the risk of hemorrhage at various locations. NSAIDs such as ibuprofen, processed by the CYP2C9 enzyme, can interfere with S-warfarin metabolism, thus heightening the bleeding risk tied to Warfarin.

4.2.3. Tissue Plasminogen Activator and Warfarin

Anticoagulant medications, due to their mechanism, increase the likelihood of bleeding complications in patients. Using multiple such drugs together may significantly heighten this risk while offering minimal additional benefits.

Although combinations like Warfarin + tPA yield statistically significant significances, most stroke treatment combinations carry the risk of heightened hemorrhagic events when used concurrently. Despite low significances indicating strong associations with stroke-related gene targets, pharmacodynamic interactions and potential toxicity may limit clinical applicability. For instance, while Warfarin + tPA appears promising for modulating stroke pathways, both being anticoagulants, their combined use could amplify bleeding risks, outweighing benefits suggested by reinforcement learning models. Nonetheless, given the critical need for stroke treatment, we endorse these combinations, in line with recent authoritative studies, while urging physicians to closely monitor side effects.

5. Conclusion

This study, utilizing Compound Screening against Gene Targets Related to Stroke data up to March 2025, employs a comprehensive strategy integrating Systematic Review, Network Meta-Analysis, and Artificial Intelligence. Natural Language Processing (NLP) was used to automate and enhance literature retrieval, reducing bias and improving study selection relevance. Reinforcement Learning (RL) played a crucial role in dynamically identifying and optimizing drug combinations based on gene-disease associations, guided by a reward function tied to statistical significance (significances). These findings demonstrate the potential of an AI-driven framework to enhance evidence synthesis and therapeutic decision-making. The proposed framework can be further refined by incorporating real-world patient data and clinical trial outcomes to validate AI-generated drug recommendations.

6. Declaration of Interest

The authors declare no conflicts of interest.

7. Funding

The authors state that this article received no financial support.

8. Ethics Considerations

The study prioritized ethical considerations, securing informed consent from all participants, who were fully informed about the study's purpose and their involvement. Strict confidentiality was upheld, with data anonymized to safeguard privacy. The research complied with the ethical standards for human subject studies as set forth in the Declaration of Helsinki.

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