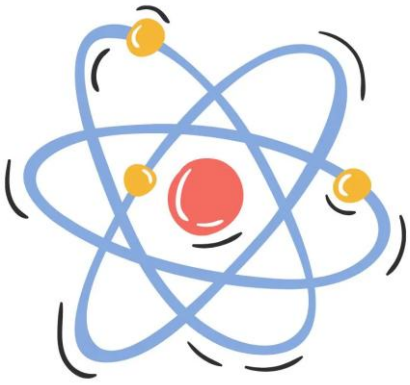

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EMERGING NETWORK BASED PHARMACOLOGY APPROACHES FOR SEQUENTIAL BLOCKADE OF SIGNALING PATHWAYS OF PERIPHERAL NEUROPATHY

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Abstract: *The global burden of PN continues to increase owing to the rising prevalence of diabetes mellitus, cancer chemotherapy, metabolic disorders, autoimmune diseases, infections, and neurodegenerative conditions. Despite substantial progress in understanding the molecular basis of neuropathy, currently available pharmacotherapies primarily provide symptomatic relief and often fail to halt disease progression or promote nerve regeneration. One of the major limitations of conventional therapeutic approaches is their reliance on single-target interventions for a disease driven by multiple interconnected molecular networks. Recent advances in systems biology and network pharmacology have transformed the understanding of complex neurological disorders by enabling the identification of multitarget therapeutic strategies. Emerging evidence indicates that peripheral neuropathy evolves through a sequential activation of pathological signaling cascades involving oxidative stress, mitochondrial dysfunction, NF-κB-mediated neuroinflammation, NLRP3 inflammasome activation, ion-channel sensitization, apoptosis, and impaired neuroregeneration. These interconnected pathways collectively establish a self-sustaining cycle of neuronal injury and chronic pain. Consequently, therapeutic strategies capable of temporally targeting distinct signaling modules may provide greater efficacy than simultaneous or single-target inhibition. This review discusses the molecular pathogenesis of peripheral neuropathy and highlights recent developments in network pharmacology, artificial intelligence-assisted target identification, protein–protein interaction networks, molecular docking, and multi-omics integration. Furthermore, a novel framework of sequential pathway blockade is proposed, involving early suppression of oxidative stress pathways, subsequent inhibition of inflammatory and inflammasome signaling, modulation of nociceptive ion channels, and activation of neuroregenerative mechanisms. Particular emphasis is placed on phytochemical-based multitarget therapeutics capable of regulating ROS/Nrf2, NF-κB, NLRP3, TRPV1, SIRT1, and PI3K/Akt signaling networks. The integration of network pharmacology with precision medicine approaches may facilitate the development of next-generation therapeutics for peripheral neuropathy and establish a new paradigm for systems-based neuropharmacology.*

Keywords: *Peripheral neuropathy; Network pharmacology; Sequential blockade; NLRP3 inflammasome; TRPV1; Oxidative stress; Neuroinflammation; SIRT1; PI3K/Akt; Phytochemicals; Systems pharmacology.*

1. Introduction

1.1 Peripheral Neuropathy: Overview and Clinical Significance

Peripheral neuropathy (PN) represents a heterogeneous group of disorders resulting from damage to peripheral sensory, motor, and autonomic nerves. It is among the most common neurological complications worldwide and affects millions of individuals, particularly patients with diabetes mellitus, cancer, autoimmune diseases, infections, nutritional

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deficiencies, and metabolic disorders. Clinically, peripheral neuropathy manifests as numbness, tingling, burning sensations, paresthesia, hyperalgesia, allodynia, muscle weakness, impaired reflexes, and autonomic dysfunction. These symptoms significantly impair quality of life and contribute to disability, depression, sleep disturbances, and reduced productivity [1,2].

The global prevalence of peripheral neuropathy has increased substantially over the last two decades due to the growing burden of diabetes, obesity, aging populations, and increasing survival rates among cancer patients receiving neurotoxic chemotherapeutic agents. Diabetic peripheral neuropathy (DPN) remains the most prevalent form, affecting approximately 50% of diabetic patients during their lifetime. Chemotherapy-induced peripheral neuropathy (CIPN), particularly associated with platinum compounds, taxanes, vinca alkaloids, and proteasome inhibitors, represents another major clinical challenge [3]. Despite significant advances in understanding the molecular mechanisms underlying neuropathy, current therapeutic approaches primarily focus on symptom management rather than disease modification.

1.2 Causes and Risk Factors of Peripheral Neuropathy

Peripheral neuropathy arises from a wide range of etiological factors. Metabolic disorders, especially diabetes mellitus, are the leading causes worldwide. Chronic hyperglycemia induces oxidative stress, mitochondrial dysfunction, advanced glycation end-product (AGE) accumulation, and vascular impairment, collectively contributing to neuronal damage. Cancer chemotherapy constitutes another major cause of neuropathy [4]. Agents such as paclitaxel, oxaliplatin, cisplatin, vincristine, and bortezomib disrupt microtubule dynamics, mitochondrial function, and axonal transport, leading to sensory neuron degeneration.

Additional risk factors include autoimmune disorders such as Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, rheumatoid arthritis, and systemic lupus erythematosus. Infectious diseases including HIV, herpes zoster, hepatitis viruses, and leprosy have also been implicated. Nutritional deficiencies involving vitamins B1, B6, B12, folate, and vitamin E contribute significantly to neuropathic manifestations. Environmental toxins, alcohol abuse, heavy metals, and hereditary mutations further increase susceptibility to peripheral nerve injury [4,5].

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1.3 Hallmarks of Peripheral Neuropathy

The pathophysiological hallmarks of peripheral neuropathy include- **(a)**. Axonal degeneration; **(b)**. Demyelination; **(c)**. Neuro-inflammation; **(d)**. Mitochondrial dysfunction; **(e)**. Oxidative stress; **(f)**. Impaired axonal transport; **(g)**. Altered ion-channel activity; and **(h)**. Neuronal apoptosis [6]. One of the earliest pathological events is disruption of mitochondrial homeostasis. The mitochondria serve as critical regulators of neuronal energy metabolism, calcium signalling, and apoptosis. Excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) results in lipid peroxidation, DNA damage, protein oxidation, and activation of pro-inflammatory signalling pathways. Another hallmark is chronic neuroinflammation characterized by activation of macrophages, Schwann cells, microglia, and infiltrating immune cells. Elevated concentrations of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), and nuclear factor-kappa B (NF-κB) have been reported in numerous neuropathic conditions. In addition, sensory hypersensitivity is frequently associated with dysregulation of transient receptor potential vanilloid 1 (TRPV1) [7,8] transient receptor potential ankyrin 1 (TRPA1) [9], purinergic receptors [10], and voltage-gated sodium channels [11]. These alterations increase neuronal excitability and contribute to chronic nerve pain states.

1.4 Molecular Pathogenesis of Peripheral Neuropathy

The pathogenesis of peripheral neuropathy involves complex interactions among oxidative stress, inflammation, immune activation, mitochondrial dysfunction, and neurodegeneration.

Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is widely recognized as a central driver of neuropathic pathology. Excessive ROS generation damages mitochondrial DNA and disrupts ATP production. Hyperglycaemia-induced activation of polyol pathways, AGE-RAGE interactions, and NADPH oxidase activity further exacerbate oxidative injury. The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) functions as a master regulator of antioxidant defence. Activation of Nrf2 promotes expression of heme oxygenase-1 (HO-1), superoxide dismutase, catalase, and glutathione-related enzymes. Impaired Nrf2 signaling has been consistently associated with progression of diabetic and chemotherapy-induced neuropathy [12-14].

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Neuroinflammation

Persistent oxidative stress activates NF-κB signaling pathways, leading to increased transcription of pro-inflammatory mediators. Activated NF-κB induces expression of TNF-α, IL-1β, IL-6, inducible nitric oxide synthase (iNOS), and COX-2. These mediators amplify neuronal injury and promote recruitment of immune cells into peripheral nerves.

NLRP3 Inflammasome Activation

The NLRP3 inflammasome has emerged as a critical molecular hub connecting oxidative stress and inflammation. Activation of NLRP3 leads to recruitment of apoptosis-associated speck-like protein containing a CARD (ASC), caspase-1 activation, and maturation of IL-1β and IL-18. Excessive inflammasome activation contributes to neuroinflammation, pyroptosis, and sensory dysfunction [15-17].

Ion Channel Dysregulation

TRPV1, TRPA1, Nav1.7, Nav1.8, and P2X7 receptors play important roles in peripheral sensitization. Inflammatory mediators lower activation thresholds of these receptors, resulting in exaggerated pain responses. TRPV1 has become a particularly attractive therapeutic target because of its central role in neuropathic pain transmission [18, 19].

Apoptosis and Neurodegeneration

Mitochondrial dysfunction triggers intrinsic apoptotic pathways involving Bax, Bcl-2, cytochrome c, caspase-9, and caspase-3. Progressive neuronal loss and axonal degeneration ultimately impair nerve conduction and sensory function [20].

1.5 Concept and Principles of Network Pharmacology

Network pharmacology represents a systems-level approach that integrates pharmacology, bioinformatics, systems biology, computational chemistry, and omics technologies. Unlike conventional pharmacology, which focuses on single targets, network pharmacology recognizes diseases as complex biological networks involving multiple interconnected pathways. The workflow typically involves disease-target identification, active compound screening, target prediction, protein-protein interaction (PPI) network construction, Gene Ontology (GO) analysis, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment, molecular docking, molecular dynamics simulation, and experimental validation. The network pharmacology is particularly suitable for peripheral neuropathy because the

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disease involves multiple signaling pathways including oxidative stress, inflammatory cascades, inflammasome activation, ion-channel dysregulation, and regenerative signaling [21, 22].

2. Role of Network Pharmacology Approach in Development of Drugs and Polyherbal Formulations for Peripheral Neuropathy

The emergence of network pharmacology has transformed the discovery and development of therapeutics for complex diseases. In peripheral neuropathy, traditional single-target drugs frequently fail to provide sustained clinical benefits because multiple molecular pathways contribute simultaneously to disease progression. Network pharmacology enables researchers to identify hub genes and key signaling nodes that regulate disease networks. Frequently identified targets in neuropathy include AKT1, TNF, IL6, TP53, CASP3, PTGS2, NFKB1, SIRT1, NLRP3, and TRPV1. These targets participate in interconnected pathways governing inflammation, oxidative stress, apoptosis, and neuro-regeneration [23,24].

An important advantage of network pharmacology is its ability to investigate polyherbal formulations. Herbal medicines typically contain hundreds of bioactive compounds capable of interacting with multiple targets. Conventional reductionist approaches often fail to explain their therapeutic effects. By integrating compound-target networks with disease-associated pathways, network pharmacology provides mechanistic insights into herbal formulations. Recent studies have demonstrated that compounds such as curcumin, resveratrol, quercetin, berberine, asiaticoside, crocin, and withanolides modulate multiple neuropathy-associated targets simultaneously. For example, curcumin regulates Nrf2, NF-κB, COX-2, NLRP3, and PI3K/Akt signaling pathways [25-27], thereby exerting antioxidant, anti-inflammatory, and neuroprotective effects.

Network pharmacology also facilitates rational design of polyherbal combinations. Rather than relying solely on traditional knowledge, researchers can identify complementary compounds targeting distinct stages of disease progression. Such approaches may support the development of sequential therapeutic interventions involving early antioxidant protection, subsequent anti-inflammatory effects, inflammasome suppression, pain modulation, and regenerative stimulation.

Moreover, integration of network pharmacology with molecular docking, machine learning, transcriptomics, metabolomics, and artificial intelligence is accelerating drug discovery. These technologies enable prediction of novel drug-target interactions,

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identification of biomarkers, and optimization of formulation composition. Consequently, network pharmacology has become an indispensable tool for modern phytopharmaceutical development and precision medicine approaches in peripheral neuropathy.

3. Formulations Developed Using Network Pharmacology-Based Approaches for Peripheral Neuropathy

The increasing adoption of network pharmacology has revolutionized the scientific evaluation of traditional herbal medicines and polyherbal formulations used in peripheral neuropathy. Unlike conventional pharmacological approaches that focus on single active ingredients and individual molecular targets, network pharmacology investigates the synergistic interactions among multiple compounds, targets, signaling pathways, and biological processes. This approach is particularly valuable for peripheral neuropathy because disease progression involves numerous interconnected pathological mechanisms including oxidative stress, mitochondrial dysfunction, neuroinflammation, inflammasome activation, ion-channel sensitization, and neuronal apoptosis.

Huangqi Guizhi Wuwu Decoction (HGWD)

Huangqi Guizhi Wuwu Decoction is a classical Traditional Chinese Medicine (TCM) prescription extensively investigated for diabetic peripheral neuropathy. The formulation consists primarily of *Astragalus membranous, Cinnamomum cassia, Paeonia lactiflora, Zingiber officinale, and Ziziphus jujuba*. The network pharmacology studies have identified more than 100 bioactive constituents including quercetin, kaempferol, β-sitosterol, formononetin, and astragaloside IV. Protein–protein interaction analysis revealed several key targets including AKT1, IL6, TNF, VEGFA, CASP3, and TP53. The KEGG enrichment analysis demonstrated involvement of PI3K/Akt, TNF, NF-κB pathway, MAPK, AGE-RAGE and HIF-1. The molecular docking studies demonstrated strong binding affinities of quercetin and kaempferol toward AKT1, TNF-α, IL-6, and NF-κB proteins [28, 29]. Experimental studies further confirmed reductions in oxidative stress markers, inflammatory cytokines, and neuronal apoptosis [30, 31].

Huangqi Guizhi Wuwu Decoction (HGWD) is among the most extensively investigated Traditional Chinese Medicine (TCM) formulations for diabetic peripheral neuropathy (DPN). Recent network pharmacology studies identified quercetin, kaempferol, naringin, and astragaloside IV as major bioactive constituents. Core targets included IL6, MAPK3, VEGFA, JUN, ESR1, AKT1, TNF, and TP53. KEGG pathway enrichment demonstrated significant

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involvement of the TNF signaling pathway, MAPK signaling pathway, AGE-RAGE signaling pathway, and PI3K/Akt signaling pathway [32, 33].

Molecular docking studies confirmed strong binding interactions between quercetin and several neuropathy-associated targets, supporting the multitarget therapeutic potential of HGWD [2]. Clinical evidence and meta-analyses have further demonstrated improvements in nerve conduction velocity, glycemic control, and neuropathic symptoms in patients with DPN [34, 35].

Beyond diabetic neuropathy, HGWD has been investigated for oxaliplatin-induced peripheral neurotoxicity. Network pharmacology and molecular docking analyses identified quercetin, β-sitosterol, kaempferol, and formononetin as key active ingredients. The major therapeutic targets included AKT1, VEGFA, IL6, CASP3, and TNF. Functional enrichment analysis indicated involvement of neuroinflammatory pathways, apoptosis regulation, and oxidative stress signaling [36].

Taohong Siwu Decoction (THSWD)

THSWD decoction has traditionally been used for improving blood circulation and alleviating pain-associated disorders. It contains sunflower, peach kernel, prepared Rehmannia root, white peony, Szechuan lovage root and angelica has found its clinical utility in treatment of paclitaxel-induced CIPN and malignant tumors [37-40]. Network pharmacology investigations have identified quercetin, luteolin, kaempferol, and baicalein as major active constituents. The formulation primarily targets: (AKT1, TP53, IL6, TNF, MAPK14, RELA, and ESR1). The pathway enrichment analysis suggests modulation of neuroactive ligand-receptor interaction; PI3K/Akt signaling; calcium signaling; inflammatory mediator regulation of TRP channels. The animal studies indicate improvements in nerve conduction velocity, reduced inflammatory infiltration, and enhanced nerve regeneration.

These genes are implicated in five main signaling pathways: PI3K-Akt signaling pathway, MAPK signaling pathway, TNF signaling pathway, IL-17 signaling pathway, and NF-κB signaling pathway. This network pharmacology study reveals the potential multitarget and multi-component mechanisms of THSWD in treatment of peripheral neuropathy and provides a scientific basis for further research into its therapeutic mechanisms.

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Goshajinkigan

Goshajinkigan is a Japanese Kampo formulation extensively investigated for chemotherapy-induced peripheral neuropathy. The formulation consists of Rahmanian root; Achyranthes root; Plantago seed; Cornus fruit; Alisma rhizome; Mountain bark. Network pharmacology analyses identified multiple targets associated with oxidative stress; Inflammatory responses; Calcium homeostasis; and Neurotrophic signaling. Experimental studies demonstrated reductions in oxaliplatin-induced neuropathic pain and preservation of sensory nerve function [42].

Xuebifang

Xuebifang has recently emerged as a promising polyherbal intervention for diabetic neuropathy. Network pharmacology studies identified major compounds including- Berberine; Curcumin; Quercetin; Kaempferol; Luteolin and these phytochemicals targets (AKT1, IL6, TNF, STAT3, NFKB1, PTGS2 which are enriched in signaling pathways such as NF-κB signaling, NLRP3 inflammasome activation, oxidative stress response, apoptosis pathways, etc [43-45].

Emerging Polyherbal Formulations

Recent network pharmacology investigations have evaluated several additional formulations including Buyang Huanwu Decoction, Jiawei Huangqi Guizhi Wuwu Decoction, Danggui Sini Decoction, and Yiqi Huoxue Tongluo Formula. These formulations exhibit multitarget regulation of Nrf2, NF-κB, NLRP3, PI3K/Akt, and BDNF signaling pathways, suggesting potential utility in preventing neurodegeneration and promoting nerve regeneration [42].

Conclusion

On conclusory note, peripheral neuropathy is a multifactorial disorder involving complex interactions among oxidative stress, neuroinflammation, inflammasome activation, ion-channel dysregulation, apoptosis, and impaired neuroregeneration. Network pharmacology provides a powerful systems-level framework for understanding these interactions and identifying multitarget therapeutic strategies. Emerging evidence suggests that sequential blockade of pathological signaling pathways may offer superior therapeutic benefits compared with conventional single-target interventions. By integrating bioinformatics, molecular docking, artificial intelligence, and experimental validation, network pharmacology is expected

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to accelerate the development of next-generation drugs and polyherbal formulations for peripheral neuropathy. Future studies should focus on clinical translation, precision medicine approaches, and validation of network-derived therapeutic hypotheses.

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