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Review

Exosomes, a potential approach to enhance the therapeutic effects of traditional Chinese medicine

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ABSTRACT

Traditional Chinese medicine (TCM) exerts unique therapeutic effects, while some unfavorable physicochemical properties limit its therapeutic potential. Exosomes are involved in cellular communication and may enhance the efficacy of TCM. The relationship between TCM and exosomes is supported by the connection between exosomes and the theory of "Qi, Xue and Ye" (one of the basic theories of TCM). Also, the functional resemblance between exosomes and Qi, which is less researched. We fill this gap by systematically summarizing exosomes from different sources with therapeutic effects and exploring the mechanisms and implications of exosomes in TCM treatment. TCM and exosomes undergo two-way communication, with TCM affecting exosomes and exosomes loading TCM monomers. The dual roles of exosomes as destructive agents in disease development are also emphasized; current obstacles and future scope of TCM–exosome therapeutic strategies are fully discussed. The objective of this review is to stimulate further investigation and create a new application of TCM.

Introduction

Traditional Chinese medicine (TCM) is applied to enhance the physiological functions or treat pathological conditions of the organism, guided by the basic theory of TCM. TCM plays unique therapeutic roles in treating complex diseases with the characteristics of multi-components, multi-targets, multi-pathways, and multi-effects [1]. With the development of network pharmacology and omics sequencing, a better understanding of the multi-pathway therapeutic properties of TCM and subtypes of diseases has been gained, and the clinical application of TCM is more promising [2]. However, the physicochemical properties of TCM limit its therapeutic effects, including low stability and weak targeting ability [3].

Exosomes are 40–160 nm extracellular vesicles of endosomal origin that are secreted from almost all eukaryotic cells and distributed in nearly all body fluids, including peripheral blood and breast milk [4]. The biological functions of exosomes have been continuously revealed, indicating an important bridge for intercellular information exchanging and material transfering [5]. Notably, the phospholipid bilayer structure of exosomes forms a protective barrier that shields loaded TCM bioactive compounds from harsh gastrointestinal pH conditions and enzymatic degradation in circulation, while their membrane properties facilitate efficient cellular uptake, thereby enhancing delivery efficiency [6].

There is some degree of commonality between exosomes and TCM theory, including Qi (dynamic functional process), Xue (circulatory-nutritive system) and Ye (body fluid systems) that originated from the Yellow Emperor's Classic of Internal Medicine [7]. Qi is conceptualized not as a discrete material substance or a measurable form of energy, but as a dynamic functional process beyond its literal association with air, functioning as the integrative force underlying physiological transmission and regulatory activities throughout the organism [8]. Xue circulates within the vascular system as the primary nutritive medium to nourish the organism [9]. Ye to be the general term for all the normal water and fluids in the organism. They are intermingled and liaise with each other to maintain the health of the organism [10, 11]. The material properties described in TCM concepts exhibit notable parallels with contemporary biomedical descriptions of exosomes. Exosomes, widely spread in blood and fluids, significantly affect biological function. Adipose tissue-released exosomes, as the major source of circulating exosomes, have been shown to carry miRNAs that alert brain-adipose crosstalk [12]. This long-distance crosstalk and cargo-transport capacity suggest that exosomes can exert regulatory effects beyond their cellular origin. This functional capacity of exosomes bears similarity to Qi [13]. Further, exosomes may also act as a material basis for interpreting some effects attributed to Qi [14]. This may shed more light on the potential relevance of exosomes to TCM. We propose that exosomes are circulating bioactive carriers present in Xue and Ye, and diffuse between individual cells by interacting in ways similar to Qi, thus helping maintain the homeostatic balance of the whole.

Interestingly, TCM shapes exosome-mediated intercellular and microenvironmental communications through regulating exosome biogenesis, secretion, and cargo [15, 16]. Exosomes encapsulate TCM bioactive compounds, and then their natural nanoparticle properties regulate complex signaling networks [17]. This two-way interaction offers an integrative perspective to explore

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the complex mechanisms of the clinical treatment process of TCM.

This review focuses specifically on clarifying the TCM-exosomes' bidirectional interaction. We examine exosomal structure, noncoding RNAs, properties, therapeutic effects, and interactions with TCM. The relationship between TCM and exosomes allows us to further clarify the mechanism of exosomes in the therapeutic application of TCM. The negative roles of exosomes, challenges and future perspectives of exosome-based TCM strategies are also summarized. As research and technology progress deeper, the bidirectional interaction of TCM-exosomes is expected to bring more opportunities for the clinical application of TCM.

1. The structure, noncoding RNAs, and properties of exosomes

Exosomes, nanoscale extracellular vesicles, are characterized by a cup-shaped structure composed of lipid bilayers. The surface biomarkers of exosomes include tetraspanins (CD63, CD9, CD81), heat shock proteins (HSP70, HSP90), fusion-related proteins, and Ras-associated binding (RAB) proteins. Exosomes serve as a medium for intercellular communication, involving in cellular communication and signal transduction processes [18].

Exosomes carry a variety of substances such as lipids, functional proteins, and nucleic acids, among which noncoding RNAs (ncRNAs) play a significant role in modulating intercellular communication [19]. NcRNAs mainly include miRNAs, long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), regulating gene expression at transcriptional, post-transcriptional, and translational levels [20]. Accumulated evidence indicates that the therapeutic effects of TCM are achieved partly by modulating exosome-carried ncRNAs, especially miRNAs [21–23].

MiRNAs, short RNAs of 21–23 nucleotides in length, combine with assembly proteins to form the miRNA-induced silencing complex (miRISC) and then silence their target gene by binding to the mRNA 3′ untranslated region, leading to inhibition of translation or mRNA degradation [24]. A single miRNA can bind to multiple mRNAs, and each mRNA with a 3' UTR can be regulated by numerous miRNAs [25, 26]. MiRNAs are regulators in essentially all biological processes, including apoptosis and angiogenesis, and are involved in various diseases, including cancer [24].

LncRNAs are a set of ncRNAs over 200 nucleotides in length, which can be transcribed but do not encode proteins and have regulatory roles in biological processes, including the regulation of cell proliferation, migration, inflammation, apoptosis, and autophagy [27]. LncRNAs can be protected and delivered by exosomes to exert various functions, including sponging miRNAs, regulating transcription and the stability of mRNAs, and interacting with proteins [20, 24, 27].

CircRNAs, a subclass of ncRNA with higher stability than linear RNA, are generated through exon skipping or back-splicing with the ability to modulate the transcription of their parental genes and even be translated into proteins [26]. CircRNAs are involved in many biological processes, including apoptosis and metastasis, and act as significant biomarkers and therapeutic targets in human diseases. CircRNAs can also affect the stability of lncRNAs and mRNA [28]. Furthermore, both lncRNAs and circRNAs can act as miRNA sponges, and their expression is regulated by the binding of transcription factors to their promoters [29, 30]. Collectively, these ncRNAs form an lncRNA/circRNA-miRNA-mRNA competing endogenous RNA (ceRNA) network, and further create a more intricate closed-loop network with transcription factors (Fig. 1).

Exosomes retain the membrane structure of the parental cells, and the nanoscale lipid bilayer structure allows them to penetrate biological barriers [31]. The vesicular structure of natural origin makes them stable and biocompatible, and the lipids and adhesion molecules ensure their natural targeting ability based on donor cells [32]. Exosomes from different sources have different compositions, reflecting their parental cell origin, which underpins the functional diversity of the cargos they carry [33].

Exosomes, owing to their diverse bioactive constituents, particularly ncRNAs, serve as important mediators of intercellular communication and represent promising targets for regulation by TCM. Meanwhile, the structure of exosomes confers pharmaceutically favorable properties such as biostability, biocompatibility, and low immunogenicity, which enable exosomes to be a potential TCM delivering pathway to target tissue.

2. The therapeutic effects of different source-derived exosomes and their interactions with TCM

Exosomes, nanoscale vesicles carrying heterogeneous bioactive contents, exhibit functional diversity determined by their parental cells [18]. Such heterogeneity may affect TCM-exosome interactions and mediate different therapeutic mechanisms in different diseases. Mesenchymal stem cells (MSCs), macrophages, endothelial cells (ECs), and astrocytes are implicated in tissue repair, immune modulation, angiogenesis, and neuroprotection, which are crucial to disease pathogenesis and therapy [34–37]. Therefore, we focus on exosomes derived from these cells to evaluate not only their intrinsic therapeutic effects but also their interactions with TCM. Interest has also grown in the use of plant- and herb-derived exosome-like nanoparticles (ELNs) as novel therapeutics. Moreover, we summarize other exosomes derived from non-autologous biological fluids, such as blood and milk, to broaden this section (Table 1 and Fig. 2).

2.1. MSC-derived exosomes

MSCs and their exosomes can modulate the immune response and induce tissue regeneration [38]. Adipose tissue-derived MSC (AD-MSC) exosomes promote mouse skeletal muscle regeneration (SMR) by upregulating the expression of myogenic differentiation (MYOD) and myogenin (MYOG) and enhancing the proliferation of satellite cells [39]. Bone marrow-derived MSC (BM-MSC) exosomes are capable of suppressing pancreatic cancer (PC) cell proliferation, migration, and invasion through their content of miR-1231, and decreasing of miR-1231 in circulating exosomes of PC patients was observed [40]. Human umbilical cord-derived MSC (Huc-MSC) exosomes release miR-129-5p, alleviating inflammatory bowel disease (IBD) through inhibiting ferroptosis and lipid peroxidation, with ACSL4 identified as a downstream target [41].

TCM interventions can positively change the properties of MSC-derived exosomes. For instance, GuiLu-ErXian Glue (GLEXG) and Artemisia argyi (mugwort, AA) enhance MSC-derived exosome release and yield [16, 42]. AA also increases exosome size and inhibits the NF-κB pathway, showing anti-inflammatory and antioxidant effects. DanShen Decoction (DSD) and Danshensu (DSS), which is a monomer of DSD that comes from *Salvia miltiorrhiza* (Danshen, SM), modulate miRNAs in MSC-derived exosomes. DSD upregulates miR-93-5p and subsequently ameliorates myocardial ischemia/reperfusion injury (MI/RI) by suppressing the TXNIP/NLRP3/Caspase-1 pathway [43]. Besides, DSS elevates miR-27a-5p to counteract peritoneal fibrosis (PF) *via* inhibiting STAT3/HIF-1α/VEGF signaling [44]. Loading schisandrol A into MSC-derived exosomes enhances diabetic wound healing (DWH) through modulating the FTO/miR-21/WNT5A pathway [45].

2.2. Macrophage-derived exosomes

Macrophages, playing a crucial role in the development and maintenance of homeostasis, polarize into pro-inflammatory M1

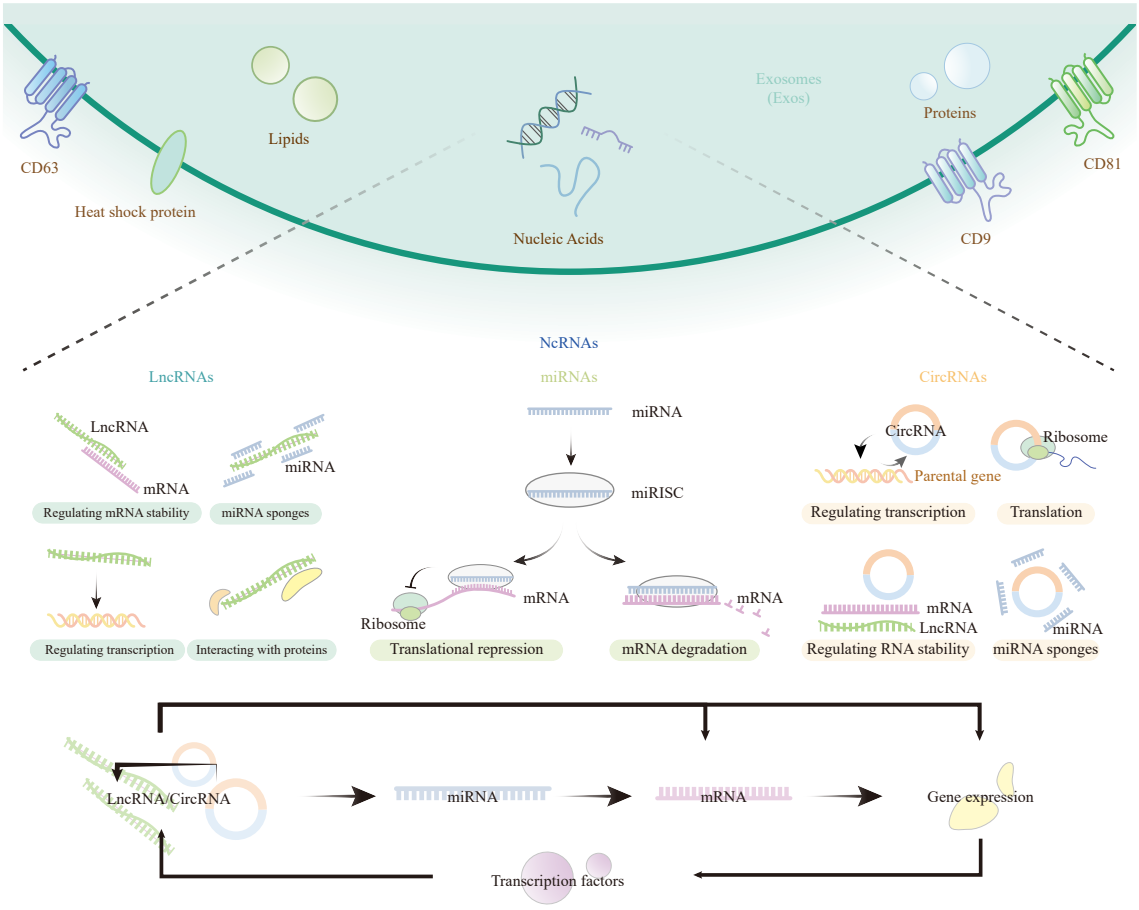


Fig. 1 The functions and interactions of major noncoding RNAs in exosomes. Notes: the noncoding RNAs (ncRNAs) in exosomes mainly include microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs). LncRNAs can regulate mRNA stability, sponge miRNAs, regulate transcription, and interact with proteins. Mature miRNAs bind assembly proteins to form the miRNA-induced silencing complex (miRISC), leading to either translation inhibition or mRNA degradation. The functions of circRNAs include regulating transcription and translation, regulating RNA stability, and sponging miRNAs. Transcription factors can both regulate the expression of ncRNAs and be regulated by ncRNAs. These ncRNAs form an lncRNA/circRNA-miRNA-mRNA competing endogenous RNA (ceRNA) network and further create a more intricate closed-loop gene regulatory network with transcription factors.

or anti-inflammatory M2 phenotypes in different tissue microenvironments [46]. Different phenotypes of macrophage-derived exosomes exhibit distinct functions in cancer, infectious diseases, tissue fibrosis, and chronic inflammatory diseases [47, 48]. M1-type macrophage-derived exosomes deliver miR-628-5p to downregulate the circFUT8/miR-552-3p/CHMP4B pathway and suppress hepatocellular carcinoma (HCC) [49]. Contrary to this, M2-type macrophage-derived exosomes promote diabetic fracture healing by shifting macrophages from the M1 to M2 phenotype, creating an anti-inflammatory osteoimmune microenvironment [50]. They also contribute to immune modulation *via* PI3K/AKT, yet their active components remain unknown. Apart from that, M2-type macrophage-derived exosomes relieve rat MI/RI *via* the delivery of miR-148a that targets thioredoxin-interacting protein (TXNIP) and thus inactivates the TLR4/NF-κB/NLRP3 signaling pathway [51]. It has been shown that exosomes from macrophages contribute to immune modulation. The variations in macrophage phenotype thereby cause variations in exosomal composition and downstream effects.

Especially, recent studies show that TCM can regulate macrophage polarization and reshape the cargo of macrophage-derived exosomes to mediate intercellular communication. Jiedu Yangxin Decoction (JDYXD) promotes M2 macrophage polarization and enriches miR-23b-3p in macrophage-derived exosomes, which subsequently inhibit Smad3 signaling in ECs and suppress endothelial-to-mesenchymal transition (EndMT) and post-infarction fibrosis [52]. Similarly, Yi-Shen-Hua-Shi (YSHS) Granule inhibits M1 macrophage polarization and reduces the level of miR-21a-5p in exosomes, which alleviates podocyte injury and delays the progression of diabetic nephropathy (DN) [53]. Protocatechuic acid (PCA) upregulates miR-10 in efferocytic macrophage-derived exosomes, thereby inhibiting endothelial inflammation via suppression of the MAP3K7/β-TrCP/NF-κB pathway [54].

2.3. EC-derived exosomes

Exosomes released from ECs can facilitate angiogenesis, axonal regeneration, and wound healing (WH), while also exerting neuroprotective effects, including protection against ischemic stroke (IS) [55, 56]. Hypoxic EC-derived exosomes deliver lncHAR1B, which binds the transcription factor basic helix-loop-helix family member e23 (BHLHE23) to promote KLF4 expression, shifting macrophages toward to an M2 phenotype and accelerating DWH through enhanced angiogenesis [57]. EC-derived exosomes also regulate Schwann cell repair phenotypes *via* miR-199-5p delivery, activating PI3K/AKT/PTEN signaling to support axonal regeneration and angiogenesis in peripheral nerve injury (PNI) [58]. Endothelial progenitor cell (EPC)-derived exosomes contribute to DWH through miR-182-5p, which targets the PPARG 3′ UTR to suppress PPAR expression [59], and decrease neuronal apoptosis in HT22 cells through targeting Bcl2l11 *via* miR-221-3p [60].

EC-derived exosomes regulate vascular homeostasis and intercellular communication, and TCM can further shape their cargo and signaling output. Astragaloside IV (ASIV) promotes EPC-derived exosomal miR-21 secretion, which induces autophagy and inhibits apoptosis in high-glucose-damaged ECs *via* the miR-

Table 1 The therapeutic effects of different source-derived exosomes and their interactions with TCM.

Source type	Source detail	Pathological Condition	Key content	Mechanism	Relevance to TCM
MSC	AD-MSC [39]	SMR	-	Upregulate the expression of MYOD and MYOG	AA [15]; GLEXG [42]; DSD [43]; DSS [44]; Schisandrol A [45]
	BM-MSC [40]	PC	miR-1231	Inhibit the proliferation, migration, invasion, and adhesion of PC cells	
	Huc-MSC [41]	IBD	miR-129-5p	Inhibit lipid peroxidation and ferroptosis by targeting ACSL4	
Macrophage	THP-1 cell (M1-type) [49]	HCC	miR-628-5p	Inhibit the m6A modification of circFUT8, and the circFUT8/miR-552-3p/CHMP4B pathway	JDYXD [52]; YSHS [53]; PCA [54]
	BMDM (M2-type) [50]	Diabetic fracture healing	-	Activate the PI3K/AKT pathway	
	Peritoneal Macrophage (M2-type) [51]	MI/RI	miR-148a	Inhibit the expression of TXNIP, and the TLR4/NF-κb/NLRP3 pathway	
EC	HUVEC [57, 58]	DWH	LncHAR1B	Upregulate the BHLHE23/KLF4 axis	ASIV [61]; Chrysin [62]; CUR [63]
		PNI	miR-199-5p	Activate the PI3K/AKT/PTEN pathway	
	EPC [59, 60]	DWH	miR-182-5p	Inhibit the expression of PPARG	
		Neuronal apoptosis	miR-221-3p	Inhibit the expression of Bcl2l11	
Astrocyte	1321N1cell and Primary astrocyte [66]	OS	Apo D	Mitigate oxidative damage	Ber [70]; SIN [71]; ZXBZD [72]; BYHWD [73]
	Primary astrocyte [67–69]	IS	miR-378a-5p	Inhibit the expression of NLRP3	
		PND	miR-26a-5p	Upregulate the AKT/GSK3-β/CRMP2 pathway through NCAM	
		TBI	LncRNA4933431K23Rik	Sponge miR-10a-5p to upregulate E2F7 and TFAP2C, thereby increasing Smad7 expression.	
Plant and herb	IG [76]	OS-induced cellular dysfunction	-	Inhibit the p38/JNK MAPK pathway	-
	ZO [78]	PD		Inhibit the NF-κB pathway	
	ACap [79]	NAFLD		Inhibit the NF-κB pathway	
	PoC [80]	MAFLD		Inhibit the NLRP3 inflammasome pathway	
	PT [81]	LC		Activate the JAK/STAT pathway.	
	LB [82, 83]	Bone fracture		Activate the PI3K/Akt/mTOR/p70S6K/4EBP1 pathway	
		Sarcopenia		Activate the AMPK/SIRT1/PGC1α pathway	
	PG [84–86]	IBD		Inhibit the TLR4/MAPK pathway; Activate the Nrf2 pathway	
		WH		Activate the ERK and AKT/ mTOR pathways	
		CDDP-induced cardiotoxicity		Inhibit the MAPK pathway	
Others	Plasma [89, 90]	ACS	miR-1237g-3p, miR-20b-5p	Biomarkers	Que [92, 93]; SIN [94]
		SICM	miR-3130-3p	Inhibit the expression of LPCAT3	
	Bovine milk [91]	Obesity	miR-11987	Induce the browning of white adipocytes	CUR [95, 96]; RSV [96]; PTX [97]

"-" means not available.

21/PTEN axis [61]. Additionally, Chrysin downregulates miR-92a in human coronary artery EC-derived exosomes, thereby alleviating atherosclerotic balloon injury [62]. Curcumin (CUR)-primed mouse brain EC-derived exosomes reduce the permeability of ECs via upregulating tight junctions [63].

2.4. Astrocyte-derived exosomes

Astrocytes are among the most abundant cells in the central nervous system (CNS). These cells help maintain ionic and lipid homeostasis and modulate neuronal activity [64]. Astrocyte-derived exosomes function as crucial mediators of intercellular communication between astrocytes and neighboring cells, which are closely implicated in CNS disorders [65]. Primary astrocyte-derived exosomes carry Apo D (apolipoprotein D) and can be internalized into neurons, attenuating oxidative stress (OS) damage [66]. In IS, rat astrocyte-derived exosomes deliver miR-378a-5p to neurons, where it inhibits NOD-like receptor protein 3 (NLRP3) and alleviates pyroptosis and neuronal injury [67]. Mouse primary astrocyte-derived exosomes confer neuroprotection through miR-26a-5p, which mitigates sevoflurane-induced neuronal apoptosis and dendritic abnormalities *via* neural cell adhesion molecule (NCAM) and the AKT/GSK3-β/CRMP2 axis [68]. These effects are particularly relevant to perioperative neurocognitive disorders (PND). Beyond direct neuronal protection, these exosomes modulate microglial responses. The lncRNA 4933431K23Rik, packaged in mouse astrocytic exosomes, sponges miR-10a-5p to upregulate E2F7 and TFAP2C, increasing Smad7 expression while inhibiting cognitive impairments induced by traumatic brain injury (TBI) [69].

TCM can precondition astrocytes, thereby modulating the molecular cargo of their exosomes and influencing neuron-glia as well as neurovascular communication in neurological disorders. Berberine (Ber)-pretreated primary astrocyte-derived exosomes attenuate cerebral ischemic injury and neuroinflammation *via* the miR-182-5p/Rac1 axis [70]. Sinomenine (SIN)-pretreated astrocyte-derived exosomes mitigate morphine dependence-like behaviors by inhibiting the NMDAR1/CaMKII/CREB signaling pathway [71]. ZeXieBaiZhu Decoction (ZXBZD) modulates astrocyte-derived exosomal miR-200a-3p/141-3p, upregulating SIRT1 in brain ECs

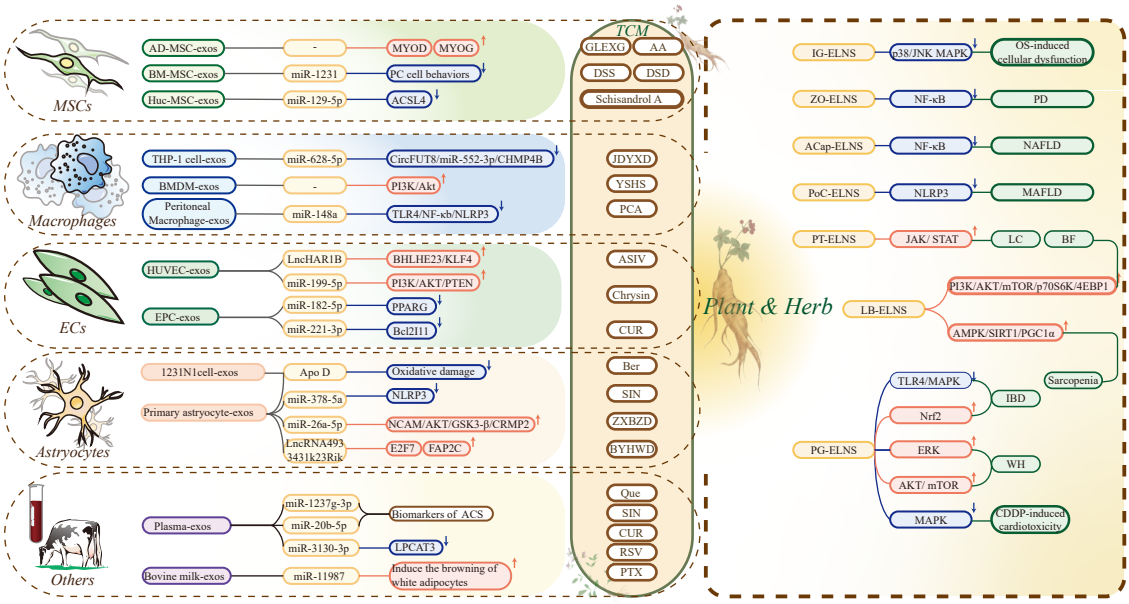


Fig. 2 The therapeutic effects of different source-derived exosomes. Notes: Different source-derived exosomes exert diverse therapeutic effects through distinct cargos and mechanisms. Exosomes derived from mesenchymal stem cells (MSCs), macrophages, endothelial cells (ECs), astrocytes, and other sources mediate therapeutic effects *via* different bioactive cargos and signaling pathways and are associated with TCM (left). Plant- and herb-derived exosome-like nanoparticles (ELNs) also exhibit therapeutic potential through multiple mechanisms (right). "-" means not available.

and ameliorating cerebral ischemia/reperfusion injury (CI/RI) [72]. Glycosides from Buyang Huanwu Decoction (BYHWD), together with astrocyte-derived exosomes, synergistically alleviate cerebral infarction by suppressing neuronal pyroptosis *via* miR-378b_L + 1-mediated inhibition [73].

2.5. Plant and herb-derived ELNs

Plant and herb-derived ELNs can be isolated based on differences in size, density, and solubility, with the most commonly used methods being ultracentrifugation, filtration, and size exclusion chromatography [74, 75]. Using these approaches, *Iris germanica* (German iris, IG)-derived ELNs have been shown to exert antioxidant and anti-senescence effects by influencing p38/JNK MAPK pathway in primary normal human epidermal keratinocytes (nHEKs) [76].

ELNs derived from herbal medicines share similar characteristics with mammalian cell-derived counterparts, including comparable size distribution, surface charge, morphology, and the presence of bioactive components [74, 77]. These ELNs often mirror or even surpass the pharmacological effects of their parent compounds. *Zingiber officinale* (ginger, ZO)-derived ELNs are less pungent and more oxidation-resistant than ginger juice, and they restore periodontal tissue in rats by suppressing NF-κB and reactive oxygen species (ROS) [78]. Similarly, Artemisia capillaris (capillary wormwood, ACap)-derived ELNs quell hepatic inflammation in non-alcoholic fatty liver disease (NAFLD) through NF-κB inhibition [79]. *Poria cocos* (Poria, PoC) and Pinellia ternata (Banxia, PT) ELNs, meanwhile, tune immune responses in NAFLD and lung cancer (LC) through NLRP3 and JAK/STAT pathways [80, 81]. Among the best-characterized herb-derived ELNs are those from *Lycium barbarum* (goji berry, LB) and *Panax ginseng* (ginseng, PG). ELNs from LB promote bone fracture healing *via* activation of the PI3K/AKT/mTOR/p70S6K/4EBP1 signaling axis and improve skeletal muscle function through AMPK/SIRT1/PGC1α-mediated mitochondrial regulation [82, 83]. ELNs from PG exert broad cytoprotective effects: they suppress TLR4/MAPK, activate Nrf2-dependent antioxidant responses [84], drive WH through ERK and AKT/mTOR [85], and mitigate cisplatin cardiotoxicity *via* MAPK inhibition [86]. These examples demonstrate that herb-derived ELNs preserve the multi-target nature of TCM formulas, providing a molecular entry point to bridge holistic concepts with experimentally testable frameworks.

2.6. Other source-derived exosomes

Apart from cell-derived exosomes, exosomes from various bodily fluids such as blood and milk have shown therapeutic potential [87, 88]. Plasma exosomal miRNAs function as both diagnostic biomarkers and therapeutic agents. MiR-1273g-3p and miR-20b-5p are validated biomarkers for acute coronary syndrome (ACS), whereas miR-3130-3p from healthy human plasma exosomes ameliorates sepsis-induced cardiomyopathy (SICM) by targeting LPCAT3 to inhibit ferroptosis [89, 90]. Milk-derived exosomes exert therapeutic effects upon oral administration, and their encapsulated miR-11987 induces browning of white adipocytes to counteract obesity [91]. Beyond these direct effects, they also serve as delivery vehicles for TCM monomers, including Que [92, 93], SIN [94], CUR [95, 96], RSV [96], and PTX [97].

Exosomes isolated from various cells and plants possess therapeutic potential for diverse diseases and also interact with TCM. Exosomes function as carriers for TCM monomers, while TCM modifies their biogenesis and cargo. The intrinsic bioactivities of herbal medicines ELNs, in particular, are similar to the multi-target and multi-pathway effects of TCM [98–100]. Non-autologous sources (e.g. plasma, milk) are not the focus here due to their heterogeneous nature and a lack of mechanistic evidence on their TCM interactions. The therapeutic heterogeneity of exosomes is predominantly determined by their molecular cargo, especially non-coding RNAs, which are closely related to their cellular origin. These source-dependent differences may influence disease-specific therapeutic efficacy and shape exosome–TCM interactions.

3. Mechanisms and therapeutic implications of exosomes in enhancing TCM efficacy

TCM actively shapes exosomal cargo and release, while exosomes in turn improve the pharmacokinetic profiles of TCM compounds. The following sections explore the underlying mechan-

isms and the translational opportunities arising from this bidirectional crosstalk (Fig. 3).

3.1. TCM exerts therapeutic effects through exosome-mediated mechanisms

3.1.1. TCM formulas modulate exosomes to exert therapeutic effects

TCM formulas, the main form of TCM clinical application, such as TCM decoctions, are composed of aqueous extracts of herbs with multiple active constituents and may exert diverse effects through modulating exosomes [101]. Several TCM formulas (including DSD [43], JDYXD [52], YSHS granule [53], and ZXBZD [72]) have been shown to regulate the cargo composition of exosomes as discussed in Section 2. Certain formulas, such as GLEXJ, can promote the release of MSC-derived exosomes [42]. Beyond these previously described examples, emerging evidence suggests that TCM formulas can also regulate exosomes derived from a broader range of cell types and influence multiple aspects of exosome biology. Yiwei Decoction (YWD) treated rat spleen-derived exosomes was taken up by gastric cancer (GC) cells *in vitro* and significantly induce cell apoptosis [102]. YWD could influence exosome production across multiple splenic cell types, which merits further investigation [103]. More recent studies have provided direct mechanistic evidence that TCM formulas regulate exosome release. Jiedu Recipe (JR) inhibits hypoxia-induced HCC cell-derived exosome release, with quercetin (Que) being a key active component acting *via* the EGFR/TFEB axis [104]. Jianpi Yangzheng Xiaozheng Decoction (JPYZXZ) alleviates GC *via* suppressing GC cell exosomal programmed cell death ligand 1 (PD-L1) mediated expansion of myeloid-derived suppressor cells (MDSCs), downregulating the expression of interleukin (IL)-6 and IL-10, and remodeling the immunosuppressive tumor microenvironment [105]. This effect is supported by decreased plasma exosome PD-L1 levels in GC patients. WenShen TongLuo ZhiTong Decoction (WSTLZT) exerts anti-osteoporosis effects in mice by regulating adipocyte-derived exosomal miR-122-5p, which is internalized by bone marrow mesenchymal stem cells (BMSCs) to downregulate SPRY2 expression and regulate the bone-fat balance [21]. TCM formulas modulate exosome biogenesis, secretion, and molecular cargo, including both proteins and miRNAs. These changes alter intercellular signaling, thereby driving therapeutic efficacy in a range of diseases.

3.1.2. TCM monomers modulate exosomes to exert therapeutic effects

TCM monomers, the bioactive ingredients of TCM, exert effects through multiple mechanisms. As outlined in Section 2, several TCM monomers, including DSS [44], PCA [54], Chrysin [62], and Ber [70], regulate the cargo composition of exosomes. ASIV can promote EPC miR-21-loaded exosome secretion, which highlights the ability of TCM monomers to modulate exosome secretion [61]. TCM monomers modulate exosome biology in a more defined manner than multi-component formulas, primarily by regulating exosome secretion and miRNA cargo. Shikonin (SHK) from *Lithospermum erythrorhizon* (LE) reduces the secretion of exosomes and the delivery of miR-128 from human breast cancer cells (MCF-7) to upregulate BCL-2-associated X protein (BAX), thus inhibiting the proliferation of tumor cells [22]. Tanshinone IIA (TSA) from *Salvia miltiorrhiza* (SM) upregulates miR-223-5P in MSC-derived exosomes, inhibiting CCR2 activation and monocyte infiltration, and promoting angiogenesis, ultimately alleviating MI/RI in rats [23]. Pretreatment with TSA also enhances exosomal bioavailability and therapeutic efficacy. Moreover, Panax notoginseng sap-

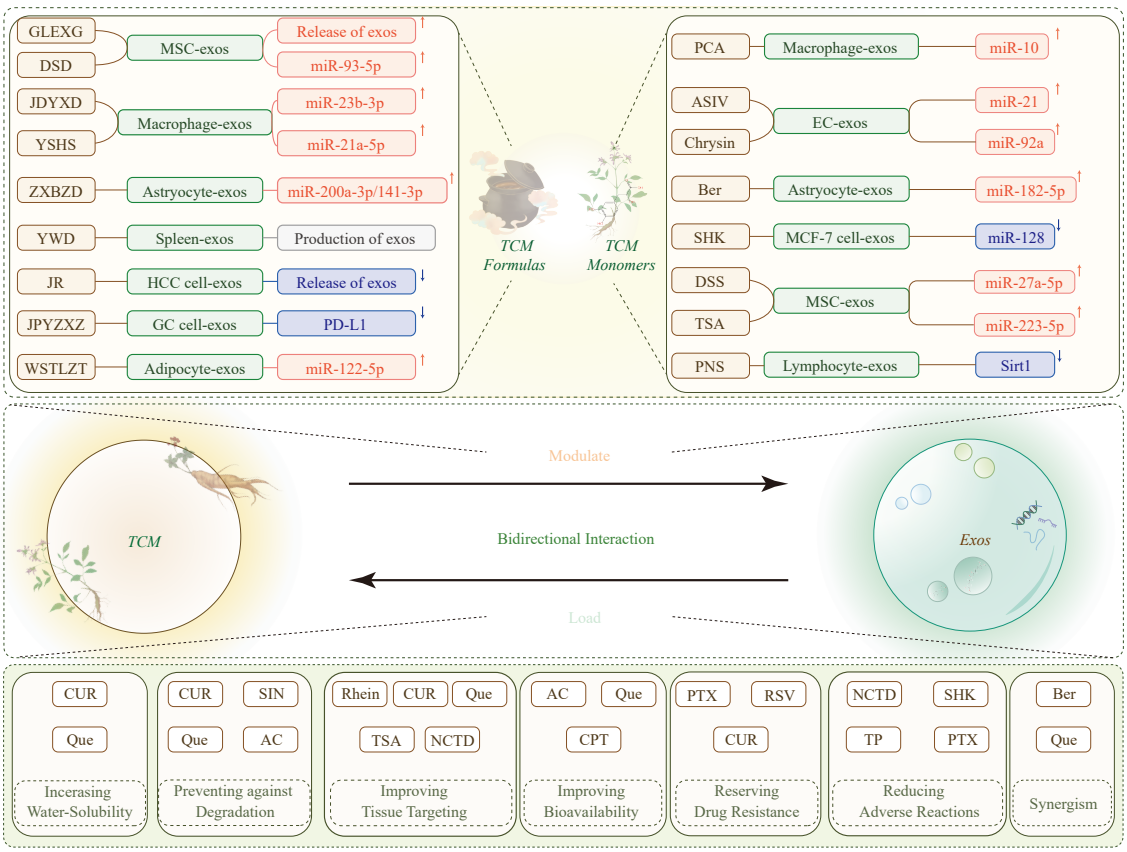


Fig. 3 Mechanisms and therapeutic implications of exosomes in enhancing TCM efficacy. Notes: The bidirectional relationship between exosomes and traditional Chinese medicine (TCM): TCM regulates exosomes, and exosomes transport TCM monomers. TCM formulas and monomers modulate exosomes to exert therapeutic effects (upper), while exosomes, in turn, enhance TCM efficacy by increasing water solubility, preventing against degradation, improving tissue targeting and bioavailability, reversing drug resistance, reducing adverse reactions, and working synergistically (lower).

onins (PNS), bioactive compounds from PG, reverse steroid resistance in lupus nephritis by modulating lymphocyte-derived exosomes, which carry silent information regulator-related enzyme 1 (Sirt1)–multidrug resistance gene 1 (MDR1)–P-glycoprotein (P-gp) signaling to glomerular endothelial cells [106]. PNS interferes with this exosomal transfer, restoring renal steroid sensitivity.

3.2. How do exosomes enhance the efficacy of TCM monomers

In addition to mediating TCM actions, exosomes act as delivery vehicles for TCM monomers. Encapsulation within the exosomal lipid bilayer improves their water solubility, stability, targeting, bioavailability and safety, collectively boosting their therapeutic efficacy (Table 2 and Fig. 3).

3.2.1. Increasing water-solubility

Poor water solubility limits the oral bioavailability of TCM monomers such as CUR and Que. Exosomal loading offers a viable approach to overcome this limitation. Mouse lymphoma cells (EL-4)-derived exosomes increase the water stability of CUR by 5-fold compared with phosphate-buffered saline (PBS) [107]. Similarly, surface-engineered plasma exosomes enhance the solubility of Que, with concentrations rising from 30.15 μg·mL^{-1} in PBS to 86.97 μg·mL^{-1} upon encapsulation, showing a 2.87-fold solubility increase [92].

3.2.2. Preventing against degradation

The therapeutic effects of TCM monomers can be limited by low stability, which prolongs the time to reach the target site and impairs accumulation there. Sun et al. reported that EL-4 cell-derived exosomes significantly increase the stability of CUR [107]. Eighty percent of the residual CUR concentration remained in PBS for the exosomal loading protocol, while only 25% remained after 150 min for the free CUR protocol. Moreover, rat plasma exosomes are revealed to slow down the oxidative degradation of Que [92]. After dispersing the free Que and Que-loaded exosomes in PBS and plasma for 24 h, the remaining ratios of free Que in each solution remained about 30%, whereas that of Que-loaded exosomes increased significantly to 73% and 79%, respectively. SIN, an alkaloid from *Sinomenium acutum* (Qingfengteng, SA) with anti-tumor activity, is revealed to be encapsulated in plasma exosomes, slowing down the release rate [94]. The cumulative release of free SIN is 86.15% in the normal body fluid environment of the human body, while that of SIN-loaded exosomes decreased to 58.63% after 24 h. *Astragalus membranaceus* (Astragalus, AM) is composed of Formononetin, Astragaloside IV, Calycosin, etc.,

Table 2 How do exosomes enhance the efficacy of TCM.

Monomer	Exosome Source	Pathological Condition	Experimental subject	Dosage/Concentration	Routes of administration	Enhancement Mechanism
CUR	EL-4 cell [95, 107]	Experimental autoimmune encephalomyelitis	C57 BL/6 mice	10 μg	Intranasal administration	Targeting
		Inflammatory disorders		100 mg·kg^{-1}	i.p.	Water-solubility; Stability; Targeting; Bioavailability
	Raw bovine milk [96, 109]	Lung cancer	SD rats	2.5 mg·kg^{-1}	i.g.	Targeting
		Breast cancer	MCF-7 cells	2.5%	Co-culturing	Stability
Que	Plasma [92, 93]	CI/RI	SD rats	3.4 mg·mL^{-1}	i.v.	Water-solubility; Stability; Targeting;
		AD	C57 BL/6 mice	12 mg·kg^{-1}	i.v.; i.p.	Targeting; Bioavailability
	BMSCs [117]	OA	C57 BL/6 mice	2 μg	intra-articular injection	Synergism
			Primary mouse chondrocytes	10 μg·mL^{-1}	Co-culturing	
SIN	Plasma [94]	HCC	HepG2 cells	0.9 mmol·L^{-1}	Co-culturing	Stability
AC	*Curcumae rhizoma* [6]	Colonic adenocarcinoma	SD rats	1.875 g·kg^{-1}	i.g.	Stability; Bioavailability
TSA Rhein	NCI-H1299 cell [108]	Sepsis	RAW264.7 cells	2 mg·mL^{-1}	Co-culturing	Targeting
NCTD	BM-MSC [110]	HCC	Balb/c mice	2 mg·kg^{-1}	i.v.	Targeting; Safety
			L02 cells	10–40 μg·mL^{-1}	Co-culturing	
CPT	Patient tumor samples [111]	Cervical cancer	Balb/c nude mice	5 mg·kg^{-1}	i.v.	Targeting
RSV	Raw bovine milk [96]	Breast cancer	MCF-7 cells	2.5%	Co-culturing	Stability
	RAW264.7 cell [112]	-	MDCK cells	-		
PTX	T cell [113]	TNBC	SD rats and female Balb/c mice	5 mg·kg^{-1}	i.v.	
			PTX-resistant TNBC cells	1 μg·mL^{-1}	Co-culturing	
TP	Raw milk [97]	Lung cancer	Balb/c mice	2.4 mg·kg^{-1}	i.g.	Safety
	DC2.4 cell [114]	UC	C57BL/6 mice	350 μg	i.v.	
SHK	HCT116 cell [115]	CRC	Balb/c mice	100 μg		
Ber	HplMSC [116]	UC	C57BL/6 mice	5 mg·kg^{-1}	i.v.	Synergism
			RAW264.7 cells	20 μg·mL^{-1}	Co-culturing	
			OVCA433 cells	50 μg·mL^{-1}		

"-" means not available.

which is commonly used to treat sepsis in the clinic. AM-derived exosomes prevent the degradation of Astragalus components (AC) in simulated gastric fluid and simulated intestinal fluid [6]. The content of Formononetin in the free AC decreased to 66% and 40% of the initial concentration in the two solutions after 2 h, while there was almost no change after exosome loading.

3.2.3. Improving tissue targeting

Rheinic acid (Rhein) and TSA are derived from *Rheum palmatum* (rhubarb, RP) and SM, respectively, which both exhibit anti-inflammatory and anti-oxidant effects. Wu et al. established an exosomal hybrid nanosystem containing rhein and TSA with the loading of NCI-H1299 cell-derived exosomes, and cocultured with murine macrophages (RAW264.7 cells). The exosomal hybrid nanosystem shows a higher co-localization rate with the macrophage scavenger receptor, from 33.52% to 42.36%, indicating higher macrophage targeting [108]. Moreover, EL-4 cell-derived exosomes and bovine milk-derived exosomes are revealed to improve the brain targeting of CUR. CUR-loaded EL-4 cell-derived exosomes can be rapidly transported to the olfactory bulb and maintained at 2.6 nmol·g^{-1} of brain tissue with twice-daily dosing after intranasal administration, and brain tissue staining showed that more than 60% of microglia co-localized well with exosomes [95]. The accumulation of CUR in the brain tissues increased 6-fold after being loaded in raw bovine milk-derived exosomes [109]. Moreover, the concentration of Que is boosted 2.5-fold in the cerebrum and 1.5-fold in the cerebellum, and fluorescence localizes well in the hippocampus after being loaded in plasma exosomes [93]. Guo et al. designed an engineered plasma exosome conjugated with a monoclonal antibody against GAP43 to deliver Que, and the accumulation of Que in the rat brain tissues was increased 6-fold [92]. Norcantharidin (NCTD) is a demethylated derivative of cantharidin (CTD), which is a bioactive compound derived from *Mylabris phalerata* (Mylabris, MP) and possesses anticancer effects. MSC-derived exosomes could enhance the tumor targeting of NCTD, as shown by NCTD-loaded exosomes mainly concentrated in liver tumor areas, while free NCTD was not enriched there [110].

3.2.4. Improving bioavailability

The low bioavailability of TCM may lead to delays in biological activities. Studies indicated that plasma exosomes improve the pharmacokinetic profile of Que [93]. The half-life time ($t_{1/2}$) prolonged from 36.47 to 89.14 min, the maximum blood concentration (C_{max}) increased from 1.31 mg·L^{-1} to 2.5 mg·L^{-1}, and the area under the plasma concentration-time curve from zero time to infinity ($AUC_{0\text{-}t}$) increased to 7.5 times after exosome loading. Moreover, AM-derived exosomes significantly increase the C_{max}, *AUC*, and bioavailability of AC, including Formononetin, Astragaloside IV, and Calycosin [6]. The exosomes of tumor cells from patients with advanced stage IIIc cervical cancer are proven to improve the bioavailability of Camptothecin (CPT) [111], with the concentration of CPT in the peripheral blood increased from 15 μg·mL^{-1} to 20.3 μg·mL^{-1} after exosome loading.

3.2.5. Reversing drug resistance

Combining exosomes with TCM can reverse drug resistance. Raw bovine milk-derived exosomes enable CUR and Resveratrol (RSV) to escape from ATP-binding cassette (ABC) transporter protein-mediated chemoresistance of breast adenocarcinoma cells, exerting stronger anticancer effects [96]. The intervention of CUR-loaded exosomes (48 nmol L^{-1}) and RSV-loaded exosomes (375 nmol L^{-1}) in MCF-7 cells exert a robust antiproliferative activity regardless of the presence or absence of the ABC inhibitors. However, the free CUR and RSV do not exert antiproliferative activity in MCF-7 cells, and the activity is even less in the presence of the ABC inhibitors. Paclitaxel (PTX) is extracted from the *Taxus chinensis* (Chinese yew, TC) with anticancer activity. RAW264.7 cell-derived exosomes enable PTX to bypass P-gp-mediated drug efflux, reversing multiple drug resistance (MDR) [112]. The cytotoxicity of PTX against P-gp expressing MDR Madin-Darby canine kidney ($MDCK_{MDR1}$) increases more than 50-fold after exosome loading. Kim et al. applied the doxorubicin (DOX)-loaded exosomes to $MDCK_{MDR1}$ cells and their sensitive counterparts, and exosomes could significantly increase drug accumulation levels. The presence of the P-gp inhibitors does not affect the accumulation of DOX-loaded exosomes in MDR cells, suggesting that exosomes may reverse tumor MDR through regulating drug efflux. Furthermore, Chen et al. employed activated T cell–derived exosomes for co-delivery of AXL-siRNA and a glutathione-responsive PTX prodrug to reverse PTX resistance in triple-negative breast cancer (TNBC) [113]. This system enables tumor-specific uptake *via* PD-1/PD-L1 interaction, suppresses AXL-mediated EndMT and immune evasion pathways, thereby synchronizing reactivation of chemotherapy sensitivity and antitumor immune responses.

3.2.6. Reducing adverse reactions

The adverse reactions of TCM monomers can not be ignored, although commonly low. Research showed that BMSC-derived exosomes reduce the hepatotoxicity and nephrotoxicity of NCTD, as evidenced by no obvious damage was seen in the liver and kidney tissue sections after the intervention of NCTD-loaded exosomes, while extensive damage was seen after free NCTD was given [110]. Triptolide (TP), a natural extract from *Tripterygium wilfordii* (thunder god vine, TW), possesses anti-inflammatory properties with high toxicity. Murine dendritic cells (DC2.4 cells)-derived exosomes reduce TP's hepatic, renal, and cardiotoxicity, improving its safety profile [114]. The exosomes counteract the focal necrosis of the liver and kidneys, the infiltration of inflammatory cells, and the myocardial swelling, denaturation, cytolysis, and contraction band necrosis caused by TP alone in the mouse heart. Human colorectal cancer cells (HCT116 cells)-derived exosomes counteract the hepatic and renal injuries caused by SHK alone, significantly reducing the expression of serum alanine aminotransferase (ALT) and aspartate transaminase (AST) [115]. Moreover, raw milk-derived exosomes attenuate the systemic and immunotoxicity of PTX in mice [97]. The exosomes abrogate the reduction of the total number of bone marrow cells and macrophages and the increase of neutrophils induced by PTX alone.

3.2.7. Synergism

Synergism is typically defined as the combined effect of agents exceeding the sum of their individual effects. TCM and exosomes can exert therapeutic effects individually, and they may synergism when combined. Ber, a bioactive monomer isolated from Coptis chinensis (Coptis, CC), exhibits anti-inflammatory and antibacterial activities. Exosomes derived from human placental mesenchymal stem cells (HplMSCs) that are loaded with berberine (Ber) can lower levels of TNF-α, IL-6, and nitric oxide (NO) in ulcerative colitis (UC) mice more effectively than Ber or exosomes alone [116]. Pretreatment with Que enhances the therapeutic efficacy of MSC-derived exosomes in an osteoarthritis mouse model, as seen by better cartilage protection than unprimed exosomes [117]. Mechanistically, Que-pretreated exosomes inhibited matrix metallopeptidase 9 (MMP9) and cyclooxygenase-2 (COX-2) more strongly than unprimed ones, and upregulated collagen II expression in IL-1β-stimulated BMSCs.

TCM formulas and monomers modulate the production and secretion of exosomes in diverse cell types. They also modulate the content of the exosome (e.g., miRNAs and proteins), as well as their functional properties. Exosomes act as TCM monomer distribution agents to optimize their pharmacokinetics and safety profile. This mutual interaction builds a bidirectional synergistic

mechanism, providing a theoretical basis for the integration of TCM and nanomedicine. There is a clinical translation potential to this synergistic paradigm. The multi-target characteristics of TCM combined with the exosome biocompatibility may enhance efficacy and reduce side effects. A finished clinical trial has studied the oral use of ginger-derived exosomes loaded with CUR for IBD (NCT04879810). One ongoing clinical trial is studying plant-derived exosome-mediated curcumin delivery in a trial of colon cancer patients (NCT01294072). Nonetheless, there have been no reported results for either study, and no details for the plant-derived exosomes appear in clinical trial NCT-01294072. As a result of the current clinical data do not allow for sufficiently systematic analyses, this field appears to still be in its infancy.

4. Exosomes as participants in disease progression

Exosomes benefit TCM and also have direct therapeutic effects. However, it is also increasingly recognized that they play a harmful role in disease progression. Exosomes have been implicated in the progression of chronic inflammatory diseases such as chronic prostatitis (CP) and oral lichen planus (OLP) [118, 119]. Exosomes from the prostatic fluid of type IIIA CP patients induce the expression of IL-8 and tumor necrosis factor-α (TNF-α) in prostatic stromal cells through the action of miR-155. The abnormal cytokine profile of T cell-derived exosomes in OLP is capable of inducing apoptosis of oral keratinocytes, but the pathogenic role of this exosome remains to be identified. Exosomes from arecoline-treated epithelial cells and mesenteric adipose tissue (MAT) contribute to oral submucous fibrogenesis and intestinal fibrosis in Crohn's disease *via* distinct cargo-mediated mechanisms [120, 121]. Dipeptidyl peptidase-4 (DPP-4) is enriched in the exosomes responsible for oral fibrosis, whereas tubulointerstitial nephritis antigen-like 1 (TINAGL1) is enriched in the exosomes responsible for intestinal fibrosis. The latter activates the TGF-β pathway via interaction with SMAD4.

Accumulating evidence also indicates that exosomes may have a key role in neurodegenerative diseases. In Parkinson's disease (PD), it has been shown that cathepsin L (CTSL) from exosomes derived from microglia activated by α-synuclein promotes progression of the disease by activating the P2X7R/PI3K/AKT pathway [122]. Similarly, in tauopathies, exosome-packaged pathological tau is not just a marker but an active pathogenic agent that facilitates the long-distance propagation of tau pathology and causes neurodegeneration *in vivo* [123].

Furthermore, exosomes modulate the tumor microenvironment and create pre-metastatic micro-ecological niches to aggravate the growth and targeting of PC [124]. M2 macrophage-derived exosomes miR-23a-3p could enhance HCC metastasis by inducing epithelial-mesenchymal transition, angiogenesis, and increasing vascular permeability [125]. Tumor-derived exosomes also contain enzymes that are related to amino acid metabolism and contain distinct nucleic acid species from those of normal cells. These exosomes induce angiogenesis, metastasis, and immunosuppression that contribute to tumor growth [126]. Exosomal miR-410-3p derived from hypoxic colorectal cancer cells promotes colorectal cancer proliferation, migration, invasion, and metastasis by targeting PTEN to activate the PI3K/AKT signaling pathway [127].This process occurs in a HIF1α/HIF2α-dependent manner. Remarkably, amiloride reduces the release of tumor-derived exosomes in cachexia model mice and improves metabolic disturbances. This suggests that the detrimental effects of exosomes are not irreversible [128].

These findings show that exosomes play an active role in disease pathology, not merely passive carriers of NcRNAs and proteins in inflammatory diseases, fibrotic diseases, neurodegenerative diseases, and malignancies.

5. Discussion and future challenges

5.1. Conceptual relevance between TCM theory and exosome biology

The relationship between the "Qi, Xue, and Ye" theory and exosome biology links TCM and modern biomedicine together and also suggests that TCM herbs that have functions of replenishing Qi, nourishing blood, generating fluid, and moistening dryness may also act on exosomes. The integration of "Qi, Xue and Ye" theory with exosome biology at the mechanistic level may help to further elucidate the pharmacological mechanism of TCM. The suggested relationship between various theoretical constructs in TCM (Qi, Xue, and Ye) and exosome-mediated intercellular communication is largely conceptual, as the TCM constructs are dynamic functioning states rather than natural substances that can be precisely measured directly [7, 13]. Thus, proxies that can be operationalized and measured are needed for linking to modern biomedicine. Exosome parameters, including vesicle quantity, cargo composition (miRNAs, proteins), as well as release and delivery to cells, may serve as measurable parameters that reflect some aspects of Qi flow and material movement. For example, better secretion and direct targeting of exosomes may correlate to Qi signaling processes as their functioning, while the diversity and amount of cargo may compare to Xue and Ye as their material basis. While such mappings are basic, they may provide a platform for translating abstract TCM notions into experimentally testable models. Future studies that integrate multi-omics profiling with TCM syndrome classification may further cement these similarities.

5.2. Challenges in TCM–exosome therapeutic strategies

5.2.1. Mechanistic ambiguity and experimental validation

Though TCM significantly changes the exosomal miRNA profiles [54, 72], the upstream regulatory mechanism is not well defined, including the selective sorting and cell specificity [129–131]. For example, specific epigenetic modifications such as DNA methylation and histone acetylation are essential in miRNA transcription [132, 133]. However, whether TCM uses a specific epigenetic modification process to modulate exosomal miRNAs, particularly selective sorting and loading in exosomes, remains unclear. The proposed bidirectional interaction framework between TCM and exosomes still needs more systematic experimental verification. Further mechanistic studies incorporating gene knockout models, epigenetic regulation, multi-omics profiling, lineage tracing and functional validation are warranted to elucidate the reciprocal regulatory relationships of TCM–exosome interactions.

5.2.2. Biosafety and translational barriers

Non-autologous exosomes, including herb-derived ELNs, may trigger immunogenicity, inflammation, or unintended biological effects due to their heterogeneous cargos [134–136]. Although current studies have generally reported low toxicity and favorable biocompatibility [137, 138], systematic evaluations of their long-term safety, immunogenicity, and pharmacokinetic properties are still lacking. In addition, native exosomes remain limited by insufficient targeting specificity and poorly controlled biodistribution. Various engineering strategies have been developed to improve delivery precision, such as chemical modification (e.g., conjugating targeting moieties such as receptor proteins, peptides, or polymers to the surface of exosomes), physical modification (e.g., encapsulating magnetic nanoparticles), and genetic engineering (e.g., fusing targeting protein genes with exosomal membrane protein genes) [139, 140]. The addition of targeting pep-

tides or TRAIL into engineered exosomes has increased the delivery efficiency in TCM-therapeutic systems [141, 142]. However, such modifications raise relevant issues with respect to altered biodistribution, altered immunogenicity, as well as the use of single-target vehicles for multi-component TCM formulas. For chronic disease management, long-term safety is particularly concerning due to organ-specific accumulation, off-target effects, and chronic biological modulation specifically in tissues such as the liver, spleen, and brain [143, 144]. The aforementioned challenges are more relevant for the case of TCM-derived ELNs or TCM-loaded exosomes. This is due to their compositional complexities and variabilities by nature. Nevertheless, information on chronic toxicity, pharmacokinetics, and the complete safety profile for these systems is limited [145, 146].

5.2.3. Methodological standardization and reproducibility

Although there has been some development in general exosome isolation methods, protocols concerning TCM–exosome strategies remain poorly defined [147]. In particular, no standards are referring to "exosome-TCM" formulations in the literature (their source definition, preparation process, functional evaluation). This is resulting in a lot of variability and poor reproducibility, which makes it difficult to interpret the mechanism of action and develop them for use in translational studies. Overcoming these bottlenecks requires standardization of protocols for production, purification, characterization, and functional testing.

5.3. Bidirectional interaction framework and future perspectives

The interactions between TCM and the exosomes are regulated in two distinct ways. TCM monomers and formulas modulate exosomal biogenesis, cargo loading, and biological functions of exosomes. Exosomes are also natural nanocarriers of TCM monomers and optimize the pharmacokinetics, biosafety, and tissue-targeting of TCM monomers to augment efficacy.

To bring this combinatorial framework a step closer to clinical implementation, two research priorities require thorough consideration. Tools that integrate multiple omics allow for the quantitative profiling of molecular interactions. The preclinical pharmacokinetic advantages of exosomal delivery require thorough validation in large-animal models with standardized dosing regimens. Meeting these specifications will convert the current theoretical hypothesis into clinical protocols for TCM-exosome combination therapy.

6. Conclusion

TCM and exosomes interact bidirectionally. This interplay bridges holistic TCM theories with experimentally measurable molecular processes. We should further clarify mechanisms, validate long-term safety, and standardize production and functional evaluation. These steps will accelerate the clinical translation of TCM–exosome strategies.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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