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RESEARCH ARTICLE

Title: Chinese and Mongolian Medicines in Remodeling the Metastatic Tumor Microenvironment From Pre-metastatic Niche Formation to Immune Escape and Colonization

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Abstract：Metastasis is the clinical expression of an ecological failure in which disseminating cancer cells encounter permissive immune, stromal, vascular and metabolic conditions rather than an inert distant organ. This review examines Chinese and Mongolian medicines through that ecological lens. Instead of treating herbal medicines as general cytotoxic agents, the review asks whether they can remodel the microenvironmental states that permit metastatic dissemination, immune escape, pre-metastatic niche formation, dormancy escape and distant colonization. We classified the literature into direct antimetastatic evidence, TME-remodeling evidence, and predictive evidence to avoid overinterpreting migration assays or network pharmacology predictions as proof of antimetastatic activity. Chinese medicine has a broader mechanistic base, especially in EMT, macrophage polarization, myeloid suppression, inflammatory signaling, angiogenesis and selected models of metastatic burden. Mongolian medicine offers a distinctive materia medica resource and plausible immunoinflammatory and vascular regulatory potential, but direct evidence linking classical Mongolian formulas to metastatic niche biology remains limited. The central argument is that a credible field must move from simple migration assays and network prediction toward orthotopic and spontaneous metastasis models, cell resolved microenvironmental profiling, spatial validation, pharmacokinetic exposure, quality control and clinically relevant recurrence or metastasis endpoints.

Keywords: Chinese medicine Mongolian medicine metastasis metastatic tumor microenvironment pre-metastatic niche immune escape tumor associated macrophage angiogenesis colonization

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1. Introduction

Cancer remains a growing global burden. GLOBOCAN 2022 estimated about 20 million new cancer cases and 9.7 million cancer deaths worldwide, and international projections indicate that annual new cases may exceed 35 million by 2050 if demographic growth and exposure patterns continue [1,2,3]. These numbers matter for a review on metastasis because mortality in many solid tumors is not determined only by the size of the primary lesion. It is often determined by whether tumor cells disseminate, survive treatment pressure, adapt to distant tissue constraints and form clinically significant secondary lesions. The popular statement that almost all cancer deaths are caused by metastasis should be used carefully, because death certificates and cancer registries vary in how they encode metastatic disease. The more defensible scientific statement is that metastasis and metastatic organ failure remain dominant barriers to durable cancer control in solid tumors. A review of Chinese and Mongolian medicines therefore becomes meaningful only if it is placed within the metastatic process itself, not within a generic anticancer frame.

The intellectual origin of metastatic ecology is the seed and soil hypothesis. Paget's observation that breast cancer metastases display organ preference proposed that cancer cells need a receptive tissue environment, while Fidler later transformed this idea into an experimental and mechanistic framework [4,5]. Modern cancer biology has widened that soil from a passive organ surface to a dynamic field made of

extracellular matrix, endothelial and lymphatic vessels, fibroblasts, resident immune cells, recruited bone marrow derived cells, platelets, metabolites, microbiota associated signals and neural or endocrine inputs. Hallmark models of cancer also show that invasion, immune evasion, inflammation, angiogenesis, metabolic plasticity and phenotypic plasticity are not independent traits. They converge during metastatic progression and create the ecological conditions that allow a rare disseminated cell to become a lethal colony [6,7].

Metastasis is not a single step. It contains local invasion, epithelial plasticity, stromal remodeling, intravasation, survival in circulation, arrest at distant capillary beds, extravasation, dormancy, immune escape, metabolic adaptation and eventual outgrowth. Foundational reviews have emphasized that each stage is inefficient, context dependent and shaped by both cancer cell intrinsic programs and host tissue cues [8,9,10,11,12,13,14,15]. This inefficiency is precisely why microenvironmental intervention matters. A drug or formula may have modest direct cytotoxicity but still alter metastatic probability if it weakens one ecological requirement such as macrophage mediated intravasation, vascular leakiness, myeloid cell recruitment, collagen crosslinking, immune exclusion or niche priming. Conversely, a compound may inhibit migration in vitro yet fail as an antimetastatic agent if it does not reach the relevant tissue compartment or if it does not alter the host niches that metastasis requires.

The tumor microenvironment should therefore be treated as a system with stage specific functions. Classic studies on microenvironmental regulation, tumor organs and tissue restraint showed that nonmalignant cells can control tumor behavior as strongly as tumor cell mutations in some contexts [16,17,18,19]. Inflammation and immune regulation add an additional level of systemic control. Chronic inflammation can supply growth factors, proteases, survival signals, angiogenic mediators and immune suppressive circuits, while immune cell populations can either eliminate disseminated cells or escort them through the metastatic cascade [20,21,22,23]. The term metastatic tumor microenvironment is therefore narrower and more demanding than tumor microenvironment. It asks whether a microenvironmental change contributes to invasion, dissemination, niche formation, colonization or metastatic relapse.

Chinese and Mongolian medicines are often described as multicomponent and multitarget systems. That description is too vague unless connected to a biological problem that truly requires network regulation. Metastasis is such a problem. It depends on immune suppression, inflammatory persistence, vascular abnormality, stromal mechanics, hypoxia, acidosis, metabolic adaptation and distant organ priming. These layers match the kinds of distributed regulation that complex herbal preparations are claimed to provide. The review therefore does not ask whether a herb is anticancer in the broad sense. It asks whether specific medicines, compounds or formulas have evidence for remodeling the metastatic soil. It also asks where evidence stops. Chinese medicine has numerous studies of EMT, TAMs, angiogenesis and inflammatory pathways. Mongolian medicine has cultural and pharmacological distinctiveness, but the direct antimetastatic literature is much thinner. A rigorous synthesis must preserve that asymmetry rather than hide it.

2. Search Strategy and Evidence Classification

Databases searched included PubMed, Web of Science, Scopus, Embase, Google Scholar, CNKI, Wanfang Data and VIP. The search covered publications from database inception to June 2026, with emphasis on studies published after 2015 and with older landmark papers retained when they defined metastasis biology, pre-metastatic niche theory, tumor immunity or traditional medicine methodology. Google Scholar was used for citation trail discovery and for books or regional sources relevant to Mongolian materia medica, while biomedical evidence and reference metadata were verified against indexed databases or journal records whenever possible.

Search terms combined medicine related terms with metastasis and microenvironment terms. The medicine block included traditional Chinese medicine, Chinese herbal medicine, Chinese medicine, Chinese formula, Chinese materia medica, Mongolian medicine, Mongolian materia medica, Mongolian medicinal plant, natural compound and ethnopharmacology. The metastatic microenvironment block included metastasis, metastatic microenvironment, tumor microenvironment, tumor immune microenvironment, pre-metastatic niche, colonization, dormancy, EMT, invasion, angiogenesis, lymphangiogenesis, tumor associated macrophage, myeloid derived suppressor cell, regulatory T cell, NK cell, CD8 T cell, cancer associated fibroblast, extracellular matrix, hypoxia, lactate, exosome and extracellular vesicle.

Inclusion criteria were peer reviewed original studies, systematic reviews, mechanistic reviews, authoritative books and official reports that addressed at least one of the following domains. These domains were Chinese medicine or Mongolian medicine in cancer models, metastatic endpoints, tumor microenvironment remodeling, pre-metastatic niche formation, immune suppression, angiogenesis, stromal remodeling, metabolism, pharmacokinetics, safety or modern evidence methods. Priority was given to studies using orthotopic, spontaneous or organotropic metastasis models, clinical recurrence or metastasis endpoints, immune or spatial biomarkers, and experiments that connected a medicine to both metastatic burden and microenvironmental mechanism. Exclusion criteria were studies without identifiable medicine composition or source, studies limited to nonspecific cytotoxicity without metastatic or TME relevance, duplicate records, papers with insufficient bibliographic information, purely promotional reports, and network pharmacology or docking studies that lacked experimental validation when they were used to support a mechanistic claim. Prediction only studies were retained only when they helped define candidate pathways or future hypotheses. Direct antimetastatic evidence

was defined as evidence showing an effect on metastatic nodule number, metastatic burden, organ colonization, vascular invasion, lymph node metastasis, recurrence, metastasis free survival, spontaneous metastasis from an orthotopic tumor, or growth of established micrometastatic disease. TME-remodeling evidence was defined as evidence showing a medicine related change in TAMs, MDSCs, Tregs, CD8+ T cells, NK cells, CAFs, endothelial or lymphatic cells, ECM, vessel leakage, hypoxia, lactate, cytokines, chemokines, exosomes or spatial tissue architecture. Predictive evidence was defined as network pharmacology, molecular docking, molecular dynamics, public omics reanalysis or machine learning prioritization without direct experimental validation of the predicted target or pathway. Evidence grades were assigned conceptually as follows. Grade A required both a metastatic endpoint and a TME mechanism in an in vivo or clinical setting. Grade B required a metastatic endpoint with incomplete TME characterization. Grade C required TME-remodeling evidence without a direct metastatic endpoint. Grade D described in vitro migration, invasion, EMT, coculture or organoid evidence. Grade E described prediction only evidence. Grade F described Mongolian medicine candidate evidence based on traditional use, materia medica documentation, phytochemistry or general pharmacology without cancer metastasis validation. This framework was used to avoid interpreting migration assays or network predictions as proof of antimetastatic activity.

3 Biological Basis of the Metastatic Tumor Microenvironment

The metastatic cascade can be read as a sequence of ecological bottlenecks. A cell must loosen epithelial constraints, communicate with fibroblasts and macrophages, cross matrix and basement membrane barriers, enter abnormal vessels or lymphatics, resist shear stress and immune attack, reach a distant organ, survive in a foreign tissue, remain dormant or restart proliferation, and then organize a new vascular and immune environment. summarizes this cascade and the intervention points that are most relevant to Chinese and Mongolian medicines.

Metastatic cascade and microenvironmental intervention points of Chinese and Mongolian medicines.

3.1 EMT and Invasive Plasticity

EMT is often introduced as a switch from an epithelial phenotype to a mesenchymal phenotype, but metastasis research now treats it as a plastic spectrum rather than a binary event. During EMT and partial EMT, tumor cells reduce epithelial junctional programs, increase motility, change cytoskeletal organization, acquire resistance to anoikis and interact more efficiently with extracellular matrix and stromal cells. TGF-β Smad, Wnt/β-catenin, PI3K/AKT, MAPK, Notch and NF-κB signaling can converge on transcriptional regulators such as Snail, Slug, Twist and ZEB family factors. E cadherin loss, N cadherin gain, vimentin expression and MMP2 or MMP9 activation are useful markers, but they are not sufficient by themselves to define metastatic competence. The deeper point is that EMT gives disseminating cells a temporary language for moving through tissue, surviving stress and communicating with the metastatic soil [24,25,26,27].

This matters for herbal medicine research because many studies report reversal of EMT markers after treatment with baicalein, berberine, curcumin, ginsenosides, tanshinones or formulas. Such studies are relevant but incomplete if they end at marker expression. A metastatic TME review should ask whether the treatment reduces invasion through a matrix barrier, alters macrophage assisted invasion, changes collective migration, restores anoikis, reduces circulating tumor cell survival, or prevents colonization in vivo. Partial EMT may be more dangerous than complete EMT in some contexts because it preserves cell cell cohesion while gaining motility. Therefore, a medicine that simply increases E cadherin in cultured cells may not fully suppress the hybrid states that travel as clusters, evade immune attack and seed metastases. Deep evidence requires linking EMT modulation to the host compartments that enable dissemination.

3.2 CAFs and Extracellular Matrix Remodeling

Cancer associated fibroblasts are not a uniform stromal population. They include inflammatory, myofibroblastic, antigen presenting and tissue specific states that can restrain or promote cancer depending on context. In metastatic progression, CAFs and related stromal cells can deposit collagen, fibronectin and hyaluronan, secrete TGF-β, IL-6, CXCL12 and VEGF, activate MMPs and create tracks that guide cancer cell movement. Matrix stiffness is not a passive biomechanical feature. It can activate integrin, FAK, Src and YAP/TAZ signaling, promoting survival, invasion and resistance to therapy. LOX mediated collagen crosslinking adds a long range function by preparing distant organs for tumor cell arrival, especially when combined with myeloid recruitment and inflammatory priming [28,29,30,31,32].

For Chinese and Mongolian medicines, the stromal question is underdeveloped. Many compounds are reported to reduce MMP2 or MMP9, but fewer studies test collagen alignment, matrix stiffness, CAF subtype switching, fibroblast tumor cell crosstalk or LOX dependent niche formation. This is a missed opportunity because traditional medicines are often framed as systems regulators. A systems regulator should be evaluated where systems regulation is visible. For example, a formula that lowers inflammatory cytokines, decreases M2 like macrophages and reduces CAF activation may weaken the matrix and immune scaffold of metastasis even without strong direct cytotoxicity. Conversely, a medicine that reduces tumor size but increases fibrosis or hypoxia might worsen some aspects of the metastatic soil. Therefore, stromal endpoints should become routine in future antimetastatic studies.

3.3 Angiogenesis, Lymphangiogenesis and Vascular Leakage

Angiogenesis supports primary tumor growth, but its metastatic relevance is more specific. Abnormal vessels create

routes for intravasation, supply hypoxic gradients, alter immune cell trafficking and generate leakiness that can help tumor cell escape. HIF-1α and VEGF signaling are central, but tumor vessels are shaped by endothelial cells, pericytes, macrophages, platelets and matrix stiffness. Vessel normalization is therefore distinct from simple vessel inhibition. Normalization can improve perfusion, reduce hypoxia and potentially increase immune cell entry, whereas excessive vessel pruning may increase hypoxia and selection pressure. Lymphangiogenesis adds another metastatic route. VEGF-C and VEGFR-3 driven lymphatic remodeling can promote nodal dissemination and systemic spread [33,34,35,36].

Many Chinese medicine studies report downregulation of VEGF, HIF-1α or microvessel density. These results are useful only if interpreted in relation to metastatic function. The more informative endpoints include vascular permeability, pericyte coverage, tumor hypoxia, intravasation frequency, lymphatic vessel density, lymph node metastasis and extravasation into distant organs. Mongolian medicine studies that show anti inflammatory or antioxidant activity may also be relevant to endothelial biology, but they need direct vascular assays. A high level review should therefore distinguish antiangiogenic signaling from antimetastatic vascular remodeling. The former is a pathway change. The latter is a biological outcome linked to dissemination.

3.4 Immune Suppression in Metastasis

Immune suppression is one of the strongest bridges between tumor microenvironment and metastasis. TAMs can support invasion by producing EGF, MMPs and cathepsins, promote angiogenesis through VEGF family signals, suppress T cell function through interleukin 10, TGF-β and checkpoint pathways, and prepare distant niches through inflammatory mediators. MDSCs expand under tumor derived growth factors and cytokines, consume arginine and cysteine, generate reactive oxygen or nitrogen species, and suppress cytotoxic T cell function. Tregs restrain antitumor immunity and may facilitate metastatic outgrowth. Exhausted CD8 T cells and impaired NK cells complete a suppressive field in which disseminated tumor cells are less likely to be eliminated [37,38,39,40,41,42,43,44].

This immune layer is especially important for Chinese medicine because several compounds and formulas are reported to shift macrophage polarization, reduce myeloid suppression or improve cytotoxic immunity. Yet macrophage labels such as M1 and M2 are too simple for current metastasis biology. Single cell studies show multiple macrophage states with angiogenic, lipid handling, interferon responsive, matrix remodeling or suppressive programs. Future herbal studies should move from the binary M1 M2 vocabulary toward functional macrophage states, spatial position and ligand receptor communication with tumor, endothelial and fibroblast cells. The same caution applies to MDSCs and Tregs. Changes in spleen size or peripheral blood percentages are not enough. The key question is whether suppressive immune cells in the metastatic organ are reduced or reprogrammed at the moment when tumor cells try to survive and expand.

Table 1. Core components of the metastatic tumor microenvironment and their roles in metastasis.

Component	Metastatic function	Representative targets	Relevant evidence direction
EMT and invasive plasticity	Permits migration, matrix entry, anoikis resistance and cluster dissemination.	TGF-β, Wnt/β-catenin, PI3K/AKT, MMP2, MMP9	Mostly Chinese medicine evidence through EMT markers and invasion assays. Stronger evidence requires in vivo metastasis endpoints.
CAF and ECM remodeling	Creates tracks, stiffness, collagen alignment and stromal barriers that support invasion and immune exclusion.	LOX, collagen, fibronectin, FAK, YAP/TAZ, CXCL12	Understudied for both Chinese and Mongolian medicines. Important for niche biology.
Angiogenesis and lymphangiogenesis	Controls vascular leakiness, intravasation, extravasation, hypoxia and lymph node dissemination.	HIF-1α, VEGF, VEGFR, Ang2, VEGF-C, VEGFR-3	Common Chinese medicine endpoint, but often measured as microvessel density rather than metastatic vascular function.
Immune suppression	Allows circulating and seeded cells to escape cytotoxic T cells and NK cells while recruiting TAMs, MDSCs and Tregs.	CSF1R, CCL2 CCR2, STAT3, PD-1/PD-L1, interleukin 10	Strong conceptual and mechanistic basis for Chinese medicine. Mongolian evidence is mostly candidate or general immunoregulation.

Component	Metastatic function	Representative targets	Relevant evidence direction
Hypoxia and metabolism	Links poor perfusion to glycolysis, lactate, acidosis, immune suppression and niche formation.	HIF-1α, GLUT1, LDHA, AMPK, mTOR, LOX	Promising but needs organ specific metabolic and immune readouts.
Pre-metastatic niche	Primes distant organs before tumor cell arrival through exosomes, myeloid recruitment, matrix deposition and vascular leakiness.	VEGFR1, LOX, CXCL12 CXCR4, S100A8 A9, exosome integrins	Highest novelty area. Direct evidence for Chinese and especially Mongolian medicines remains limited.

3.5 Hypoxia, Acidosis and Metabolic Adaptation

Hypoxia and metabolic stress do not merely reflect poor perfusion. They shape metastatic selection. HIF signaling can induce VEGF, CXCR4, MMPs, glycolytic enzymes and LOX, connecting oxygen tension to invasion, angiogenesis, niche formation and collagen remodeling. Glycolysis and lactate accumulation acidify the microenvironment, suppress effector T cell and NK cell functions, promote macrophage polarization and alter endothelial behavior. Lipid metabolism, oxidative stress and mitochondrial flexibility also influence the ability of disseminated cells to survive in distant organs. Cancer metabolism is therefore not only a tumor cell intrinsic engine. It is a language shared with immune and stromal compartments [45,46,47,48].

The metabolic dimension offers a deeper interpretation of traditional concepts that are sometimes translated too loosely into modern biomedical language. Rather than asserting that a formula restores balance in an abstract sense, investigators can ask whether it lowers lactate, normalizes perfusion, reduces hypoxia, changes macrophage lipid handling, shifts AMPK mTOR signaling, or changes nutrient competition between tumor and immune cells. This also provides a bridge to organ specificity. Liver, lung, bone and brain metastases expose disseminated cells to different oxygen levels, nutrients, immune surveillance and stromal architecture. A medicine that suppresses metabolic adaptation in one metastatic organ may not work in another. Therefore, metabolic claims should be organ and model specific.

3.6 Premetastatic Niche and Colonization

The pre-metastatic niche is the conceptual center of this review. It explains how a primary tumor can educate distant tissues before tumor cells arrive. Tumor derived soluble factors and extracellular vesicles can mobilize bone marrow derived cells, increase vascular permeability, deposit fibronectin, alter resident immune cells and change stromal architecture. VEGFR1 positive bone marrow progenitors, exosome integrins, pancreatic cancer derived exosomes, LOX dependent collagen remodeling and MMP9 dependent lung tropism illustrate how distant organs can become receptive soils. Colonization is the next bottleneck. Disseminated cells must survive foreign tissue constraints, sometimes enter dormancy, sometimes evade immune surveillance, and eventually rebuild a local vascular and immune ecosystem suitable for growth [49,50,51,52,53,54,55,56,57,58,59,60].

This biology changes how Chinese and Mongolian medicines should be studied. A preventive treatment may appear weak in a late stage tumor volume assay but still block niche priming. A treatment given after tumor cell dissemination may not prevent arrival but could keep cells dormant or vulnerable to immune elimination. A treatment that reduces primary tumor inflammation may indirectly alter exosome cargo or myeloid mobilization. The experimental design must therefore state which stage is being tested. Preventive niche studies should sample lung, liver, bone or brain before detectable metastases appear. Colonization studies should separate extravasation, early survival and outgrowth. Without this temporal clarity, claims of metastatic TME remodeling remain conceptually attractive but experimentally vague.

Organotropism is also central. Breast cancer often metastasizes to lung, bone, liver and brain, colorectal cancer frequently seeds liver, prostate cancer has a strong bone tropism, and lung cancer can colonize brain, adrenal gland and bone. These patterns reflect both tumor cell programs and organ soils. Exosome integrins, chemokines, resident macrophages, endothelial barriers, metabolic nutrients and matrix composition all shape where disseminated cells survive. For herbal medicine research, organotropism means that a positive lung metastasis study should not be generalized to liver or brain without additional evidence. It also means that formula selection might eventually be matched to organ niche biology rather than only primary tumor type.

4 Traditional Chinese Medicine in Remodeling the Metastatic Microenvironment

Chinese medicine has the larger evidence base. Modern studies include formulas, injections, single herbs, extracts and purified compounds, and they are often connected to systems pharmacology, immune modulation, angiogenesis, EMT and inflammatory networks. General reviews and clinical oriented

discussions support the relevance of traditional Chinese medicine and natural products in cancer therapy, but they also show the translational problem that motivates this article. Many studies describe broad anticancer activity, adjunctive benefit or pathway modulation without asking whether the intervention changes metastatic burden or metastatic niche biology [61,62,63,64,65,66,67,68]. The key task is therefore not to list all herbs. It is to place representative medicines into the metastatic sequence and grade the evidence.

4.1 Chinese Medicine Targeting EMT and Invasive Plasticity

EMT and partial EMT provide a central entry point for Chinese medicine research because they connect tumor cell plasticity with matrix invasion, macrophage crosstalk and survival after dissemination. Ginsenoside Rg3, berberine, curcumin, baicalein, baicalin, wogonin, tanshinone IIA, matrine, oxymatrine, beta elemene and artemisinin related compounds are repeatedly discussed in cancer literature and often converge on TGF-β/Smad, Wnt/β-catenin, PI3K/AKT, NF-κB, STAT3 and MMP signaling [69,70,71,72,73,74,75,76,77,78,79,80,81,82,83]. The important interpretation is not that these compounds are equivalent antimetastatic drugs. Rather, they identify a recurring biological space in which epithelial plasticity, inflammatory transcription factors and protease activity are coupled. If an extract or formula lowers Snail, vimentin and MMP-9 while restoring E-cadherin, it provides a mechanistic clue. If the same treatment reduces lung metastasis, liver metastasis or lymph node spread in an orthotopic model and changes macrophage or fibroblast crosstalk, it becomes stronger evidence for metastatic TME remodeling.

For formal evidence grading, EMT studies should be separated into at least three levels. The lowest level is marker reversal in cultured tumor cells. The intermediate level is invasion, anoikis resistance, spheroid, organoid or coculture evidence showing that tumor cell plasticity changes in a microenvironmental context. The strongest level connects EMT suppression to metastatic burden in vivo. This distinction is particularly important for Chinese medicine because many papers stop at wound healing or transwell assays. Such assays are useful screens, but they do not prove that the medicine interrupts a metastatic bottleneck in vivo.

4.2 Chinese Medicine Regulating TAMs and Myeloid Suppression

TAMs are among the most plausible microenvironmental targets for Chinese medicine because they link inflammation, angiogenesis, ECM remodeling and immune escape. A medicine may reduce invasion by acting directly on tumor cells, but it may also work by preventing macrophages from supplying EGF, VEGF, IL-10, TGF-β or proteases. A stronger study therefore asks whether Chinese medicine shifts macrophage state within the primary tumor, circulation or metastatic organ, whether that shift changes T cell exclusion or vessel structure, and whether the altered macrophage compartment is necessary for the antimetastatic effect. Depletion, adoptive transfer, conditioned medium rescue and spatial profiling can distinguish direct tumor cell effects from macrophage mediated effects.

Myeloid suppression extends beyond macrophages. MDSCs participate in pre-metastatic niche formation, suppress cytotoxic T cell function and can cooperate with neutrophils, platelets and endothelial cells. Chinese medicines that modulate IL-6/STAT3, CCL2/CCR2, CXCL12/CXCR4, GM-CSF, COX-2/PGE2 or PD-1/PD-L1 circuits should be interpreted within this myeloid geography. A peripheral blood reduction in MDSCs is suggestive, but a metastatic TME claim requires tissue evidence in lung, liver, bone or lymph node niches and ideally a link to reduced seeding or colonization.

4.3 Chinese Medicine Modulating Tregs, CD8+ T Cells, NK Cells and Immune Checkpoints

Many traditional medicine studies report improved immune function, but metastatic immunology demands more precise endpoints. It is not enough to state that CD4 or CD8 ratios improved. The relevant question is whether Tregs are reduced near disseminated tumor cells, whether CD8+ T cells recover interferon γ or granzyme activity, whether NK cells eliminate early seeded cells, and whether PD-1/PD-L1 or other checkpoint circuits are changed in the organ where colonization occurs. Chinese medicines that reduce myeloid suppression or macrophage derived IL-10 may indirectly improve T cell and NK cell function, so immune readouts should be interpreted as a network rather than isolated cell counts.

The immune checkpoint era makes this module translationally important. A treatment that lowers PD-L1 or improves CD8+ T cell infiltration may be more relevant as an immunotherapy partner than as a standalone antimetastatic agent. The metastatic setting is demanding because checkpoint response depends on antigen presentation, T cell priming, effector entry, stromal barriers, myeloid suppression and organ specific immune tolerance. Combination models with checkpoint blockade are therefore more informative than simple PD-L1 expression assays.

4.4 Chinese Medicine Targeting Angiogenesis, Lymphangiogenesis and Vascular Leakage

A large number of Chinese medicine studies report downregulation of HIF-1α, VEGF or microvessel density. In metastatic biology, this observation should be converted into more precise vascular questions. Does the treatment reduce vascular leakage that permits intravasation or extravasation. Does it normalize pericyte coverage. Does it reduce VEGF-C/VEGFR-3 dependent lymphangiogenesis and nodal spread. Does it decrease hypoxia and improve immune entry, or does excessive vessel pruning worsen hypoxia. These distinctions matter because antiangiogenic and vascular normalizing effects can have different consequences for metastasis.

This module is particularly relevant for Chinese medicine because many compounds have anti inflammatory and endothelial effects at the same time. A formula that reduces

IL-6/STAT3 and HIF-1α/VEGF signaling may alter both myeloid recruitment and vascular function. Strong evidence should include vascular permeability, pericyte coverage, lymphatic vessel density, intravasation frequency, extravasation assays or organ colonization endpoints rather than VEGF expression alone.

4.5 Chinese Medicine Regulating CAFs, ECM Remodeling and Stromal Stiffness

CAF and ECM evidence is less developed than EMT or angiogenesis evidence, but it is essential for the novelty of this review. CAFs supply TGF-β, IL-6, CXCL12, collagen, fibronectin, MMPs and VEGF, while stiff and aligned matrix activates integrin/FAK, Src and YAP/TAZ signaling. Chinese medicine studies that report MMP suppression are relevant but not sufficient. The field needs measurements of CAF activation states, collagen deposition, LOX dependent crosslinking, matrix stiffness, YAP/TAZ activity and immune exclusion barriers. This module links primary invasion to pre-metastatic niche formation because ECM remodeling is not confined to the primary tumor.

A useful evidence table should therefore include whether a medicine acts on tumor cells, fibroblasts or both. If a formula reduces α-SMA+ CAFs, collagen I deposition and CXCL12 while increasing CD8+ T cell entry, it supports stromal remodeling. If it also lowers metastatic burden, it becomes direct antimetastatic evidence. If it only reduces MMP-9 in tumor cells, it remains invasion related evidence. This distinction gives the manuscript more depth than a pathway list.

4.6 Chinese Medicine Targeting Hypoxia, Lactate and Metabolic Adaptation

Inflammation and metabolism are not background features of metastasis. They determine whether macrophages become suppressive, whether endothelial barriers leak, whether fibroblasts remodel matrix and whether cytotoxic lymphocytes retain function. Chinese medicines that suppress NF-κB, IL-6/STAT3, TNF-α, COX-2, NLRP3, HIF-1α, glycolytic enzymes or lactate accumulation may influence metastatic soil even when direct tumor killing is modest. The biological claim should be expressed as immunometabolic remodeling rather than as a vague restoration of balance.

This section also creates a bridge to oral formulas. Many herbal compounds have limited systemic bioavailability, yet they may act through gut, liver, immune or microbial metabolism. If oral treatment changes lactate, bile acids, microbial metabolites, myelopoiesis or liver inflammatory tone, it may affect metastatic organ permissiveness. Metabolomics, microbiome profiling and tissue exposure studies are therefore not optional decorations. They are needed to explain how orally administered medicines influence distant metastatic niches.

4.7 Chinese Medicine and Pre-metastatic Niche Formation

Pre-metastatic niche formation is the most innovative but least fully validated Chinese medicine module. Theoretically, Chinese medicines could interfere with extracellular vesicle release or uptake, reduce myeloid mobilization, lower LOX mediated collagen remodeling, alter CXCL12/CXCR4 dependent recruitment, suppress S100A8/A9 inflammatory priming or maintain NK cell surveillance in distant organs. Some studies imply these mechanisms indirectly, but few place pre-metastatic niche formation as the primary endpoint. Future research should collect distant organs before tumor cell arrival, measure fibronectin, LOX, myeloid cells, vascular permeability and exosome markers, and then test whether these changes predict lower metastatic burden.

Extracellular vesicle biology deserves special attention. Tumor extracellular vesicles can carry integrins, proteins, nucleic acids and metabolites that educate bone marrow cells, endothelial cells and resident stromal cells. A medicine may reduce metastatic potential by changing vesicle quantity, cargo, uptake or downstream response in distant organs. Testing this possibility requires more than measuring serum exosome markers. Investigators should isolate vesicles, define their cargo, test recipient cell effects and determine whether vesicles from treated tumors lose niche forming ability in vivo. This design would connect Chinese medicine mechanisms directly to pre-metastatic niche theory.

Table 2. Chinese medicine evidence map for metastatic microenvironment remodeling.

Medicine or compound	Cancer type	Model or setting	Metastatic endpoint	Microenvironmental target	Main signaling	Evidence grade	Main interpretation
Ginsenoside Rg3 and related red ginseng saponins	Melanoma and experimental metastasis models	Mouse metastasis assays reported in early pharmacology studies	Metastatic burden reduced	Tumor cell dissemination and vascular or immune context not fully resolved	VEGF, invasion associated signaling, stress pathways	B	Direct antimetastatic endpoint exists, but cell resolved TME mechanism remains incomplete.

Medicine or compound	Cancer type	Model or setting	Metastatic endpoint	Microenvironmental target	Main signaling	Evidence grade	Main interpretation
Astragalus based Chinese herbal combinations	Advanced non-small cell lung cancer	Clinical meta-analysis with platinum chemotherapy	Survival and response outcomes rather than metastasis specific endpoints	Host immune support and treatment tolerance inferred	Immune and inflammatory modulation	C	Clinical relevance is plausible, but direct metastatic TME biomarkers are generally absent.
Berberine	Multiple solid tumors	Cell and animal studies summarized in pharmacology reviews	Mostly invasion and growth endpoints	EMT, inflammation, metabolism and immune related pathways	NF-κB, STAT3, AMPK, PI3K/AKT, MMPs	C to D	Best treated as a mechanistic candidate unless metastasis endpoints and tissue exposure are shown.
Curcumin	Multiple solid tumors	Preclinical and clinical literature summarized across cancer studies	Mostly invasion, angiogenesis and adjunctive endpoints	Inflammation, angiogenesis, EMT and immune tone	NF-κB, STAT3, HIF-1α/VEGF, COX-2	C to D	Broad TME relevance but bioavailability and metastatic endpoint limitations must be stated.
Baicalein, baicalin and wogonin	Multiple cancer types	Scutellaria constituent studies and reviews	Mostly invasion and EMT related endpoints	EMT, inflammatory signaling, apoptosis and angiogenesis	TGF-β/Smad, Wnt/β-catenin, NF-κB, MMPs	D	Useful for EMT and invasion hypotheses, but direct pre-metastatic niche evidence is limited.
Tanshinone IIA and Danshen derived constituents	Solid tumors and vascular biology contexts	Pharmacology and cancer mechanism literature	Mostly invasion, angiogenesis or growth endpoints	Endothelial function, EMT, inflammatory signaling	PI3K/AKT, STAT3, VEGF, MMPs	C to D	Relevant to vascular and invasion modules but needs organotropic metastasis validation.

Medicine or compound	Cancer type	Model or setting	Metastatic endpoint	Microenvironmental target	Main signaling	Evidence grade	Main interpretation
Matrine and oxymatrine	Solid tumor preclinical models	Literature review and mechanism studies	Mostly invasion, apoptosis and growth endpoints	EMT, inflammatory signaling and immune modulation	NF-κB, PI3K/AKT, MMPs	D	Mechanistic candidate for invasion and immune modules, with limited direct metastatic TME evidence.
β-elemene and elemene formulations	Multiple solid tumors	Drug delivery and cancer therapy literature	Metastasis related claims vary by model	Tumor cell plasticity, immune modulation and treatment sensitization	PI3K/AKT, MAPK, apoptosis and EMT pathways	C to D	Potential translational candidate, but evidence should be separated by formulation and model.
Artemisinin related compounds	Multiple solid tumors	Natural product cancer pharmacology literature	Mostly growth, invasion and angiogenesis endpoints	Oxidative stress, angiogenesis and immune context	ROS, NF-κB, VEGF, apoptosis pathways	D	Mechanistic support is broad, but metastatic niche claims remain insufficient.
Formula level candidates	Breast, colorectal, liver and lung cancer contexts	Formula studies with variable standardization	Metastatic endpoints inconsistent or absent	TAMs, MDSCs, CAFs, angiogenesis, metabolism and exosomes	IL-6/STAT3, CCL2/CCR2, CXCL12/CXCR4, LOX, HIF-1α/VEGF	C to E	Most important future direction. Claims require chemistry, exposure, metastasis burden and TME readouts in the same evidence chain.

5 Mongolian Medicine and the Metastatic Microenvironment

Mongolian medicine is the distinctive feature of this review, but it must be handled with more restraint than Chinese medicine. Mongolian medicine has a long medical tradition and materia medica shaped by Inner Asian ecology, Tibetan medicine, Chinese medicine, regional folk practice and local botanical resources. Authoritative materia medica sources and plant compendia document medicinal plants used in Mongolia and Mongolian medical contexts, while selected phytochemical studies show that individual species contain alkaloids, flavonoids, phenolics, polysaccharides or terpenoids with plausible anti inflammatory or immunoregulatory activity [84,85,86,87,88,89,90]. This

resource base is real. The direct evidence that classical Mongolian medicines remodel metastatic niches is not yet strong.

5.1 Classical Mongolian Formulas and Mongolian Medicinal Materials

The first and most stringent evidence layer includes classical Mongolian formulas, clearly documented Mongolian medicinal materials and studies that explicitly test a medicine within a Mongolian medical context. This layer should include formula name, Latin source, plant part, traditional use, processing, extraction method and chemical markers. At present, this layer is rich in materia medica documentation but thin in metastatic TME models. This is not a reason to exclude Mongolian medicine. It is a reason to define its current evidentiary position honestly.

A modern Mongolian medicine program should begin with a small number of well authenticated formulas or herbs, establish chemical fingerprints, use orthotopic breast, colorectal, liver or lung cancer models, and sample both primary tumor and distant organs. The readouts should include metastatic burden, macrophage and myeloid subsets, vascular permeability, ECM deposition, exosome markers and spatial immune organization. This design would move Mongolian medicine from ethnopharmacological promise toward direct antimetastatic evidence.

5.2 Cross-used Materia Medica

The second evidence layer includes cross-used materia medica. Taraxacum mongolicum is the clearest example in the current reference set because it is botanically and culturally relevant and has been studied in breast cancer cell and macrophage associated contexts. In one study, Taraxacum mongolicum extract affected malignant phenotypes in a TAM related microenvironment through IL-10/STAT3/PD-L1 signaling, which is directly relevant to immune escape even though it should be classified as cross-used materia medica rather than definitive classical Mongolian formula evidence. This distinction prevents the manuscript from borrowing all Chinese medicine or general natural product studies and calling them Mongolian medicine evidence.

Cross-used materials are scientifically valuable precisely because they create bridges among Chinese medicine, Mongolian medicine and regional ethnopharmacology. They should be labelled transparently. The table should state whether the study tested a Mongolian formula, a Mongolian medicinal material, a cross-used plant, a purified compound or a general natural product. This makes the evidence map more convincing and turns the limited Mongolian literature into a structured research agenda.

5.3 General Natural Product Evidence and Candidate-only Evidence

The third layer includes general natural product evidence. If a compound exists in a Mongolian medicinal plant but the experiment was not performed in a Mongolian medicine context, the study should not be counted as Mongolian medicine evidence. It can be used as candidate support, especially for anti inflammatory, immune, vascular or metabolic hypotheses, but it remains indirect. This distinction is particularly important for purified flavonoids, alkaloids, phenolics and polysaccharides that appear across many medicinal plants.

There is also a practical collection and conservation dimension. Some Mongolian medicinal materials are tied to grassland or desert ecologies, and chemical profiles may vary with geography, climate, harvest season and processing. Sustainable sourcing is therefore not only an environmental issue but also a scientific issue. If the chemical fingerprint changes, the immune or vascular effect may change. A future research platform should integrate botany, ecology, chemistry and cancer biology rather than treating plant identity as a footnote.

The absence of direct pre-metastatic niche studies should be written as a research opportunity rather than as a rhetorical weakness. A Mongolian candidate with anti inflammatory activity could be tested in a breast cancer lung niche model by measuring lung vascular permeability, fibronectin, S100A8/A9, Ly6C myeloid cells, macrophage states and early tumor cell seeding. A candidate that affects endothelial function could be tested in lymphangiogenesis and lymph node spread models. These designs would decide whether Mongolian medicine can move beyond candidate status.

Table 3. Evidence hierarchy for Mongolian medicine and metastatic TME research.

Evidence class	Examples or scope	Antitumor evidence	Antimetastatic evidence	TME evidence	Current status	Required next validation
Classical Mongolian formula	Formulas clearly recorded and tested in Mongolian medicine context	Limited and uneven	Rare or absent	Rare or absent	True Mongolian evidence but underdeveloped for metastasis	Formula authentication, chemical fingerprint, orthotopic metastasis model and immune stromal profiling

Evidence class	Examples or scope	Antitumor evidence	Antimetastatic evidence	TME evidence	Current status	Required next validation
Mongolian medicinal material	Authenticated plant, mineral or animal material documented in Mongolian materia medica	Variable, often general pharmacology	Usually absent	Possible anti inflammatory or immunoregulatory signals	Candidate Mongolian evidence	Taxonomy, voucher specimen, source region, extract standardization, metastatic endpoint
Cross-used materia medica	Taraxacum mongolicum and other materials shared with Chinese or regional medicine	Some cancer related studies exist	Usually not direct	TAM related IL-10/STAT3/PD-L1 evidence is relevant for Taraxacum mongolicum	Valuable but must be labelled cross-used	Separate Mongolian provenance from Chinese or general natural product evidence
Purified compound from a Mongolian medicinal plant	Flavonoids, alkaloids, phenolics, polysaccharides or terpenoids	May exist in broader natural product literature	Not Mongolian medicine evidence by itself	Mechanistic clues only	Candidate only	Show the compound is present, absorbed and active at relevant exposure in a Mongolian preparation
General natural product evidence	Studies unrelated to Mongolian medical use but involving similar compounds	Often broad	Variable	May involve inflammation, VEGF, macrophages or oxidative stress	Indirect background evidence	Do not count as Mongolian evidence unless preparation and provenance are established
Validated future Mongolian candidate	Well defined formula or material tested in metastasis models	To be determined	Required	Required	Research goal	Metastatic burden plus TAM, MDSC, CAF, ECM, vascular, exosome and spatial immune endpoints

6 Integrative Mechanisms Across Medicines and Metastatic Stages

The value of placing Chinese and Mongolian medicines together is not that both traditions have equal evidence. They do not. The value is that both can be interpreted through a multistage metastatic ecology. Figure 1 organizes the possible mechanisms into six modules. Immune remodeling includes TAM repolarization, myeloid suppression, Treg reduction and restoration of CD8 T cell or NK cell function. Inflammation control includes NF-κB, IL-6 STAT3, COX2 PGE2 and inflammasome related circuits. Vascular regulation includes HIF-1α VEGF, VEGFR, Ang2, lymphangiogenesis and endothelial leakiness. Invasion control includes TGF-β Smad, Wnt/β-catenin, PI3K/AKT and MMP activity. Metabolic state includes hypoxia, lactate, acidosis and AMPK mTOR balance. Matrix and stromal control includes CAF activation, collagen deposition, LOX and stiffness.

6.1 From Multitarget Claims to Stage Specific Mechanisms

Multitarget action is often presented as an advantage of traditional medicines, but it becomes scientifically meaningful only when targets are mapped to metastatic stages. In early invasion, EMT, matrix proteases and CAF interaction dominate. During intravasation and extravasation, vascular leakiness, macrophage assistance and platelet protection matter. During niche formation, exosomes, myeloid recruitment, fibronectin, LOX and inflammatory signals matter. During colonization, immune surveillance, dormancy escape, metabolic fit and angiogenic restart matter. A formula that touches many pathways is not automatically useful. It is useful if its pathway combination weakens a bottleneck that metastatic cells must cross.

This view also changes how figures and tables should be read. A table of compounds and pathways is not enough. The table must say whether a pathway has been linked to a metastasis endpoint, whether the evidence comes from a primary tumor or a metastatic organ, and whether the study shows direct antimetastatic activity or only TME regulation. The same pathway can have different meanings across stages. VEGF suppression in a primary tumor may indicate antiangiogenesis. VEGF suppression in lung pre-metastatic tissue may indicate niche prevention. VEGF suppression during immunotherapy may either improve or worsen immune entry depending on vascular normalization. Therefore, stage, timing and tissue site must be reported.

A stage resolved synthesis also clarifies why some herbal studies seem inconsistent. If treatment begins before tumor implantation, the result may reflect host conditioning, inflammation reduction or immune priming rather than direct tumor cell action. If treatment begins when the primary tumor is established, the result may reflect effects on invasion, angiogenesis and intravasation. If treatment begins after tumor cells have been injected intravenously, the result largely tests circulation survival, arrest, extravasation and colonization. If treatment begins after micrometastases are established, the result tests outgrowth and therapeutic control. These designs answer different questions. A review that merges them will produce confusion. A review that separates them can explain why the same medicine may appear strong in one model and weak in another.

The strongest conceptual claim of this manuscript is that the metastatic soil can be remodeled at several distances from the primary tumor. The local soil surrounds the invasive front and contains macrophages, fibroblasts, vessels and matrix. The systemic soil includes circulating cytokines, platelets, neutrophils, myeloid cells, metabolites and extracellular vesicles. The distant soil includes resident macrophages, endothelial cells, fibroblasts, hepatocytes, osteoblast lineage cells, astrocytes or other organ specific populations. Chinese and Mongolian medicines may act at any of these distances. This broader geography is more faithful to metastasis biology than the common practice of measuring only the primary tumor mass.

The concept of balance, frequently used in traditional medicine writing, can be made scientifically rigorous if it is translated into dynamic constraints. Immune balance can mean reduced suppressive myeloid tone with preserved cytotoxic function. Vascular balance can mean reduced leakiness with improved perfusion. Matrix balance can mean less pathological stiffness without complete loss of tissue structure. Metabolic balance can mean less lactate accumulation and hypoxia with improved immune cell fitness. These translations give traditional language a precise experimental form and prevent the manuscript from drifting into vague rhetoric.

Figure 1. Six mechanistic modules linking Chinese and Mongolian medicines to metastatic TME remodeling.

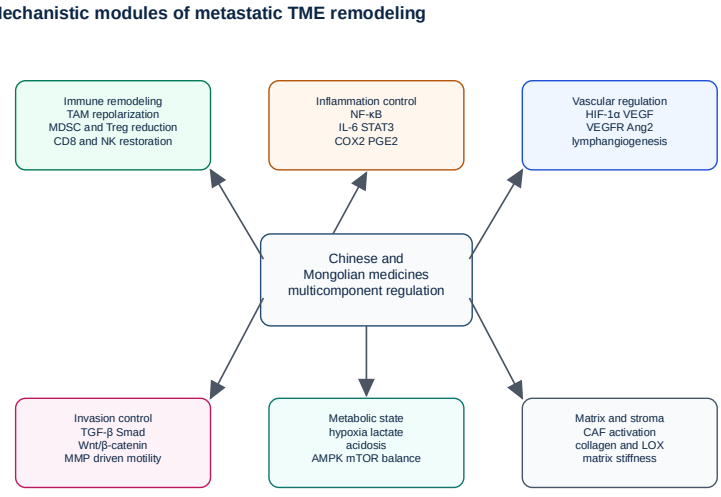
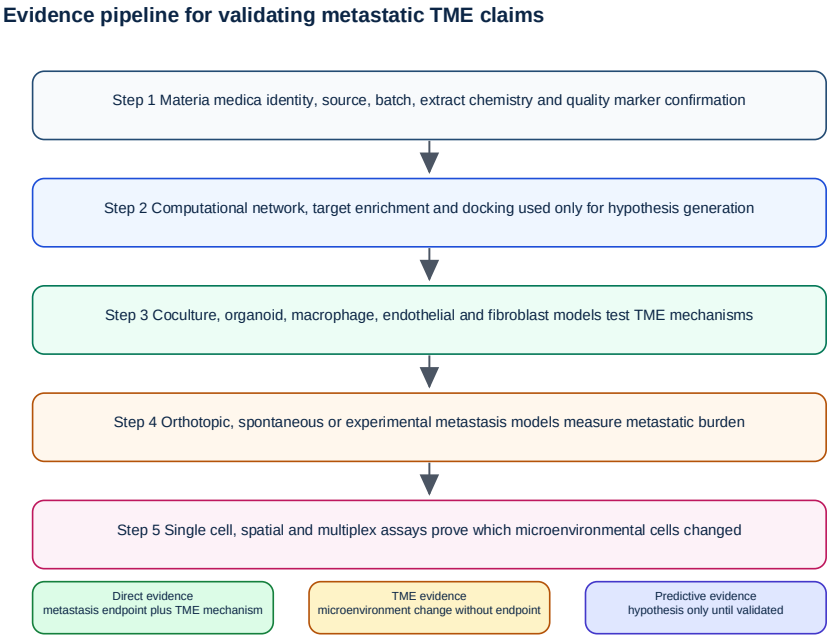


Table 4. Signaling pathways and metastatic TME interpretation.

Pathway	Metastatic interpretation	Evidence caution
TGF-β Smad	Controls EMT, immune suppression, CAF activation and tissue fibrosis.	Marker reversal alone does not prove metastasis inhibition.
Wnt/β-catenin	Supports plasticity, stemness and immune exclusion in selected tumors.	Context dependent and may vary by tumor type.
PI3K/AKT mTOR	Links survival, metabolism, invasion and therapy resistance.	Common pathway hits need dose and exposure validation.
NF-κB and IL-6 STAT3	Connect inflammation to myeloid expansion, EMT, angiogenesis and cachexia.	Inflammation suppression must be tied to metastatic endpoints.
HIF-1α VEGF	Connects hypoxia to angiogenesis, vascular leakage and niche priming.	Vessel pruning and normalization should be distinguished.
LOX ECM integrin FAK	Links stiffness, collagen crosslinking and distant niche formation.	Often missing in herbal medicine studies.
PD-1/PD-L1 and suppressive myeloid circuits	Shape immune escape during colonization.	Requires functional immune assays, not only expression data.

Figure 2. Evidence pipeline for validating Chinese and Mongolian medicines that claim metastatic TME remodeling.



7 Computational Discovery and Multilevel Validation

Network pharmacology and systems pharmacology are widely used in Chinese medicine research. TCMSP, BATMAN TCM, ETCM and related systems pharmacology frameworks make it possible to link herbs, compounds, predicted targets, pathways and disease modules. Network medicine can also help prioritize herbal candidates whose targets fall near metastasis related modules in protein

interaction space [91,92,93,94,95,96,97]. These tools are useful because herbal medicines contain many compounds and because metastasis is a network problem. They help generate hypotheses that would be difficult to discover by reading single pathway studies alone.

However, computational prediction must not be written as mechanistic proof. Docking a compound to STAT3 or VEGFR does not show that the compound reaches a metastatic organ, binds the target at relevant concentration, changes immune or stromal cells, or reduces metastasis. Transcriptomic reanalysis can identify pathway associations, but it cannot prove causality. The correct pipeline is shown in Figure 2. Materia medica identity and quality come first. Computational methods then generate hypotheses. In vitro coculture, organoid, macrophage, endothelial and fibroblast systems test microenvironmental interactions. Orthotopic or spontaneous metastasis models test metastatic burden. Single cell, spatial and multiplex methods identify the cell states and tissue architecture that changed.

Figure 2. Evidence pipeline for validating Chinese and Mongolian medicines that claim metastatic TME remodeling.

7.1 Cell Resolved and Spatial Evidence

Single cell and spatial methods are particularly important for this field because traditional medicines rarely act through one cell type. A treatment may reduce tumor cell EMT, but the same sample may show changes in macrophages, endothelial cells, fibroblasts and T cells. Bulk tissue assays average these signals and can mislead interpretation. Single cell RNA sequencing can identify which populations respond. Spatial transcriptomics, multiplex immunofluorescence or imaging mass cytometry can show whether cytotoxic cells enter tumor nests, whether macrophages cluster near vessels, whether CAFs form exclusion barriers and whether disseminated cells are surrounded by suppressive niches.

For Mongolian medicine, these methods are a way to accelerate evidence building. Instead of testing many herbs in shallow assays, investigators could choose a small number of authenticated candidates and perform deep profiling in a metastasis model. If a candidate reduces lung metastatic burden and simultaneously lowers suppressive macrophage states, decreases fibronectin deposition and restores NK cell proximity to tumor cells, it would create a strong mechanistic signature. If it only changes predicted targets in a network, it remains a candidate. This hierarchy should be explicit.

Spatial evidence is also a safeguard against misleading averages. A treatment may not change the total number of macrophages in a tumor, but it may move them away from vessels or away from invasive fronts. It may not change total CD8 T cell abundance, but it may allow T cells to cross a CAF rich exclusion barrier. It may not reduce overall collagen, but it may disrupt aligned collagen fibers that guide invasion. These spatial effects are directly relevant to metastatic behavior and are often invisible in western blotting or bulk PCR. Future Chinese and Mongolian medicine studies should therefore combine molecular assays with spatial pathology whenever possible.

Computational methods should be integrated after, not before, careful evidence classification. A network can prioritize candidate pathways, but the evidence map determines which claims can be made. For example, a formula predicted to target VEGF, STAT3 and MMP9 may be described as a candidate for vascular, immune and invasion modules. It should not be described as proven to inhibit metastasis unless an appropriate model shows reduced metastatic burden. This distinction is especially important for review writing because readers may mistake large network diagrams for strong evidence. A well written review should make prediction look useful but provisional.

Multiomics can help solve the problem of component complexity. Metabolomics can identify absorbed compounds and host metabolites changed by treatment. Proteomics can identify secreted factors and matrix proteins. Single cell transcriptomics can identify responding cell states. Spatial methods can identify tissue architecture. Microbiome analysis can test whether oral medicines change systemic immunity through gut ecology. These layers should not be added as fashionable decoration. They should answer a specific causal question, such as whether a formula prevents lung niche formation by reducing myeloid recruitment or whether it improves checkpoint response by changing macrophage T cell communication.

8 Translational Considerations Rather Than Established Clinical Evidence

Clinical translation is the point at which many promising herbal mechanisms lose clarity. Traditional Chinese medicine has entered adjunctive oncology discussions, and modernization debates emphasize standardization, evidence quality and integration with conventional therapy [98,99,100]. For the metastatic TME topic, clinical endpoints must match the claim. Tumor response, symptom relief and immune marker changes are useful but insufficient. The relevant endpoints include recurrence rate, time to distant metastasis, metastasis free survival, progression free survival in metastatic disease, circulating tumor cells, extracellular vesicle markers, immune cell subsets and tissue biomarkers from primary and metastatic lesions.

Combination therapy requires special caution. A medicine that reduces MDSCs or TAM mediated suppression could in principle improve immune checkpoint blockade. A medicine that normalizes vessels could improve drug delivery or immune infiltration. A medicine that lowers inflammatory cytokines could reduce cachexia or treatment related inflammation. Yet these same interventions could also alter drug metabolism, transporter activity, hepatic or renal exposure, coagulation, bleeding risk or immune related adverse events. Therefore, combination studies should include pharmacokinetics, toxicity, herb drug interaction assessment and immune safety.

Quality control is not a technical appendix. It is central to the biology. If an extract is chemically undefined, the study cannot be reproduced. If the dose is far above achievable exposure, the mechanism may be irrelevant. If the batch varies, a macrophage or VEGF effect may disappear. For Mongolian medicine, taxonomic authentication and local name standardization are especially important because cross use of plants across medical traditions can blur attribution. The review should encourage a reporting standard that includes Latin binomial, plant part, voucher specimen, source region, processing, extraction method, fingerprint, marker compounds, dose, route, schedule and exposure where possible.

Clinical studies also need better timing. Metastasis prevention, adjuvant recurrence reduction, treatment of established metastatic disease and symptom support are different clinical aims. A formula given after surgery to prevent recurrence should be evaluated through recurrence and metastasis free survival. A formula given with chemotherapy in metastatic disease should be evaluated through progression free survival, organ specific response, toxicity and biomarkers of immune or vascular change. A formula used for supportive care may improve quality of life without being antimetastatic. The manuscript should respect these distinctions because they prevent exaggerated clinical interpretation.

Biomarker strategy is another weakness in current translation. Peripheral cytokines or lymphocyte subsets are easy to measure, but they may not represent the metastatic organ. Liquid biopsy may help by tracking circulating tumor DNA, extracellular vesicle cargo, CTC clusters or inflammatory proteins, but tissue validation remains important when the claim is TME remodeling. In neoadjuvant or surgical settings, paired tissue can reveal whether a medicine altered macrophages, CAFs, vessels or hypoxia. In metastatic settings, biopsies are harder but more informative. A mature field will need both accessible blood markers and tissue anchored mechanisms.

Safety deserves a central position because TME remodeling can be double edged. Dampening inflammation may reduce myeloid recruitment and cachexia, but excessive immunosuppression could weaken tumor surveillance. Reducing angiogenesis may limit dissemination, but excessive vascular pruning can increase hypoxia and resistance. Modulating coagulation or platelet activity may affect circulating tumor cell survival, but it may also increase bleeding risk. Herbal medicines can also interact with cytochrome enzymes, transporters and immune therapies. The safest translational path is not to assume benignity, but to measure interaction, exposure and adverse events prospectively.

Table 6. Clinical and translational evidence framework for Chinese and Mongolian medicines.

Formula or medicine	Cancer type	Clinical setting	Outcome type	TME or immune biomarker	Safety issue	Evidence limitation
Astragalus based Chinese herbal combinations	Advanced non-small cell lung cancer	Combination with platinum based chemotherapy	Response and survival related outcomes	Mostly systemic immune inference rather than metastatic tissue biomarkers	Herb drug interaction and chemotherapy tolerance require monitoring	Not designed as a metastasis prevention or metastatic TME trial
General Chinese herbal adjuvant therapy	Multiple cancers	Chemo or radiotherapy adjunctive use	Quality of life, toxicity, response or survival outcomes	Variable immune markers in peripheral blood	Hepatic, renal, marrow and interaction monitoring needed	Heterogeneous formulas and limited metastatic endpoints
Potential recurrence prevention formulas	Postoperative solid tumors	Adjuvant setting after primary treatment	Recurrence, distant metastasis and metastasis free survival should be prioritized	CTCs, extracellular vesicles, TAM or MDSC markers, cytokines and tissue immune profiles	Long term exposure and standardization required	Often discussed mechanistically but rarely tested with rigorous metastatic endpoints

Formula or medicine	Cancer type	Clinical setting	Outcome type	TME or immune biomarker	Safety issue	Evidence limitation
Potential immunotherapy combinations	Metastatic solid tumors	Combination with immune checkpoint blockade	Progression free survival, response durability and organ specific control	CD8+ T cells, NK cells, TAMs, MDSCs, Tregs and PD-1/PD-L1 axis	Immune related adverse events and immunosuppressive effects must be tracked	Most claims remain preclinical or hypothetical
Mongolian medicine candidates	Not yet established	Future translational studies	Metastasis incidence, organ colonization or recurrence should be defined prospectively	Macrophage, myeloid, vascular, ECM and exosome biomarkers	Authentication, dose, toxicity and sustainability must be established first	Clinical metastatic TME evidence is currently insufficient

9 Challenges and Future Perspectives

Evidence grading and overclaiming remain the first challenge. Anticancer, anti-invasive, TME-remodeling and antimetastatic claims are not interchangeable. A cell viability result is not evidence of metastatic TME remodeling, a migration assay is not proof of metastasis prevention, and a pathway prediction is not a mechanism. The review therefore concentrates evidence caution in the Methods and Challenges sections and uses tables to show which claims are direct, which are TME related and which are predictive.

Model mismatch is the second challenge. Subcutaneous tumors are convenient but often poor models of spontaneous metastasis and organ specific niches. Tail vein models test survival, arrest and colonization but bypass invasion and intravasation. Orthotopic and spontaneous models are more demanding but better suited to Chinese medicine studies that claim multistage regulation. Preventive niche studies require distant organ sampling before tumor arrival, whereas therapeutic colonization studies require treatment after dissemination.

Mongolian medicine standardization is the third challenge. The field needs an independent evidence system rather than borrowing strength from Chinese medicine or general natural product literature. A Mongolian evidence table should include name, Latin source, traditional use, formula context, active constituents, model, TME endpoint, metastasis endpoint and evidence grade. This will reveal gaps but also protect the originality of Mongolian medicine by defining what has and has not been shown.

Pharmacokinetics and quality control are the fourth challenge. In vitro concentrations may exceed achievable exposure, and undefined extracts cannot be reproduced. Studies should report plant identity, voucher specimen, origin, processing, extraction, fingerprint, marker compounds, route, schedule, dose conversion, absorbed components and metastatic organ exposure. These details are especially important for formulas and for Mongolian materia medica whose chemistry may vary with ecology and harvest conditions.

Multiomics and clinical translation form the fifth challenge. Single cell, spatial, proteomic, metabolomic and microbiome methods should be used to test specific causal questions rather than to decorate a manuscript. Clinical studies should distinguish supportive care, combination therapy, recurrence prevention and treatment of established metastatic disease. The most relevant endpoints are recurrence, distant metastasis, metastasis free survival, circulating tumor cells, extracellular vesicle markers and tissue anchored immune or stromal biomarkers.

Table 5. Translational challenges and future strategies.

Challenge	Why it matters	Recommended strategy
Evidence mixing	Cell viability, migration, TME markers and metastasis endpoints are often merged.	Use explicit grades for direct antimetastatic, TME, predictive and candidate evidence.
Model mismatch	Subcutaneous tumors cannot answer many metastatic niche questions.	Use orthotopic, spontaneous, organotropic and time staged niche models.

Challenge	Why it matters	Recommended strategy
Mongolian medicine standardization	Ambiguous plant identity and formula provenance weaken reproducibility.	Report Latin name, voucher, origin, processing, fingerprint and marker compounds.
Pharmacokinetics	In vitro concentrations may exceed achievable tissue exposure.	Measure absorbed components and metastatic organ exposure.
Cellular resolution	Bulk assays cannot identify the responding microenvironmental cells.	Use single cell, spatial and multiplex immune assays.
Clinical endpoints	Symptom or response endpoints do not prove antimetastatic effect.	Use recurrence, metastasis free survival, CTCs, exosomes and tissue biomarkers.

10 Conclusion

The metastatic tumor microenvironment offers a deeper and more original framework for reviewing Chinese and Mongolian medicines than a general TME theme. Metastasis is not merely movement of malignant cells. It is a multistage ecological transition in which immune suppression, vascular abnormality, stromal remodeling, hypoxia, acidosis, metabolic plasticity, pre-metastatic niche formation and colonization cooperate to create receptive soil. Chinese medicine already has a broad body of mechanistic evidence across EMT, TAMs, MDSCs, Tregs, angiogenesis, inflammation and metabolism. Some of that evidence is directly antimetastatic, much of it is TME related, and some remains predictive. Mongolian medicine has distinctive resource value and plausible immunoinflammatory or vascular regulatory potential, but direct metastatic TME evidence remains insufficient.

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