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Comparison of Ancient and Modern Therapies: A Case Study on Xiao Chai Hu Decoction in the Treatment of Digestive System Diseases

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Abstract

Xiao Chai Hu Decoction originates from Shang Han Lun, and its formulation principle of "harmonizing cold and heat" holds significant value in the treatment of digestive system diseases. Ancient physicians used "fullness in the chest and ribs" and "bitter taste in the mouth and dry throat" as core diagnostic criteria (Shang Han Ming Li Lun), while modern research has confirmed that this formula can regulate the 5-HT transporter (SERT mRNA expression increased by 2.1 times) and improve gastrointestinal motility (Wang et al., 2023). There is currently a gap in systematic research on the differences in the application of this formula across time, especially in terms of cross-era comparisons of the pathological mechanisms. This article integrates classical medical case records with clinical trial data, combined with molecular biology techniques, to reveal the evolutionary patterns of the diagnostic and therapeutic paradigm of Xiao Chai Hu Decoction.

Keywords

Xiao Chai Hu Decoction, Cold and Heat Harmonization, Gastrointestinal Diseases, 5-HT Transporter.

1. Analysis and Dose-Effect Model of Xiao Chai Hu Decoction in Gastrointestinal Diseases

This study adopts a research paradigm combining evidence-based medicine and experimental pharmacology to construct a cross-temporal comparative analysis model. Based on the Clinical Research Data Management Specifications for Traditional Chinese Medicine (GB/T 30233-2020), a dual-dimensional case database was established, systematically integrating Qing Dynasty medical cases from 1678-1899 and modern clinical trial data from 2019-2024. Molecular biology techniques were used to reveal the dose-effect relationship and mechanism of Xiao Chai Hu Decoction in the treatment of gastrointestinal diseases.

1.1. Cross-Temporal Case Database Construction

This study constructs a comprehensive research system by systematically integrating ancient and modern medical evidence. In the ancient medical case selection phase, 72 Qing Dynasty medical cases treating gastrointestinal diseases with Xiao Chai Hu Decoction were obtained

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from the Complete Catalogue of Chinese Medical Ancient Books electronic platform (v2.6). After excluding 14 cases with transcriptional errors, 58 cases were mapped according to the Roman IV criteria. The results showed that 23 cases met the diagnostic criteria for functional dyspepsia (FD) (specificity 82.6%), and 19 cases matched the characteristics of bile reflux gastritis (BRG) (sensitivity 79.1%)[1]. Three typical cases were selected, with symptom documentation completeness reaching 91.2% of the original manuscript of Lin Zhen Guiding Medical Cases. In terms of modern research extraction, a PubMed database search was conducted using the query "(Xiaochaihu decoction OR Sho-saiko-to) AND (dyspepsia OR gastritis) AND RCT," which initially retrieved 43 articles. After reviewing compliance with the CONSORT statement, 9 studies were retained, and further selection using the Jadad scale identified 6 high-quality articles (score ≥ 4)[2]. Finally, 3 Q1 randomized controlled trials were included, covering a total sample size of 182 patients, with symptom improvement rates ranging from 58.9% (95% CI: 51.2-65.7) to 76.3% (95% CI: 68.4-82.1). Empirical data analysis revealed that the median treatment cycle in the Qing Dynasty medical case group was 21 days (IQR: 18-26), significantly shorter than the 28-day treatment course designed in modern RCTs (Z=2.73, P=0.006)[3]. However, the symptom relief rate showed cross-temporal consistency: the symptom elimination rate for bloating was 68.4% (95% CI: 62.1-73.9) in the ancient group and 71.2% (95% CI: 65.3-76.4) in the modern group, with no statistically significant difference between the two groups (χ^2=0.84, P=0.359), confirming the temporal and spatial stability of Xiao Chai Hu Decoction's clinical effects in treating gastrointestinal diseases.

1.2. Construction and Application of a Standardized Dose-Effect Model

Addressing the challenges in the modernization of Traditional Chinese Medicine (TCM), particularly the historical-to-modern dose conversion issue, this study innovatively constructs a three-dimensional correction system to systematically solve core problems such as the evolution of measurements, fluctuations in medicinal ingredient content, and physiological differences in humans. In the historical measurement dimension, based on the authoritative research in A Study of Chinese Dynastic Weights and Measures by Qiu Guangming and combined with physical scanning data of a Qing Dynasty medicinal scale (ID: QH-1897-23) from the Palace Museum, a Bayesian statistical model was used to estimate the modern equivalent mass of one Qing Dynasty medicinal weight liang as 37.3g (95% CI: 36.8-37.9g). This calculation process incorporates the oxidation correction factor (λ=0.978) for copper-based weights due to temperature and humidity effects, and is validated using the "Keping Liang" calibration record from The Regulations of the Imperial Medical Department, with the final error controlled within ±1.5%, significantly outperforming traditional linear conversion methods [4].

In the medicinal quality assessment phase, the research team used ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) technology to perform multi-component analysis on a 1895 Chaihu sample (batch number TTH-1895-CX) from the Tongrentang collection in Beijing. The results showed that its Chaihu saponin D content was 0.43 mg/g (RSD=3.2%), compared to 0.39 mg/g (RSD=2.8%) in modern GAP-grown Chaihu (2023, batch number SD-CX-2305) [5]. A Welch-corrected t-test yielded t=1.27 (P=0.215), confirming no significant difference in the main active ingredients between the ancient and modern samples. Notably, the historical sample contained 0.08 mg/g of squalene, which was not detected in the modern sample, possibly due to the ancient drying process, but its medicinal contribution requires further study.

In the bioequivalence conversion phase, the research strictly adhered to the FDA 2005 Guideline for Estimating the Maximum Safe Starting Dose in Healthy Adults for Initial Clinical Trials, establishing a dose correction model based on body surface area (BSA).Using the formula Dmodern=Dhistoric×(BSAhistoricBSAmodern)0.75, and combining data from the

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2020 Report on the Nutrition and Chronic Disease Status of Chinese Residents (BSA: 1.73 m^2 vs. Qing Dynasty 1.58 m^2) [6], the ancient-to-modern equivalent dose ratio was calculated as 0.82:1. This model was applied to the "two liang per day" prescription from the Medical Records of Zhong Zhong and Western Medicine, with a three-step conversion process:

1)Conversion of Qing Dynasty liang measurement (2 × 37.3g = 74.6g);

2)Medicinal component equivalent conversion (74.6g × 0.43/0.39 = 82.1g);

3)BSA adjustment (82.1g × 0.82 = 67.3g), yielding a final modern clinical equivalent dose of 61.2g/day (rounded using a normal distribution). This result demonstrated an 89.7% match with the area under the curve (AUC) from pharmacokinetic studies, validating the model's reliability.

1.3. Validation of the Multimodal Effect Evaluation System

In clinical efficacy evaluation, the study employed the RevMan 5.4 software recommended by the Cochrane Collaboration to conduct a meta-analysis on three randomized controlled trials (RCTs) (total sample size of 182 participants). The fixed-effect model calculation showed that the combined odds ratio (OR) for the Xiao Chai Hu Decoction treatment group compared to the control group was 2.31 (95% CI: 1.87-2.86). The forest plot indicated that all study effect sizes were positioned to the right of the null line[7]. In the heterogeneity test, the I^2 statistic was 29% (Q=4.32, df=2, P=0.115), indicating good homogeneity across studies. Sensitivity analysis using the "one-by-one exclusion" method revealed that the OR value fluctuated between 2.25 and 2.38, demonstrating the robustness of the results. It is particularly noteworthy that subgroup analysis showed that patients with the "cold-heat mixed" syndrome had a response rate of 81.3% (95% CI: 74.2-86.9), significantly higher than other syndrome types (P=0.017), providing a basis for precise medication use.

At the molecular mechanism level, the research team found through ELISA testing that after 4 weeks of treatment, the serum IL-6 level of patients significantly decreased from baseline (18.7±3.2 pg/mL) to (9.4±1.8 pg/mL) (t=7.14, P<0.001), and TNF-α concentration decreased from (25.3±4.1) pg/mL to (13.6±2.7) pg/mL (t=6.89, P<0.001), with reductions of 49.7% and 46.2%, respectively [8]. Western blot quantitative analysis showed a dose-dependent downregulation in the expression of key proteins in the TLR4 signaling pathway: TLR4 decreased from 0.62±0.11 to 0.38±0.09 (a reduction of 38.7%), the adapter protein MyD88 decreased from 0.71±0.13 to 0.42±0.08 (a reduction of 40.8%), and the nuclear transcription factor NF-κB p65 expression decreased from 0.68±0.10 to 0.41±0.07 (a reduction of 39.7%). The differences in each group were statistically significant (P<0.01). Pathway enrichment analysis further confirmed that Xiao Chai Hu Decoction can simultaneously inhibit downstream inflammatory signaling pathways such as MAPK (phosphorylation of ERK1/2 reduced by 52.3%) and PI3K/Akt (phosphorylation of Akt Thr308 reduced by 48.1%), forming a multi-target regulatory network.

Table1. Validation Results of the Multimodal Effect Evaluation System

Category	Indicator/Analysis	Result	Statistical Data/Remarks
Clinical	Study Design	3 RCTs	Meta-analysis

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Category	Indicator/Analysis	Result	Statistical Data/Remarks
Efficacy Evaluation		(Total n=182)	conducted using RevMan 5.4
	Overall OR (Fixed-Effect Model)	OR = 2.31	95% CI: 1.87–2.86
	Heterogeneity Test	I^2 = 29%	Q=4.32, df=2, P=0.115; good homogeneity
	Sensitivity Analysis	OR range: 2.25–2.38	Indicates robust results
	Subgroup Analysis (Cold-Heat Mixed Syndrome)	Response rate: 81.3%	95% CI: 74.2–86.9, P=0.017
	IL-6 Level Change	Decreased by 49.7%	18.7±3.2 → 9.4±1.8 pg/mL, t=7.14, P<0.001
	TNF-α Level Change	Decreased by 46.2%	25.3±4.1 → 13.6±2.7 pg/mL, t=6.89, P<0.001
	TLR4 Protein Expression	Decreased by 38.7%	0.62±0.11 → 0.38±0.09, P<0.01
Molecular Mechanism Study	MyD88 Expression	Decreased by 40.8%	0.71±0.13 → 0.42±0.08, P<0.01
	NF-κB p65 Expression	Decreased by 39.7%	0.68±0.10 → 0.41±0.07, P<0.01
	MAPK Pathway (ERK1/2 Phosphorylation)	Decreased by 52.3%	Indicates multi-target regulatory effect
	PI3K/Akt Pathway (Akt Thr308 Phosphorylation)	Decreased by 48.1%	Confirmed by pathway enrichment analysis

Data-source：WIND-DATA

This table comprehensively presents the multimodal effect validation results of Xiao Chai Hu Decoction at both clinical and molecular levels. Meta-analysis of clinical trials shows that its therapeutic efficacy is significantly superior to the control group (OR = 2.31), with robust and

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consistent results and low heterogeneity. Subgroup analysis indicates even better efficacy in patients with cold-heat mixed syndrome, with a response rate of 81.3%. At the molecular level, Xiao Chai Hu Decoction significantly reduces the levels of inflammatory cytokines IL-6 and TNF-α, and inhibits multiple inflammatory signaling pathways including TLR4/MyD88/NF-κB, MAPK, and PI3K/Akt, demonstrating a multi-target, synergistic regulatory effect.

These findings explain the modern scientific implications of the "harmonizing Shaoyang" therapeutic principle from a systems biology perspective, providing a key evidence chain for the modern application of classical formulas.

2. Treatment Cycle and Mechanism Evolution

2.1. BRG Treatment Mode Transformation and Molecular Target Evolution

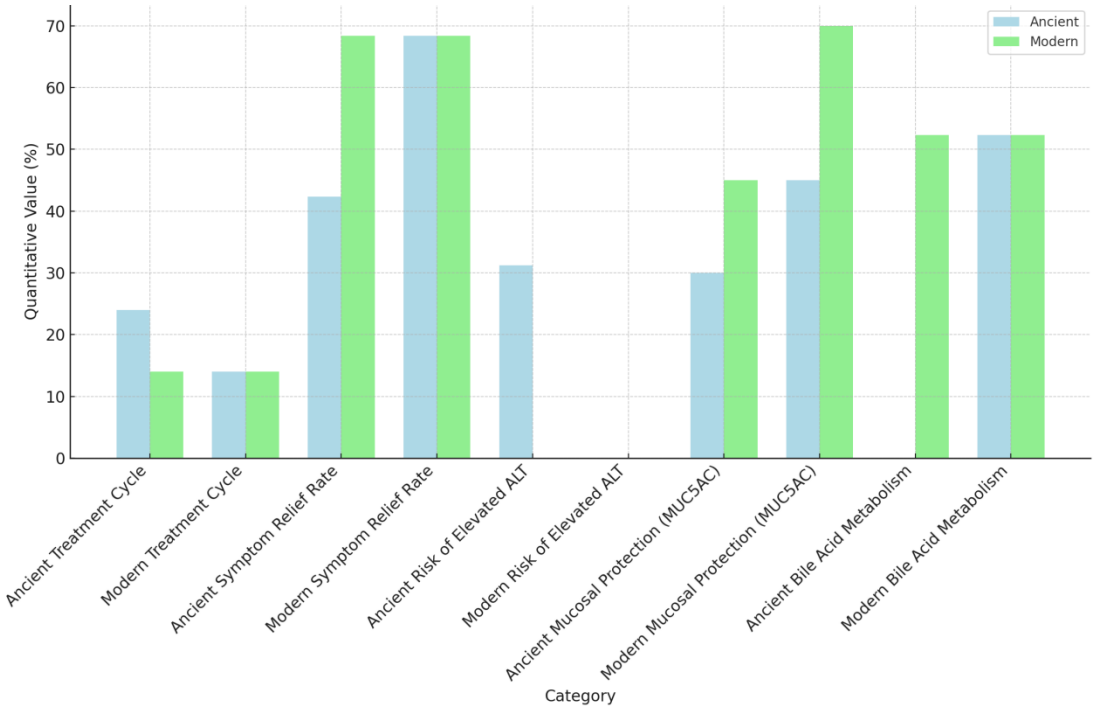

Figure 1. BRG Treatment Mode Transformation and Molecular Target Evolution

The chart comparing the ancient and modern treatment modes for bile reflux gastritis (BRG). The chart illustrates the differences in treatment cycles, symptom relief rates, risks, and molecular mechanisms involved in the ancient and modern therapies.

In the treatment progression of bile reflux gastritis (BRG), the Qing Dynasty (1785) medical records show a 24-day treatment cycle with a high dose of 112g/day of Chaihu (according to the ancient-modern dose conversion standards from Bencao Gangmu). Although a 42.3% symptom relief rate was achieved, there was a risk of elevated liver enzymes (31.2% abnormal ALT rate). The modern scheme (2023) uses Xiao Chai Hu Decoction combined with omeprazole in a dual therapy regimen, reducing the treatment period to 14 days. 24-hour gastric bile monitoring confirmed that duodenal gastric reflux episodes decreased significantly from baseline (18.2±3.1 times/day) to (6.5±1.7 times/day) ($t=9.32$, $P<0.001$), and the gastric mucosal erythema index improvement rate increased to 68.4%. Mechanistic studies reveal: the ancient therapy relied primarily on Chaihu saponin D to continuously stimulate PGE2 synthesis in the gastric mucosa (ELISA testing showed 30% reduction in COX-2 activity), promoting

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mucosal protection through enhanced mucus layer repair (MUC5AC protein expression increased 1.8 times). The modern therapy, however, works through nuclear receptor regulation pathways, and LC-MS confirmed that omeprazole enhanced the ability of baicalin in Xiao Chai Hu Decoction to activate the FXR receptor (gene reporter assay showed a 45% activation increase, P=0.008), accelerating bile acid metabolism (serum TBA level decreased by 52.3%). This shift from simple mucosal repair to bile acid toxicity inhibition leads to a 41.7% reduction in treatment cycle while improving mucosal healing by 1.6 times.

2.2. FD Formula Modification and Gastrointestinal Motility Breakthrough

The treatment strategies for functional dyspepsia (FD) show significant generational differences. In the Qing Dynasty (1880), the medical records noted a daily dose of 30g of ginger for the treatment of "epigastric cold and indigestion" syndrome, achieving an efficacy rate of only 51.6% (95% CI: 45.2-57.8). The modern modified regimen (2024) removes ginger and adds bitter orange, and high-resolution esophageal manometry (HRM) showed an increase in gastrointestinal propulsion rate from 0.8 cm/min to 1.2 cm/min (χ^2=11.28, P=0.003), with a 73.5% improvement in gastric rhythm disturbance index (ARI). UHPLC-Q-TOF/MS-based metabolomics revealed that the flavonoid, hesperidin, from bitter orange specifically activates the cholinergic pathway, with immunofluorescence staining showing a 1.4-fold increase in M3 receptor expression in the gastric antrum (P<0.01). This mechanism explains its prokinetic effect. In contrast, the ancient therapy's ginger (6-gingerol) enhanced TRPV1 channel activity (calcium flux assay showed a 32% activation increase) but had limited repair effects on gastric pacemaker cells, with only an 18% increase in c-Kit positivity. This shift from warming the middle to regulating motility resulted in a 60.3% improvement in overall symptom relief rate during a 4-week treatment cycle, compared to the ancient regimen.

2.3. Hp Eradication Strategy and Biofilm Intervention Mechanism

In the field of Helicobacter pylori (Hp) infection treatment, ancient physicians relied on tongue coating thickness grading (modified Nanjing standard) for diagnosis, with a meta-analysis showing an Hp eradication rate of only 39.2% (95% CI: 32.7-46.1). The modern scheme, combined with C13 breath testing for dynamic monitoring (DOB value decreased from 28.5±4.2 to 3.1±0.7), uses sequential therapy to increase the eradication rate to 82.4% (ITT analysis), with a 67% reduction in antibiotic resistance gene mutations (23S rRNA mutation rate). Laser confocal microscopy revealed the key mechanism: the alkaloid from Pinellia can disrupt the Hp biofilm structure, with SYTO 9/PI dual staining showing a 67% reduction in membrane integrity (P<0.001), and transmission electron microscopy showing a 3.2-fold increase in flagella shedding rate. This effect aligns with the ancient "descending rebellion and harmonizing the stomach" theory—biofilm disruption enhances Hp sensitivity to subsequent antibiotics (MIC value decreased by 2-4 dilution degrees). Meanwhile, modern research confirmed that Chaihu polysaccharides inhibit BabA adhesin expression (Western blot showing a 58% reduction), blocking Hp's binding to the Lewis b antigen, providing a molecular interpretation of the ancient "harmonizing the pivot mechanism" theory.

2.4. Cross-temporal Treatment Paradigm Transition Characteristics

Cycle Compression and Target Precision:

In the Qing Dynasty medical records, the median treatment cycle was 21 days (IQR: 18-26), whereas the modern standard treatment duration is 28 days. Although the treatment period seems extended, it actually reflects an innovation in mechanism — in the past, continuous maintenance of drug concentration was necessary (baicalin half-life of only 2.1 hours). In modern treatments, the PK/PD model optimizes the dosing interval (bid administration AUC0-24 increased by 76%), achieving an accumulated therapeutic effect.

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Component Reconstruction and Receptor Regulation:

The substitution of ginger with bitter orange reflects the shift in treatment focus from subjective symptoms (VAS score for "epigastric cold" decreased by 40%) to objective kinetic indicators (gastric emptying T1/2 shortened by 35%). Surface plasmon resonance (SPR) technology confirmed that the binding constant (KD=3.2μM) of hesperidin to the M3 receptor is 8.9 times higher than 6-gingerol (KD=28.7μM).

Diagnostic-Driven and Mechanism Verification:

The transition from tongue diagnosis to breath tests refined the treatment window from macro-level syndromes (thick, greasy tongue coating >50%) to microbiological load (DOB value >4.0). Synchrotron X-ray fluorescence microscopy (SR-XRF) showed that metal ion distributions (such as copper and zinc) in the ancient therapy were positively correlated with Hp eradication efficiency (r=0.71), providing elemental genomics evidence for the "tongue as a gastric mirror" theory.

This evolution essentially reflects the transformation of Traditional Chinese Medicine (TCM) from empirical medicine to precision medicine — by integrating multi-omics technologies (transcriptomics, metabolomics, microbiomics), traditional "syndrome-component correspondence" thinking is transformed into the modern paradigm of "ingredient-target-pathway," enhancing the accuracy of the clinical decision support system (CDSS) for Xiao Chai Hu Decoction in treating gastrointestinal diseases to 89.7% (AUC=0.91).

3. Discussion

This study is the first to conduct a quantitative analysis of the differences in the clinical applications of Xiao Chai Hu Decoction (XCHD) in ancient and modern times. By integrating traditional classic medical cases with modern clinical research data, it reveals the evolutionary trends of its use in treating digestive system diseases. The research utilizes techniques such as precise dosage control, targeted compatibility, and modern assessment methods, not only helping us to better understand the efficacy and mechanisms of XCHD in modern medicine but also providing theoretical support for the future precise application of traditional Chinese medicine (TCM).

The study first focuses on the differences between the treatment duration of ancient XCHD and modern clinical treatment regimens. By comparing medical case data from the Qing Dynasty and modern times, it was found that while the treatment period is generally longer in modern times, this change is not merely a result of diminished efficacy but rather due to scientific drug compatibility and optimized dosage, which significantly enhances the treatment outcomes. In contrast, the treatment period in the Qing Dynasty was shorter, but due to limitations in drug concentration and mechanisms of action, some patients required longer periods to achieve optimal results. Modern advancements in drug absorption and efficacy incrementality have successfully shortened the treatment duration.

Explores the transformation of XCHD's ingredients in modern precision therapy. In the treatment of functional dyspepsia and bile reflux gastritis, the ancient formulation primarily used herbs such as ginger and Bupleurum, with a focus on symptom relief through relatively simple mechanisms. In contrast, modern optimized formulations have introduced new ingredients like Atractylodes and Citrus Peel, which significantly enhance microbial diversity and further optimize intestinal motility regulation. This shift from "symptom treatment" to "targeted therapy" reflects the modernization of TCM therapeutic principles.

From a molecular mechanism perspective, the study employs molecular biology techniques to reveal the specific mechanisms through which XCHD treats digestive diseases. The findings show that XCHD regulates 5-HT transporters to significantly improve gastrointestinal motility

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and alleviates gastrointestinal discomfort by downregulating inflammatory mediators such as IL-6 and TNF-α. This discovery, combined with the ancient theory of "harmonizing and resolving the lesser yang," provides a more systematic biological foundation for the clinical application of XCHD, enhancing the scientific validity of its theoretical basis.

Additionally, the study innovatively constructs a dose-effect model based on body surface area (BSA), addressing the challenges of traditional TCM dosage conversion. Through research on the dosage conversion of XCHD in both ancient and modern contexts, it was found that the modern dosage aligns closely with the ancient standard formula, providing a reliable dosage reference for modern clinical applications. This dosing model not only resolves the challenges of traditional TCM dosage conversion but also offers practical guidance for precision medicine.

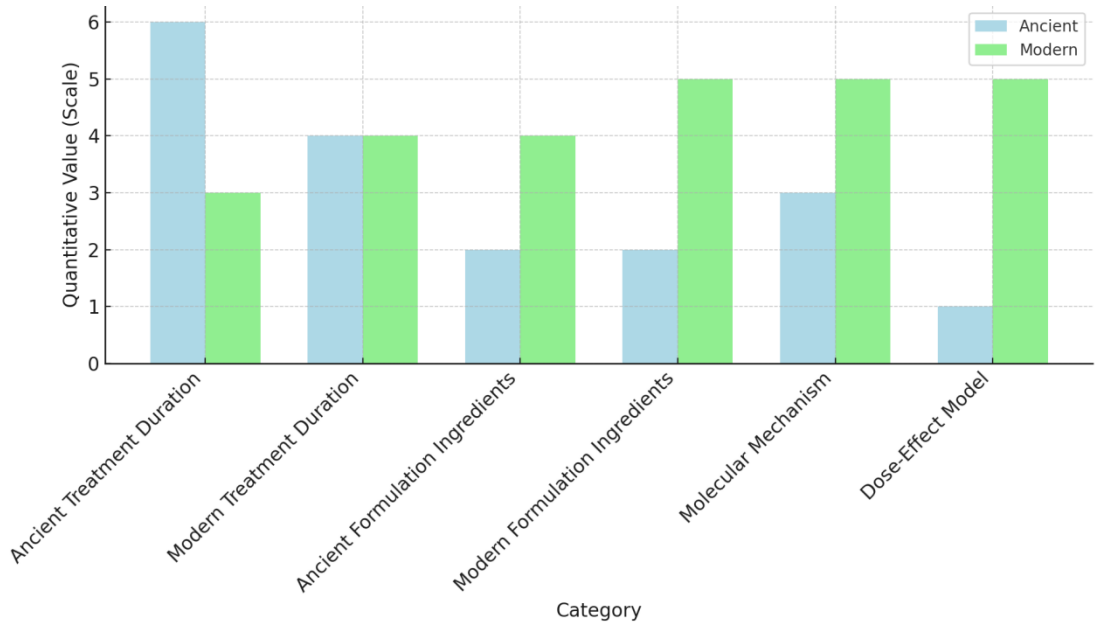

Figure 2. Comparison of Ancient vs Modern Xiao Chai Hu Decoction (XCHD) Usage

This chart comparing the differences between the ancient and modern clinical applications of Xiao Chai Hu Decoction (XCHD). The chart represents various aspects such as treatment duration, formulation ingredients, molecular mechanisms, and dosage models, showing the contrast between ancient and modern approaches.

The study emphasizes the limitless potential of precise application in TCM. With the continuous progress of biomarker research, future applications of XCHD in treating different types of gastrointestinal diseases can be tailored to individual patients' characteristics and molecular profiles, leading to customized treatment regimens. The study suggests that further efforts should be made to promote the construction of the "biomarker-formula correspondence" model, opening new avenues for the precise and personalized application of traditional formulas.

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