RESEARCH ARTICLE

Application of network pharmacology and molecular docking to explore the mechanism of metronidazole in treating paronychia

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Paronychia, a periungual infection often involving anaerobic bacteria and marked inflammation, is usually managed with broad-spectrum antibiotics. However, metronidazole's selective anti-anaerobic activity and anti-inflammatory properties may offer a superior therapeutic option. This research aimed to elucidate the potential therapeutic targets and molecular mechanisms by which metronidazole exerted its effects in paronychia. Network pharmacology approaches were used to predict metronidazole's candidate targets for paronychia followed by molecular docking using AutoDock software to assess binding interactions between metronidazole and the predicted proteins. The results showed that heat shock protein 90 alpha family class A member 1 (HSP90AA1) and hematopoietic cell kinase (HCK) were identified as key molecular targets, exhibiting stable binding conformations and favorable binding free energies with metronidazole, which suggested that the efficacy of metronidazole in paronychia might involve dual regulatory mechanisms through modulation of HSP90AA1 and HCK signaling pathways. This study provided both a theoretical foundation and a methodological framework for further exploration of metronidazole's pharmacological actions in inflammatory dermatological disorders.

Keywords: metronidazole; paronychia; network pharmacology; molecular docking; target prediction.

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Introduction

Paronychia is an inflammation of the periungual skin and underlying soft tissues affecting toenails or fingernails, which exhibits a high incidence across all age groups including infants and young children [1]. Chronic paronychia defined as inflammation persisting for over six weeks is characterized by fluctuating discomfort and variable disease severity, alternating between mild and severe phases. Common complications include recurrent pain, granulation tissue hyperplasia, nail matrix damage, and scarring, while, in severe cases, amputation may be necessary [2–5], significantly impairing patient quality of life [6].

Although the pathogenesis of chronic paronychia remains incompletely understood, studies reveal a transition from aerobic bacterial predominance in mild cases to an enrichment of anaerobic microorganisms such as *Anaerococcus* in more severe stages accompanied by a decline in beneficial aerobic flora [7]. This dysbiotic shift may hinder colonization by protective bacteria and exacerbate the condition. Metronidazole

may serve as a supplementary treatment option for paronychia [8]. Current standard management of acute paronychia includes warm-water soaks, topical antiseptics or antibiotics, and, when indicated, surgical drainage [9]. Systemic therapy often involves Cephalexin and, in cases of methicillin resistant *Staphylococcus aureus* (MRSA) suspicion, trimethoprim-sulfamethoxazole [10]. Chronic paronychia often requires avoidance of irritants and topical antifungal agents with or without corticosteroids, but many patients experience prolonged inflammation and frequent relapse [11]. These limitations highlight the need for alternative or adjunctive therapies [12]. Network pharmacology, first introduced by Hopkins *et al*. in 2007, integrates pharmacology, bioinformatics, network analysis, and systems biology to investigate drug actions at the systems level [13, 14]. By modeling drugs and biological systems as interconnected networks, it enables identification of interactions among compounds, targets, and disease pathways, facilitating prediction of therapeutic effects and adverse reactions and guiding drug discovery and repurposing strategies [15]. This approach constructs multilayer "drug–target–disease" and protein–protein interaction networks, from which key nodes are identified using network topology parameters such as degree centrality and betweenness centrality, revealing the multi-target mechanisms of drug action. Molecular docking is a computational strategy that simulates the interaction between ligands and target receptors to predict binding modes and affinities, providing insight into molecular recognition and guiding rational drug design [16, 17].

This study employed network pharmacology to predict metronidazole's potential targets and enriched pathways in paronychia followed by molecular docking analysis to evaluate metronidazole–target interactions, thereby preliminarily elucidating the molecular mechanism of metronidazole treatment for paronychia. This research provided a theoretical rationale for the clinical application of metronidazole in paronychia management, potentially informing optimized dosing strategies and improving patient outcomes.

Materials and methods

Prediction of metronidazole targets

The simplified molecular input line entry system (SMILES) structure of metronidazole was obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), then input into the similarity ensemble approach (SEA) database (http://sea.bkslab.org/) and PharmMapper database (http://lilab.ecust.edu.cn/pharmmapper/) to predict potential drug targets. After removing duplicate entries, a comprehensive target gene set for metronidazole was established.

Acquisition of paronychia-related target genes

Paronychia-associated genes were retrieved using the keywords "paronychia," "nail," and "inflammation" from the GeneCards database (https://www.genecards.org). After deduplication, UniProt (https://www.uniprot.org) was used to verify and correct gene annotations, yielding a curated dataset of paronychia-related targets.

Identification of intersection targets between metronidazole and paronychia

The refined target lists for metronidazole and paronychia were combined using an online Venn diagram analysis tool (Venny 2.1) (https://bioinfogp.cnb.csic.es/tools/venny) to identify shared targets, representing putative therapeutic targets of metronidazole in paronychia.

Construction of a multilayer network model of "Metronidazole–intersection targets–paronychia"

A multilayer network integrating metronidazole, intersection targets, and paronychia was constructed and analyzed for topological features using Cytoscape 3.9.1 (https://cytoscape.org).

Protein-protein interaction (PPI) network construction

The intersection targets were imported into the search tool for the retrieval of interacting genes/proteins (STRING) (v11.5) (https://string-db.org) database with the species limited to homo sapiens and interaction score threshold set above 0.400. After removing isolated nodes, Cytoscape 3.9.1 was used to visualize the PPI network. Core therapeutic genes were then identified by intersecting the top candidates from maximum clique centrality (MCC), degree centrality, and betweenness centrality algorithms *via* the CytoHubba (version 0.1) (http://apps.cytoscape.org/apps/cytohubba).

Molecular docking study

The 3D structures of proteins encoded by key genes were retrieved from the research collaboratory for structural bioinformatics (RCSB) protein data bank (https://www.rcsb.org). In PyMOL 2.5 (https://pymol.org/2), redundant ligands and unrelated protein chains were removed. Receptor models were prepared in AutoDock by deleting water molecules and adding polar hydrogens. The metronidazole ligand was similarly dehydrated and protonated. Docking simulations were performed with AutoDock Vina (version 1.1.2) (http://vina.scripps.edu) using a grid box centered on the binding site and 20 docking runs per complex. Final docking poses were visualized in PyMOL 2.5.

Results

Acquisition of common targets

In this study, 70 metronidazole-related targets were retrieved from the SEA and PharmMapper databases with duplicates removed and entries curated. Paronychia-associated targets were obtained from the GeneCards database and similarly filtered, yielding 8,276 unique disease-related targets. Venn diagram analysis then revealed 49 overlapping targets (Figure 1).

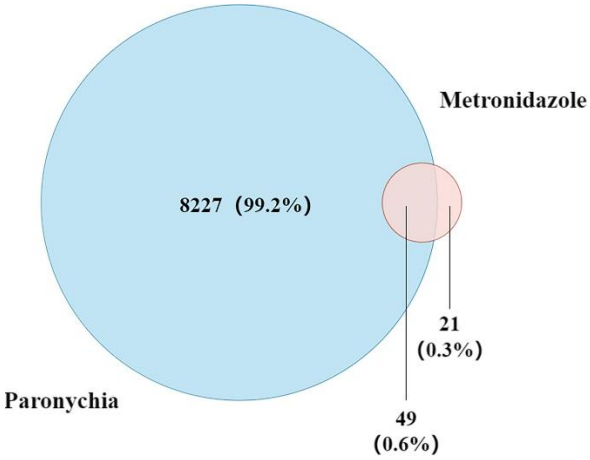

Figure 1. Venn diagram of metronidazole and paronychia related pathogenesis target.

Construction of the metronidazole–target–paronychia network diagram

A network map linking metronidazole, its 49 intersection targets, and paronychia was generated, which demonstrated that metronidazole engaged multiple paronychia-associated proteins, reflecting its therapeutic efficacy through coordinated, multi-target modulation (Figure 2).

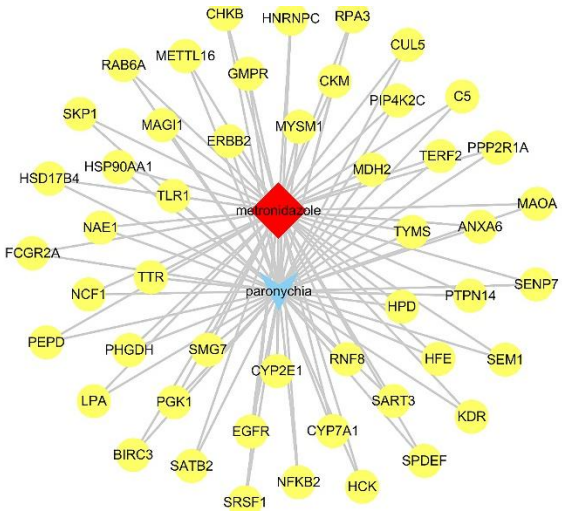

Figure 2. Metronidazole-target-paronychia network diagram.

Protein-protein interaction (PPI) network analysis

The 49 intersection targets were imported into the STRING database to construct the protein–protein interaction (PPI) network. This network comprised 49 nodes and 68 edges with a clustering coefficient of 0.431, indicating a pronounced modular structure (Figure 3). Enrichment analysis yielded a *P* value of 0.0108, confirming that these targets clustered non-randomly within common biological processes or pathways. Core genes *HSP90AA1*, *EGFR*, *SKP1*, and *HCK* were identified *via* CytoHubba, representing potential key mediators of metronidazole's effects in paronychia treatment.

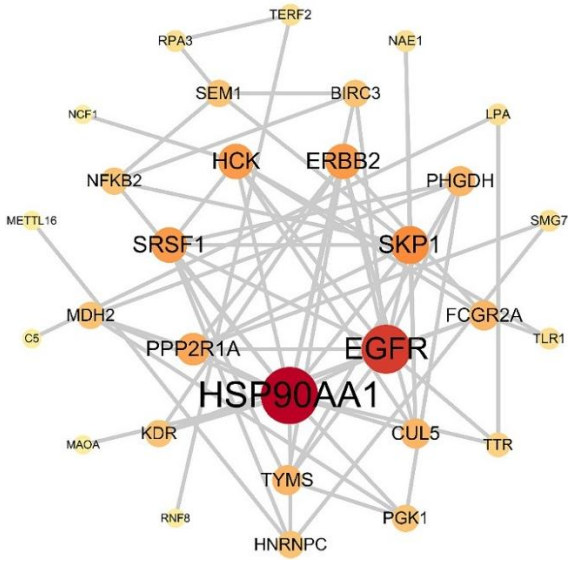

Figure 3. PPI network diagram of paronychia treated with metronidazole.

Molecular docking analysis of metronidazole with core target proteins

Molecular docking of metronidazole with the core proteins HSP90AA1 (Figure 4), epidermal growth factor receptor (EGFR), SKP1, and hematopoietic cell kinase (HCK) (Figure 5) was performed using AutoDock Vina. The lowest binding free energies were −5.6, −4.9, −4.3, and −5.2 kcal/mol for HSP90AA1, EGFR, SKP1, and HCK, respectively, indicating strong and stable ligand–receptor interactions. Generally, binding energies below −5.0 kcal/mol are considered to reflect favorable binding affinity.

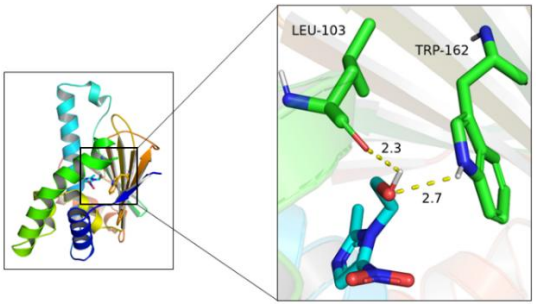

Figure 4. Docking of metronidazole with HSP90AA1.

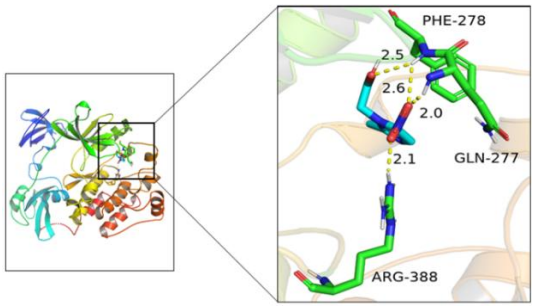

Figure 5. Docking of metronidazole with HSK.

Discussion

Chronic paronychia is typified by recurrent periungual erythema and edema, resulting in persistent discomfort and delayed resolution. It is a multifactorial condition driven by interactions among diverse microorganisms and mechanical factors. Standard treatments primarily employ topical antifungal agents and corticosteroid creams. However, the efficacy of antifungal therapy remains contentious [18, 19], and prolonged corticosteroid use can lead to adverse effects such as skin atrophy [20]. Our previous work demonstrated that anaerobic bacteria exacerbated the severity of paronychia [7]. A clinical study of metronidazole in paronychia treatment reported significant efficacy and a favorable safety profile. Despite its empirical use, the precise mechanisms underlying metronidazole's therapeutic action remain unclear due to challenges in establishing reliable *in vitro* and *in vivo* models of paronychia. This study employed network pharmacology and molecular docking to identify the target genes of

metronidazole in paronychia treatment. Network pharmacology, an emerging interdisciplinary approach, integrates the polypharmacological properties of drugs with the network architecture of biological systems to elucidate complex drug–system interactions [21]. Due to the lack of subtype classification in existing databases, this study retrieved disease-related targets for both metronidazole and paronychia without distinguishing between acute and chronic forms. A total of 49 overlapping targets were identified, and a multilayer "metronidazole–target–paronychia" network alongside a PPI network was constructed. Core genes *HSP90AA1*, *EGFR*, *SKP1*, and HCK were selected. Molecular docking revealed strong interactions between metronidazole and the proteins HSP90AA1 and HCK. HSP90AA1 encodes the inducible heat shock protein HSP90α, a molecular chaperone that is markedly upregulated under stress conditions such as hyperthermia, infection, and inflammation [22]. HSP90 proteins are evolutionarily conserved chaperones that assist nascent client proteins in achieving their native conformations, orchestrate assembly and disassembly of macromolecular complexes, facilitate refolding of misfolded proteins, and promote clearance of protein aggregates. They cooperate with the ubiquitin–proteasome system to degrade irreversibly misfolded proteins and ensure correct subcellular localization, thereby maintaining protein homeostasis [23]. EGFR is a well-characterized HSP90 client whose stability is regulated by HSP90α [24]. Upon binding its ligand epidermal growth factor (EGF), EGFR modulates inflammatory responses, promotes angiogenesis, and stimulates fibroblast and keratinocyte proliferation and migration, thereby enhancing wound contraction and epithelialization to facilitate healing [25]. Recent evidence indicated that EGF also exerted anti-inflammatory effects in skin by inhibiting interferon-γ–induced expression of pro-inflammatory genes including the chemokine CXCL10, cytokines IL-6 and IL-1A, the MHC class II antigen–associated gene HLA-DMA, and the inflammasome activator GBP5, thus preserving immune homeostasis in the cutaneous microenvironment [26]. Clinical observations further revealed that use of EGFR inhibitors (EGFRIs) and tyrosine kinase inhibitors targeting EGFR (EGFR-TKIs), which reduced EGFR signaling, could induce paronychia in treated patients [27, 28]. HCK, a Src family tyrosine kinase, is predominantly expressed in hematopoietic cells including macrophages, monocytes, and neutrophils, where it mediates pivotal immune signaling processes [29]. HCK regulates macrophage function by inhibiting autophagy pathways, skewing differentiation toward a pro-inflammatory phenotype, and enhancing secretion of cytokines such as CD54 (ICAM-1), IL-6, CXCL10, and TNF-α [30]. Importantly, the HSP90AA1/HSP90α axis and HCK signaling pathways functionally synergize to regulate CXCL10 and IL-6 expression. Based on these mechanisms, metronidazole might exert anti-inflammatory effects *via* a dual regulatory pathway, which included that it upregulated HSP90AA1 to stabilize EGF/EGFR signaling and suppressed the IFN-γ–mediated inflammatory cascade, while it inhibited HCK-driven pro-inflammatory macrophage differentiation, synergistically reducing key inflammatory mediators. Metronidazole not only retains its potent activity against anaerobic bacteria but also leverages its anti-inflammatory properties to provide a combined therapeutic effect in paronychia. This dual action overcomes the limitations of corticosteroid monotherapy that lacks antimicrobial efficacy and antifungal treatment that lacks anti-inflammatory benefit. This study offered a theoretical framework and experimental direction for further elucidation of metronidazole's mechanisms in paronychia management.

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