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Acupoint drug delivery: An integrative strategy for multimorbidity treatment

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The rising prevalence of multimorbidity exposes the critical limitations of conventional single-disease treatment approaches. Multimorbidity involves complex pathological interactions across multiple organ systems, often generating conflicting therapeutic demands and necessitating a shift from isolated interventions toward integrated treatment strategies. Acupoints, characterized by unique microvascular networks and enriched neuroimmune components, function as dynamic bio-interfaces on the body surface. These specialized regions provide distinct pharmacokinetic advantages for drug delivery: they enhance drug permeability, enable targeted distribution, and can be engineered for sustained release through advanced formulation strategies. Recent studies have demonstrated that acupoint drug delivery systems, such as nanocomposite hydrogels, microneedle patches, and magnetically responsive implants, not only increase local drug concentration but also leverage the neuroimmune interface properties of acupoints to achieve systemic regulatory effects. This article synthesizes the microenvironmental advantages of acupoint drug delivery, advances in carrier platforms, and mechanisms for modulating multiple organ networks, proposing acupoint-targeted drug delivery as a novel integrative intervention approach for the treatment of multimorbidity.

INTRODUCTION

Multimorbidity, defined as the presence of two or more coexisting conditions in an individual, represents a growing global healthcare challenge with significant implications for patients, caregivers, and society.[1,2] In this context, the limitations of conventional single-target therapeutics are increasingly apparent, as such strategies are inherently unable to modulate the complex, interconnected pathological networks that underlie multimorbidity. For instance, patients with both type 2 diabetes and severe depression often encounter a clinical dilemma: antidiabetic drugs can exacerbate mood fluctuations, while antidepressants may disrupt metabolic control by affecting appetite and promoting weight gain. This multimorbidity highlights the inherent limitations of single-target therapies in addressing complex, multi-system dysfunctions. Furthermore, systemic administration of therapeutic agents frequently results in suboptimal bioavailability at target sites and unavoidable off-target toxicities, thereby complicating the treatment of patients with multiple comorbidities who already face polypharmacy challenges.

Acupoint-based drug delivery offers a paradigm shift from conventional systemic administration to localized, organ-specific therapeutic intervention. Rooted in traditional meridian theory, key acupoints (e.g., Neiguan (PC6), Zusanli (ST36)) serve as anatomical hubs linking to visceral systems (Figure 1A). Anatomical studies have shown that acupoints are sites of dense neurovascular convergence, characterized by increased microcirculatory blood flow, enriched sensory innervation, and unique lymphatic drainage patterns.[3] Leveraging these features, acupoint-based delivery via nanocarriers, hydrogels, or microneedles can establish localized drug depots for sustained release and targeted distribution, concomitantly activating endogenous neuroimmune regulatory networks to generate pharmaco-acupuncture synergy (Figure 1B). This method of administering drugs through acupoints enables the distribution of drugs to key physiological systems (such as the brain, heart, liver, and kidneys), thereby coordinating regulatory interactions among multiple systems to address the complex pathophysiological issues associated with multimorbidity (Figure 1C). This review synthesizes recent advances in acupoint drug delivery, focusing on the acupoint microenvironment for targeted delivery, carrier platforms enabling controlled delivery, and mechanisms underlying systemic multi-organ modulation. By integrating these insights, we propose acupoint-based drug delivery as a promising integrative strategy for multimorbidity management and discuss the future directions in advancing its clinical translation.

THE ACUPOINT MICROENVIRONMENT FOR TARGETED DRUG DELIVERY

The fundamental advantage of acupoint drug delivery lies in the specialized local microenvironment that facilitates targeted drug distribution and acts as a gateway for systemic regulation.[4] The uniqueness of this microenvironment is manifested in three interconnected characteristics:

(1) Enhanced Permeability: The high density of intercellular connections, increased capillary permeability, and unique extracellular matrix composition at acupoints facilitate superior transdermal drug penetration compared to surrounding skin.[5]

(2) Specificity: Structural and molecular heterogeneity across acupoints defines their organ-targeting therapeutic profiles. Anatomically, distinct acupoints differ in neurovascular bundle distribution, fascial structure, and local innervation patterns. For instance, ST36 is rich in Prokineticin Receptor 2 (PROKR2) sensory neurons and exhibits vagal–adrenal neural pathways that mediate gastrointestinal and metabolic regulation; PC6 features dense cardiac-related afferent fibers and specialized microvasculature for cardiovascular modulation. At the molecular level, acupoints exhibit differential expression of transient receptor potential vanilloid-1 (TRPV1), acid sensing ion channel subunit 3 (ASIC3), adenosine receptors, and cytokine receptors, which govern site-specific drug–target interactions and signal transduction. These unique anatomical and molecular signatures establish the acupoint–organ axis that underlies selective drug targeting and organ-specific regulation.

(3) Depot Functionality: The dense connective tissue and fascial layers at acupoints enable sustained retention of injected or implanted drug delivery systems, creating localized "drug reservoirs" that enable controlled release over extended periods.

These characteristics jointly constitute the structural and functional basis for acupoints in drug delivery and systemic regulation.[6] Pharmacokinetic studies have demonstrated that acupoints exhibit significantly higher drug delivery efficiency compared to non-acupoint skin regions.[7] For example, research quantifying aminophylline transdermal absorption demonstrated that acupoints such as "Feishu" (BL13), "Geshu" (BL17), and "Danzhong" (CV17) exhibit drug delivery coefficients substantially higher than those in non-acupoint areas, with different acupoints displaying distinct delivery characteristics.[6] These pharmacokinetic characteristics provide a scientific basis for targeted drug administration.

DIVERSE ACUPOINT DRUG DELIVERY PLATFORMS FOR MULTIMORBIDITY MANAGEMENT

The acupoint microenvironment serves as an optimal substrate for diverse advanced drug delivery modalities. Among these, injectable nanocomposite

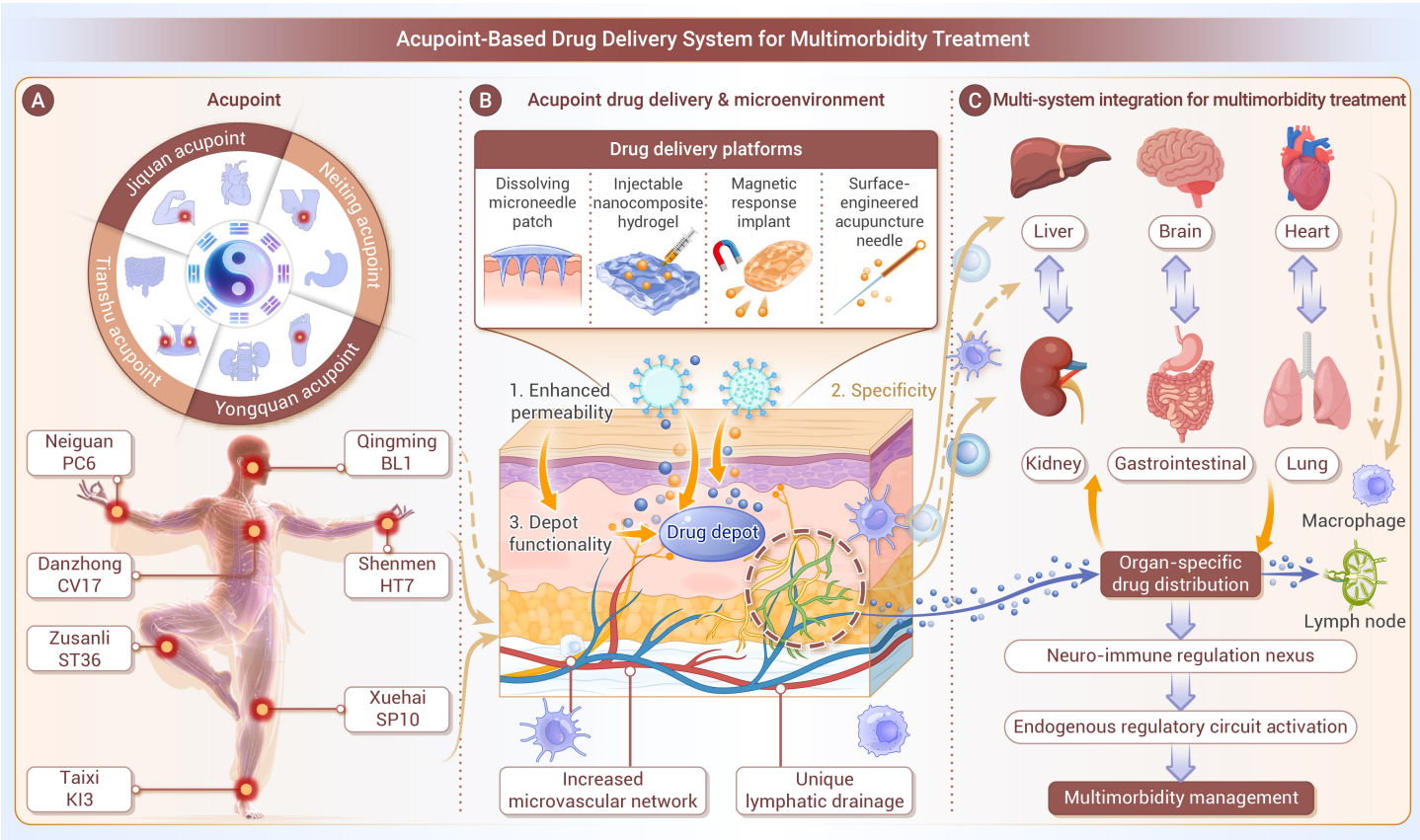

Figure 1. Schematic diagram of an acupoint-based drug delivery system for multimorbidity treatment (A) Distribution of key acupoints and their corresponding target organs. (B) Existing acupoint-based drug delivery approaches and their core mechanisms of action. (C) Multi-organ targeted drug delivery mediated by acupoints for synergistic treatment of multimorbidity.

hydrogels represent a strategy that integrates pharmacological effects with acupoint-specific stimulation for multimorbidity management, a concept termed pharmaco-acupuncture synergy. For example, Ren et al. developed an acupoint-targeted nanocomposite hydrogel (TP@HSA NPs) co-delivering triptolide and 2-Chloro-N^6-cyclopentyladenosine (CCPA), achieving simultaneous anti-inflammatory, analgesic, and acupuncture-mimetic effects. Acupoint administration enhanced mechanical and thermal pain thresholds by 4.9- and 1.6-fold compared with non-acupoint sites. Notably, acupoint administration increased the accumulation of the nanomedicine in arthritic paws, with a 13.5% increase observed at 48 h compared with non-acupoint administration, which may account for the better therapeutic efficacy and reduced toxicity.[7]

Beyond hydrogels, emerging modalities offer complementary advantages for multimorbidity treatment. Dissolving microneedles enable minimally invasive transdermal delivery at acupoints, enhancing patient compliance for chronic inflammatory mutimorbidities requiring frequent administration.[8] Magnetic-responsive implants enable on-demand drug release in response to physical stimulation, addressing both neuropathic pain and systemic inflammation in pain-inflammation multimorbidity.[9] Surface-engineered acupuncture needles integrate traditional stimulation with localized drug delivery, providing precise intervention for articular disorders and their associated systemic mutimorbidities.[10] These diversified platforms allow the customization of acupoint interventions to distinct pathological dimensions of mutimorbidities (inflammation, neural injury, metabolic dysregulation, and impaired tissue repair), establishing the technological foundation for integrative acupoint pharmacotherapy.

NETWORK REGULATION: THE INTEGRATIVE MECHANISM OF ACUPOINT DRUG DELIVERY FOR MULTISYSTEM MULTIMORBIDITY

How does local acupoint drug delivery translate into the regulation of distant organs and systemic mutimorbidities? The answer lies in the convergence of enhanced local pharmacokinetics, targeted distribution through neurovascular networks, and activation of endogenous regulatory circuits.

At the pharmacokinetic level, acupoint administration alters drug biodistribution. Acupoint injection of nanocomposite hydrogels results in distinct biological distribution compared to conventional routes, as the unique lymphatic drainage and vascular connectivity of acupoints facilitate preferential drug accumulation in target organs connected through somatotopic neural circuits. This "acupoint-target organ" axis enables organ-specific drug delivery while minimizing systemic exposure.

At the neural pathway level, acupoints are dense convergence areas of nerve fibers, capillaries, and deep fascia. In the deep fascia of limb acupoints (such as ST36), abundant PROKR2-expressing sensory neurons form a specific afferent gateway for transmitting somatic signals to the central nervous system. Crucially, the enhanced microcirculatory oscillation and increased mean blood flow at acupoint regions facilitate accelerated drug absorption into systemic circulation and lymphatic drainage, while the dense neurovascular network enables targeted conduit effects on specific organs through established somatotopic neural connections. When combined with drug delivery, local release of neuromodulatory agents (such as CCPA) can potentiate these neural pathways, creating "chemical–neural" synergistic activation. For instance, acupoint delivery of adenosine receptor agonists can amplify the vagal-adrenal anti-inflammatory reflex, while simultaneously providing local analgesia.

At the immunoregulatory level, the vagus–adrenal axis activates catecholamine release to inhibit macrophage pro-inflammatory factors, while drug carriers and their therapeutic agents interact with local immune sentinels, promoting antigen-presenting cell migration to lymph nodes and establishing "acupoint–lymph node" immune regulation. This local initiation, systemic dissemination model makes acupoints an ideal target for regulating inflammatory multimorbidity through localized drug delivery.

At the tissue repair level, acupoint delivery of regenerative agents bridges localized pharmacotherapy with systemic regenerative processes. For example, acupoint injection of stem cell-laden hydrogel microspheres accelerates wound healing by modulating local immune responses and promoting tissue remodeling. This convergence of acupoint stimulation with cellular and biomaterial therapies exemplifies the potential of integrated regenerative

medicine approaches.

Collectively, acupoint-targeted drug delivery establishes a distinct "pharmaco-neuro-immune" regulatory nexus. By leveraging the acupoint microenvironment and neurovascular networks, drug carriers achieve organ-specific targeted distribution and sustained release; concomitantly, activation of neural reflex circuits initiates multilevel responses, including immunity, endocrine function, metabolism, and tissue repair, thereby enabling integrated regulation of multi-system dysfunctions. For instance, in diabetes mellitus complicated with cardiovascular disease, electroacupuncture at PC6 and ST36 activates the PI3K/Akt/eNOS, AMPK/PGC-1α, and inhibits NF-κB pathways to improve vascular function, glucose/lipid metabolism, and suppress inflammation. In trigeminal neuralgia complicated with anxiety and depression, electroacupuncture at Baihui (DU20) and ST36 exerts frequency-specific effects: high-frequency stimulation relieves pain, whereas low-frequency stimulation ameliorates mood disturbances, with DU20 demonstrating superior regulation of brain circuits, including the ventral tegmental area. These examples provide a mechanistic foundation for applying acupoint drug delivery to the treatment of multimorbidity. However, specific acupoint–carrier–drug combinations for these multimorbidity phenotypes remain unexplored, representing a key direction for future research.

CONCLUSION AND OUTLOOK

Acupoint-targeted drug delivery represents a synergistic integration of traditional medicine knowledge and modern pharmaceutical technology. Insights into acupoint-specific pharmacokinetics and the neuroimmune interface have established a foundation for its application in the regulation of multiple system diseases. The development of precision carrier technologies, including nanocomposite hydrogels, dissolving microneedles, and magnetically responsive implants, enables controlled release, targeted distribution, and reduced systemic toxicity, positioning acupoint pharmacotherapy as a promising intervention strategy for managing mutimorbidity.

Translational challenges for clinical applications

Despite its potential, several critical challenges must be addressed to enable clinical translation. Fewer than ten acupoints have been rigorously investigated for drug delivery optimization, and the optimal combinations of acupoint, carrier, and drug for specific comorbidity profiles remain undefined. The dose-response relationship requires systematic quantification, as the mathematical relationships linking carrier formulation, stimulation parameters, and therapeutic outcomes have yet to be established. Additionally, individual variability in acupoint drug absorption, including genetic background, sex, skin condition, and disease status, remains poorly understood. Furthermore, formulation stability and batch-to-batch reproducibility of nanocarriers, hydrogels, and microneedles are insufficient for scalable Good Manufacturing Practice (GMP) production. Finally, comprehensive safety assessments, clear regulatory pathways for product classification, and rigorous clinical trial frameworks adapted to multimorbidity remain absent for validating efficacy, safety, and reliability.

Future directions

Progress will require concerted efforts along four interconnected avenues:

(1) Predictive models linking multimorbidity subtypes to optimal acupoint-carrier-drug combinations should be developed by integrating clinical pharmacokinetic data with multi-omics analyses and machine learning, thereby enabling a transition from empirical selection to data-driven precision.

(2) Intelligent closed-loop acupoint delivery systems, enabled by advances in flexible electronics, micro-nano sensors, and implantable microfluidics, should be engineered to monitor local drug concentrations and physiological responses in real time, thereby allowing on-demand parameter adjustment.

(3) Mechanism-based clinical validation should be pursued through N-of-1 trials to generate individual-level pharmacokinetic and efficacy data, and through adaptive platform trials targeting specific multimorbidity subtypes, with both approaches grounded in explicit mechanistic hypotheses regarding drug–neuroimmune interactions.

(4) Acupoint–drug synergy modalities should be developed using injectable, smart-responsive materials that release anti-inflammatory, neurotrophic, or metabolic regulatory factors in response to local microenvironmental cues, thereby achieving spatiotemporal coordination between targeted delivery and endogenous regulatory mechanisms.

Integrating acupoints with pharmaceuticals shows potential for the treatment of complex diseases. This strategy combines localized, targeted drug delivery with acupoint-triggered neuroimmune modulation, offering the potential for enhanced therapeutic efficacy in the management of multimorbidity. By mapping acupoint–pharmacokinetic functional landscapes, developing intelligent delivery systems, conducting mechanism-based clinical validation, and pioneering smart acupoint–drug coupling platforms, this strategy has the potential to transform the heritage of Eastern medicine into an effective approach for managing multimorbidity.

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AUTHOR CONTRIBUTIONS

X. C. and R. X. contributed equally to this paper. X.C. and R.X. wrote and supervised the original manuscript. X.C. and X.C. edited the manuscript. T.Y. revised and edited the manuscript. Q.Z. proposed the concept, revised, and edited the manuscript. All authors contributed to the article and approved the submitted version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable.

DATA AND CODE AVAILABILITY

Not applicable.