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Prediction of Quality Markers (Q-Markers) for the Mongolian Medicine Naru-3 Based on Chemical Composition, Pharmacological Effects, and Network Pharmacology

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Abstract: Naru Sanwei Pill, also known as Naru-3, a Mongolian medicine originating from *Zhigao Pharmacopoeia*, is a classic prescription used in the treatment of rheumatism. It is composed of *Terminalia chebula*, processed *Aconitum kusnezoffii Reichb.*, and *Piper longum*, and is known for its effects in eliminating "mucus," relieving pain, and reducing swelling, with significant efficacy in treating joint effusion and lumbar pain. In recent years, researchers have summarized its chemical components and pharmacological effects, and employed network pharmacology methods based on the core theory of Traditional Chinese Medicine quality markers (Q-Markers) to analyze and predict its markers. The results identified potential Q-Markers for Naru-3, providing a scientific basis for quality control and further research.

Keywords: Mongolian medicine Naru-3; Network pharmacology; Quality markers; Chemical components; Pharmacological effects

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1. Introduction

Naru Sanwei Pill, also known as Naru-3, was first recorded in *Zhigao Pharmacopoeia* and is one of the classic formulas in Mongolian medicine. It consists of *Terminalia chebula*, *Piper longum*, and processed *Aconitum kusnezoffii Reichb.*, and is a unique and effective remedy in Mongolian medicine for treating rheumatism. The prescription originates from *Zhigao Pharmacopoeia* [1] and is included in the *Mongolian Medicine Standards of the Ministry of Health of the People's Republic of China* [2]. The formulation functions to eliminate "mucus," reduce swelling, dry "Xieri Wusu" (also known as "yellow water disease"), dispel wind, relieve pain, and eliminate cold.

It is used to treat rheumatism, joint pain, lumbar and leg cold pain, toothache, diphtheria, and other conditions. Warm in nature, this formula is particularly effective for cold-induced yellow water diseases.

In this formulation, *Aconitum kusnezoffii Reichb.* serves as the primary component for eliminating mucus, relieving pain, and drying yellow water. *Terminalia chebula* acts as an auxiliary to regulate bodily humidity, while *Piper longum* supplements gastric fire and expels "Badagan" (the sticky materials inside humans characterized by coldness) and "Heyi" (the moving energy of the body, directing language, thinking, and outer and inner physical activity) diseases. Together, these three ingredients effectively treat cold-induced "yellow water diseases," parasitic skin diseases, diphtheria, anthrax, and other mucus-related conditions [1,2].

Mongolian medicine has gained increasing recognition nationwide for its unique efficacy, but quality concerns remain a major challenge. Due to its multi-component, multi-target characteristics, establishing a unique quality and bioactivity evaluation system remains an arduous task. The pharmacopeia's quality monographs, which are based on chemical markers, deviate from the theoretical framework of Mongolian medicine. The concept of quality markers (Q-Markers), proposed by academician Changxiao Liu, integrates multiple principles and multidisciplinary technologies, offering an approach to building a scientific quality control system [3,4].

Network pharmacology aligns well with the mechanisms of Mongolian medicine. This study comprehensively analyzes the chemical composition and pharmacological effects of Naru-3. Based on the Q-Marker theory, network pharmacology was employed to predict its quality markers, providing a basis for its quality control.

2. Chemical composition

2.1. Chemical composition of single ingredients

Naru-3 is a Mongolian medicine prescription composed of three single ingredients with functions such as expelling wind-dampness and relieving pain. It is the preferred medication for treating cold-damp arthralgia [5]. The chemical compositions of each single ingredient differ, and their synergistic effects contribute to the overall therapeutic efficacy. Therefore, a thorough understanding of the chemical composition of each ingredient is a prerequisite for studying the quality control and efficacy evaluation of traditional medicine.

2.1.1. *Aconitum kusnezoffii Reichb.*

Li *et al.* [6] used chromatographic methods, including silica gel, Sephadex LH-20, and high-performance liquid chromatography (HPLC), to isolate and identify compounds such as neoline, norditerpenoid alkaloids, dehydrosonchifoline, songorine, neoline, talatisamine, isotalatisine, hokbusine A (isolated for the first time), neoline base, 8-acetyl-14-benzoylaconine, and 8-methoxy-14-benzoyl-beiwutinine (both isolated for the first time). Peng [7] employed thin layer chromatography (TLC), nuclear magnetic resonance (NMR), mass spectrometry (MS), and infrared (IR) techniques to identify compounds such as Dzunghar alkaloid (isolated for the first time), Dzunghar amine (isolated for the first time), talatisamine, multiroot alkaloid (isolated for the first time), and 3-deoxyaconitine. Zhi *et al.* [8] used ultra-high performance liquid chromatography (UPLC) with high-resolution mass spectrometry (Orbitrap-MS) to identify compounds such as hypaconitine, benzoylneoline, benzoylaconine, benzoylhypaconine, and aconitine.

2.1.2. *Piper longum*

Liu *et al.* [9] used UPLC-Q-Exactive-MS to identify compounds such as piperine, piplartine, piperlonguminine,

and methylpiperate. Zhang *et al.* [10] used silica gel, MCI, TLC, and preparative HPLC for isolation and purification, identifying compounds based on their physicochemical properties and spectral data, such as 1β,6α-dihydroxy-4(15)-eudesmene, (+)-aphanamol I, 1,2-dihydroxy-3,10-bisaboladien-4-one, 3',4'-dihydroxy-1,10-bisaboladien-4-one, 1α-hydroxy-4-eudesmaldehyde (isolated for the first time), commiphorane I (isolated for the first time), black pepper lactam R (isolated for the first time), dihydropiperlonguminamide A (isolated for the first time), hydroxydihydro-bovistolide (isolated for the first time), 3R-chloro-4S-hydroxy-2-pyrrolidone (isolated for the first time), 3S-chloro-4R-hydroxy-2-pyrrolidone (isolated for the first time), guinea piperine, pseudo-piperlonguminamide D, wallamine, pseudo-piperlonguminamide C, pseudo-piperlonguminamide A, dihydropiperlongumine, zanthoxylamide, trans-zanthoxylamide, and (2E-N-2-isobutyl)-3-phenylpropenamide.

2.1.3. *Terminalia chebula*

Zhou *et al.* [11] used UPLC-Q-Exactive Orbitrap-MS to identify compounds such as gallic acid, methyl gallate, ellagic acid, corilagin, rugosin A, geraniin, rutin, arjunglucoside, and arjunolic acid. Wang *et al.* [12] used HPLC to determine the content of chebulagic acid and chebulinic acid. Yang and Tang [13] employed 1H-NMR, 13C-NMR, and IR to identify quercetin in *Terminalia chebula*.

2.2. Compound chemical composition

Compared to single ingredients, the compound components in Mongolian medicine formulations are richer and more complex, forming the basis for their multi-component, multi-target, and holistic regulation effects. Research on compounds such as aconitine in Naru-3 is extensive, and advanced techniques like HPLC have introduced new approaches to quality control. For instance, a study employing HPLC-triple quadrupole mass spectrometry combined with chemical pattern recognition revealed six differential markers [14]. Cao *et al.* [15] established a fingerprint profile for Naru-3 using UPLC combined with diode array detection (DAD), providing a basis for controlling the quality of compound medicinal materials.

3. Pharmacological effects

3.1. Analgesic effects

Yue *et al.* [16] observed that in patients receiving pregabalin combined with nerve block therapy for neuropathic pain (NP), the addition of Naru-3 significantly reduced interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) levels compared to conventional treatment, demonstrating its efficacy in NP treatment. Naru-3 may alleviate pain by modulating neuroinflammation and inhibiting the release of inflammatory factors. Zong *et al.* [17] pointed out that peripheral nerve injury induces central sensitization to pain. Naru-3 intervention blocked MMP2/IL-1β signaling, inhibited related expression and chemokine release, and potentially acted through the negative regulation of the dorsal root ganglion (DRG)-spinal cord pathway to manage sustained NP.

3.2. Anti-inflammatory effects

Multiple studies have demonstrated the anti-inflammatory effects of Naru-3. Bai *et al.* [18] found that it reduced IL-1 and TNF-α levels in the joint tissues of rats with adjuvant arthritis. Zhao *et al.* [19] constructed a collagen-induced arthritis (CIA) rat model and observed that different doses of Naru-3 reduced serum VEGF and TNF-α levels. High doses also reduced IL-1 levels and improved synovial membrane structure. E'nirile [20] reported that

Naru-3 alleviated synovitis and joint damage by inhibiting synovial angiogenesis and inflammatory cytokines and regulating MMP2 expression.

4. Network pharmacology-based Q-Marker prediction analysis of Naru-3

4.1. Screening of candidate compounds based on measurability and modifiability

Li *et al.* [21] analyzed 16 batches of Naru-3 using HPLC-MS/MS and identified nine components with good linearity and precision (RSD < 3.0%), recovery rates between 95.91% and 102.92%, and stable content. These nine components from *Aconitum carmichaelli*, *Terminalia chebula*, and *Piper longum* exhibit pharmacological activity and measurability, making them viable candidates for Naru-3 compounds after a comprehensive evaluation.

4.2. Target prediction of Q-Marker candidate components

Target information for gallic acid, corilagin, benzoylaconine, benzoylmesaconine, benzoylhypaconine, aconitine, mesaconitine, hypaconitine, and piperine was predicted using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://old.tcmsp-e.com/tcmsp.php) and SwissTargetPrediction (http://www.swisstargetprediction.ch). Protein and gene names were converted using the UniProt database (http://www.uniprot.org/). A total of 157 targets were identified after removing duplicates.

4.3. Construction of protein-protein interaction (PPI) networks

The 157 identified targets were imported into the STRING database (http://string-db.org) to construct a PPI network, with the species set as "Homo sapiens," a minimum required interaction score of > 0.4, and unconnected nodes hidden. The remaining parameters were kept as default. The PPI network of 157 target proteins was generated (see **Figure 1**). The analysis results were then imported into Cytoscape 3.7.2, and the "Centiscape2.2" plugin was used for topological analysis. Key targets were identified by selecting those with the degree, betweenness centrality, and closeness centrality values greater than the median, and a degree value of ≥ 10. A total of 38 key targets were obtained through this filtering process (see **Table 1**).

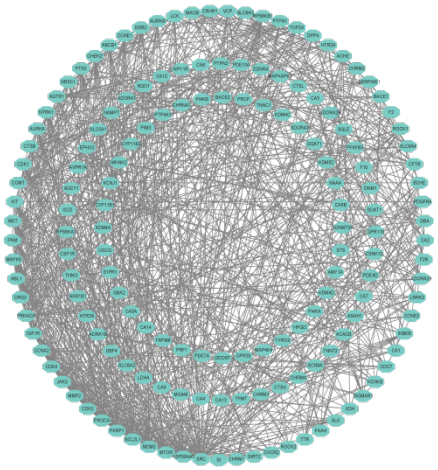

Figure 1. PPI network

Table 1. Topological properties of the PPI network

Target name	Betweenness centrality	Closeness centrality	Degree
SRC	4,118.2901	0.0036	57
HSP90AA1	1,757.5726	0.0035	47
MTOR	1,183.9132	0.0032	39
MDM2	564.0807	0.0031	37
BCL2L1	819.8547	0.0032	36
PARP1	412.9712	0.0030	32
PIK3CA	468.1337	0.0029	30
MMP2	618.6497	0.0030	29
CDK2	574.6500	0.0030	29
JAK2	483.7640	0.0031	28
CDK4	373.6547	0.0029	26
DRD2	666.4660	0.0028	24
PRKACA	1,139.4346	0.0030	24
KIT	600.3463	0.0029	23
MET	621.4489	0.0030	23
PKM	1,317.7946	0.0029	23
COMT	797.7177	0.0028	22
CDK1	366.7417	0.0027	21
CTSB	1,145.5314	0.0029	21
NR3C1	668.5234	0.0030	20
NTRK1	511.6742	0.0029	20
AGTR1	781.0390	0.0028	20
ABCB1	330.1906	0.0029	19
ESR2	1,221.2748	0.0029	19
LCK	336.3792	0.0029	18
MAOB	322.9984	0.0027	18
PTPN1	529.7860	0.0029	17
SLC6A3	335.3646	0.0027	17
CRHR1	413.0155	0.0028	17
VCP	544.2264	0.0028	17
DPP4	970.8921	0.0028	16
ACHE	596.3169	0.0026	15
SERPINE1	613.7177	0.0029	14
CFTR	703.8496	0.0029	13
BACE1	500.3856	0.0028	13
GBA	1,324.3972	0.0027	13
BCHE	354.9683	0.0027	13
CA2	939.2063	0.0027	12

4.4. GO and KEGG pathway enrichment analysis

The DAVID 2021 database (https://david.ncifcrf.gov/) was used to conduct Gene Ontology (GO) functional enrichment and KEGG pathway analyses on the 157 identified targets. GO analysis identified 25 terms, including 8 related to biological processes (BP), 6 related to cellular components (CC), and 11 related to molecular functions (MF). A selection of 15 significant terms was visualized (see **Figure 2**).

The Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis identified 14 significant pathways, with a focus on statistically significant entries ($P \leq 0.01$ and Benjamini ≤ 0.01). The results are visualized in **Figure 3**.

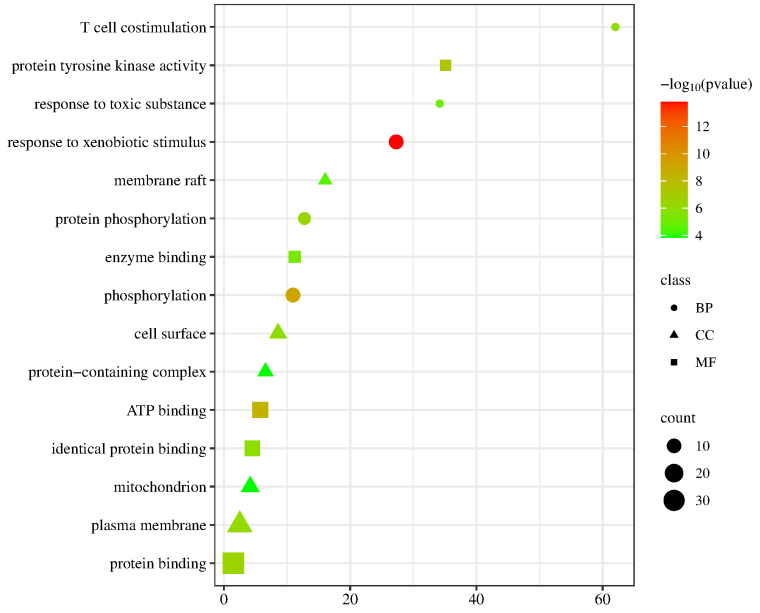

Figure 2. GO functional enrichment analysis of core targets

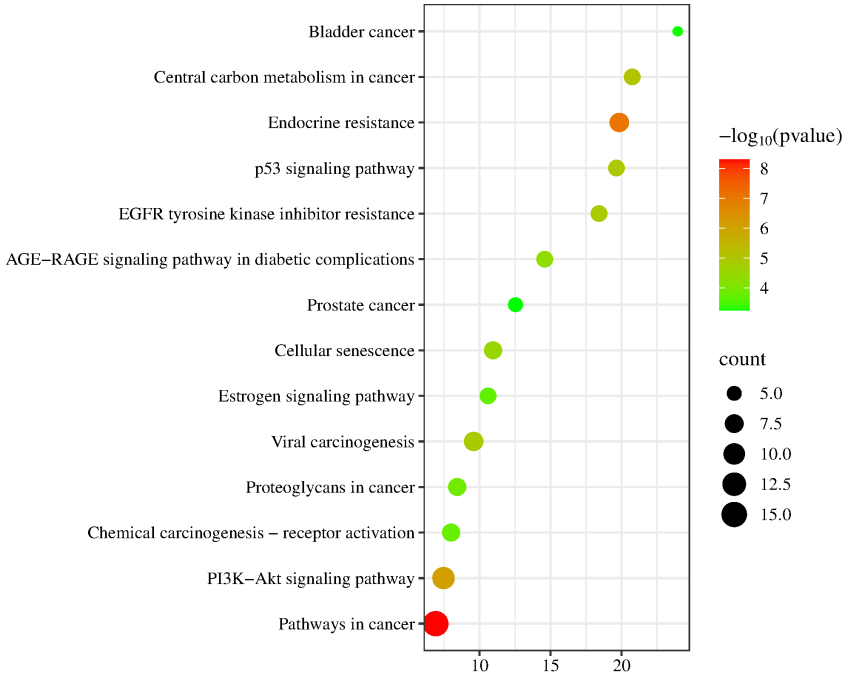

Figure 3. KEGG pathway enrichment analysis of core targets

4.5. Construction of the component-target-pathway network

The nine identified components of Naru-3, 38 key targets, and top-ranked pathways were integrated into a "Component-Target-Pathway" network using Cytoscape 3.7.2. The network was analyzed using the CentiScape2.2 plugin, and the topological analysis results are summarized in **Table 2**. The network visualization is provided in **Figure 4**.

Table 2. Topological properties of the component-target-pathway network

Name	Betweenness centrality	Degree
Piperine	954.3284	25
Gallic acid	339.4962	16
Aconitine	145.3234	14
Mesaconitine	163.7608	14
Benzoylaconitine	197.2629	14
Hypaconitine	140.1783	13
Corilagin	361.1974	13
Benzoylmesaconitine	164.5092	11
Benzoylhypaconitine	54.6823	8

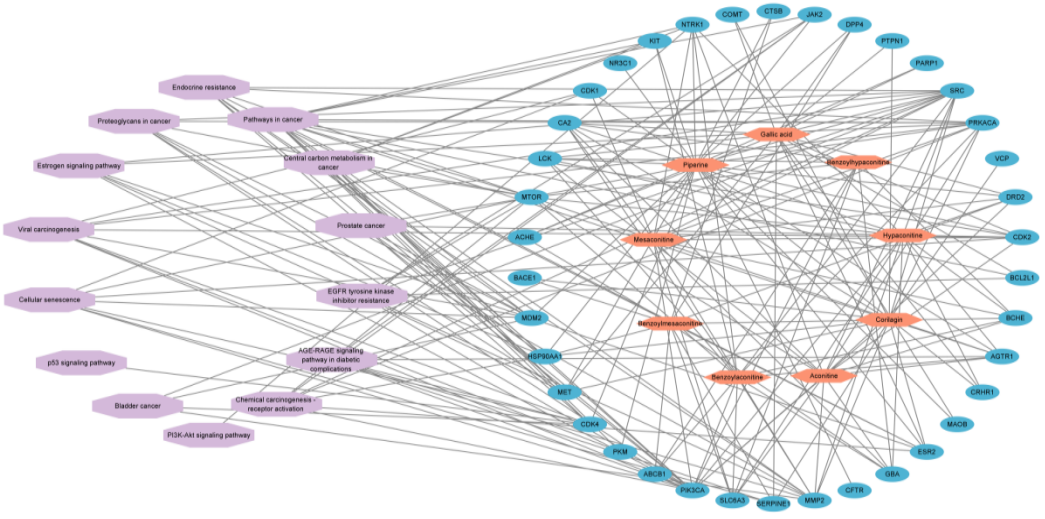

Figure 4. Component-target-pathway network of Naru-3

4.6. Analysis of Q-Marker

Naru-3 is primarily used clinically for treating joint pain, rheumatic diseases, rheumatoid arthritis (RA), and neuropathic pain, demonstrating significant anti-inflammatory and analgesic effects along with a favorable safety profile.

The network pharmacology analysis revealed that corilagin, benzoylaconitine, and aconitine might act on MMP2, a matrix metalloproteinase capable of degrading extracellular matrix (ECM) components such as collagen and laminin. This degradation disrupts the normal structure and barrier function of joint tissues, facilitating the migration and invasion of inflammatory cells and thus promoting the development of inflammation [22].

Gallic acid has been found to suppress inflammation induced by LPS in THP-1 macrophages, potentially by modulating the MAPK and NF-κB signaling pathways [23]. Piperine significantly inhibits the release of the inflammatory cytokine IL-1β, highlighting its anti-inflammatory mechanism through multi-target and multi-pathway effects [24].

HSP90AA1, a member of the heat shock protein 90 family, plays a role in inhibiting inflammation by downregulating inflammatory signaling pathways, thereby reducing inflammatory responses [25]. PIK3CA, a catalytic subunit of PI3K, activates the PI3K/Akt signaling pathway, which is implicated in the pathogenesis of RA. Abnormal activation of this pathway leads to excessive production of inflammatory mediators, reduced autophagy, enhanced osteoclast differentiation and activity, and increased angiogenesis and vascular permeability. These effects collectively contribute to the progression and severity of RA. Targeting the PI3K/Akt pathway is thus a promising strategy for controlling inflammation, alleviating joint damage, and improving patient quality of life [26,27].

GO functional enrichment analysis indicated that Naru-3 can regulate processes such as gene expression and enzyme binding. KEGG pathway enrichment analysis revealed that Naru-3 is involved in pathways such as cancer signaling, the P53 signaling pathway, and the PI3K/Akt signaling pathway. The P53 signaling pathway plays a critical role in regulating cell survival and inflammation. Its protective effect against inflammation is primarily achieved by suppressing the activity of the transcription factor NF-κB and enhancing the polarization of M2 macrophages. Numerous studies have demonstrated a reciprocal regulatory relationship between NF-κB and P53, which is key to controlling inflammation [28,29].

These findings are consistent with previously reported data, suggesting that the network pharmacology approach used in this study is both reliable and valid.

5. Conclusion

Mongolian medicinal preparations are natural remedies formulated through the combination of different Mongolian medicinal materials under the guidance of traditional Mongolian medical theories. The aim of developing quality control methods for these preparations is to ensure the safety and consistent efficacy of their use.

Naru-3 is a commonly used Mongolian medicinal preparation in clinical practice, employed for the treatment of conditions such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, and related disorders [5]. Long-term clinical experience in Mongolian medicine has demonstrated that this preparation has the effects of dispelling excess mucus, relieving pain, reducing swelling, and drying “Xieri Wusu” (a traditional Mongolian medical term).

Network pharmacology is an emerging interdisciplinary field that integrates systems biology, network science, and computational technologies into pharmacological research. Given the multi-component and multi-target characteristics of Mongolian medicinal compounds, network pharmacology provides a means to simulate and analyze the pharmacological mechanisms of various components. This approach helps elucidate the material basis of their efficacy and facilitates the prediction of quality markers (Q-Markers), laying a theoretical foundation for establishing quality control methods for Mongolian medicine.

Based on a literature review of Naru-3, this study selected nine compounds associated with anti-rheumatoid arthritis effects: gallic acid, corilagin, benzoylmesaconine, benzoylaconine, benzoylhypaconine, mesaconine, hypaconine, aconitine, and piperine. A network pharmacology study was conducted on these

compounds, constructing a "component-target-pathway" network to provide a theoretical basis for elucidating the pharmacological mechanisms of Naru-3.

The network pharmacology analysis indicated that these nine compounds are active components and may serve as potential Q-Markers of Naru-3. To ensure the reliability of these predicted Q-Markers, experimental validation is currently underway. The results of this study provide a theoretical basis for establishing quality control methods for the Mongolian medicinal preparation Naru-3.

Disclosure statement

The authors declare no conflict of interest.

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