TMR

REVIEW

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Enhancing bioavailability in traditional Chinese medicine: Exploring strategies for optimized therapeutic efficacy

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Author contributions

Thomas JO conceptualized the review and wrote the paper. Idowu IM collected data and analyzed relevant studies. Rudrapatna SG directed the drawing and critically reviewed the article. All authors read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

ADG, andrographolide; ADME, absorption, distribution, metabolism, and the elimination; AE, aloe emodin; ALI, acute lung injury; ART, artemisinin; ATR-FTIR, attenuated total reflectance-fourier transform infrared spectroscopy; AUC, area under the curve; BMC, bisdemethoxycurcumin; BP, butylidenephthalide; CA-VO, volatile oil combination; CH, chrysophanol; CLM, chrysophanol-loaded micelles; CPP, cell-penetrating peptides; CRF, chronic renal failure; CU1, curcumin derivative; DAD, iode Array detectors; Dio, diosgenin; DRIFTS, Diffuse reflectance mid-infrared Fourier transform spectroscopy; FMN, Formononetin; FPC, forsythin-phospholipid complex; FZ, radix aconiti lateralis praeparata; GC, gas chromatography; HILIC-RPLC-SRM, hydrophilic interaction liquid chromatography coupled with reversed-phase liquid chromatography and selected reaction monitoring; HPE, herpetrione; HPLC, high-performance liquid chromatography; HPLC-MS/MS, high-performance liquid chromatography tandem mass spectrometry; HPLC-PDA-MS/MS, high-performance liquid chromatography photodiode array detection tandem mass spectrometry; HPLC-QTOF MS, high-performance liquid chromatography quadrupole time of flight mass spectrometry; HP-β-CD, hydroxypropyl-β-cyclodextrin; HSYA, Hydroxy-safflower yellow A; IC, icaritin; ICP-MS, inductively coupled plasma mass spectrometry; IGFBPs, insulin-like growth factor binding proteins; IPC, icariin-phospholipid complex; LDA, Linear discriminant analysis; LMWP, low molecular weight protamine; MS, mass spectrometry; Pae, paeoniflorin; PCA, principal component analysis; PF, pueraria flavones; P-gp, P-glycoprotein; PLS-DA, partial least squares discriminant analysis; PN, Panax notoginseng (Burkill) F.H.Chen; PSO, psoralen; QC, quality control; rTCS-LMWP, recombinant Cell-penetrating trichosanthin; SA, sodium alginate; SBP, Shexiang Baoxin Pill; SDs, solid dispersions; SHL, Shuang Huang Lian Injection; SOMA, self-orienting millimeter-scale applicators; TA, bioavailability of Tanshinone IIA; TCM, traditional Chinese medicine; TCS, trichosanthin; TDG, Tetrastigma hemsleyanum Diels & Gilg; TLC, thin-layer chromatography; TNBC, triple-negative breast cancer; UHPLC-QqQ MS/MS, ultra-high-performance liquid chromatograph triple quadrupole tandem mass spectrometry; ZT, Zhenwu Tang.

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Abstract

Traditional Chinese medicine (TCM) offers diverse therapeutic compounds but faces challenges like poor bioavailability and instability. Recent innovations in drug delivery systems, including nanotechnology-based drug delivery systems have shown potential to enhance solubility, stability, and therapeutic efficacy. This review examines these advancements, focusing on their mechanisms and applications in improving TCM formulations. Cutting-edge techniques, such as microneedles, iontophoretic patches, and self-orienting applicators, are also discussed for their potential to revolutionize TCM delivery. By bridging traditional wisdom with modern innovations, this review emphasizes the transformative role of these strategies in advancing TCM's integration into contemporary medicine.

Keywords: traditional Chinese medicine; bioavailability enhancers; drug delivery; nanocarriers; therapeutic efficacy

Introduction

Traditional Chinese medicine (TCM), with its origins deeply rooted in ancient Chinese philosophies such as Daoism and Confucianism [1-3], emphasizes a holistic approach aimed at restoring balance and harmony within the body, as outlined in foundational texts like the Yellow Emperor's Inner Canon [4-7].

This system integrates natural therapies including herbal remedies, acupuncture, and qigong, which collectively address physical and mental well-being while aligning with modern trends toward complementary and integrative healthcare practices [5, 8, 9].

In TCM practices, multi-component TCM formulas are employed based on the syndrome differentiation theory of Chinese medicine. However, its preparations suffer from drawbacks like instability, low bioavailability, and poor solubility [10-12].

Recent advancements in pharmaceutical technologies aim to address these challenges by improving the stability and delivery of TCM formulations, thereby enhancing their therapeutic efficacy [13-16].

This review aims to provide a comprehensive overview of recent advancements in the field of enhancing the bioavailability of TCM. By synthesizing findings from a diverse range of studies, we highlight the potential of nanocarriers, absorption enhancers, solid dispersions, and other innovative approaches in overcoming the challenges associated with TCM delivery. Furthermore, we discuss the challenges and proposed solutions for improving therapeutic outcomes and advancing the integration of TCM into modern healthcare practices.

Ensuring bioavailability through quality control in TCM

The bioavailability of active compounds in traditional Chinese medicine is inherently influenced by the variability in raw materials, preparation methods, and manufacturing processes. Quality control (QC) is essential for maintaining consistency and ensuring that TCM formulations are both safe and therapeutically effective. By standardizing bioactive compounds, optimizing extraction techniques, and verifying ingredient authenticity, QC plays a pivotal role in ensuring the reproducibility of pharmacokinetics and maximizing bioavailability.

Impact of quality control on bioavailability

Chromatography has become a cornerstone of TCM quality control, with techniques such as high-performance liquid chromatography (HPLC), gas chromatography (GC), and thin-layer chromatography (TLC) being extensively employed [17-19]. The continuous refinement of these methods, underscores their pivotal role in ensuring the reproducibility and authenticity of TCM products [20, 21]. Advancements in these techniques are particularly critical in the context of some TCM products such as injections, inhalations, decoctions, herbal supplements, where safety and efficacy are paramount concerns [22].

HPLC, in particular, has gained prominence for its sensitivity and versatility. It serves as the primary tool for detecting active ingredients, impurities, and adulterants in TCM formulatons [23]. Recent advancements, including the integration of HPLC with diode Array detectors (DAD) and mass spectrometry (MS), have expanded its capabilities, enabling comprehensive profiling of complex herbal mixtures [24]. For instance, HPLC-MS is widely used to quantify active compounds such as astragaloside IV in *Astragali radix* [25, 26], ginsenosides in *Panax ginseng* C.A.Mey. [27], and curcumin in *Curcuma longa Lynn.* [28] ensuring therapeutic efficacy and consistency. Moreover, combining HPLC with newer technologies like tandem mass spectrometry (MS/MS) allows for the simultaneous analysis of multiple analytes, further enhancing its utility in quality control processes [29].

Zhao et al. used HPLC-MS/MS to study the pharmacokinetics and bioavailability of galgravin, a compound found in certain TCM formulations, following oral and intravenous administration to rats. The method used allowed for rapid analysis, with a runtime of just 6 minutes, facilitating efficient determination of galgravin levels in biological samples [30].

Chromatographic fingerprinting is another vital technique, offering a holistic approach to quality assessment by capturing the complete chemical profile of a TCM product [31]. This method is particularly effective for multi-component formulations, such as Qingkailing Injection, where multiple bioactive markers are analyzed simultaneously to maintain batch consistency [31, 32]. In the case of TCM injections, tablets, and tinctures, multidimensional fingerprinting techniques have proven especially valuable, combining chromatographic and spectrometric methods like ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS) [33-35].

For instance, fingerprinting methods for Shenqi Fuzheng Injection and Danhong Injection provide detailed chemical profiles, ensuring consistent quality [33, 36]. Similarly, the fingerprinting developed for Tianma Toutong Tablet identifies bioactive compounds like gastrodin, chlorogenic acid, and ferulic acid, supporting its antioxidant activity and quality evaluation [34]. Xiaozhong Zhitong Tincture employs multidimensional fingerprinting, combining HPLC, GC, and electrochemical techniques with advanced tools like hierarchical clustering analysis and grey relation analysis to quantify key compounds and predict reducing potency [35]. Bazhen Yimu Pill is evaluated using HPLC fingerprints alongside ultraviolet and differential scanning quantum fingerprints, further enhancing its quality control framework [32].

Corydalis yanhusuo W.T.Wang, a TCM herb renowned for its analgesic properties, has been the subject of quality assessment using HPLC fingerprinting techniques. Lu et al. developed an HPLC method to establish a comprehensive chemical fingerprint of *C. yanhusuo*, enabling the identification and quantification of its major alkaloid components. This approach facilitated the differentiation of *C. yanhusuo* from related species and ensured consistency across different batches. The study demonstrated that HPLC fingerprinting is a reliable and effective method for the quality control of *C. yanhusuo*, ensuring its authenticity and therapeutic efficacy in TCM applications.

Ensuring therapeutic consistency through fingerprinting

Fingerprinting techniques also play a pivotal role in bioavailability studies by ensuring the consistency and reproducibility of materials used in pharmacokinetic evaluations [37-42]. For instance, fingerprinting helps standardize the chemical variability of herbal extracts, enabling accurate assessment of their absorption and metabolism. A study by Li et al. comparing dispensing granules of Chinese herbal medicines, such as *Gardenia jasminoides* Ellis, with traditional decoctions used HPLC fingerprinting and multi-component quantification to evaluate chemical similarity. Pharmacokinetic profiling further assessed bioequivalence through concentration-time curves and key parameters, revealing no significant differences between the two forms [43]. This has direct implications for TCM products, as bioavailability studies rely on consistent and reproducible materials to ensure the safety and efficacy of these formulations.

Licorice (*Glycyrrhiza spp.*) is a widely used herb in TCM, often prepared as a decoction. To establish a robust quality control method, Zhang et al. developed a chromatographic fingerprint for licorice standard decoction using a quality by design approach. They employed HPLC to analyze the decoction, focusing on critical method attributes such as peak resolution, total peak number, and capacity factor distributions. By optimizing these parameters, the study established a reliable HPLC fingerprint method that ensures the consistency and quality of licorice decoctions, thereby maintaining their therapeutic efficacy [44].

Advanced analytical techniques for bioavailability optimization

Traditional single-marker approaches often fall short in capturing the complexity of TCM formulations [45]. Pattern-oriented techniques, such as chromatographic fingerprinting combined with multivariate data analysis (chemometrics), have proven effective in overcoming

these limitations [46, 47]. Multivariate analysis offers robust tools for comparing and classifying TCM products by analyzing entire chemical profiles [48]. Chemometrics is particularly valuable for detecting adulteration, ensuring consistent therapeutic properties, and differentiating high-quality formulations from substandard products. Techniques like principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA) have been successfully applied in these contexts [49-51]. Linear discriminant analysis (LDA), another chemometric technique, further enhances classification accuracy by identifying patterns that distinguish between sample groups, making it an invaluable tool in quality control and authentication studies [52].

Fraud detection is another critical application of advanced analytical techniques. Herbal medicines such as *Radix astragali* are often adulterated with less expensive materials to increase yield and profit margins [53]. Diffuse reflectance mid-infrared Fourier transform spectroscopy (DRIFTS), combined with chemometric methods, has proven highly effective for identifying adulteration. For instance, DRIFTS detected the presence of Jin Quegen (the root of *Caragana sinica* (Buc'hoz) Rehd.) in *Radix astragali* samples, with high classification accuracy using PLS-DA. Techniques like PCA and LDA also demonstrated high prediction accuracy, ensuring the integrity and safety of the herbal formulation [53].

A study by Yan et al. used attenuated total reflectance-fourier transform infrared spectroscopy (ATR-FTIR) with first-order derivative processing to enhance spectral clarity and identification. This method allowed for the rapid analysis of *Panax ginseng* C.A.Mey., *Panax notoginseng* (Burkill) F.H.Chen (PN), and *Panax quinquefolius* polysaccharides. By integrating chemometric models such as PCA, PLS-DA, and LDA, the study achieved accurate differentiation of these polysaccharides. Further refinement with two-dimensional ATR-FTIR improved the precision of quantitative models, providing a fast, non-destructive, and cost-effective approach to Panax polysaccharide analysis [52].

Quality control's role in enhancing bioavailability

The identification of active components is a cornerstone of quality control in TCM. Simultaneously quantifying diverse constituents such as alkaloids, flavonoids, and terpenes provides a holistic understanding of their pharmacological contributions, enabling the development of more effective formulations [54, 55]. Advanced techniques such as HPLC-MS, including methods such as high-performance liquid chromatography photodiode array detection tandem mass spectrometry (HPLC-PDA-MS/MS) and high-performance liquid chromatography quadrupole time of flight mass spectrometry (HPLC-QTOF MS), are essential for identifying active ingredients. For instance, hydrophilic interaction liquid chromatography coupled with reversed-phase liquid chromatography and selected reaction monitoring (HILIC-RPLC-SRM) has been successfully applied to analyze complex components in TCM injections like Shenfu and Xingxiong, ensuring comprehensive identification and quantification of pharmacologically active compounds [33]. These methods enhance the reproducibility of therapeutic effects by ensuring consistency in quality.

Further advancements, such as hybrid stationary phases in column technology, have improved the separation of polar and non-polar components, addressing the challenges of complex TCM matrices [56]. A practical application of these techniques is demonstrated in the study of Zhenwu Tang (ZT), a TCM formulation primarily composed of *Radix aconiti lateralis praeparata* (FZ). Known for its pharmacologically active diterpenoid alkaloids, ZT was analyzed using HPLC-MS/MS to investigate the pharmacokinetics of six key alkaloids: hypaconitine, mesaconitine, aconitine, benzoylmesaconitine, benzoylaconitine, and benzoylhypaconitine. Notably, ZT administration significantly enhanced the bioavailability of benzoylmesaconitine, showing 3.5- and 5.5-fold increases compared to the FZ extract alone, underscoring the formulation's potential for improved therapeutic efficacy [57].

The study of Jia-Wei-Qi-Fu-Yin, another TCM formulation, further illustrates the potential of modern analytical techniques. An et al. used ultra-high-performance liquid chromatograph triple quadrupole tandem mass spectrometry (UHPLC-QqQ MS/MS) to measure 20 bioactive compounds, including saponins, flavonoids, oligosaccharide esters, and phenolic acids, in rat plasma and brain. The pharmacokinetic analysis revealed distinct absorption patterns, compounds like ferulic acid were absorbed quickly, while ginsenosides showed slower absorption. Importantly, ferulic acid and ginsenosides stood out as key contributors to the formulation's therapeutic effects, owing to their high levels of exposure in both blood and brain [58].

Safety evaluation and its influence on bioavailability

Safety evaluation is a key component of quality control, as adverse drug reactions can severely impact the bioavailability and therapeutic efficacy of TCM formulations [59-62]. Adverse drug reactions, such as anaphylactic shock, have highlighted the urgent need for robust safety evaluation methods. Injectable products, such as Shuang Huang Lian Injection (SHL), have been widely used to treat acute respiratory infections, pneumonia, and influenza but are often associated with severe allergic or anaphylactoid reactions that limit their clinical applications. Identifying the components and mechanisms underlying these reactions is crucial for improving safety [63].

Feng et al. addressed SHL's safety concerns by utilizing spectrum-effect relationships and ultra-performance liquid chromatography time of flight mass spectrometry UPLC–TOF–MS to identify potential anaphylactoid agents. Chromatographic fingerprint analysis pinpointed specific peaks associated with elevated levels of β-hexosaminidase and plasma histamine, which were linked to allergic responses [63].

Complementing this, Gu et al. employed metabonomics to explore the pathological mechanisms of SHL-induced allergic reactions. By analyzing endogenous metabolites in a rat model, the study identified 15 biomarkers and implicated metabolic pathways, including linolenic acid metabolism, phenylalanine metabolism, and purine metabolism, in the allergic response. Elevated serum histamine and tryptase levels, alongside histological changes, further clarified the allergic mechanisms, providing insights that could guide future safety research [64].

Lianhua Qingwen Capsule, another widely used TCM formulation, also highlights the importance of safety evaluation. Using inductively coupled plasma mass spectrometry (ICP-MS), Li et al. quantified 26 inorganic elements across 22 batches, revealing significant quality variations. Chemometric analysis identified elements like uranium, cesium, and thallium as key contributors to inconsistency, while health risk assessments raised concerns about elevated vanadium levels in certain batches. This underscores the necessity of elemental analysis and health risk assessments to ensure both safety and consistency in TCM formulations [65].

Relevance of bioavailability in TCM efficacy

Bioavailability refers to the proportion of a drug that reaches its intended site of action or enters the bloodstream to exert its therapeutic effects. In the context of TCM, bioavailability plays a crucial role in determining the efficacy of herbal formulations. Many TCM compounds face challenges like poor solubility, instability, and low absorption, which directly impact their therapeutic potential [66-68].

Bioavailability is an integral part of the pharmacokinetic paradigm, which studies the movement of drugs through the body which entails absorption, distribution, metabolism, and the elimination (ADME) of drugs from the body [69-73]. The route of administration significantly influences bioavailability, as seen in oral formulations subjected to gastrointestinal absorption and hepatic first-pass metabolism, compared to intravenous (IV) administration, which bypasses these processes [74-76]. For example, oral TCM formulations often require higher doses to achieve therapeutic effects due to lower bioavailability, potentially increasing the risk of toxicity [77, 78]. Drug clearance, or the removal of active compounds from systemic circulation, further impacts bioavailability. This process is governed by mechanisms like first-order and zero-order kinetics, with first-order

kinetics involving the elimination of a constant drug fraction over time, proportional to its plasma concentration. Understanding these pharmacokinetic mechanisms is essential for optimizing dosing regimens and minimizing risks [79-81].

Factors influencing bioavailability of TCM

Preparation method

Traditional methods such as steaming, roasting, and fermenting aim to enhance the therapeutic effects of raw herbs while reducing toxicity [82, 83]. However, these methods can also introduce inconsistencies in bioavailability. Modern techniques like spray-drying and freeze-drying provide greater precision and reproducibility, ensuring consistent therapeutic outcomes [84].

Interactions in TCM formulations

TCM formulations often involve interactions between herbs or with conventional drugs. Herb-drug interactions can influence pharmacokinetics through shared metabolic pathways involving enzymes like CYP450 and transporters like P-glycoprotein (P-gp). For example, *Schisandra chinensis* (Turcz.) Baill. regulates P-gp and other transporters, potentially affecting the bioavailability of co-administered drugs. Herb-herb interactions, on the other hand, may alter bioavailability synergistically or antagonistically. For instance, combinations like stilbene glucoside and emodin in Radix Polygoni Multiflori enhance absorption, while others may decrease it. Understanding these interactions is critical for ensuring safety and efficacy [85-88].

Health conditions and bioavailability

Chronic conditions like liver disease, diabetes, and stroke can significantly impact the bioavailability of TCM compounds. For example, liver injury alters drug metabolism, while diabetes can affect gastrointestinal absorption and renal clearance. These pathological states highlight the need to consider individual patient conditions when prescribing TCM formulations [89-95].

Physical and chemical modifications

Modifying the physical and chemical properties of natural products can enhance their bioavailability. Techniques such as particle size reduction and chemical derivatization improve solubility and absorption. For example, certain insoluble compounds can be made more bioavailable through nanotechnology-based modifications [96]. By addressing these factors and incorporating advanced quality control measures, the bioavailability of TCM formulations can be optimized to ensure consistent, safe, and effective therapeutic outcomes.

Strategies to improve the bioavailability of TCM

In the following subsections, various approaches designed to improve the bioavailability of TCM will be reviewed. Table 1 summarizes the advantages and disadvantages of various drug delivery systems employed in TCM formulations, highlighting their potential in enhancing bioavailability while addressing associated challenges.

Table 1 Advantages and disadvantages of drug delivery systems in TCM

Drug delivery system	Advantages	Disadvantages	Reference
Nano-suspensions	Improves solubility and dissolution rate; enhances drug absorption and bioavailability; allows for targeted delivery.	High production cost; potential stability issues; risk of particle aggregation.	[97]
Solid dispersions	Enhances drug solubility and bioavailability; prevents drug recrystallization; improves dissolution rate.	Requires careful selection of carriers; possible phase separation; thermal instability.	[98]
Phospholipid complexes	Enhances membrane permeability; improves oral bioavailability; bypasses first-pass metabolism.	Complex formulation process; potential stability issues during storage.	[99]
Cyclodextrin complexes	Increases water solubility; stabilizes active ingredients; enhances drug absorption.	May require high cyclodextrin concentration; potential toxicity concerns at high doses.	[100]
Liposomes	Biocompatible and biodegradable; enables targeted drug delivery; reduces systemic toxicity.	Expensive manufacturing process; limited stability; risk of drug leakage.	[101]
Lipid nanoparticles (SLNs/NLCs)	Improves drug stability and controlled release; high biocompatibility; protects drug from degradation.	Risk of particle aggregation; limited drug-loading capacity.	[102]
Polymeric micelles	Enhances solubility of hydrophobic drugs; improves drug stability; facilitates sustained release.	Possible cytotoxicity; potential instability under dilution conditions.	[103]
Microemulsions	Enhances drug solubility; increases bioavailability; provides thermodynamic stability.	Requires high surfactant concentration; limited drug-loading capacity.	[104]
Microneedles	Minimally invasive; enables transdermal drug delivery; reduces systemic side effects.	Limited drug load capacity; may cause irritation at the application site.	[105]
CPP (Cell-penetrating Peptides)	Enhances intracellular drug delivery; facilitates crossing of biological membranes.	Stability issues; potential off-target effects; needs optimization for efficiency.	[106]
Absorption enhancers	Improves drug transport across membranes; enhances bioavailability.	Potential for irritation or toxicity; variable effects depending on patient physiology.	[107]

Pre-processing

TCM often relies on complex pre-processing techniques to enhance the therapeutic properties of herbs. These techniques can involve processes like drying, slicing, and, importantly, fermentation [108].

Cheng et al. explored the impact of pre-processing on *Polygonatum cyrtonema* Hua, the study investigated the effects of solid-state fermentation by *Bacillus subtilis* on the polysaccharides derived from this TCM. Their study revealed that fermentation significantly altered the structure of the polysaccharides. This modification led to enhanced antioxidant activity and immune-boosting properties in in vivo models, suggesting improved bio accessibility and potential bioavailability of the fermented polysaccharides [108].

Processing methods also play a pivotal role in the pharmacokinetics and tissue distribution of bioactive compounds. Li et al. examined the effects of different ginseng processing techniques on the pharmacokinetics and tissue distribution of key ginsenosides (Rg1, Re, Rb1, and Rd) in rats. Their findings revealed that these methods significantly influenced the absorption and distribution of ginsenosides, with red ginseng extracts showing enhanced accumulation in vital organs such as the heart, lungs, and kidneys [109].

Furthermore, Yoo et al. compared the pharmacokinetics of red ginseng and black ginseng, focusing on the impact of their respective processing techniques. Black ginseng undergoes repeated steaming and drying, resulting in a higher concentration of low molecular weight ginsenosides, such as Rg3, Rg5, and Rk1. These compounds demonstrated superior absorption and systemic exposure compared to the high molecular weight ginsenosides prevalent in red ginseng. Consequently, black ginseng's unique processing method appears to enhance bioavailability and may offer greater therapeutic potential [110].

Micronization

Reducing the particle size of drugs, a process known as micronization, is a crucial technique for enhancing their bioavailability. This is particularly important for TCMs, where the absorption of bioactive compounds can be limited by their inherent properties. Figure 1 Provides a visual overview of common micronization methods. These techniques can be broadly categorized into top-down approaches, such as jet milling and high-pressure homogenization, where larger particles are physically broken down, and bottom-up approaches, like spray drying and controlled crystallization, where small particles are formed from a dissolved or dispersed state. Stabilizing agents are often necessary to prevent aggregation and maintain the stability of these newly created small particles.

Recent research has illuminated the significant impact of micronization on improving the bioavailability and therapeutic efficacy of various TCMs. For example, a study explored the effects of micronization on PN, a popular TCM in Asia. By reducing the particle size of PN powder to a range of 60 to 214 μm, researchers observed a marked improvement in its in vitro dissolution and in vivo pharmacokinetics. Notably, PN powder with a particle size of approximately 90 μm exhibited the most significant enhancement in absorption. Further optimization was achieved through hydrothermal treatment at 40 °C, which further boosted PN saponin release and bioavailability [111].

In another study, Zhang et al. [112] investigated the effects of particle size reduction on *Tetrastigma hemsleyanum* Diels & Gilg (TDG), another widely used TCM. Their meticulous analysis of physical properties, dissolution rates, antioxidant activity, and hepatoprotective properties revealed that micronization significantly enhanced the dissolution and bioavailability of key bioactive compounds in TDG. This led to improved antioxidant activity and liver protection in in vivo models.

Similar to the findings with PN and TDG, Liu et al. [113] tackled the issue of mangiferin's low oral bioavailability by employing supercritical antisolvent technology to produce mangiferin microparticles. This approach yielded spherical microparticles with significantly reduced particle size and crystallinity, resulting in a dramatic improvement in solubility and dissolution rate. Consequently, the oral bioavailability of mangiferin was more than doubled, accompanied by a substantial increase in antioxidant capacity, comparable to that of vitamin C.

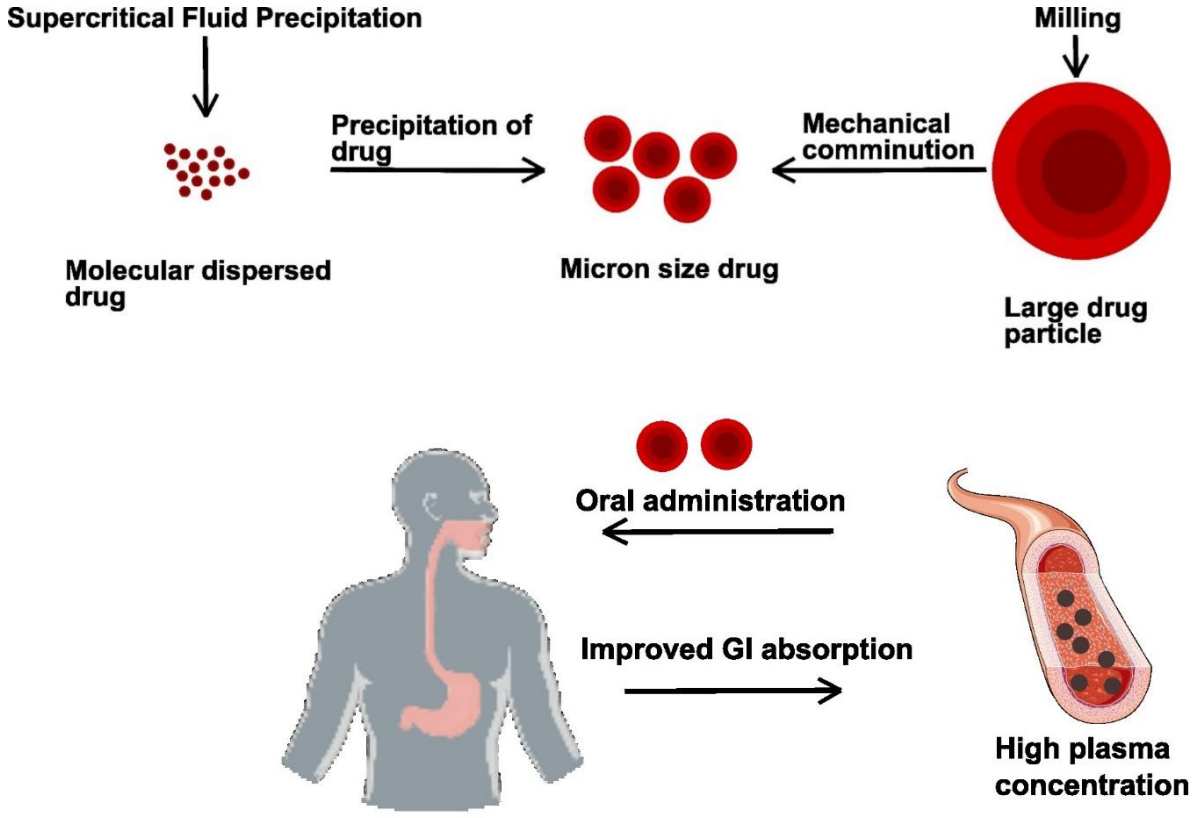

Figure 1 Illustration of the two principal methods for the production of a micron-size TCM drug

Solid dispersion

Solid dispersion technology is an effective strategy for enhancing the dissolution rate and bioavailability of poorly water-soluble drugs. This approach has evolved to incorporate advanced polymeric carriers and surfactants, improving drug solubility, stability, and wettability. Rather than focusing on historical classifications, current research prioritizes the application of solid dispersions in optimizing TCM formulations[114, 115].

As illustrated in Figure 2, the application of solid dispersion techniques has shown significant promise in TCM formulations. To address the poor solubility and bioavailability of Tanshinone IIA (TA), a key active compound in *Salvia miltiorrhiza* Bunge (Danshen), Luo et al. [116] investigated the use of sodium alginate (SA) as a carrier. SA, a biocompatible polymer, can suppress crystal growth, making it a suitable matrix for preparing TA solid dispersions (SDs). The researchers developed these TA-SA-SD formulations using a rapid one-pot method. Pharmacokinetic studies demonstrated that the solid dispersion formulations significantly improved the oral absorption and bioavailability of TA. Specifically, TA-SA-SD (1:6) and TA-SA-SD (1:8) exhibited relative bioavailability values 2.08-fold and 2.75-fold higher, respectively, compared to unmodified TA.

Liu et al. [117] tackled the challenge of improving the solubility and bioavailability of diosgenin (Dio), a TCM with promising therapeutic effects, including anti-tumor, anti-infective, and anti-allergic properties. However, Dio's poor aqueous solubility and low bioavailability have limited its wider application. To overcome these limitations, the researchers developed Soluplus-mediated Dio amorphous solid dispersions, leveraging Soluplus's ability to enhance solubility and inhibit crystallization. Pharmacokinetic studies in rats demonstrated that the bioavailability of the optimized Dio formulation was approximately five times higher than that of the unmodified drug.

To enhance the solubility, bioavailability, and therapeutic efficacy of baicalein, a flavonoid hindered by poor aqueous solubility and efflux mechanisms, Tong et al. [118] developed a solid dispersion formulation by incorporating PVP-VA64 as a polymeric carrier with d-α-tocopherol polyethylene glycol 1000 succinate (TPGS) as both a plasticizer and an efflux inhibitor. Pharmacokinetic assessments in rats demonstrated the superiority of this approach. The optimized baicalein solid dispersion exhibited a significantly higher Cmax and greater overall drug exposure, culminating in a 2.88-fold increase in bioavailability compared to raw baicalein. Furthermore, a reduced time to reach maximum concentration indicated more rapid absorption.

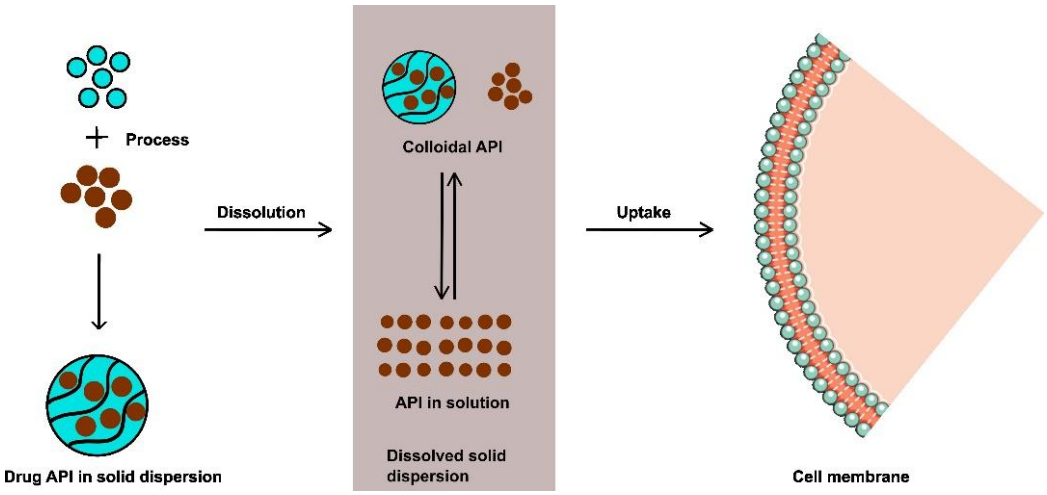

Figure 2 Illustration of solid dispersion technique in enhancing the aqueous solubility of poorly aqueous soluble TCM

Nanotechnology-based systems

Nano-suspensions

Nano-suspensions, colloidal dispersions of nanosized drug particles stabilized by surfactants, represent a pivotal advancement in pharmaceutical formulation. They constitute a biphasic system wherein pure drug particles disperse in an aqueous medium, each particle measuring less than 1 μm in diameter [119].

There are two main methods for producing nano-suspensions: top-down and bottom-up approaches. Top-down techniques, such as high-pressure homogenization and media milling, break down larger drug particles into nanometer-sized forms. These methods are widely used but require high energy inputs and careful material selection to avoid degradation. Bottom-up approaches, including precipitation and solvent evaporation, form nanoparticles from drug solutions, offering an alternative for heat-sensitive compounds [120].

Addressing the poor solubility of honokiol, a TCM with diverse pharmacological activities, researchers employed nano-suspensions prepared using bovine serum albumin and polyvinylpyrrolidone as stabilizers in a solvent precipitation-ultrasonication method. Importantly, analysis revealed that Honokiol existed in an amorphous state in the nano-suspensions, unlike in bulk Honokiol powder. In vivo studies in rats showcased a significant enhancement in oral bioavailability of Honokiol when administered as nano-suspensions, with a 3.94-fold increase in Cmax and a 2.2-fold increase in AUC(0-t). Intraperitoneal administration of Honokiol nano-suspensions demonstrated notable alteration in biodistribution, leading to substantially higher drug levels and tissue bioavailability in the blood, heart, and brain, potentially benefiting the treatment of cardio-cerebro-vascular diseases [121].

Hang et al. [122] developed herpetrione (HPE) nanosuspensions stabilized by glycyrrhizin (HPE NSs/GL) using wet media milling to enhance HPE's bioavailability and hepatoprotective effects. Compared to HPE coarse suspensions, HPE NSs/GL significantly improved drug dissolution and AUC. Additionally, HPE NSs/GL showed superior hepatoprotective effects by reducing serum ALT and AST levels and lowering hepatic IL-1β, IL-6, and TNF-α. These findings highlight the substantial potential of HPE NSs/GL in enhancing HPE's bioavailability.

Microemulsion

Microemulsions, consisting of two immiscible fluids, are transparent systems stabilized by a surfactant or a blend of surfactants, often with a co-surfactant.

Their classification whether water-in-oil, bicontinuous, or oil-in-water is determined by their microstructure, which is influenced by their physicochemical properties and ingredient proportions. These systems exhibit ultra-low interfacial tension between the immiscible phases and possess several advantages: spontaneous formation, thermodynamic stability, ease of production, high solubilization capacity for lipophilic, hydrophilic, and amphiphilic solutes, enhanced solubilization and bioavailability of hydrophobic drugs, a high surface

area-to-volume ratio facilitating mass transfer, and potential for enhancing permeation [123].

Zhang et al. [124] investigated the therapeutic potential of a volatile oil combination (CA-VO) derived from the TCM herbs *Ligusticum Chuanxiong* Hort. and *Angelica sinensis* (Oliv.) Diels for treating acute lung injury (ALI). To address the challenges of poor water solubility and low oral bioavailability, the researchers developed a CA-VO-loaded microemulsion. This formulation significantly improved the bioavailability of CA-VO, achieving more than a twofold increase compared to the unformulated oil. In ALI models, the formulation effectively reduced inflammation and enhanced lung function, highlighting its potential as a promising therapeutic approach for this serious condition.

Similarly, Zou et al. [125] aimed to enhance the solubility and bioavailability of Formononetin (FMN), a poorly soluble drug, by developing a microemulsion drug delivery system combined with nanocrystal technology. The in vivo studies demonstrated a remarkable increase in FMN bioavailability, with the formulation exhibiting a 5.5-fold improvement compared to the raw drug.

Zeng et al. [126] investigated enhancing hepatocellular carcinoma treatment by combining icaritin (IC) with coix seed oil. To maximize the therapeutic potential of this combination, they developed an icaritin-loaded microemulsion utilizing coix seed oil as the base. This formulation demonstrated synergistic anti-tumor activity against HepG2 cells, significantly outperforming the effects of either agent alone. The improved efficacy was attributed to enhanced apoptosis induction. Additionally, the microemulsion greatly increased IC bioavailability and promoted targeted liver accumulation. In vivo studies using a HepG2 xenograft mouse model further validated the superior anti-tumor performance of the formulation, highlighting its promise as an effective therapeutic strategy.

Polymeric micelles

Polymeric micelles, formed by amphiphilic block copolymers in aqueous solutions, represent self-assembled nanostructures. These micelles comprise a hydrophobic core and a hydrophilic shell. While the core facilitates the solubilizing of poorly water-soluble drugs, the shell stabilizes the micelles and prevents aggregation [127].

Shen et al. [128] tackled the challenge of improving the oral bioavailability of paeoniflorin (Pae), a promising natural compound with poor absorption. To address this, they developed a micelle-based drug delivery system using glycyrrhizic acid as a carrier. The in vivo experiments in rats demonstrated significantly enhanced intestinal permeability and a nearly fourfold increase in oral bioavailability compared to a conventional Pae solution.

Gu et al. [129] focused on improving the therapeutic efficacy of chrysophanol (CH), a natural compound with potential for treating chronic renal failure (CRF), by developing a micellar drug delivery system. Using a thin-film dispersion technique, they prepared chrysophanol-loaded micelles (CLM) with nano-sized particles and high encapsulation efficiency. This formulation significantly enhanced the dissolution rate and achieved a 3.4-fold increase in oral bioavailability compared to free CH. Additionally, CLM demonstrated improved kidney accumulation and superior renoprotective effects in a CRF rat model.

Shi et al. [130] enhanced the therapeutic potential of aloe emodin (AE), a natural compound with established anti-hyperuricemic activity but limited bioavailability. The researchers formulated AE-loaded mixed micelles using Soluplus® and glycyrrhizic acid, producing nanoparticles with improved solubility and high encapsulation efficiency. Pharmacokinetic studies revealed a threefold increase in oral bioavailability compared to free AE. Additionally, in a gouty arthritis rat model, the micellar formulation significantly reduced uric acid levels and inflammation.

Liposomes

Liposomes, serve as biocompatible and biodegradable carriers for drug delivery, efficiently encapsulating a range of substances, including low molecular weight drugs, peptides, proteins, and nucleic acids. Their ability to enhance solubility and protect bioactive molecules from degradation makes them ideal for improving TCM formulations [131].

Tang et al. [132] developed sodium deoxycholate-decorated liposomes to enhance the oral bioavailability of pueraria flavones (PF), a key component of Pueraria lobata used in traditional Chinese medicine for cardiovascular and cerebrovascular diseases. Pharmacokinetic evaluation demonstrated significant enhancements in PF bioavailability, with a 1.34-fold and 1.543-fold increase in AUC respectively, compared to free PF.

Wang et al. [133] developed a liposomal formulation of bisdemethoxycurcumin (BMC), a key component of turmeric with diverse therapeutic effects but limited clinical utility due to poor solubility and bioavailability. By conjugating BMC with TPGS, the researchers created liposomes that exhibited a 10-fold increase in oral bioavailability compared to free BMC and sustained drug release rates in both acidic and neutral environments. In vivo studies using potassium oxonate-induced hyperuricemic rats demonstrated that the liposomes significantly reduced serum uric acid levels by acting as a xanthine oxidase inhibitor.

Lin et al. [134] addressed the challenge of improving the therapeutic efficacy of butylidenephthalide (BP), an anticancer agent with poor bioavailability, for treating drug-resistant brain tumors. The researchers developed a cyclodextrin-encapsulated BP liposomal formulation designed to enhance bioavailability. In vivo intranasal administration of the liposomal formulation in nude mice with temozolomide-resistant glioblastoma multiforme resulted in a 10-fold increase in BP brain accumulation compared to oral delivery, as determined by liquid chromatography–mass spectrometry.

Lipid nanoparticles

Lipid nanoparticles, comprising lipids such as fats, oils, and waxes, have garnered considerable attention across various domains, notably in medicine, for their utility in drug delivery. These nanoparticles serve as protective carriers, encapsulating drugs to shield them from degradation and enabling targeted delivery within the body. This encapsulation enhances drug solubility and stability, improves bioavailability, and allows for controlled release kinetics [135].

Liu et al. [136] developed injectable psoralen polymer lipid nanoparticles to address the limitations of psoralen (PSO), a hydrophobic compound with potent anti-tumor activity against triple-negative breast cancer (TNBC). TNBC is the most aggressive subtype of breast cancer with limited treatment options and poor prognosis. The formulations were designed to enhance PSO solubility, improve bioavailability, and enable targeted drug delivery.

In vivo pharmacokinetic studies in rats revealed that the formulation significantly enhanced PSO bioavailability by increasing blood drug concentration and plasma protein binding rates compared to free PSO.

Li et al. [137] tackled the challenge of enhancing the therapeutic efficacy of andrographolide (ADG), a potent anti-cancer compound hindered by poor solubility and bioavailability. By encapsulating ADG within solid lipid nanoparticles, the researchers achieved a significant improvement in its bioavailability and anti-cancer activity. In vitro studies using a model of head and neck squamous cell carcinoma development demonstrated the superior performance of the formulation in inhibiting cancer cell growth at lower concentrations compared to free ADG.

Wei et al. [138] developed long-circulating solid lipid nanoparticles loaded with a curcumin derivative (CU1) to enhance its pharmacokinetic properties and anti-cancer efficacy against MHCC-97H liver cancer cells.

In vivo pharmacokinetic studies revealed that CU1 loaded nanoparticle formulation dramatically prolonged drug retention time and significantly increased bioavailability, with a 69.9-fold and 85.9-fold increase in the area under the curve (AUC) for curcumin and CU1, respectively, compared to free formulations.

Complexation-based systems

Cyclodextrin complex

Cyclodextrins are widely used as complexing agents to enhance the solubility, dissolution rate, and stability of poorly soluble drugs. Their unique molecular structure enables the encapsulation of hydrophobic

compounds within their cavities, improving drug bioavailability [139, 140].

Li et al. [141] explored the use of cyclodextrin inclusion complexes to enhance the solubility and bioavailability of Ginsenoside Re (G-Re), a bioactive compound with known therapeutic potential but limited water solubility. Among the different cyclodextrins tested, gamma cyclodextrin (γ-CD) proved most effective, forming a stable complex with G-Re. This complex exhibited a 9-fold increase in dissolution rate and a nearly 3-fold increase in peak blood concentration compared to free G-Re. Furthermore, the relative bioavailability of G-Re was significantly improved.

Zhu et al. [142] encapsulated antimalarial drug artemisinin (ART) within hydroxypropyl-β-cyclodextrin (HP-β-CD) and subsequently loading it into porous starch. This resulted in a significant increase in both drug loading and entrapment efficiency. The optimized formulation exhibited enhanced solubility and a remarkable improvement in bioavailability compared to both free ART and commercially available artemisinin-piperaquine tablets. Furthermore, the formulation demonstrated superior antimalarial activity both in vitro and in vivo.

Zeng et al. [143] sought to overcome the limitations of curcumin, a promising natural compound with potential anti-epileptic properties, by addressing its poor bioavailability. Researchers developed a curcumin-HP-β-CD inclusion complex using a simple solvent evaporation method. This resulted in a dramatic increase in curcumin solubility and a nearly threefold improvement in bioavailability. Importantly, brain concentrations of curcumin were enhanced by 38.7 times, leading to significantly greater anti-epileptic effects in preclinical models.

Phospholipid complex

Recently, there has been a preference for lipid-drug complexes as potential vehicles for drug delivery. These phospholipid complexes offer significant advantages such as ease of formulation development, high encapsulation efficiency, long-term stability, and scalability for industrial production [144].

Phospholipids form molecular complexes with TCM through weak hydrogen bonding or van der Waals interactions. These phospholipid complexes have been instrumental in enhancing the solubility of various poorly soluble molecules and aiding in the bypassing of first-pass metabolism by transporting drugs into the bloodstream through the lymphatic pathways [144-147].

Yu et al. [148] focused on enhancing the pulmonary delivery and therapeutic efficacy of icariin by developing an icariin-phospholipid complex (IPC). This formulation significantly improved bioavailability and sustained therapeutic effects. In a murine model of lipopolysaccharide (LPS)-induced acute lung injury, IPC demonstrated a 4.61-fold increase in lung tissue drug exposure and a 39.5-fold increase in immune cell drug concentration within the epithelial lining fluid. These results culminated in significantly prolonged and enhanced local anti-inflammatory effects compared to free icariin.

Forsythin, another TCM compound, faces challenges related to poor solubility and permeability, resulting in inadequate lung exposure. To address this, Wei et al. [149] developed a forsythin-phospholipid complex (FPC) to improve dissolution properties and lung affinity. The FPC demonstrated superior dissolution, cellular uptake, and lung targeting in vitro. In a murine model of LPS-induced acute lung injury, intratracheal administration of FPC resulted in a 39.6-fold increase in lung tissue drug exposure and a 198-fold increase in drug concentration within the epithelial lining fluid compared to intraperitoneal injection. Moreover, FPC instillation significantly outperformed both instilled forsythin and injected FPC in anti-inflammatory efficacy and survival rates, making it a promising strategy for treating acute respiratory distress syndrome.

Absorption enhancers

Absorption enhancers play a crucial role in enhancing the effectiveness of drugs by improving their absorption or bioavailability in the body [107]. These substances can increase membrane permeability, inhibit drug efflux pumps, or enhance solubility, especially for drugs with poor solubility or absorption. By using absorption enhancers, the therapeutic effect of a drug can be increased, potentially reducing the required dosage and minimizing side effects [150].

Bao et al. [151] tackled the challenge of enhancing the oral bioavailability of Hydroxy-safflower yellow A (HSYA), a promising cardioprotective compound with poor absorption. The researchers developed a composite formulation incorporating absorption enhancers to improve HSYA's transport across intestinal barriers. This study demonstrated enhanced cellular uptake and permeability in Caco-2 cell models. Furthermore, the composite effectively overcame energy-dependent and P-glycoprotein-mediated efflux mechanisms, leading to a significant improvement in HSYA's oral bioavailability.

Shao et al. [152] evaluated the role of borneol, a bioavailability enhancer known for modulating the BBB and inhibiting P-gp efflux, in improving the release profile and pharmacokinetics of a compound Danshen colon-specific osmotic pump capsule.

Pharmacokinetic studies in beagle dogs revealed that the inclusion of borneol in the formulation further enhanced the relative bioavailability of key compounds, including salvianolic acid B, tanshinone IIA, notoginsenoside R1, ginsenoside Rg1, and ginsenoside Re, exceeding the bioavailability achieved by standard tablet formulations.

Discussion: Current challenges and emerging perspectives

In today's fast-paced world, where medicine demands precision, efficacy, and adaptability, TCM stands at a crossroads. To stay relevant, it must overcome long-standing challenges like bioavailability enhancement, standardization, and global acceptance while embracing modern technological advancements. The good news? Emerging innovations are not just helping TCM catch up, they're giving it the tools to redefine itself as a scientifically validated, impactful therapeutic approach.

Let's face it: TCM's biggest hurdle has always been variability in bioavailability. Two patients can receive the same herbal formula, but with differences in sourcing, preparation methods, and active compound concentrations, the extent of systemic absorption and therapeutic outcomes can vary significantly. Add to that global skepticism about its scientific rigor, and it's clear why TCM struggles to break into mainstream medicine. To truly step onto the global stage, TCM needs consistent bioavailability optimization strategies, rigorous pharmacokinetic data, and universal standards.

Challenges in enhancing bioavailability in TCM

One of the most pressing challenges in optimizing bioavailability in TCM is variability in pharmacokinetics. Differences in herb sourcing, processing, and extraction methods lead to inconsistent absorption profiles. Unlike synthetic drugs, where pharmacokinetics can be tightly controlled, the bioavailability of TCM formulations varies significantly due to plant metabolism, enzymatic degradation, and complex multi-component interactions.

Another critical issue is limited solubility and permeability of active compounds. Many key TCM bioactives suffer from poor water solubility (e.g., flavonoids, alkaloids, terpenes), rapid metabolism, and low intestinal permeability, leading to suboptimal therapeutic effects. First-pass metabolism further reduces systemic exposure, particularly for oral formulations.

Scientific validation and standardization remain major barriers. Bridging traditional knowledge with pharmacokinetic modeling is essential for improving absorption profiles, yet few studies provide rigorous bioavailability assessments using validated methodologies such as PBPK (physiologically based pharmacokinetic) modeling.

Cutting-edge strategies to enhance bioavailability

Technology is rewriting the rulebook for TCM, opening doors to innovations that were unimaginable just a decade ago.

AI is at the forefront of this transformation, turning centuries of TCM knowledge into precision medicine. Algorithms analyze complex

datasets to pinpoint synergistic herb combinations, optimize formulations, and predict how well they'll be absorbed [153]. This streamlining ensures that what's on the label matches what's in the bottle, every single time. AI even enables virtual simulations of herb-drug interactions, significantly cutting down on trial-and-error processes [154].

Nanotechnology is another game-changer, revolutionizing how TCM compounds work in the body. Picture nanoparticles carrying herbal compounds directly to problem areas, whether inflamed lungs, tumors, or the gut. These tiny carriers enhance solubility, stability, and bioavailability while minimizing side effects [155]. Personalized nanoformulations tailored to individual patients make TCM treatments as unique as the people using them [156].

Another major breakthrough in targeted TCM delivery is the use of CPPs. CPPs have emerged as a powerful tool for intracellular drug delivery, addressing one of the major challenges in bioavailability [157]. While traditionally studied for their role in protein and nucleic acid transport, recent research has demonstrated their potential in enhancing the efficacy of TCM-derived therapeutics.

An example is IHP5, a tumor-targeting CPP derived from insulin-like growth factor binding proteins (IGFBPs). IHP5 exhibited 13-fold greater penetration than the classical TAT peptide in HeLa cells and selectively accumulated in cancer cells over normal human cells. When conjugated with trichosanthin (TCS), an active component of TCM, IHP5 enhanced TCS-mediated tumor cell killing by 19-fold without increasing cytotoxicity in normal cells. This study highlights the potential of tumor-targeted CPPs in precision TCM drug delivery applications [158].

Furthermore, in a separate study, a recombinant Cell-penetrating trichosanthin (rTCS-LMWP) was developed by fusing a CPP (LMWP) with trichosanthin to improve tumor penetration and intracellular delivery. The rTCS-LMWP formulation not only enhanced trichosanthin uptake but also synergized with anti-PD-1 checkpoint blockade therapy, leading to increased dendritic cell activation, macrophage repolarization, and enhanced T-cell-mediated immune responses in CT26 tumor-bearing mice [159].

These findings reinforce the critical role of CPPs in TCM bioavailability enhancement. Future research should focus on optimizing TCM-CPP conjugates for broader applications in oncology, neurodegenerative diseases, and inflammation-related disorders.

Beyond CPPs, self-orienting millimeter-scale applicators (SOMA), microneedles, and the RaniPill are emerging as next-generation drug delivery systems, providing minimally invasive yet highly effective alternatives for improving bioavailability in TCM formulations.

SOMA technology introduces a self-aligning drug delivery system designed to maximize absorption in the intestine. Unlike conventional oral formulations that face bioavailability limitations due to enzymatic degradation, SOMA automatically orients itself for optimal adhesion to the intestinal wall, allowing direct drug absorption into systemic circulation. This eliminates first-pass metabolism, a major barrier for many bioactive compounds in TCM. Current research suggests that SOMA could be a game-changer for delivering poorly soluble herbal extracts with improved pharmacokinetics [160].

Transdermal microneedle patches are another breakthrough that could revolutionize non-invasive TCM drug delivery. These tiny, painless needles penetrate the outer skin barrier, enabling direct systemic absorption of bioactive TCM compounds. Unlike traditional oral formulations, microneedles bypass gastrointestinal breakdown, enhancing bioavailability and prolonging drug circulation time. Recent studies have demonstrated the effectiveness of microneedle patches in delivering curcumin, resveratrol, and berberine,compounds known for their therapeutic potential but hindered by poor bioavailability [161].

RaniPill is a swallowable, robotic drug delivery capsule that allows for needle-free, painless subcutaneous drug delivery via the intestine. Upon reaching the small intestine, the pill automatically injects bioactive compounds through a dissolvable microneedle, ensuring direct absorption into systemic circulation without enzymatic degradation. This innovative system is currently under clinical evaluation for biologics and peptide-based drugs, but its application in TCM-derived bioactive compounds holds significant promise for oral formulations of traditionally injectable TCM treatments [162].

Beyond these advancements, lab-on-a-chip technology has introduced novel methodologies for evaluating TCM effects at the cellular level, offering a powerful tool for studying bioavailability. A recent study by Chen et al. developed a microfluidic chip-based hepatocyte model to assess emodin toxicity. This system seamlessly integrates HepG2 cells within a simulated microenvironment, utilizing rat tail collagen type I and gelatin to mimic physiological conditions, thereby enhancing the accuracy of toxicity and metabolic evaluations. With its favorable applicability in assessing emodin, this model provides a valuable platform and a promising in vitro tool for studying the metabolism and bioavailability of TCM active components [163].

Spatial transcriptomics is not only advancing our understanding of TCM pharmacology but also shaping its optimization for enhanced bioavailability. By mapping gene expression changes at a cellular level, this technology provides critical insights into how herbal formulations interact with specific tissues, aiding in the development of precision-targeted therapies. A recent study using single-nucleus RNA sequencing and spatial transcriptomics on Shexiang Baoxin Pill (SBP) provided mechanistic insights into its cardioprotective effects in myocardial ischemia-reperfusion. By identifying critical pathways related to endocardial angiogenesis and fibroblast regulation, these findings pave the way for optimizing SBP formulations to enhance its absorption, distribution, and therapeutic efficacy in cardiovascular applications [164].

Future directions in bioavailability enhancement

The future of TCM doesn't lie in replacing its roots with technology, it's in marrying ancient practices with modern innovations. Hybrid approaches like combining nanoformulations with absorption enhancers or using stimuli-responsive systems for precise drug delivery align TCM's holistic principles with the demands of precision medicine.

Emerging techniques such as microneedles, iontophoretic patches, and electroporation represent transformative advancements in TCM delivery, promising improved permeability, stability, and site-specific delivery. Additionally, CPPs offer potential for overcoming membrane permeability barriers, though stability optimization remains a key focus. By embracing these multidisciplinary collaborations, TCM can transcend cultural and scientific barriers. It has the opportunity not just to survive but to lead the way in integrating tradition with cutting-edge innovation.

The road ahead is clear: TCM must embrace multidisciplinary collaboration between scientists, clinicians, and technologists to fully realize its therapeutic potential. By leveraging modern innovations to enhance bioavailability, TCM can transition from traditional herbal medicine to a globally recognized, scientifically validated system of medicine.

Conclusion

The quest to enhance the bioavailability of TCM compounds represents a pivotal frontier in modern pharmaceutical research. Significant strides have been made through advanced delivery strategies such as nanoformulations and absorption enhancers, addressing challenges like poor solubility and limited absorption. Nanoformulations, including nanoparticles and liposomes, have shown promise in encapsulating TCM compounds, protecting them from degradation, and facilitating targeted delivery. These carriers enhance stability and therapeutic efficacy, though challenges like toxicity and complex production processes remain. Absorption enhancers, while effective in increasing membrane permeability and gastrointestinal absorption, require further research to mitigate concerns over long-term safety and variability. By integrating these innovations with robust quality control measures, these strategies not only improve bioavailability but also ensure consistency and safety, enabling reproducibility across applications.

Looking ahead, emerging techniques such as microneedles, iontophoretic patches, and electroporation represent transformative advancements in TCM delivery, promising improved permeability, stability, and site-specific delivery. Additionally, CPPs offer potential for overcoming membrane permeability barriers, though stability optimization remains a key focus. Future advancements in quality control, such as chromatographic fingerprinting and metabolomics, will play a vital role in standardizing and refining these innovative strategies. Collaborative efforts bridging traditional wisdom with modern science, including multi-omics approaches and AI-driven drug discovery, hold the potential to unlock new therapeutic possibilities. Continued research, rigorous preclinical studies, and innovative optimization efforts are essential to translate these advancements into clinical practice, ensuring improved patient outcomes and advancing the field of TCM pharmacotherapy.

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