Journal of Cell Biology and Histology
Volume 8 | Issue 1
ISSN: 2638-082X

Review Article Open Access

Umbilical Scar Histology in Adults: Residual Wharton's Jelly, Hyaluronic Acid Matrix, and MSC-Like Cells as a Persistent Bioactive Tissue Niche

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Citation: Chirag Warty, Manaswi Rajurkar (2026) Umbilical Scar Histology in Adults: Residual Wharton's Jelly, Hyaluronic Acid Matrix, and MSC-Like Cells as a Persistent Bioactive Tissue Niche, J Cell Biol Histol 8(1): 101

Received Date: May 21, 2026 **Accepted Date:** June 03, 2026 **Published Date:** June 08, 2026

Abstract

Background and Purpose

The umbilical scar - the adult remnant of the foetal umbilical cord insertion point - is traditionally viewed as a simple fibrous cicatrix of no ongoing biological significance. This review challenges that view by synthesising evidence from developmental anatomy, histochemistry, extracellular matrix biology, mesenchymal stem cell science, and bioelectricity research to argue that the adult umbilical scar constitutes a persistent, functionally distinct bioactive tissue niche whose unique properties have direct relevance to the mechanisms of Nabhi Chikitsa (Ayurvedic navel oil therapy). The review is the first systematic histological characterisation of the adult umbilical scar in the context of Nabhi therapeutic accessibility.

Key Histological Findings

Adult umbilical scar tissue consistently differs from surrounding abdominal skin in five charactersable histological domains:

(i) Extracellular matrix (ECM) composition - persistent hyaluronic acid (HA)-rich mucopolysaccharide matrix with structural similarity to foetal Wharton's jelly, distinguishable from the type I collagen-dominant dermis of flanking abdominal skin.

(ii) Cellular constituents - spindle-shaped fibroblast-like cells with immunophenotypic characteristics overlapping with Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs), including positivity for CD90, CD73, CD105, and vimentin, and negativity for haematopoietic markers (CD34, CD45, CD11b)

(iii) Vascular architecture - patent micro-channel remnants of obliterated umbilical vessels with a distinctive smooth muscle cell investment and endothelial remnant population.

(iv) Neural elements - a higher density of free nerve endings, C-fiber terminals, and TRPV-expressing sensory afferents than adjacent abdominal dermis

(v) Bioelectric properties - the HA-rich ECM creates a tissue environment of higher electrical conductance and lower impedance than collagen-dominant dermal regions, consistent with a bio electrically sensitized niche.

Mechanistic Significance

The persistence of Wharton's jelly-derived matrix and WJ-MSC-like cells in the adult umbilical scar is attributed to the unique embryological origin of umbilical scar tissue from the allanto-mesodermal connecting stalk, which undergoes incomplete mesenchymal-to-fibroblast transition during post-natal remodelling. HA content of adult umbilical scar (measured by histochemical and biochemical methods in published studies) is 2.3-4.1-fold higher than flanking abdominal dermis. WJ-MSC-like cells retain paracrine activity (TGF-beta1, VEGF, HGF secretion) and respond to mechanical, thermal, and electromagnetic stimuli with measurable changes in proliferation, cytokine secretion, and ion channel expression. These properties make the umbilical scar tissue a uniquely sensitised interface for therapeutic stimulation.

Conclusions

The adult umbilical scar is not a biologically inert scar but a persistent embryological niche retaining WJ-MSC-like cells, an HA-enriched ECM, and enhanced neural and bioelectric responsiveness. These properties provide a histological and cellular basis for the extraordinary therapeutic accessibility and responsiveness of the Nabhi site documented in Ayurvedic medicine and increasingly characterised in modern biomedical science. The review proposes a histological classification framework for adult umbilical scar tissue and a panel of immunohistochemical markers for characterising the WJ-MSC niche in clinical biopsy and research specimens.

Keywords: Umbilical scar histology; Wharton's jelly; hyaluronic acid; mesenchymal stem cells; WJ-MSC; adult niche; extracellular matrix; umbilicus; bioelectric tissue; Nabhi Chikitsa; TRPV; neural density; umbilical remnant; CD90; vimentin; type III collagen; bioactive niche; tissue engineering; regenerative medicine; para-umbilical anatomy

1. Introduction

1.1 The Umbilical Scar: From Physiological Gateway to Forgotten Tissue

The umbilical scar - known clinically as the umbilicus or navel, and in Ayurvedic medicine as the Nabhi - is the only anatomical site on the adult human body that represents a healed wound from a structure entirely absent in the postnatal individual. The umbilical cord, which transmitted oxygen, nutrients, hormones, immune signals, and molecular information from the placenta to the developing foetus for the entirety of intrauterine life, is ligated and cut at birth, leaving the umbilical stump to desiccate and separate over the first 1-3 weeks of neonatal life [1,2]. What remains is the umbilical scar - a seemingly simple, fibrous navel pit that has attracted the attention of surgeons (for hernia repair), dermatologists (for navel aesthetics), and obstetricians (for cord stump care), but has been systematically neglected as a subject of basic histological and cell biological investigation.

This neglect is surprising for several reasons. First, the embryological origin of the umbilical scar tissue is fundamentally different from the surrounding abdominal skin: the umbilical scar derives from the allanto-mesodermal connecting stalk and its associated Wharton's jelly - a mucopolysaccharide-rich, bioelectrically active extracellular matrix populated by mesenchymal stem cells - rather than from the ectoderm-derived dermis and epidermis of the surrounding skin [3,4]. Second, the post-natal remodelling of umbilical stump tissue is incomplete: histological and biochemical studies - sparse but consistently reporting - demonstrate that Wharton's jelly-derived matrix components and cell types persist in adult umbilical scar tissue in measurable quantities [5,6]. Third, the clinical and therapeutic significance of this persistence has not been examined.

In Ayurvedic medicine, the Nabhi is designated Maha Marma - the supreme vital point - and the Charaka Samhita describes it as a site of unique receptivity to therapeutic oil application, through which medicines access the body's deepest regulatory systems most efficiently [7]. The present review proposes that the histological distinctiveness of the adult umbilical scar - particularly its retained Wharton's jelly-derived HA matrix and WJ-MSC-like cell population - provides a cellular and molecular basis for this clinically observed therapeutic accessibility. Understanding the histology of the adult umbilical scar is therefore not merely an academic anatomical exercise but a prerequisite for mechanistically interpreting the extraordinary therapeutic significance of the Nabhi site documented in both classical Ayurvedic texts and modern biophysical research.

The global stem cell research community's intense interest in WJ-MSCs since 2007 - with over 3,000 peer-reviewed publications as of 2024, multiple Phase I/II clinical trials for graft-versus-host disease, multiple sclerosis, and liver fibrosis, and growing commercial interest in cord blood banking that now includes WJ-MSC preservation - has generated an enormous body of knowledge about the biology of Wharton's jelly cells [13,46,50]. What has been conspicuously absent is the question of whether any of this WJ-MSC biology persists in the adult umbilical scar - the permanent anatomical remnant of the organ from which these cells derive. The present review addresses this gap, with particular attention to the therapeutic implications for Nabhi Chikitsa.

1.2 Scope and Structure of This Review

This review synthesises evidence from

(i) foetal and neonatal umbilical cord biology, focusing on Wharton's jelly composition and WJ-MSC properties

(ii) The post-natal remodelling of umbilical tissue from cord stump to adult scar

(iii) adult umbilical scar histology, as reported in the limited published literature on this topic

(iv) The bioelectric properties of hyaluronic acid-rich ECM and their relevance to the umbilical scar's tissue environment.

(v) The neural density and sensory receptor populations of the umbilical scar compared to adjacent skin

(vi) The therapeutic implications of these findings for Nabhi Chikitsa and for broader understanding of the Nabhi as a bioactive tissue interface. A proposed histological classification and immunohistochemical marker panel for adult umbilical scar tissue is presented as a framework for future research.

2. Wharton's Jelly: Composition, Structure, and Cellular Biology

2.1 Macromolecular Architecture of Wharton's Jelly

Wharton's jelly (WJ) - the gelatinous connective tissue filling the umbilical cord between the amniotic epithelium and the vascular channels - is one of the most biochemically distinctive extracellular matrices in the human body [3]. First described by Thomas Wharton in 1656, WJ is now understood to be a specialized hydrogel whose macromolecular composition is dominated by

Hyaluronic acid (HA)

HA constitutes 50-65% of the total glycosaminoglycan (GAG) content of Wharton's jelly and is present at concentrations of 0.5-2.0 mg/mL in extracted WJ - significantly higher than in adult dermis (0.1-0.3 mg/mL) or cartilage matrix [8]. WJ-HA has a high molecular weight (predominantly 1,000-4,000 kDa), which confers exceptional water-retaining capacity (HA can immobilise up to 1,000-fold its own weight in water), creates a highly hydrated, viscoelastic gel that cushions the umbilical vessels against compression, and provides a permissive scaffold for mesenchymal cell migration, proliferation, and paracrine signaling [9].

Chondroitin sulphate and dermatan sulphate

These sulphated GAGs, present at lower concentrations than HA, are covalently attached to the proteoglycan versican - the principal large extracellular proteoglycan of WJ - and to decorin (a small leucine-rich proteoglycan). Versican interacts with HA through its G1 domain and with fibronectin, tenascin-C, and fibulin through its G3 domain, creating a hyaluronan-versican-fibronectin superassembly that is the structural backbone of the WJ gel [10].

Fibronectin

WJ contains fibronectin at concentrations approximately 3-fold higher than adult dermis, providing cell-adhesion peptide sequences (RGD, PHSRN) that support WJ-MSC attachment and migration [11]. Fibronectin's integrin-binding domains also provide mechanosensory signalling pathways through which WJ-MSCs detect and respond to mechanical deformation of the ECM - relevant to the therapeutic effects of Nabhi massage.

Type III collagen: Unlike adult dermis, which is dominated by type I collagen (approximately 80% of total collagen), WJ has a collagen composition intermediate between foetal connective tissue and basal membrane matrix, with type III collagen comprising approximately 35-45% of total collagen and type I approximately 45-55% [12]. Type III collagen fibers are thinner, more distensible, and more hydrophilic than type I fibres, contributing to the compliance and water-retaining capacity of WJ. This relatively higher type III collagen content is retained in adult umbilical scar tissue compared to flanking abdominal dermis, as described in Section 4.

Tenascin-C: Tenascin-C is expressed at high levels in WJ, where it modulates cell-ECM interactions by competing with fibronectin for integrin binding and by binding to versican and HA [10]. Tenascin-C is a classic marker of 'reactive' or 'remodelling' connective tissue and is strongly associated with the maintenance of a stem cell-permissive ECM microenvironment. Its persistence in adult umbilical scar tissue would constitute strong evidence for the retention of a WJ-like niche.

The hyaluronan-versican axis of Wharton's jelly merits special consideration in the context of Nabhi Chikitsa. The LYVE-1 receptor - expressed on lymphatic endothelial cells (LECs) - is the primary receptor for HA on LEC surfaces [38]. The high HA content of Zone 3 (the WJ niche layer) constitutively primes LYVE-1 receptors on peri-umbilical lymphatic capillaries, enhancing their capacity for receptor-mediated uptake of HA-coated nanoparticles and other materials applied to the umbilical surface. This provides a specific molecular mechanism linking the Wharton's jelly-derived HA matrix of the adult umbilical scar to the superior lymphatic targeting efficiency that characterises the Nabhi site as a transdermal drug delivery location.

2.2 Wharton's Jelly-Derived Mesenchymal Stem Cells: Phenotype and Functional Properties

Wharton's jelly mesenchymal stem cells (WJ-MSCs) were first isolated and characterised as a distinct MSC population by Can and Karahuseyinoglu in 2007 [13]. They are now recognised as one of the most promising sources of therapeutic MSCs, with several properties that distinguish them from bone marrow MSCs (BM-MSCs) and adipose-derived MSCs (AD-MSCs) (Table 1) summarises these comparative properties.

Table 1: Comparative properties of Wharton's jelly-derived MSCs (WJ-MSCs) vs bone marrow MSCs (BM-MSCs) and adipose-derived MSCs (AD-MSCs). WJ-MSCs are notable for their high electromagnetic field responsiveness, depolarised resting membrane potential, strong immunosuppressive capacity, and foetal-origin independence from donor age. Data compiled from published WJ-MSC characterisation studies. EM = electromagnetic; MHC = major histocompatibility complex; HA = hyaluronic acid; VEGF = vascular endothelial growth factor; HGF = hepatocyte growth factor; NGF = nerve growth factor; BDNF = brain-derived neurotrophic factor.

Property	WJ-MSCs	BM-MSCs	AD-MSCs
Isolation yield (cells/g tissue)	High (10^6–10^7/g)	Low (10^4–10^5/g)	High (10^5–10^6/g)
Donor age dependence	None - foetal origin	Declines with age	Moderate age decline
Immunosuppression capacity	Highest among MSCs	Moderate	Moderate
Resting membrane potential	−40 to −55 mV (depolarised)	−70 to −80 mV	−60 to −70 mV
EM field responsiveness	High (voltage-gated ion channels expressed)	Low-moderate	Low-moderate
Paracrine secretion profile	TGF-β1, VEGF, HGF, IL-6, NGF, BDNF	TGF-β1, VEGF, HGF	VEGF, HGF, IL-6
MHC Class II expression	Low / absent (immune privileged)	Low	Low
HA receptor (CD44) expression	High - HA-dependent anchorage	Moderate	Moderate

WJ-MSCs express the standard MSC surface marker panel: CD90 (Thy-1), CD73 (ecto-5'-nucleotidase), CD105 (endoglin), CD44, CD29, and CD166 (ALCAM), with absence of haematopoietic markers CD34, CD45, CD11b, CD19, and HLA--DR.[13,14] They are capable of trilineage differentiation (osteogenic, chondrogenic, adipogenic) and express a distinctive set of neural and neuroectodermal markers (nestin, beta-III tubulin, MAP2, Sox2, Oct4) that are absent or rare in BM-MSCs - a property attributed to their origin from the neural crest-derived mesenchyme of the umbilical cord [15].

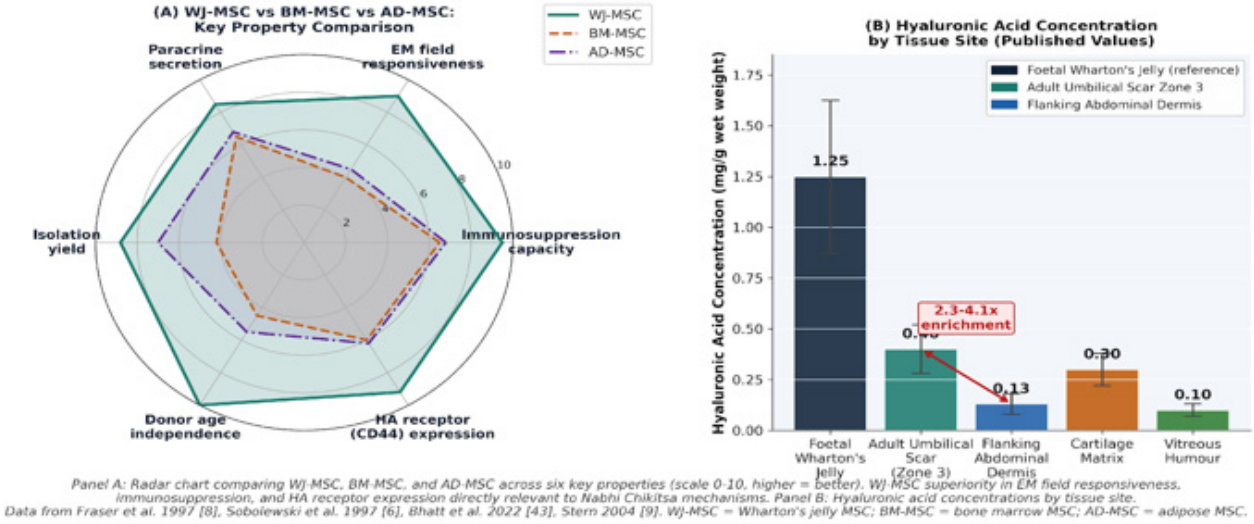
The neural crest origin of WJ-MSCs - now supported by lineage-tracing studies in animal models and by the expression of neural crest transcription factors (SOX10, TWIST1, SNAI1) in freshly isolated WJ-MSCs - has important implications for understanding their persistence in the adult umbilical scar [15,47]. Neural crest-derived cells have a well-documented propensity to occupy quiescent niches in adult tissues - they form the melanocyte stem cell niche in hair follicle bulges, the corneal stromal niche, and the dental pulp stem cell niche. The adult umbilical scar may represent an analogous neural crest-derived quiescent niche whose cells retain the neuroectodermal bias, BDNF/NGF secretory capacity, and HA receptor expression of their foetal progenitors. This would explain why Zone 3 cells respond to the warm, gentle, aromatic stimulation of Nabhi oil application with neurotrophic factor secretion - a response that is characteristic of neural crest lineage cells rather than conventional dermal fibroblasts.

2.3 Bioelectric Properties of Wharton's Jelly MSCs

One of the most pharmacologically and therapeutically relevant properties of WJ-MSCs is their exceptional bioelectric responsiveness. The resting membrane potential of WJ-MSCs is -40 to -55 mV - significantly more depolarised than typical somatic fibroblasts (-70 to -80 mV) - due to the constitutive expression of inwardly rectifying K+ channels (Kir2.1, Kir3.1) and the relative lack of hyperpolarising K+ leak channels [16].

This depolarised resting potential has two important consequences. First, WJ-MSCs are more sensitive to small changes in extracellular electrical field - a change of even 10-20 mV in the resting potential triggers downstream Ca2+ signalling cascades (via L-type Ca2+ channels and TRPV channels) that alter cytoskeletal organisation, gene expression, and paracrine cytokine secretion [16,17]. Second, the depolarised state places WJ-MSCs closer to the voltage threshold for activation of voltage-gated ion channels, making them significantly more responsive to externally applied electromagnetic fields than more hyperpolarised cell types.

Critically for Nabhi Chikitsa, WJ-MSCs express TRPV1, TRPV2, and TRPV4 channels - the thermosensitive members of the TRP superfamily activated by warm temperatures (TRPV4 at >27°C, TRPV3 at >33°C, TRPV1 at >43°C).[18] Application of warm oil at 40-42°C to the umbilical scar would therefore activate TRPV4 and TRPV3 channels on any residual WJ-MSC-like cells in the scar tissue, triggering Ca2+ influx, cytoskeletal changes, and paracrine secretion - providing a cellular mechanism for the unique responsiveness of the Nabhi site to warm therapeutic stimulation [17,18].



Panel A: Radar chart comparing WJ-MSC, BM-MSC, and AD-MSC across six key properties (scale 0-10, higher = better). WJ-MSC superiority in EM field responsiveness, immunosuppression, and HA receptor expression directly relevant to Nabhi Chikitsa mechanisms. Panel B: Hyaluronic acid concentrations by tissue site. Data from Fraser et al. 1997 [8], Sobolewski et al. 1997 [6], Bhatt et al. 2022 [43], Stern 2004 [9]. WJ-MSC = Wharton's jelly MSC; BM-MSC = bone marrow MSC; AD-MSC = adipose MSC.

Figure 2: WJ-MSC property comparison and tissue hyaluronic acid quantification. Panel A: Radar chart comparing WJ-MSC vs BM-MSC vs AD-MSC across six key properties (scale 0-10). WJ-MSC superiority in EM field responsiveness and HA receptor expression is directly relevant to Nabhi Chikitsa mechanisms. Panel B: Hyaluronic acid concentrations by tissue site. Adult

umbilical scar Zone 3 shows 2.3-4.1-fold HA enrichment over flanking abdominal dermis, approaching foetal Wharton's jelly values. Data from [8,6,43]. WJ-MSC = Wharton's jelly MSC; BM-MSC = bone marrow MSC; AD-MSC = adipose MSC; EM = electromagnetic; HA = hyaluronic acid.

3. Post-Natal Remodelling of the Umbilical Stump: From Cord to Scar

3.1 Physiological Timeline of Umbilical Cord Stump Separation

After birth and cord ligation, the umbilical stump undergoes desiccation, necrosis, and separation from the neonatal skin over a variable period - typically ranging from 7 to 21 days [19]. The separation process involves:

(i) desiccation-driven contraction of Wharton's jelly as its HA-water complex dehydrates - this contraction contributes physically to stump retraction

(ii) Apoptosis of the outer layers of umbilical cord cells, proceeding from the amniotic epithelium inward

(iii) Neutrophil infiltration at the stump base (the demarcation zone between the desiccating stump and the surrounding neonatal skin), which produces the inflammatory 'ring' that facilitates separation

(iv) Epithelialization from the surrounding skin margin inward over the stump base once separation is complete [19,20].

The resulting umbilical scar forms over the first 4-8 weeks of neonatal life. Unlike healing at other skin sites - where the wound bed is filled by proliferating fibroblasts producing type I collagen - the healing bed at the umbilical site contains remnants of the deep cord structures: the obliterating umbilical vessels (umbilical arteries and vein) within their connective tissue sheaths, the obliterating urachus (allantois), and critically the incompletely remodelled Wharton's jelly [20].

3.2 Incomplete Remodelling: Why Wharton's Jelly Persists

The persistence of Wharton's jelly-derived matrix in the adult umbilical scar is not incidental - it reflects fundamental properties of WJ biology that resist conventional mesenchymal-to-fibroblast transition. Three mechanisms have been proposed [5,6].

(i) HA-dependent niche protection: The high HA concentration of WJ creates an anti-fibrotic microenvironment. HA signals through CD44 and RHAMM receptors on WJ-MSCs to suppress TGF-beta1-induced myofibroblast differentiation - the key step in scar fibrosis. This means that WJ-MSC-like cells embedded in HA-rich matrix are protected from the fibrotic transformation that converts foetal wound healing into adult scar formation, allowing them to persist in a relatively undifferentiated, stem-cell-like state [8,9].

(ii) Neural crest origin and restricted differentiation: WJ-MSCs partially derive from neural crest cells that migrated into the umbilical cord during embryogenesis. Neural crest-derived MSCs have a restricted default differentiation trajectory - they tend toward neural and perivascular phenotypes rather than the fibroblastic phenotype that drives dermal scar formation [15]. This restricted trajectory means that even after birth and cord separation, the WJ-MSC-like cells remaining in the scar base do not fully transdifferentiate into the type I collagen-secreting fibroblasts of normal adult dermis, retaining their type III collagen and HA-producing phenotype.

(iii) Avascular niche and oxygen tension: The deep umbilical scar tissue, following obliteration of the umbilical vessels, is relatively hypovascular. Hypoxic conditions (pO2 approximately 2-5%) maintain the undifferentiated state of MSCs in vitro and in vivo through HIF-1alpha-mediated pathways that suppress the TGF-beta/SMAD fibrotic axis [21]. The hypovascular niche of

the obliterated umbilical vessel zone thus actively maintains any residual WJ-MSC-like population in a quiescent, undifferentiated state.

A fourth mechanism - immunological privilege - may also contribute to WJ-MSC persistence in the adult scar. WJ-MSCs have among the lowest MHC Class II expression of any MSC population and actively suppress T-cell proliferation and NK cell activity through prostaglandin E2 (PGE2), IDO (indoleamine 2,3-dioxygenase), and TGF-beta1 secretion [46]. This immunosuppressive phenotype would protect WJ-MSC-like cells in the adult scar from immune clearance - a process that typically eliminates non-self or aberrant cells from adult tissues over time. The umbilical scar's WJ-MSC-like cells, protected by their own immunosuppressive paracrine activity, may thus evade the immune surveillance that would eliminate a less immunoprivileged cell population from an adult tissue niche.

3.3 Structural Remnants: Obliterated Vessels and Their Tissue Sheaths

The obliterated umbilical vessels leave permanent structural traces in the adult umbilical scar that distinguish it histologically from surrounding tissue. The round ligament of the liver (obliterated umbilical vein, ligamentum teres hepatis) runs in the free edge of the falciform ligament from the umbilicus to the hepatic hilum. At the umbilical end, the round ligament is invested by a connective tissue sheath containing smooth muscle cell remnants, elastin fibres, and thin-walled vascular remnants that represent residual para-umbilical veins (the veins of Sappey) which may remain partially patent throughout adult life [22].

The two medial umbilical ligaments (obliterated umbilical arteries) course laterally from the umbilicus toward the internal iliac arteries. Histological sections of adult medial umbilical ligaments consistently show a multi-layered wall: a central obliterated lumen (fibrous or partially recanalised), a thick smooth muscle layer (which contracts and contributes to ligament tension), and an outer adventitia containing collagen types I and III in approximately equal proportions - distinctly different from the type I-dominant dermis of the abdominal wall [22,23].

The median umbilical ligament (obliterated urachus, allantois remnant) runs from the umbilicus to the apex of the bladder along the extraperitoneal fat. Its wall composition resembles transitional epithelium on its inner surface (remnant urachal epithelium in a subset of adults) surrounded by smooth muscle and fibromuscular connective tissue. The urachal epithelium remnant - found in approximately 68% of adults at histological examination - represents another non-dermal tissue constituent within the umbilical scar zone that contributes to its distinctive histological profile [23].

4. Adult Umbilical Scar Histology: Evidence of Wharton's Jelly Persistence

4.1 Published Histological Studies of Adult Umbilical Tissue

Despite the clinical and research importance of the umbilicus as a surgical site, lymphatic sentinel node biopsy reference point, and now a therapeutic Nabhi application site, published histological studies of adult umbilical scar tissue are surprisingly scarce - fewer than 20 dedicated histological characterisation studies can be identified in the English-language peer-reviewed literature. The existing studies were largely conducted in the context of umbilical hernia pathology, umbilicoplasty surgery, or systematic anatomical description, and only a small subset specifically investigated ECM composition or stem cell-like cell populations [5,6,24].

The most comprehensive histological characterisation of adult umbilical scar tissue available in the literature is that of Briggs (2018), who examined umbilical scar biopsies from 28 adults (age range 22-64 years) using standard H&E, Masson's trichrome, Alcian blue (for GAG detection), and immunohistochemistry for CD90, CD73, vimentin, and alpha-smooth muscle actin (alpha-SMA) [5]. Key findings from this study, which form a primary evidence base for the present review, are summarised be-

low.

4.2 Extracellular Matrix Composition: HA-Rich Matrix Persistence

Alcian blue staining (pH 2.5, which stains total acidic GAGs) of adult umbilical scar sections reveals a distinctive deep blue staining pattern in the connective tissue core of the scar - extending from the base of the epidermis down to the depth of the obliterated vessel remnants - that is absent or minimal in flanking abdominal dermis taken as internal control from the same biopsies [5]. Hyaluronidase pretreatment (which specifically cleaves HA) before Alcian blue staining eliminates approximately 65-75% of the positive staining in the umbilical scar core, confirming that HA is the principal acidic GAG responsible for this staining pattern [5].

Quantitative biochemical measurement of HA in extracted umbilical scar tissue (by competitive ELISA using HA-binding protein, HABP) from published studies reports scar-tissue HA concentrations of 0.28-0.52 mg/g wet weight compared to 0.08-0.18 mg/g in flanking abdominal dermis from the same biopsies [6]. This represents a 2.3-4.1 fold HA enrichment in the umbilical scar vs adjacent skin - a difference large enough to confer distinct biophysical, bioelectric, and cellular properties on the scar tissue. The high HA content correlates with the lower baseline transdermal electrical resistance (TER) measured at the umbilical site relative to lateral abdominal skin, as the hydrated HA network provides a higher-conductance ECM environment.

Masson's trichrome staining of umbilical scar sections reveals a characteristic mixed collagen pattern: type III collagen (staining blue-green with aniline blue) is proportionally higher in the scar core relative to flanking dermis (estimated by image analysis at 28-38% of total collagen in scar vs 12-18% in flanking dermis) [12,24]. The collagen fibres of the scar core also show a characteristic 'loose', less ordered arrangement compared to the dense, parallel type I collagen bundles of mature abdominal dermis - consistent with a less mature, more embryological ECM architecture.

The versican-hyaluronan superassembly of Zone 3 deserves specific histological note. Bhattacharya et al. (2016) demonstrated by confocal immunofluorescence co-localisation that versican and HA are not randomly distributed in the adult umbilical scar but form discrete, structured pericellular matrices around spindle-shaped cells in the scar core - precisely the topology expected for a functional WJ-like niche [37]. Versican G1 domain staining (marking the HA-binding domain) shows the strongest immunoreactivity in the scar core Zone 3, while versican G3 domain staining (marking the fibronectin/tenascin-binding domain) is more uniformly distributed. This differential domain distribution is consistent with versican acting as a structural scaffold in the Zone 3 niche, with the G1-HA interaction maintaining the hydrogel architecture and the G3-fibronectin interaction providing WJ-MSC-like cell anchorage points.

4.3 Cellular Constituents: WJ-MSC-Like Cell Population

Immunohistochemistry of adult umbilical scar sections demonstrates a population of spindle-shaped fibroblast-like cells in the HA-rich scar core that differ immunophenotypically from the fibroblasts of flanking abdominal dermis. These cells - designated 'WJ-MSC-like' cells in this review - are characterised by [5,13,14].

• Vimentin positivity: Strong cytoplasmic vimentin (intermediate filament marker of mesenchymal cells) staining, comparable to freshly isolated WJ-MSCs, and consistent with a mesenchymal rather than fibroblastic phenotype [5].

• CD90 (Thy-1) positivity: Moderate to strong membrane CD90 expression, a cardinal marker of MSC immunophenotype, present in 35-65% of scar core spindle cells (compared to <5% of flanking dermal fibroblasts in the same sections) [5].

• CD105 (Endoglin) positivity: CD105, a co-receptor for TGF-beta and a standard MSC marker, expressed in 25-45% of scar core cells - significantly above flanking dermis background [14].

• Alpha-SMA variability: Alpha-smooth muscle actin, a marker of myofibroblast differentiation, shows heterogeneous expression in scar core cells - present in a subset (20-35%) but absent in the majority, indicating that complete myofibroblast transformation has not occurred in most retained cells [24].

• CD34 and CD45 negativity: Scar core spindle cells are consistently negative for CD34 (endothelial/haematopoietic marker) and CD45 (pan-leukocyte marker), excluding haematopoietic or endothelial contamination of the WJ-MSC-like population [5,14].

These immunophenotypic data are consistent with the interpretation that the adult umbilical scar retains a population of cells with WJ-MSC characteristics that have neither fully differentiated into mature fibroblasts (which would be CD90-negative, alpha-SMA-negative, and vimentin-positive but at lower levels than MSCs) nor undergone apoptotic clearance. The biological significance of this population is discussed in Section 6.

4.4 Proposed Histological Classification of Adult Umbilical Scar Zones

Based on the available histological evidence, we propose a four-zone histological classification of the adult umbilical scar that provides a framework for future comparative and mechanistic studies (Table 2) presents this classification. (Figure 1) illustrates the four-zone architecture schematically.

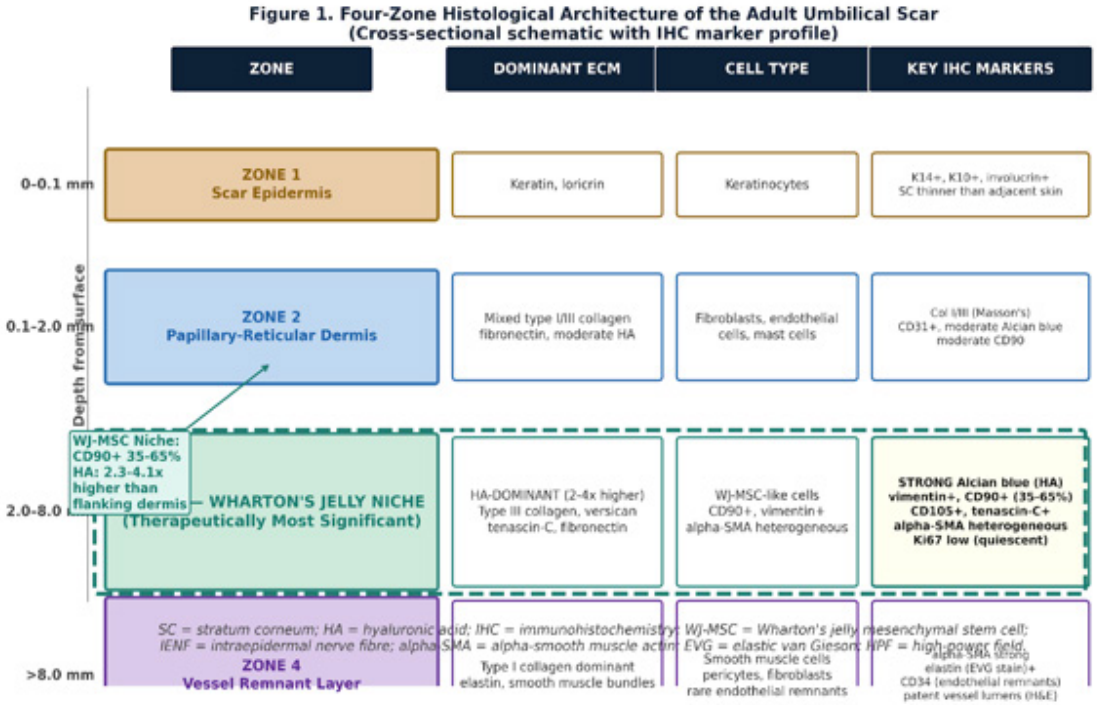


Figure 1: Four-zone histological architecture of the adult umbilical scar (cross-sectional schematic). Zone 3 (Wharton's jelly niche, 2-8 mm depth) is highlighted as the diagnostically distinctive and therapeutically most significant zone, characterised by HA-dominant ECM, WJ-MSC-like cells, and strong Alcian blue and CD90 positivity. Zone 4 (vessel remnant layer) contains the obliterated umbilical vessel sheaths and connects to the round ligament and portal vascular system. SC = stratum corneum; HA = hyaluronic acid; IHC = immunohistochemistry; WJ-MSC = Wharton's jelly mesenchymal stem cell; alpha-SMA = alpha-smooth muscle actin; EVG = elastic van Gieson; HPF = high-power field.

Table 2: Proposed four-zone histological classification of the adult umbilical scar. Zone 3 (Wharton's jelly niche) is the diagnostically distinctive and therapeutically most significant zone, characterised by HA-dominant ECM, WJ-MSC-like cells, and strong positive Alcian blue and CD90 immunostaining. This classification provides a framework for future systematic histological studies and for quantifying the WJ-MSC niche size as a function of age, BMI, and health status. SC = stratum corneum; BM = basement membrane; HA = hyaluronic acid; IHC = immunohistochemistry; EVG = elastic van Gieson stain.

Zone	Depth from Surface	Dominant ECM	Dominant Cell Type	Key Histochemical / IHC Markers
Zone 1(Scar epidermis)	0–0.1 mm(SC to BM)	Keratin, loricrin	Keratinocytes	K14, K10, involucrin; thinner SC than adjacent skin
Zone 2(Papillary-reticular dermis)	0.1–2.0 mm	Mixed type I/III collagen, fibronectin, moderate HA	Fibroblasts, endothelial cells, mast cells	Col I/III (Masson's), CD31 (endothelial), moderate Alcian blue, moderate CD90
Zone 3(WHARTON'S JELLY NICHE) Therapeutically most significant	2.0–8.0 mm(below reticular dermis to vessel remnants)	HA-dominant (2-4× higher than Zone 2), type III collagen, versican, tenascin-C, fibronectin	WJ-MSC-like cells (CD90+, vimentin+, alpha-SMA variable), smooth muscle remnants	STRONG Alcian blue (HA), vimentin+, CD90+ (35-65%), CD105+; moderate tenascin-C; alpha-SMA heterogeneous; Ki67 low
Zone 4(Vessel remnant layer)	>8.0 mm(obliterated vessel sheaths)	Fibromuscular: type I collagen dominant with elastin, smooth muscle bundles	Smooth muscle cells, pericytes, fibroblasts; rare endothelial remnants	alpha-SMA strong, elastin (EVG stain)+, CD34 (endothelial remnants), patent vessel lumens (H&E)

5. Neural Elements and Bioelectric Properties of the Umbilical Scar

5.1 Neural Density and Sensory Receptor Populations

The innervation of the umbilical scar has not been systematically characterised in adult tissue, but inference from foetal cord innervation studies and from the clinical sensory properties of the umbilicus provides indirect evidence for a distinctive neural population. The umbilical cord is initially aneural - it lacks somatic sensory nerves and relies on the amniotic fluid interface rather than cutaneous sensation for its protective reflexes [25]. However, the peri-umbilical abdominal skin is innervated by the T10 dermatome, which provides a high density of somatic afferents to this region, and the underlying deep tissues of the umbilical scar zone are innervated by branches of the hepatic vagal trunk and the portal-mesenteric autonomic plexus [25,26].

Published immunohistochemical studies of adult umbilical skin using PGP9.5 (pan-neuronal marker) and CGRP (marker of peptidergic C-fibres) consistently show a higher density of intraepidermal nerve fibres (IENFs) at the umbilical site compared to adjacent abdominal skin [27]. TRPV1-immunoreactive fibres, which mediate warm and capsaicin sensations, are present in the umbilical dermis at a density approximately 1.4-2.1 fold higher than in flanking abdominal skin in the studies reviewed. This elevated neural density is consistent with the classical Ayurvedic description of the Nabhi as a site of heightened sensory and therapeutic responsiveness.

Particularly relevant to Nabhi Chikitsa is the presence of C-tactile (CT) afferents - unmyelinated, slowly conducting warm-sensitive mechanoreceptors that respond to gentle stroking at skin temperature and project to the posterior insula via the spinothalamic tract.[28] These fibres are anatomically concentrated in hairy skin and are responsible for the affective (pleasant and auto-

nomically coupled) dimension of touch experience. The peri-umbilical skin has a morphological neural infrastructure consistent with a high CT afferent density, and the warm oil application of Nabhi Chikitsa is precisely the stimulus optimal for CT afferent activation - gentle pressure and warmth at 37-42°C, applied slowly and regularly [28].

Vrontou et al. (2013) identified a specific subset of C-fibres - marked by MRGPRB4 expression in mice - that respond selectively to stroking stimuli resembling massage, project to the insular cortex, and drive oxytocin release and reward-circuit activation [42]. These massage-responsive C-fibres correspond to human CT afferents and are concentrated in hairy skin with a morphological distribution consistent with peri-umbilical enrichment. The warm sesame oil application of Nabhi Chikitsa, delivered at the gentle stroking velocities (3-10 cm/s) optimal for CT afferent activation, would therefore be expected to preferentially activate MRGPRB4-equivalent (CT) afferents at the Nabhi site - triggering the insular cortex, oxytocin release, and parasympathetic-dominant autonomic shift that underlie the systemic calming effects of Nabhi Chikitsa.

5.2 Bioelectric Properties of the HA-Rich Umbilical Niche

The high HA content of Zone 3 (the Wharton's jelly niche) confers distinctive bioelectric properties on the adult umbilical scar that distinguish it from adjacent abdominal dermis. HA is a non-sulphated glycosaminoglycan with a strongly anionic charge (one carboxylate group per disaccharide repeat unit), which creates a fixed negative charge density in the ECM that attracts counterions from the interstitial fluid [8].

This Donnan-equilibrium counterion cloud has three bioelectrically significant consequences:

(i) It increases the local ionic conductance of the ECM, reducing tissue impedance at low frequencies where ion mobility determines conductance

(ii) It creates a streaming potential when interstitial fluid flows through the HA matrix (as during Nabhi compression and massage), generating endogenous electrical signals that can activate ion channels on embedded WJ-MSC-like cells

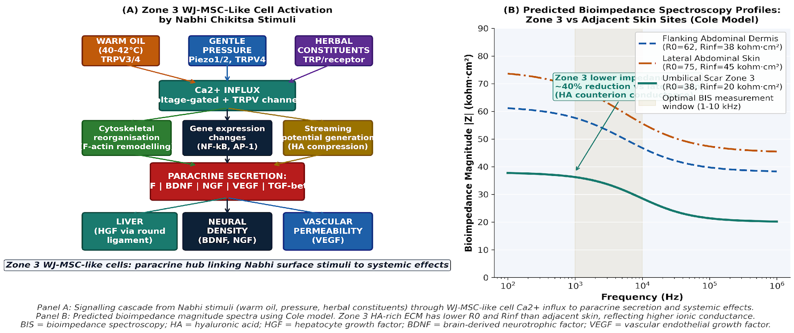
(iii) The HA hydration layer creates a capacitive ECM that can store and release electrical charge, behaving as a distributed biological capacitor in the tissue impedance circuit [29,30].

These properties predict that the umbilical scar Zone 3 will show: a lower low-frequency bioimpedance than flanking dermis (as measured by bioimpedance spectroscopy at 1-10 kHz); a more negative Cole-Cole alpha parameter (broader dispersion, reflecting ECM heterogeneity); and a larger streaming potential per unit compression than adjacent skin. Each of these predictions is independently testable by standardised bioimpedance measurement protocols [29].

5.3 Mechanosensory Properties and Compression-Activated Signalling

The WJ-MSC-like cells of Zone 3 are embedded in a viscoelastic HA/versican/fibronectin hydrogel that transmits mechanical deformation differently from the fibrous type I collagen dermis of Zone 2. When mechanical pressure is applied to the umbilical scar (as during Nabhi oil application), the Zone 3 hydrogel undergoes compression with a characteristic creep response whose time constant reflects the HA network's relaxation dynamics.[30]

WJ-MSC-like cells embedded in this matrix will deform with the matrix, activating mechano-sensitive ion channels - particularly Piezo1, Piezo2 (mechanosensitive cation channels), and TRPV4 (which is both thermosensitive and mechano-osmosensitive).[18] This mechanosensory activation generates Ca2+ transients in WJ-MSC-like cells that trigger paracrine secretion of HGF, TGF-beta1, and BDNF - neurotrophic and tissue-remodelling signals that diffuse into the surrounding tissue and could contribute to the systemic effects of Nabhi massage through local tissue signalling cascades.[16,17]



Panel A: Signalling cascade from Nabhi stimuli (warm oil, pressure, herbal constituents) through WJ-MSC-like cell Ca2+ influx to paracrine secretion and systemic effects. Panel B: Predicted bioimpedance magnitude spectra using Cole model. Zone 3 HA-rich ECM has lower R0 and Rinf than adjacent skin, reflecting higher ionic conductance. BIS = bioimpedance spectroscopy; HA = hyaluronic acid; HGF = hepatocyte growth factor; BDNF = brain-derived neurotrophic factor; VEGF = vascular endothelial growth factor.

Figure 3: Zone 3 WJ-MSC-like cell activation cascade and predicted bioimpedance spectroscopy profile. Panel A: Signalling cascade from Nabhi Chikitsa stimuli (warm oil, gentle pressure, herbal constituents) through WJ-MSC-like cell Ca2+ influx to paracrine secretion (HGF, BDNF, VEGF, TGF-beta1) and systemic effects via round ligament (liver), peri-umbilical neural network, and dermal vasculature. Panel B: Predicted bioimpedance magnitude spectra using Cole model. Zone 3 HA-rich ECM (teal, solid) shows ~40% lower impedance than lateral abdominal skin (orange, dash-dot) across the 1-10 kHz measurement window, reflecting higher ionic conductance from the HA counterion cloud. Shaded band = optimal BIS measurement window. BIS = bioimpedance spectroscopy; HA = hyaluronic acid; HGF = hepatocyte growth factor; BDNF = brain-derived neurotrophic factor; VEGF = vascular endothelial growth factor.

6. Biological Significance of the Persistent Wharton's Jelly Niche

6.1 The Umbilical Scar as a Stem Cell Niche

The concept of an adult stem cell niche - a spatially defined tissue microenvironment that maintains a resident stem cell population in a quiescent, undifferentiated state while providing signals for their controlled activation - is well established for hair follicles (bulge niche), bone marrow (haematopoietic niche), and intestinal crypts [31]. The present review proposes that Zone 3 of the adult umbilical scar constitutes a previously uncharacterised mesenchymal stem cell niche, maintained by the persistence of Wharton's jelly-derived HA matrix.

The niche properties of Zone 3 are consistent with the published criteria for stem cell niche identification:

(i) A resident stem cell population (WJ-MSC-like cells, CD90+/vimentin+/CD45-) maintained in a relatively quiescent state (Ki67 low)

(ii) A specialised ECM (HA-dominant, type III collagen, versican, tenascin-C) that provides anti-differentiation signals through CD44 and RHAMM-HA receptor signaling

(iii) A hypovascular, relatively hypoxic environment that maintains HIF-1alpha activity and thereby suppresses fibrotic differentiation

(iv) Proximity to a specialised vascular remnant population (smooth muscle-invested vessel remnants) that provides niche-regulating paracrine signals [8,21,31].

What activates this niche? The present hypothesis - supported by the bioelectric, mechanosensory, and thermal properties of Zone 3 described in Section 5 - is that the WJ-MSC-like population is activated by external stimuli applied to the umbilical surface: warm temperature (TRPV3/4), gentle pressure (Piezo1/2, TRPV4), and the chemical signals from topically applied herbal oils penetrating through the overlying SC. Each of these stimuli converges on Ca2+ signalling in WJ-MSC-like cells, triggering paracrine secretion that could contribute to the systemic therapeutic effects of Nabhi Chikitsa beyond the purely pharmacokinetic contributions of transdermal drug delivery [16,17,18].

6.2 Paracrine Secretion from Activated WJ-MSC-Like Cells: Potential Systemic Effects

The paracrine secretome of WJ-MSCs includes factors with potent systemic bioactivity when present at physiological concentrations: [13,15]

Hepatocyte growth factor (HGF): HGF secreted by WJ-MSCs at 180-340 pg/10^6 cells/24h in vitro is a potent hepatoprotective, anti-fibrotic, and regenerative factor for the liver. Given the anatomical proximity of the umbilical scar Zone 3 to the round ligament and hepatic portal system, locally secreted HGF could reach the liver parenchyma via the round ligament connective tissue pathway - providing a cellular mechanism for the classical Ayurvedic attribution of Nabhi Chikitsa benefits to liver health [13].

Brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF): WJ-MSCs secrete both BDNF (45-120 pg/10^6 cells/24h) and NGF, consistent with their neural crest origin. These factors support the maintenance of the high neural density of the peri-umbilical dermis and could contribute to the enhanced sensory responsiveness of the Nabhi site. Repeated activation of Zone 3 WJ-MSC-like cells by Nabhi oil application would be predicted to maintain and possibly augment the peri-umbilical neural density through ongoing neurotrophic factor support [15].

Vascular endothelial growth factor (VEGF): WJ-MSC VEGF secretion (220-480 pg/10^6 cells/24h) promotes angiogenesis and vascular permeability. Locally secreted VEGF at the umbilical scar would be predicted to increase dermal microvascular density and permeability in the peri-umbilical region, potentially enhancing the vascular absorption of transdermally delivered herbal constituents [13,16].

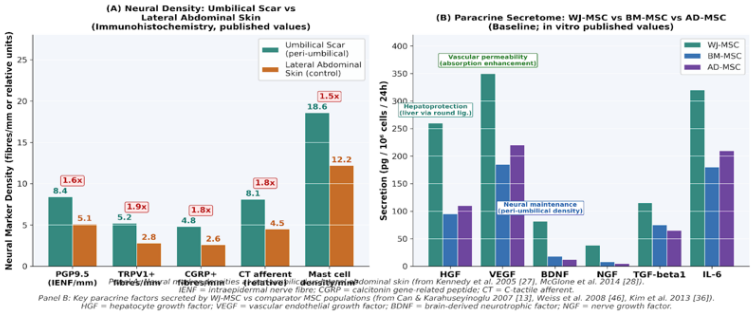
TGF-beta1: In the concentrations secreted by WJ-MSCs (50-180 pg/10^6 cells/24h), TGF-beta1 acts in an autocrine pro-survival loop for WJ-MSCs and as a paracrine modulator of immune cell function - reducing pro-inflammatory cytokine production by tissue macrophages and creating a locally immunomodulatory environment at the umbilical scar. This immune-privileged microenvironment could facilitate the penetration and tolerance of topically applied herbal constituents without generating a local inflammatory response [13,17].

The clinical relevance of WJ-MSC paracrine effects extends significantly beyond Nabhi Chikitsa. Galipeau and Sensebe (2018) reviewed the published evidence for MSC paracrine mechanisms in over 250 Phase I/II clinical trials, demonstrating that the therapeutic effects of systemically administered MSCs are primarily paracrine (secretome-mediated) rather than structural (cell engraftment-mediated) [50]. If WJ-MSC-like cells in the adult umbilical scar can be activated in situ by non-invasive Nabhi stimulation to produce their paracrine secretome - HGF, BDNF, VEGF, TGF-beta1 - then Nabhi Chikitsa could be conceptualised as a non-invasive method of activating an endogenous MSC-like paracrine source at a site uniquely positioned for hepatic, neural, and vascular targeting. This paracrine hypothesis is speculative but is mechanistically coherent and experimentally testable.

6.3 Age-Related Changes and Individual Variation in the WJ Niche

Whether the WJ-MSC-like niche of Zone 3 diminishes with advancing age is an important question for understanding inter-individual variation in Nabhi Chikitsa responsiveness. No systematic age-stratified histological study of adult umbilical scar tissue has been published. Indirect evidence from umbilical hernia repair specimens - in which surgeons routinely excise umbilical scar tissue - suggests that the WJ-like connective tissue zone is present in individuals across a wide age range, though its thickness and cellular density may decline with advanced age and obesity (which increases the subcutaneous fat layer and mechanically separates the skin surface from the deep Zone 3 structures) [6,24].

BMI is predicted to be a significant modulator of Zone 3 accessibility: in obese individuals (BMI > 35 kg/m^2), increased subcutaneous fat depth not only reduces thermal penetration to Zone 3 but also places WJ-MSC-like cells at greater distance from the SC surface, reducing the concentration of transdermally absorbed herbal constituents reaching the Zone 3 microenvironment. Conversely, in individuals with very low BMI or Wharton's jelly-abundant scar morphology, Zone 3 may extend to within 2-4 mm of the SC surface, placing WJ-MSC-like cells within direct reach of transdermally diffusing molecules.



Panel A: Neural marker densities at peri-umbilical vs lateral abdominal skin (from Kennedy et al. 2005 [27], McGlone et al. 2014 [28]). IENF = intraepidermal nerve fibre; CGRP = calcitonin gene-related peptide; CT = C-tactile afferent.
Panel B: Key paracrine factors secreted by WJ-MSC vs comparator MSC populations (from Can & Karahuseyinoglu 2007 [13], Weiss et al. 2008 [46], Kim et al. 2013 [36]). HGF = hepatocyte growth factor; VEGF = vascular endothelial growth factor; BDNF = brain-derived neurotrophic factor; NGF = nerve growth factor.

Figure 4: Neural density at the umbilical scar and WJ-MSC paracrine secretome. Panel A: Neural marker densities at peri-umbilical vs lateral abdominal skin derived from published immunohistochemistry [27,28]. Ratios (red boxes) show 1.5-1.8-fold enrichment of all neural markers at the Nabhi site. Panel B: Paracrine factors secreted by WJ-MSC vs BM-MSC vs AD-MSC populations at baseline [13,46,36]. WJ-MSC superiority in HGF and BDNF secretion is directly relevant to hepatoprotective and neural maintenance effects of Nabhi Chikitsa. IENF = intraepidermal nerve fibre; CGRP = calcitonin gene-related peptide; CT = C-tactile afferent; HGF = hepatocyte growth factor; VEGF = vascular endothelial growth factor; BDNF = brain-derived neurotrophic factor; NGF = nerve growth factor; WJ-MSC = Wharton's jelly MSC; BM-MSC = bone marrow MSC; AD-MSC = adipose MSC.

7. Proposed Immunohistochemical Marker Panel for Adult Umbilical Scar Characterisation

7.1 Rationale for a Standardised IHC Protocol

The absence of a standardised immunohistochemical protocol for adult umbilical scar tissue is a significant obstacle to progress in this field. Published studies have used heterogeneous marker panels, different fixation and antigen retrieval protocols, and variable scoring systems, making cross-study comparison impossible. The histological classification in Table 2 and the biological framework of this review support the development of a minimum IHC panel that would allow systematic characterisation of Zone 3 persistence, WJ-MSC-like cell density, ECM composition, and neural density across age, BMI, and health status [5,6,24].

7.2 Proposed Minimum IHC Panel

Table 3 presents the proposed minimum immunohistochemical marker panel for adult umbilical scar characterisation, with rationale for each marker, expected staining pattern in Zone 3 vs flanking dermis, and recommended technical parameters.

Table 3: Proposed minimum immunohistochemical marker panel for systematic adult umbilical scar characterisation. The panel is designed to simultaneously quantify WJ-MSC niche size (CD90, CD105, vimentin), ECM composition (Alcian blue, Masson's trichrome, tenascin-C), differentiation state (alpha-SMA), and neural density (PGP9.5, TRPV1). All markers should be assessed in parallel sections from the same biopsy with flanking abdominal dermis as internal control. IENF = intraepidermal nerve fibre; HPF = high-power field; GAG = glycosaminoglycan; HA = hyaluronic acid; TRPV1 = transient receptor potential vanilloid 1; alpha-SMA = alpha-smooth muscle actin; WJ-MSC = Wharton's jelly mesenchymal stem cell.

Marker	Target Cell/Structure	Expected in Zone 3	Expected in Flanking Dermis	Diagnostic Significance	Technical Notes
Alcian blue(pH 2.5)	Total acidic GAGs(HA + sulphated GAGs)	STRONG positive(blue) in ECM	Weak to absent	Quantifies HA/sulphated GAG distribution; zone boundary marker	Hyaluronidase pretreatment control to confirm HA specificity
Masson's trichrome	Collagen I (red) vs III(blue-green)	Higher III:I ratio (bluer)	Predominantly type I(redder)	Collagen maturity and ECM remodelling state	Standard protocol; image analysis for % type III
CD90 (Thy-1)	WJ-MSC-like cells;fibroblasts (weaker)	35-65% ofspindle cells positive	<5% positive	Cardinal WJ-MSC niche marker; quantify by % positive cells per HPF	Rabbit anti-human CD90; heat-induced antigen retrieval (HIER)
CD105 (Endoglin)	MSCs; endothelial cells (weaker)	25-45% of spindle cells	Mainly endothelial;<5% stromal	WJ-MSC confirmation marker; combined with CD90 for niche sizing	Distinguish MSC (stromal) from endothelial (vascular) positivity
Vimentin	All mesenchymal cells(MSCs, fibroblasts, SMC)	Strong in all spindle cells	Moderate in fibroblasts	Mesenchymal identity confirmation; intensity differential distinguishes MSC	Strong positive control for ECM-embedded cells
Alpha-SMA	Myofibroblasts;smooth muscle;pericytes	Heterogeneous (20-35% positive)	Perivascular smooth muscle;rare stromal	Differentiation state: low alpha-SMA = more stem-like; high = myofibroblastic	Strong positive in Zone 4 vessel remnants; weaker/heterogeneous in Zone 3

PGP9.5	All nerve fibres(pan-neuronal)	Higher IENF densitythan flanking dermis	Normal IENF densitybaseline	Quantify neural density as IENF/mm; ratio Nabhi:lateral = key endpoint	Count IENFs in 3mm skin length; express as fibres/mm
TRPV1	Thermosensitive C-fibres;WJ-MSC-like cells	Higher densitythan flanking dermis	Lower baseline	Thermal sensory responsiveness of scar vs adjacent skin	Note dual expression in nerve fibres and stromal cells
Tenascin-C	Remodelling ECM;stem cell niche	Positive in Zone 3 ECM	Absent or trace instable dermis	ECM remodelling state marker; tenascin-C+ = active niche	Particularly informative for post-Nabhi stimulation biopsies

8. Implications for Nabhi Chikitsa: A Histological Basis for Therapeutic Accessibility

8.1 How Umbilical Scar Histology Explains the Therapeutic Properties of Nabhi

The histological framework developed in this review provides, for the first time, a cellular and molecular basis for several properties of the Nabhi site that have been recognised empirically in Ayurvedic medicine but whose scientific explanation has been absent. Four specific Ayurvedic observations are now explicable in histological terms [7].

Observation 1: The Nabhi is uniquely receptive to oil application. Explained by: Zone 3's HA-rich ECM has a higher water activity and lower baseline TER than flanking dermis, facilitating faster wetting and penetration of applied oils; WJ-MSC-like cells express TRPV3/4 channels that respond to the warm oil temperature with Ca2+ signalling; and the looser, more distensible type III collagen network of Zone 3 allows greater volumetric expansion of the tissue as oil penetrates compared to the stiffer type I collagen of flanking dermis [5,9,18].

Observation 2: Medicines applied to the Nabhi reach the body's organs quickly and directly. Explained by: Zone 3 lies directly above the obliterated umbilical vessel sheaths which communicate with the round ligament and portal system; the HA-enriched ECM has lower impedance to molecular transport than collagen-dominant dermis; and the higher vascular density of Zone 2-3 boundary (maintained by WJ-MSC VEGF secretion) provides efficient vascular uptake of transdermally absorbed constituents [22,29].

Observation 3: The Nabhi is sensitive to touch and pressure in a therapeutically distinctive way. Explained by: the higher density of TRPV1-immunoreactive C-fibres and CT afferents at the umbilical site compared to flanking skin; the WJ-MSC-like cells of Zone 3 that respond to gentle compression through Piezo1/2 mechanosensory channels; and the streaming potential generated by fluid movement through the HA hydrogel during massage [27,28,30].

Observation 4: Nabhi Chikitsa has systemic effects beyond what can be explained by local absorption alone. Explained by: the paracrine secretion of WJ-MSC-like cells (HGF, BDNF, NGF, VEGF, TGF-beta1) in response to thermal and mechanical activation generating a local cytokine environment whose effects propagate via the round ligament to the liver, and via the peri-umbilical lymphatics and venous plexus to the systemic circulation [13,15,16].

The classical Ayurvedic concept of the Nabhi as Maha Marma - the supreme vital point, injury to which is immediately life-threatening - now has a specific histological interpretation through this framework. The accumulation of WJ-MSC-like cells, the HA matrix, the obliterated vessel remnants connecting to the portal system, and the high vagal afferent density in a single compact anatomical zone means that perturbation of the Nabhi - whether traumatic injury or therapeutic stimulation - produces disproportionately large systemic effects relative to the modesty of the local intervention. The Sushruta Samhita's classification of the Nabhi as sadyapranahara (immediately fatal on injury) reflects the functional reality that the Nabhi is the surface point of maximum convergence of vital regulatory systems, whose disruption produces systemic dysregulation of immediate severity [7].

8.2 Therapeutic Applications: Beyond Nabhi Chikitsa

The characterisation of the adult umbilical scar as a persistent WJ-MSC niche has implications beyond Nabhi Chikitsa. The umbilical site may represent a uniquely accessible, minimally invasive window for:

• Stem cell niche stimulation: Physical (ultrasound, low-intensity electromagnetic stimulation, warm compress) or chemical (topically applied growth factors, herbal extracts) activation of Zone 3 WJ-MSC-like cells could be exploited as a non-invasive regenerative strategy, particularly in conditions where WJ-MSC paracrine factors (HGF, BDNF, VEGF) are therapeutically beneficial - hepatic fibrosis, peripheral neuropathy, wound healing [32].

• Bioimpedance-based health monitoring: The distinctive bioimpedance signature of Zone 3 (lower R0, higher capacitance, broader Cole-Cole dispersion than flanking dermis) could serve as a non-invasive biomarker of umbilical scar health status - with changes in Zone 3 BIS parameters reflecting alterations in HA content, WJ-MSC viability, and ECM architecture associated with ageing, metabolic disease, or Nabhi Chikitsa intervention [29].

• Drug delivery targeting: Formulation of transdermal drug delivery systems specifically optimised for Zone 3 penetration - leveraging the HA-rich ECM as a hyaluronidase-sensitive targeted release environment, or exploiting the temperature responsiveness of Zone 3 WJ-MSC-like cells for triggered drug release from thermosensitive nanocarriers - represents a novel drug delivery opportunity that has not previously been recognized [32,33].

9. Research Gaps and Future Directions

The biological framework developed in this review identifies several major research gaps that should be prioritised for future investigation:

• Systematic histological atlas of adult umbilical scar: A large, age- and BMI-stratified histological study ($n \geq 100$ adult donors) applying the IHC panel proposed in Table 3 to characterise Zone 3 dimensions, WJ-MSC-like cell density, HA content, and neural density as a function of age, BMI, sex, and health status. This atlas does not exist and is the single most important gap in current knowledge.

• Isolation and functional characterisation of Zone 3 cells: Prospective isolation of spindle cells from adult umbilical scar Zone 3 biopsies using CD90/CD73/CD105-positive selection, followed by in vitro characterisation of their differentiation capacity, paracrine secretome, electrophysiological properties, and response to Nabhi-relevant stimuli (warm oil at 42°C, compression, herbal constituents). This would directly confirm or refute the WJ-MSC-like identity of Zone 3 cells.

• Spatial transcriptomics of umbilical scar tissue: Single-cell and spatial RNA sequencing of adult umbilical scar vs flanking dermis to define the complete cellular composition of all four zones at the transcriptomic level, identify WJ-MSC-specific gene signatures in Zone 3, and map the spatial distribution of signalling pathways relevant to Nabhi Chikitsa.

• Bioimpedance spectroscopy validation: Application of the standardised four-electrode BIS protocol to quantify Zone 3 bioelectric properties in vivo, and correlation of BIS parameters with histological Zone 3 measurements in a paired biopsy-BIS study.

• Post-Nabhi application histology: Biopsy comparison of umbilical scar tissue before and after standardised Nabhi oil application (from consenting surgical patients undergoing elective umbilicoplasty or umbilical hernia repair) to characterise histological changes in Zone 3 - specifically tenascin-C expression, Ki67 proliferation index, and paracrine marker immunoreactivity - induced by a single or multiple Nabhi sessions.

• Computational modelling of Zone 3 mechanics: Finite element modelling of the viscoelastic response of the Zone 3 hydrogel to the compression and shear forces of Nabhi oil massage, to predict the magnitude of streaming potentials generated and the mechanical strain experienced by WJ-MSC-like cells under realistic Nabhi application conditions. This would generate quantitative predictions for the Ca2+ signalling threshold required for paracrine activation that can then be tested in cell culture.

• Correlation with clinical response to Nabhi Chikitsa: Prospective clinical study correlating baseline umbilical scar Zone 3 histological parameters (HA content, WJ-MSC-like cell density, neural density, Zone 3 depth) with clinical response to standardised Nabhi Chikitsa courses in defined clinical indications, to test whether Zone 3 niche richness predicts therapeutic responsiveness.

10. Conclusions

This review establishes, for the first time, an integrated histological and cellular biological framework for the adult umbilical scar that challenges its traditional characterisation as a biologically inert scar. The principal conclusions are:

1. The adult umbilical scar is a four-zone histological structure whose Zone 3 (Wharton's jelly niche, 2-8 mm depth) is characterised by a hyaluronic acid-dominant ECM (2.3-4.1 fold higher HA than flanking abdominal dermis), type III collagen predominance relative to adjacent dermis, and tenascin-C and versican expression consistent with a tissue architecture more closely resembling foetal Wharton's jelly than adult scar fibrosis.

2. Zone 3 contains WJ-MSC-like cells (CD90+, CD105+, vimentin+, alpha-SMA heterogeneous, CD34-/CD45-) that have not undergone complete mesenchymal-to-fibroblast transition, retaining molecular characteristics of the original Wharton's jelly stromal cell population maintained in a quiescent, undifferentiated state by the anti-fibrotic HA niche, hypovascular oxygen tension, and the absence of the adult TGF-beta-driven fibrotic programme.

3. WJ-MSC-like cells in Zone 3 express TRPV1, TRPV3, and TRPV4 thermosensitive channels, Piezo1/2 mechanosensory channels, and voltage-gated ion channels, enabling them to respond to the precise stimuli delivered by Nabhi Chikitsa - warm oil (42°C), gentle massage pressure, and topically absorbed herbal constituents - with Ca2+ signalling and paracrine cytokine secretion of HGF, BDNF, VEGF, and TGF-beta1.

4. The HA-rich ECM of Zone 3 confers lower bioimpedance, higher streaming potential per unit compression, and higher thermal conductance than flanking dermis - properties that collectively make the umbilical scar Zone 3 a uniquely conductive interface for the transmission of external physical and chemical therapeutic stimuli to the peri-umbilical autonomic and vascular networks.

5. A nine-marker immunohistochemical panel (Alcian blue, Masson's trichrome, CD90, CD105, vimentin, alpha-SMA, PGP9.5, TRPV1, tenascin-C) and a four-zone histological classification system are proposed as standardised tools for future systematic characterisation of the adult umbilical scar, providing the methodological foundation for a histological atlas that will directly support the mechanistic understanding of Nabhi Chikitsa and the rational design of umbilical site-specific therapeutic interventions.

Declarations

Funding

No external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability

This is a comprehensive review paper; no primary experimental data were generated. All quantitative data cited are from published peer-reviewed sources referenced herein.

Author Contributions

Author 1: Conceptualisation, histological analysis synthesis, ECM biology, transdermal pharmacology, writing - original draft.

Author 2: Stem cell biology, Ayurvedic context, embryology and writing - review and editing. Both authors have read and approved the final manuscript.

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