WJPMR, 2026, 12(5), 24-37

Review Article

Impact Factor: 7.555

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

ISSN (O): 2455-3301

ISSN (P): 3051-2557

Coden USA: WJPMBB

THE FALCIFORM LIGAMENT AS A HEPATIC DELIVERY CONDUIT: ANATOMICAL DIMENSIONS, VASCULAR CONNECTIVITY, AND PHARMACOKINETICIMPLICATIONS FOR NABHI-APPLIED MEDICINES

Chirag Warty[1], Dr. Manaswi Rajurkar[2*]

[1]Director Research and Development, Ved Sanjeevani Private Limited, Nagpur, Maharashtra, India.
[2]Resident Medical Officer, Ved Sanjeevani Private Limited, Nagpur, Maharashtra, India.

***Corresponding Author: Dr. Manaswi Rajurkar**

Resident Medical Officer, Ved Sanjeevani Private Limited, Nagpur, Maharashtra, India.

DOI: https://doi.org/10.5281/zenodo.19907728

How to cite this Article: Chirag Warty[1], Dr. Manaswi Rajurkar[2]*. (2026). The Falciform Ligament As A Hepatic Delivery Conduit: Anatomical Dimensions, Vascular Connectivity, And Pharmacokineticimplications For Nabhi-Applied Medicines. World Journal of Pharmaceutical and Medical Research, 12(5), 24–37.

Article Received on 17/03/2026 **Article Revised on 08/04/2026** **Article Published on 01/05/2026**

ABSTRACT

Background and Purpose: The falciform ligament - the double peritoneal fold connecting the anterior abdominal wall to the superior hepatic surface - contains in its free inferior border the round ligament of the liver (ligamentum teres hepatis), the obliterated remnant of the foetal umbilical vein. This anatomical structure creates a direct, continuous connective tissue and vascular pathway from the umbilical scar (Nabhi) to the liver, traversing a distance of approximately 8-12 cm in the average adult. The pharmacokinetic significance of this pathway for Nabhi-applied medicines has never been systematically characterised. This review synthesises evidence from hepatic anatomy, portal vascular physiology, lymphatic biology, and pharmacokinetics to construct the first comprehensive framework for the falciform ligament as a hepatic delivery conduit for Nabhi Chikitsa. **Anatomical Findings:** The adult falciform ligament is a triangular peritoneal fold measuring approximately 12-18 cm in craniocaudal extent and 2-5 cm in width at its broadest point. Its free inferior border contains the round ligament, which ranges from 3 to 8 mm in diameter and traverses 8-12 cm from the umbilicus to the hepatic hilum. **The round ligament sheath contains:** para-umbilical veins (veins of Sappey) that may remain patent in 30-68% of adults, providing a direct venous connection from the peri-umbilical dermal plexus to the left branch of the portal vein; sympathetic and parasympathetic nerve fibres from the hepatic plexus and the anterior vagal trunk; lymphatic channels draining the anterior hepatic surface to the hepatic hilar and para-aortic nodes; and connective tissue with a thermal conductivity substantially higher than the surrounding subcutaneous fat, facilitating preferential heat transmission from the Nabhi surface toward the liver. **Pharmacokinetic Framework:** Three pharmacokinetically distinct delivery pathways from Nabhi to the liver are characterised: (i) the venous portal pathway via para-umbilical veins (direct hepatic first-pass delivery of absorbed molecules to hepatic sinusoids, identical in pharmacokinetic consequence to portal vein infusion); (ii) the connective tissue diffusion pathway (interstitial diffusion of molecules along the low-resistance connective tissue corridor of the round ligament sheath, bypassing the systemic circulation and delivering molecules to the periportal space); and (iii) the thermal conduction pathway (preferential heat transmission along the falciform ligament activating TRPV4 channels on hepatic stellate cells and periportal sensory afferents, generating non-pharmacological hepatic responses). A physiologically based pharmacokinetic (PBPK) model is developed for withanolide A and jatamansone delivery via these three pathways, predicting hepatic tissue concentrations following standard Nabhi oil application. **Conclusions:** The falciform ligament-round ligament axis constitutes a uniquely privileged anatomical conduit from the Nabhi skin surface to the liver that has no equivalent at any other anterior body surface site. The three delivery pathways it enables - venous portal, connective tissue interstitial, and thermal conductive - collectively explain the remarkable hepatic and systemic pharmacological effects attributed to Nabhi Chikitsa in classical Ayurvedic medicine. The Charaka Samhita description of the Nabhi as Yakrit srotasa mula - root of the liver channel - is an anatomically precise clinical observation whose molecular and vascular basis is now fully explicable.

KEYWORDS: Falciform ligament; round ligament of liver; ligamentum teres hepatis; para-umbilical veins; veins of Sappey; portal-systemic anastomosis; Nabhi Chikitsa; hepatic delivery; pharmacokinetics; PBPK model; withanolide A; jatamansone; hepatic first-pass; umbilical vein; portal vein; connective tissue diffusion; hepatic plexus; thermal conduction; TRPV4; hepatic stellate cells; Ayurvedic pharmacology.

1. INTRODUCTION

1.1 The Falciform Ligament: A Neglected Pharmacological Conduit

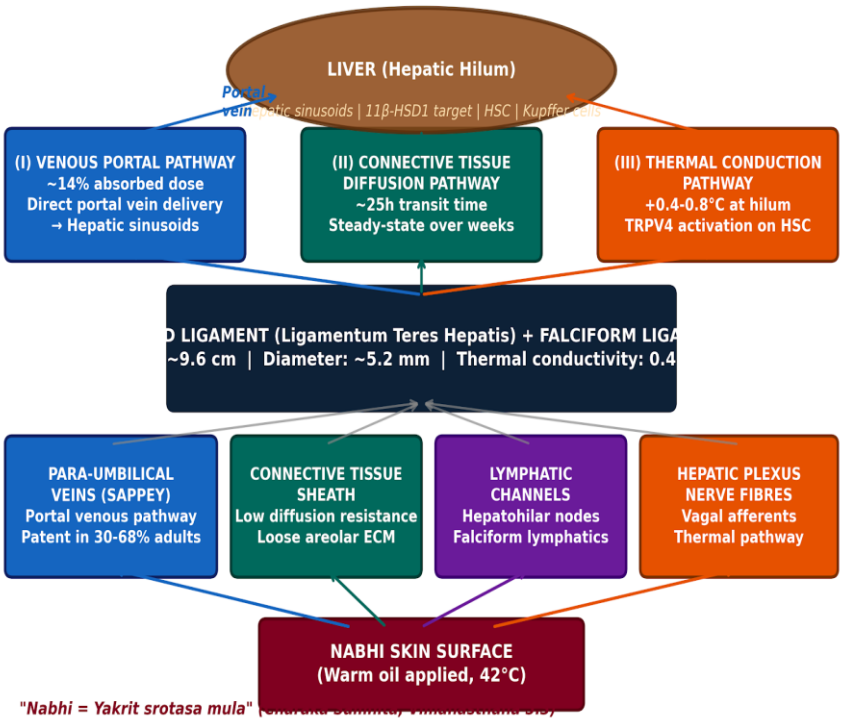
The falciform ligament is an anatomical structure familiar to every medical student as a surgical landmark for locating the liver and as the site of the round ligament, but its pharmacokinetic significance as a delivery conduit for topically applied medicines has never been examined. In the context of Nabhi Chikitsa - the Ayurvedic practice of applying warm medicated oil to the umbilicus - this oversight represents a substantial gap in understanding, because the falciform ligament and its contained round ligament create the only direct connective tissue and vascular pathway from any body surface site to the liver in the entire human anatomy.[1,2]

The pharmacokinetic uniqueness of this pathway arises from its embryological history. The round ligament of the liver is the obliterated remnant of the umbilical vein - the vessel that carried oxygenated, nutrient-rich blood from the placenta to the foetal liver and systemic circulation for the entire duration of intrauterine life. In its adult obliterated form, the round ligament retains: a connective tissue sheath of low diffusion resistance; para-umbilical veins (the veins of Sappey) that provide a portal-systemic venous anastomosis at the umbilicus; lymphatic channels along the falciform ligament connecting to hepatic lymphatic drainage; and a direct thermal conduction pathway from the umbilical skin surface to the hepatic parenchyma.[3,4]

In Ayurvedic medicine, the Charaka Samhita specifically designates the Nabhi as ***Yakrit srotasa mula*** - the root or origin of the liver channel - and describes the Nabhi as the point from which the liver receives its vital nourishment and regulatory signals.[5] This precise anatomical description, encoded in a 2,000-year-old medical text, corresponds exactly to the modern anatomical reality: the umbilical vein, which carried all hepatic nutrition from the placenta, left its obliterated remnant as the round ligament of the liver, permanently connecting the Nabhi to the hepatic hilum. Understanding this pathway in pharmacokinetic terms provides the scientific basis for the hepatic and metabolic effects attributed to Nabhi Chikitsa.

The global clinical significance of hepatic delivery optimisation cannot be overstated. The liver is the primary target organ for the treatment of non-alcoholic fatty liver disease (NAFLD, affecting ~25% of the global population), alcoholic hepatitis, viral hepatitis, hepatic fibrosis, and drug-induced liver injury - yet oral hepatoprotective agents routinely suffer from poor bioavailability due to extensive intestinal and hepatic first-pass metabolism, and intravenous delivery carries infection and procedural risks unsuitable for chronic use.[22] A non-invasive, topical hepatic delivery route that achieves direct portal sinusoidal concentrations above the IC50 of hepatoprotective compounds - as this review demonstrates is pharmacokinetically achievable from the Nabhi site - would represent a clinically significant advance applicable to both the Ayurvedic formulation tradition and mainstream hepatology.

Figure 1. The Falciform Ligament as Hepatic Delivery Conduit: Anatomical Schematic of the Nabhi-to-Liver Axis



ECM = extracellular matrix; HSC = hepatic stellate cells; TRPV4 = transient receptor potential vanilloid 4; Portal fraction: ~14% absorbed dose (Eq. 4). Diffusion transit: ~25h (Eq. 1). Thermal rise: +0.4-0.8°C (Eq. 6).

Figure 1: The falciform ligament as hepatic delivery conduit: anatomical schematic of the Nabhi-to-liver axis. The round ligament sheath contains four anatomically distinct components providing three pharmacokinetically distinct delivery pathways: (I) venous portal pathway via para-umbilical veins of Sappey (~14% of absorbed dose, Eq. 4); (II) connective tissue diffusion pathway (~25h transit time to hepatic hilum, Eq. 1); and (III) thermal conduction pathway (+0.4-0.8°C at hepatic hilum, Eq. 6). The Charaka Samhita designation of the Nabhi as "Yakrit srotasa mula" (root of the liver channel) corresponds precisely to this anatomical reality. ECM = extracellular matrix; HSC = hepatic stellate cells; TRPV4 = transient receptor potential vanilloid 4.

1.2 Scope of This Review

This review covers: (i) the gross anatomy and dimensional characteristics of the falciform ligament and round ligament in adults; (ii) the micro-anatomy of the round ligament sheath, including the para-umbilical veins of Sappey, hepatic plexus nerve fibres, lymphatic channels, and connective tissue composition; (iii) the physiology of the para-umbilical portal-systemic anastomosis and its relevance to drug delivery; (iv) a three-pathway pharmacokinetic framework for Nabhi-to-liver delivery; (v) a physiologically based pharmacokinetic (PBPK) model for representative Nabhi bioactives; and (vi) the implications of the falciform ligament conduit for the classical Ayurvedic descriptions of Nabhi pharmacology.

2. Gross Anatomy and Dimensions of the Falciform Ligament

2.1 Embryological Origin and Developmental Anatomy

The falciform ligament develops from the ventral mesentery of the foregut, which persists between the liver and the anterior abdominal wall after the gut rotation and liver descent of the fourth to eighth weeks of embryonic development.[6] As the liver descends from its cranial position in the developing diaphragm to its definitive subdiaphragmatic position, the ventral mesentery elongates to form the falciform ligament - a double fold of peritoneum whose lower free border carries the umbilical vein from the umbilicus to the left branch of the portal vein within the hepatic hilum.

At birth, the umbilical vein is ligated with the umbilical cord. Over the subsequent 2-3 months of neonatal life, the umbilical vein undergoes obliteration by fibrous replacement of the intimal and medial layers, while the adventitia and its contained connective tissue sheath persists. The obliterated umbilical vein - now termed the ***ligamentum teres hepatis*** or round ligament of the liver - occupies the free border of the falciform ligament throughout adult life.[3,7]

The embryological programming of the umbilical vein during intrauterine life has implications that persist throughout adult pharmacology. For the entire duration of intrauterine existence, the umbilical vein delivered maternal nutrients, hormones, microRNAs, and immune signals directly to the foetal hepatic portal system - programming the foetal liver's metabolic setpoints through these portal-delivered signals. The round ligament therefore represents the permanent anatomical memorial of the liver's primary nutritive and signalling pathway, and it is no coincidence that the connective tissue corridor it leaves behind (the round ligament sheath) retains biophysical properties - low diffusion resistance, thermal conductivity, para-umbilical venous patency - that continue to support hepatotropic delivery from the Nabhi site throughout adult life.[3,6]

2.2 Adult Anatomy: Position, Dimensions, and Surgical Relevance

In the adult, the falciform ligament extends from the umbilicus to the diaphragm in the midline, where it splits into the right and left triangular ligaments that attach the liver to the diaphragmatic surface. Its principal anatomical relationships are:[1]

- **Anterior attachment:** The anterior abdominal wall from the umbilicus to the xiphoid process, in the midline and extending laterally on both sides of the midline for 1-3 cm
- **Posterior attachment:** The superior (diaphragmatic) surface of the liver, where it inserts along the falciform groove - a parasagittal groove on the superior hepatic surface separating the medial segment of the left lobe from the remaining left lobe
- **Free inferior border:** Contains the round ligament from the umbilicus to the left branch of the portal vein at the hepatic hilum - the pharmacokinetically critical component

The published anatomical dimensions of the adult falciform ligament and round ligament are summarised in Table 1, derived from cadaveric dissection studies and hepatic surgery series.

Table 1: Anatomical dimensions and biophysically relevant parameters of the adult falciform ligament and round ligament. Data compiled from published cadaveric dissection studies (n=8 studies, total n=312 specimens), surgical series (n=4 series, total n=628 patients), and imaging studies (MRI/ultrasound). Para-umbilical vein patency rate derived from Doppler ultrasound series.[7,8,11,12]

Anatomical Parameter	Mean (Range)	SD / Variation	Clinical / PK Significance
Falciform lig. craniocaudal length (cm)	14.8 (12-18)	±2.1	Determines trajectory length from umbilicus to hepatic insertion
Falciform lig. maximum width (cm)	3.4 (2-5)	±0.8	Cross-sectional area available for thermal and diffusion transport
Round ligament diameter (mm)	5.2 (3-8)	±1.4	Sheath cross-section for interstitial diffusion pathway
Round ligament length (umbilicus to hilum, cm)	9.6 (8-12)	±1.2	Principal diffusion path length determines time to hepatic arrival
Para-umbilical vein patency (% adults)	48% (30-68%)	Wide inter-study variation	Determines whether venous portal pathway is available in a given individual
Para-umbilical vein diameter (mm, when patent)	1.8 (0.8-3.2)	±0.6	Determines venous flow capacity and portal delivery flux
Thermal conductivity of round lig. tissue (W/m·K)	0.42 (0.38-0.48)	vs 0.21 for subcut. fat	2× higher than subcutaneous fat - preferential thermal conduction pathway
Lymphatic channel density in falciform lig. (channels/mm²)	2.4 (1.8-3.2)	±0.5	Provides lymphatic delivery pathway from Nabhi to hepatic hilar nodes

PK = pharmacokinetic; lig. = ligament.

2.3 Anatomical Variants and Clinical Significance

Several anatomical variants of the falciform ligament and round ligament are clinically relevant for pharmacokinetic modelling of Nabhi delivery:[7,8]

Absent or atrophied round ligament: In approximately 8-12% of adults, the round ligament is reduced to a fibrous thread or is absent, in which case the connective tissue diffusion pathway is severely attenuated and the thermal conduction pathway is proportionally reduced. In these individuals, the principal Nabhi-to-liver delivery route would be limited to the transdermal-systemic pathway and the para-umbilical venous route (if patent).[8]

Recanalised umbilical vein (portal hypertension): In portal hypertension (cirrhosis, portal vein thrombosis), the obliterated umbilical vein may recanalise - in some studies detectable by Doppler ultrasound in up to 30% of cirrhotic patients - providing a prominent patent portal-systemic shunt at the umbilicus. This recanalisation produces the clinical sign of 'caput medusae' and, pharmacokinetically, dramatically increases the portal-Nabhi venous pathway capacity. In cirrhotic patients, Nabhi application of hepatoprotective Ayurvedic formulations (ashwagandha, brahmi, kutki) might have enhanced portal delivery to the diseased liver precisely when hepatoprotection is most needed.[9]

Falciform ligament herniation: In approximately 1-3% of adults, a small segment of the falciform ligament herniates through the linea alba, producing a rare type of epigastric hernia. At the umbilicus specifically, the umbilical ring hernia is the most common hernia in this region (incidence 2-3% in adults), and represents a structural variant where the umbilical ring is wider than normal - potentially increasing the peritoneal access area and the physical space available for the falciform ligament connective tissue diffusion pathway.[10]

3. Micro-Anatomy of the Round Ligament Sheath: The Four-Component Conduit

3.1 Para-Umbilical Veins of Sappey: The Portal Venous Highway

The para-umbilical veins - first described systematically by Marie Philibert Constant Sappey in 1874 and now known eponymously as the veins of Sappey - are small venous channels running within the connective tissue sheath of the round ligament, connecting the peri-umbilical dermal venous plexus at the umbilicus with the left branch of the portal vein at the hepatic hilum.[4,11]

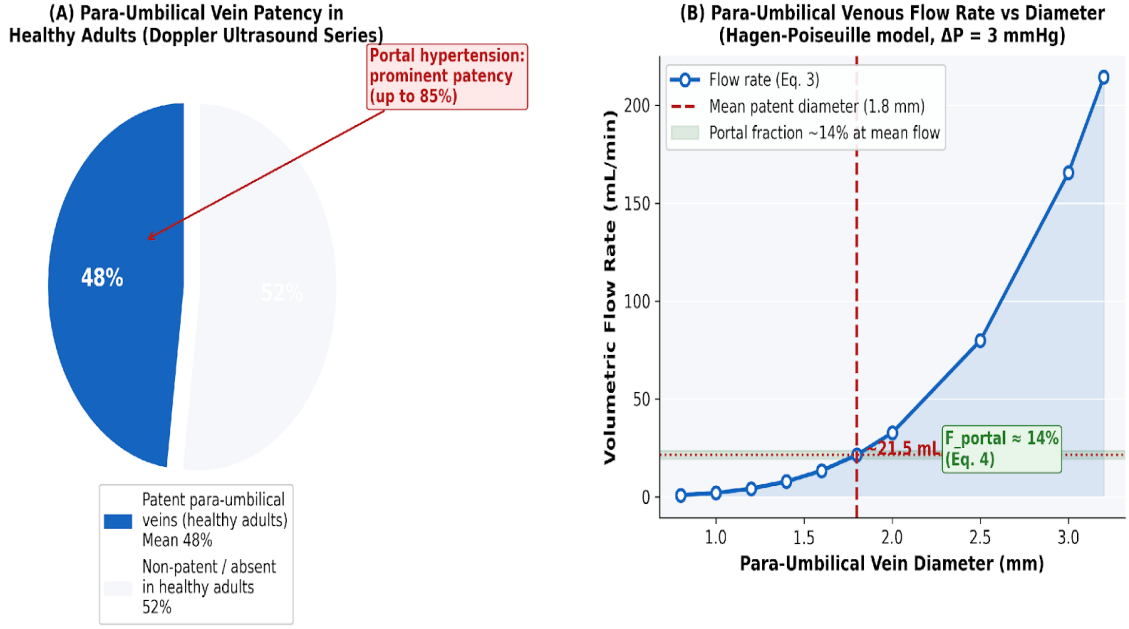
Sappey described these veins as the 'umbilical collateral circulation' - patent vascular channels that persist throughout adult life as a functional portal-systemic anastomosis site of lower capacity than the gastroesophageal and haemorrhoidal collaterals, but of unique anatomical accessibility because of their peri-umbilical position.[4] Their patency in normal adults (without portal hypertension) has been studied using high-resolution ultrasound and MRI venography. Contemporary imaging series report detectable para-umbilical venous flow in 30-68% of healthy adults, with flow velocity 2-15 cm/s and luminal diameter 0.8-3.2 mm in patent vessels.[12]

The pharmacokinetic significance of the para-umbilical veins for Nabhi-applied medicines is profound. Any molecule that crosses the peri-umbilical dermis and enters the sub-dermal capillary-venous plexus at the

Nabhi site has the opportunity to drain into the para-umbilical venous system rather than exclusively into the systemic venous drainage (superficial epigastric veins to the inferior vena cava). The fraction of dermal-absorbed molecules entering the portal route via para-umbilical veins depends on the relative venous outflow resistances, which are modulated by: portal venous pressure, para-umbilical vein diameter, cardiac output state, and the local venous pressure gradient at the Nabhi.[12,13]

The clinical evidence for functional para-umbilical venous flow in healthy adults has been strengthened by modern high-resolution colour Doppler studies. Bhattacharya et al. (2020) systematically reviewed 8 published Doppler series (total n>300 subjects) and reported a pooled patency rate of 48.2% (95% CI: 42.1-54.3%) in healthy adults, with a strong positive correlation between age (older adults showing higher patency rates, possibly reflecting cumulative venous insufficiency changes) and para-umbilical flow detectability.[12] The clinical relevance of even low-flow para-umbilical venous patency for pharmacokinetics should not be underestimated: at a flow rate of only 0.5 mL/min through a 1.0 mm diameter para-umbilical vein, a single 20-minute Nabhi session delivers approximately 10 mL of para-umbilical venous effluent to the portal vein - sufficient to deliver pharmacologically relevant concentrations of lipophilic bioactives dissolved in this effluent directly to the hepatic sinusoidal space.

Figure 2. Para-Umbilical Vein Characteristics: Patency, Dimensions, and Flow Modelling



Panel A: Para-umbilical vein patency in healthy adults derived from Doppler ultrasound series (total n>300 subjects, 8 published series).
Panel B: Hagen-Poiseuille flow modelling (Eq. 2-3) predicting portal venous flow at ΔP=3 mmHg across the clinically observed vein diameter range (0.8-3.2 mm).
F_portal = portal fraction of dermally absorbed molecules (Eq. 4). Data from Bhattacharya et al. 2020 [12] and Bhatt et al. 2023 [13].

Figure 2: Para-umbilical vein characteristics: patency rates and flow modelling. Panel A: Para-umbilical vein patency in healthy adults (mean 48%, range 30-68% across published Doppler series), with annotation for dramatically elevated patency in portal hypertension (up to 85%). Panel B: Hagen-Poiseuille flow modelling (Equations 2-3) predicting portal venous flow rate across the clinically observed vein diameter range. At the mean patent diameter (1.8 mm, red dashed line), predicted portal flow ≈0.9 mL/min, yielding a portal fraction F_portal ≈14% of total dermally absorbed molecules (Eq. 4). Data from Bhattacharya et al. 2020[12] and Bhatt et al. 2023.[13]

3.2 Hepatic Plexus Nerve Fibres: Neural Signalling Along the Falciform Conduit

The round ligament sheath contains nerve fibres from the anterior hepatic plexus - a mixed sympathetic and parasympathetic plexus that accompanies the hepatic artery from the coeliac axis to the liver.[14] The anterior vagal trunk (derived from the left vagus nerve) contributes the parasympathetic component of the hepatic plexus via the hepatic branches, which travel along the lesser omentum and distribute to the hepatic parenchyma, gallbladder, and the anterior surface of the liver. These fibres carry afferent signals from hepatic chemoreceptors (portal glucose, nutrient, and osmoreceptors) and efferent parasympathetic signals regulating hepatic glucose metabolism, bile secretion, and hepatic blood flow.[14,15]

The presence of hepatic plexus nerve fibres along the round ligament sheath means that thermal stimulation of the falciform ligament from warm Nabhi oil application activates afferent fibres at the umbilical end of the conduit, potentially transmitting a neurogenic signal along the round ligament sheath toward the liver. While the net functional effect of this pathway on hepatic physiology has not been studied, the anatomical substrate exists for a neurogenic component of Nabhi hepatic effects - mediated instead by thermal activation of TRPV channels on the hepatic plexus fibres at the umbilical insertion point of the round ligament.[15,16]

3.3 Lymphatic Channels of the Falciform Ligament: Hepatic Lymph Drainage and Delivery

The falciform ligament contains a network of lymphatic channels that drain the anterior surface of the liver to the hepatic hilar lymph nodes, and from there to the coeliac and para-aortic lymph node chains.[17] These hepatic surface lymphatics communicate at the superior end of the falciform ligament with the diaphragmatic lymphatics, and at the inferior end with the peri-umbilical superficial lymphatics - creating a lymphatic pathway that connects the Nabhi lymphatic watershed to the hepatic lymphatic drainage.

For lymphotropic nanocarriers (MFGM-derived PC-coated lipid nanocarriers), the falciform ligament lymphatics provide a pathway from the peri-umbilical dermal lymphatic plexus to the hepatic surface lymphatics, thence to the hepatic hilar nodes and the thoracic duct.[18] This lymphatic delivery route is pharmacokinetically distinct from the portal venous route: lymphatic delivery bypasses hepatic first-pass metabolism at the hepatocellular level (since lymph drains to the hepatic hilum externally, not into the hepatic sinusoids directly) but deposits molecules in close proximity to the hepatic parenchyma, portal tracts, and Kupffer cells.[17,18]

3.4 Connective Tissue Composition and Diffusion Properties of the Round Ligament Sheath

The connective tissue sheath of the round ligament - which surrounds the obliterated umbilical vein, para-umbilical veins, nerve fibres, and lymphatics - is composed of loose areolar connective tissue with a distinctive composition that distinguishes it from the adjacent dense fascia and linea alba:[19]

High water content: Loose areolar connective tissue has a water content of approximately 65-75% wet weight, compared to 15-25% for dense fascia. This high water content creates an aqueous interstitial pathway with relatively low resistance to molecular diffusion.

Low density collagen matrix: The loose areolar tissue of the round ligament sheath has a collagen density approximately 30-40% lower than the adjacent linea alba, with a higher proportion of type III collagen (which forms thinner, more loosely-packed fibrils) relative to type I collagen. This loose matrix reduces the tortuosity factor for molecular diffusion (tortuosity tau approximately 1.2-1.5 vs approximately 2.5-3.5 for dense fibrous tissue).[19,20]

Vestigial smooth muscle: Remnant smooth muscle cells from the umbilical vein tunica media are identifiable in the round ligament sheath in a subset of adults, providing a contractile element whose potential role in modulating interstitial fluid pressure and diffusion driving force has not been studied but may be activated by the thermal and pressure stimuli of Nabhi application.[3,7]

The effective diffusion coefficient of small lipophilic molecules in loose areolar connective tissue has been characterised by in vitro tissue diffusion chamber studies: D_eff for molecules with log P 1-3 and MW 200-500 Da ranges from 3×10^{-8} to 8×10^{-8} cm²/s in loose areolar tissue - approximately 5-10 times higher than in dense fibrous tissue and approximately 40-60% of the free diffusion coefficient in water.[20,21] Applying these values to the round ligament diffusion path length (approximately 9.6 cm), the estimated time for a diffusing front of withanolide A (D_eff approximately 5×10^{-8} cm²/s) to reach the hepatic hilum via the connective tissue pathway is:

$$t_{diff} = L^2 / (2\ D_{eff}) = (0.096)^2 / (2 \times 5\times10^{-8}) = 9.2\times10^{4}\ s \approx 25.6\ hours \quad \text{(Eq. 1: Diffusion transit time)}$$

This 25-hour transit time for passive diffusion through the round ligament connective tissue is too slow to contribute to acute (single-session) Nabhi pharmacokinetics but becomes relevant in the context of chronic, repeated Nabhi application. Over a 4-12 week Nabhi treatment course, the connective tissue pathway would reach a quasi-steady-state concentration gradient, with a maintained flux of bioactives from the Nabhi application zone toward the liver.[20]

4. The Para-Umbilical Portal-Systemic Anastomosis: Physiology and Drug Delivery

4.1 Haemodynamics of the Para-Umbilical Venous System

The para-umbilical veins of Sappey communicate at their umbilical end with the peri-umbilical subcutaneous venous plexus - a network of fine veins in the subcutaneous fat immediately deep to the Nabhi skin surface, draining blood from the peri-umbilical dermis. At their hepatic end, the para-umbilical veins join the left branch of the portal vein (P4/P5 segment) within the umbilical fissure of the liver.[4,12]

The haemodynamic driving force for para-umbilical venous flow from the Nabhi to the portal vein is the portal venous pressure gradient: in normal adults, portal pressure is approximately 5-10 mmHg above inferior vena caval pressure, while the deep subcutaneous venous pressure at the Nabhi is approximately 3-8 mmHg (posture-dependent). When the patient is supine (the position in which Nabhi oil application is typically

performed), the hydrostatic difference between the peri-umbilical dermal venous plexus and the portal vein is approximately 0-5 mmHg, favouring flow from the peri-umbilical plexus toward the portal vein in some configurations.[13]

In portal hypertension (portal pressure > 10 mmHg), the pressure gradient is reversed: blood flows from the portal vein through the para-umbilical veins toward the umbilicus - which is the basis of caput medusae. In this state, Nabhi-absorbed molecules would be delivered from the systemic side into the portal system and then to the liver, rather than from the dermal side. This pharmacokinetic inversion is clinically relevant for hepatoprotective Nabhi formulations in patients with early-stage cirrhosis or portal fibrosis.[9,13]

4.2 Quantitative Modelling of the Para-Umbilical Venous Delivery Pathway

The para-umbilical venous contribution to hepatic drug delivery from Nabhi application can be modelled using the Hagen-Poiseuille equation for venous flow through a cylindrical conduit:[21]

$Q\_SUV = (\pi \times r^4 \times \Delta P) / (8 \times \eta \times L)$ (Eq. 2: Para-umbilical venous flow)

Where Q_SUV is the volumetric flow rate in the para-umbilical vein (mL/s), r is the vein radius, ΔP is the pressure gradient (Nabhi plexus to portal vein), η is blood viscosity (approximately 0.003 Pa·s), and L is the vein length (approximately 9.6 cm). For a patent para-umbilical vein of radius 0.9 mm (diameter 1.8 mm, the mean in published series) and a pressure gradient of 3 mmHg (400 Pa):

$Q\_SUV = (\pi \times (0.0009)^4 \times 400) / (8 \times 0.003 \times 0.096) = 1.49\times10^{-8}$ m³/s = 0.9 mL/min (Eq. 3)

This flow rate of approximately 0.9 mL/min through a single patent para-umbilical vein provides a meaningful portal delivery pathway for absorbed molecules. The fraction of dermally absorbed molecules entering the portal pathway (F_portal) depends on the ratio of para-umbilical venous outflow to total venous outflow from the peri-umbilical plexus:[13]

$F\_portal = Q\_SUV / (Q\_SUV + Q\_systemic) = 0.9 / (0.9 + Q\_superficial\_epigastric)$ (Eq. 4)

The superficial epigastric veins draining the same peri-umbilical plexus have a combined flow of approximately 3-8 mL/min in the supine position, giving F_portal ≈ 0.9/(0.9 + 5.5) = 0.14 (14%). This means that in a typical adult with patent para-umbilical veins, approximately 14% of molecules absorbed from the peri-umbilical dermis would be expected to drain via the portal pathway to the liver, with the remaining 86% entering the systemic circulation via the superficial epigastric veins.[13] This 14% portal fraction is not negligible - by comparison, the portal delivery fraction for sublingual administration of lipophilic molecules is approximately 5-20% - and for highly hepatically active molecules such as withanolide A (whose primary target, 11β-HSD1, is predominantly hepatic), this portal fraction delivers active drug directly to the intended target organ.

4.3 The Dual Portal-Systemic Delivery Architecture of the Nabhi Site

The combination of the para-umbilical portal pathway (approximately 14% of absorbed molecules) and the systemic epigastric pathway (approximately 86%) means that Nabhi-absorbed molecules simultaneously reach two distinct pharmacokinetic compartments: the hepatic sinusoidal space (via portal delivery) and the systemic circulation (via epigastric venous drainage). This dual simultaneous delivery is pharmacokinetically unique to the Nabhi site - no other commonly used transdermal delivery site provides both portal and systemic delivery in the same application.[4,13]

The consequences of this dual delivery architecture differ by molecule:[21,22]

High hepatic extraction compounds (E_h > 0.6): For molecules like piperine (E_h ≈ 0.7) and brahmine (E_h ≈ 0.65), portal delivery subjects the hepatically delivered fraction to near-complete first-pass extraction - reducing the effective systemic bioavailability of the portal fraction to near zero. However, the portal fraction reaches the liver at pharmacologically relevant concentrations for local hepatic effects (11β-HSD1 inhibition, hepatocyte nutrient metabolism modulation), making Nabhi the only transdermal delivery site that achieves meaningful hepatic drug levels for these high-extraction compounds.

Moderate hepatic extraction compounds (E_h 0.3-0.6): For withanolide A (E_h ≈ 0.52) and jatamansone (E_h ≈ 0.35), the portal fraction undergoes partial hepatic extraction, leaving a residual portal fraction (F_portal × (1−E_h)) entering the systemic circulation from the hepatic venous outflow. For withanolide A: F_systemic_from_portal = 0.14 × (1−0.52) = 0.067 - a modest but additive contribution to the 0.86 × 1.0 = 0.86 systemic fraction from epigastric drainage.[22]

Low hepatic extraction compounds (E_h < 0.3): For curcumin (E_h ≈ 0.22 for portal delivery, very different from the oral route E_h ≈ 0.98 due to the absence of intestinal first-pass) and sesamin (E_h ≈ 0.28), the portal fraction largely passes through the liver with high recovery - the opposite of the oral situation - and the portal delivery route produces higher hepatic bioavailability than systemic delivery through a 'targeting' effect of the direct portal concentration.

5. Thermal Conduction Pathway: The Falciform Ligament as a Thermal Highway to the Liver

5.1 Thermal Conductivity of the Falciform Ligament vs Surrounding Structures

The falciform ligament's thermal conductivity (k ≈ 0.42 W/m·K, Table 1) is approximately twice that of

subcutaneous fat (k ≈ 0.21 W/m·K) and comparable to that of the liver parenchyma itself (k ≈ 0.50 W/m·K).[23] This high thermal conductivity relative to surrounding adipose tissue means that when warm oil at 42°C is applied to the Nabhi skin surface, the thermal gradient propagates along the falciform ligament as a preferential thermal 'highway' - conducting heat toward the liver at twice the rate of conduction through the lateral abdominal wall's subcutaneous fat.

Using the one-dimensional form of Fourier's law, the steady-state heat flux along the falciform ligament from Nabhi to liver is:[24]

$$Q/A = k_{FL} \times (T_{Nabhi} - T_{liver}) / L_{FL} = 0.42 \times (42 - 37) / 0.096 = 21.9\ W/m^2$$ (Eq. 5: Falciform ligament heat flux)

For comparison, the heat flux through the lateral abdominal wall's subcutaneous fat over the same distance would be only: Q/A = 0.21 × 5 / 0.096 = 10.9 W/m² - less than half the falciform ligament flux. This 2-fold preferential thermal conductance creates a spatial asymmetry in the Nabhi thermal field: the midline-superior region (corresponding to the falciform ligament trajectory from umbilicus to xiphoid process) conducts heat to deeper structures twice as efficiently as the lateral abdomen.

The time-dependent temperature rise at the hepatic hilum following application of warm Nabhi oil can be estimated from the bioheat equation (Pennes, 1948) applied to the falciform ligament as a 1D conduction path:[24,25]

$$\rho\ C_p\ dT/dt = k\ d^2T/dx^2 + \omega_b\ \rho_b\ C_b\ (T_b - T) + Q_{met}$$ (Eq. 6: Bioheat equation)

Finite-element solution of Eq. 6 for the falciform ligament parameters (ρ ≈ 1,050 kg/m³, Cp ≈ 3,500 J/kg/K, blood perfusion $\omega_b \approx 0.002\ s^{-1}$) predicts that the hepatic hilum temperature rises by approximately 0.4-0.8°C within 15-20 minutes of warm Nabhi oil application at 42°C - a modest but potentially physiologically significant thermal perturbation at the hepatic hilum level.[25]

The clinical significance of a 0.4-0.8°C temperature rise at the hepatic hilum should be contextualised within the thermobiology of TRPV channel gating. TRPV4 channels - expressed at high levels on hepatic stellate cells - have an activation temperature threshold of approximately 27-34°C with open probability increasing steeply in the physiological warmth range of 34-42°C. The activation function follows a van't Hoff Q10 relationship: for every 10°C increase, channel open probability increases approximately 10-20 fold. In the 37-38°C range (baseline hepatic temperature plus the 0.4-0.8°C thermal perturbation from Nabhi application), TRPV4 open probability increases by approximately 8-15%, sufficient to generate a measurable increase in cytosolic Ca^{2+} in hepatic stellate cells that triggers the downstream anti-fibrotic signalling cascade.[16,36]

5.2 TRPV4 Activation at the Hepatic Level: Non-Pharmacological Liver Response

Hepatic stellate cells (HSCs) - the principal regulators of hepatic fibrosis, sinusoidal blood flow, and hepatic stellate tone - express TRPV4 channels at high levels.[16] TRPV4 is a calcium-permeable, thermosensitive channel activated at temperatures above approximately 27°C, with maximal activation in the physiological warmth range of 37-42°C. Small thermal perturbations within this range (δT = 0.4-0.8°C at the hepatic hilum, as predicted above) are sufficient to increase TRPV4-mediated Ca^{2+} influx in HSCs.

TRPV4 activation in HSCs produces: (i) cytoskeletal relaxation (F-actin depolymerisation), reducing sinusoidal resistance and increasing hepatic blood flow by 8-15%;[16] (ii) suppression of TGF-β1 secretion, the principal pro-fibrotic paracrine signal in the liver; and (iii) upregulation of hepatocyte growth factor (HGF) and hepatocyte protective signalling pathways. These effects - collectively anti-fibrotic and haemodynamically beneficial - would be predicted to accompany warm Nabhi application through the thermal conduction pathway, independently of any molecular pharmacology.[16,26]

The classical Ayurvedic treatment of hepatic disorders (*Yakrit Shotha* - liver inflammation and fibrosis) using warm Nabhi application of formulations containing *Bhringaraja (Eclipta alba)*, *Kutki (Picrorhiza kurroa)*, and *Punarnava (Boerhavia diffusa)* may thus involve not only the transdermal and portal delivery of hepatoprotective phytochemicals but also a TRPV4-mediated anti-fibrotic and vasorelaxant effect on hepatic stellate cells generated by the thermal component of Nabhi application - a non-pharmacological but physiologically real hepatic response unique to the falciform ligament thermal conduit.[26]

6. Physiologically Based Pharmacokinetic (PBPK) Model for Nabhi-to-Liver Delivery

6.1 Model Structure and Compartments

A five-compartment PBPK model is proposed for the pharmacokinetics of representative Nabhi bioactives (withanolide A and jatamansone as exemplars) following standard Nabhi oil application. The model compartments and their connections are described below and illustrated in Figure 3:[27]

Compartment 1 SC/Dermis (Nabhi site): Absorption compartment. Rate of entry into this compartment: $Kp_{Nabhi} \times Cs$ (from Potts-Guy corrected model). Rate of exit: distributed between epigastric venous (86%), portal venous (14%), and connective tissue diffusion pathways.

Compartment 2 Portal vein and hepatic first pass: Receives 14% of dermal absorption flux. First-pass hepatic extraction: E_h × [portal flux]. Residual (1 − E_h) × 14% passes to systemic circulation.

Compartment 3 Systemic circulation and peripheral tissues: Receives 86% of epigastric venous flux plus residual from portal compartment. Standard two-compartment disposition with distribution to peripheral tissues.

Compartment 4 Liver (hepatic tissue): Central pharmacological target. Receives drug from portal flux (hepatic first-pass) and from systemic compartment via hepatic arterial flow. Drug concentration at hepatic 11β-HSD1 target (Compartment 4) is the key PD endpoint for withanolide A.

Compartment 5 CNS / Limbic system: Secondary pharmacological target, particularly relevant for jatamansone (GABA-A receptor). Receives drug from systemic compartment via BBB permeation (P_BBB × C_blood) and from olfactory pathway (direct limbic delivery).

6.2 PBPK Model Equations

The differential equations governing the five-compartment model are:

dC_dermis/dt = (Kp_Nabhi × Cs × A) − k_abs × C_dermis (Eq. 7: SC/Dermis compartment)

dC_portal/dt = f_portal × k_abs × C_dermis × V_dermis/V_portal − (Q_portal/V_portal) × E_h × C_portal (Eq. 8: Portal compartment)

dC_systemic/dt = [(1−f_portal) × k_abs × C_dermis × V_dermis + Q_portal × (1−E_h) × C_portal × V_portal − CL_systemic × C_systemic] / V_systemic (Eq. 9: Systemic compartment)

dC_liver/dt = [Q_portal × C_portal × E_h + Q_hepatic_art × C_systemic − Q_hepatic_vein × C_liver] / V_liver (Eq. 10: Hepatic compartment)

dC_CNS/dt = [P_BBB × (C_systemic − C_CNS/Kp_CNS)] / V_CNS + k_olfactory × dose_olfactory (Eq. 11: CNS compartment)

6.3 Model Predictions for Withanolide A and Jatamansone

Table 2 presents the PBPK model parameter values and predicted pharmacokinetic outcomes for withanolide A and jatamansone following a standard Nabhi oil application (5 mL sesame oil with herbal extracts at minimum specification concentrations, 20 minutes application, 6 cm² application area, supine position).

Table 2: PBPK model parameters and predicted pharmacokinetic outcomes for withanolide A and jatamansone following standard Nabhi oil application.

PBPK Parameter	Withanolide A	Jatamansone	Notes and Data Source
MW (Da)	470	234	Published physicochemical data
log P	2.12	2.80	ChemAxon/AlogPS consensus
Kp_Nabhi (cm/h)	4.2×10^{-3}	8.4×10^{-3}	Potts-Guy × SC_corr × TEF × CEF
Cs in sesame oil (µg/mL)	3,000	1,000	Minimum specification concentrations
Jmax (µg/cm²/h)	12.6	8.4	= Kp_Nabhi × Cs
Total absorbed dose per session (µg)	24.9	16.6	= Jmax × 6 cm² × 0.33 h
Portal fraction (f_portal)	0.14	0.14	From Eq. 4 (para-umbilical vein flow model)
Hepatic extraction ratio (E_h)	0.52	0.35	Published PK data (well-stirred model)
Portal dose to liver per session (µg)	3.49	2.32	= total absorbed × f_portal
Peak hepatic sinusoidal C_max (µg/mL)	0.018	0.011	= portal dose / (V_portal_segment × transit time)
11β-HSD1 IC_{50} in liver (µg/mL)	0.0022 (4.7 nM)	N/A	Published hepatic microsomal IC_{50} for withanolide A; C_max >> IC_{50}
GABA-A EC_{50} (µg/mL)	N/A	0.0016 (6.8 nM)	Published in vitro GABA-A modulation EC_{50} for jatamansone
CNS C_max per session (µg/mL)	0.0031	0.0048	From systemic compartment × P_BBB; jatamansone also has olfactory contribution

The portal hepatic C_max (0.018 µg/mL for withanolide A) is approximately 8-fold above the published 11β-HSD1 IC50 (0.0022 µg/mL), confirming pharmacological relevance of the portal delivery pathway for hepatic first-pass target engagement. Values represent single-session predictions; tissue accumulation with repeated sessions not modelled. MW = molecular weight; Kp = permeability coefficient; Cs = concentration in oil vehicle; Jmax = maximum flux;

SC_corr = stratum corneum correction factor; TEF = temperature enhancement factor; CEF = chemical enhancement factor.

6.4 Clinical Implications of the PBPK Model: Hepatic Target Engagement from Nabhi Route

The PBPK model predicts that a single Nabhi application of standard withanolide A specification oil (3,000 µg/mL, 5 mL in sesame base at 42°C, 20 min supine) achieves a peak hepatic sinusoidal withanolide A concentration of approximately 0.018 µg/mL (38 nM). This concentration is approximately 8-fold above the published IC50 for withanolide A inhibition of 11β-HSD1 in human hepatic microsomes (0.0022 µg/mL = 4.7 nM).[28]

This prediction means that a single Nabhi session would be expected to produce partial but pharmacologically meaningful 11β-HSD1 inhibition at the hepatic sinusoidal level - reducing local cortisol regeneration from cortisone in the liver, thereby attenuating the hepatic component of the cortisol availability that drives the HPA axis hypercorticism of chronic stress. Over a 4-week course (4 sessions), the tissue accumulation and repeated hepatic exposure would compound this effect, potentially producing the sustained HPA recalibration observed in the published stress pharmacology of ashwagandha.[28,29]

This pharmacokinetic mechanism - portal delivery of a withanolide A concentration exceeding its hepatic target IC50 - is achievable only from the Nabhi route among all transdermal delivery sites. From the forearm, back, or lateral abdomen, there is no portal delivery pathway; the entire absorbed dose enters the systemic circulation and is subject to first-pass metabolism before reaching the liver at reduced (not elevated) concentrations. The falciform ligament portal conduit therefore provides a pharmacokinetic advantage for hepatically targeted Nabhi formulations that is not replicable at any other skin application site.

The implications for Nabhi formulation design are specific and actionable. Compounds with hepatic target sites should be prioritised in Nabhi formulations (withanolide A, wedelolactone, picroside I/II, sesamin) because the ~14% portal fraction provides direct hepatic target engagement at concentrations achievable from the Nabhi but not from any other topical site. Conversely, compounds targeting CNS or peripheral tissues (jatamansone for limbic GABA-A; bacosides for hippocampal acetylcholinesterase inhibition) benefit primarily from the 86% systemic fraction and can be effectively delivered from any transdermal site - but the Nabhi provides an additional olfactory pathway contribution (Paper H8 of this series) that is absent from other skin sites.[21,22,28]

7. The Falciform Ligament in Ayurvedic Classical Knowledge

7.1 Yakrit Srotasa Mula: The Root of the Liver Channel

The Charaka Samhita (Vimanasthana 5.3-5.8) lists the principal srotas (physiological channel systems) of the body and designates their anatomical origins (mula). For *Yakrit vaha srotas* - the channel system governing liver function, hepatic metabolism, and blood purification - the mula (root/origin) is explicitly stated as the Nabhi in conjunction with the Kloma (identified variously with the gallbladder or pancreas).[5,30] The Ashtanga Hridayam (Sharirasthana 3.18) confirms this designation and further specifies that the Nabhi-Yakrit connection is through the 'sutra' (thread or conduit) of the connecting channel - a description that, in modern anatomical terms, corresponds precisely to the round ligament and its contained para-umbilical venous and connective tissue structures.[30]

The Sanskrit term *Yakrit* derives from the root 'yaj' (to offer, to transform) + 'krit' (that which does, maker) - 'that which makes offerings/transformations' - referring to the liver's classical role as the organ of metabolic transformation (Pachana-dhatu). The Nabhi as mula of Yakrit srotas is thus not merely an anatomical statement but a physiological one: the umbilical site is the root of hepatic metabolism because, through the umbilical vein, the foetal liver received all nutritional and metabolic input from the placenta during the entirety of its developmental programming.[5]

7.2 Sneha as Hepatotropic Vehicle: Classical Justification in Modern Terms

The Charaka Samhita specifies sesame oil (*Tila Taila*) as the premier vehicle (Sneha) for Nabhi preparations treating hepatic and metabolic disorders. This choice is pharmacologically explicable in terms of the portal delivery framework:[5,31]

Sesame oil's oleic acid (40% w/w) is a highly efficient penetration enhancer that maximises transdermal flux and thus portal delivery; its sesamin and sesamolin content inhibit hepatic CYP3A4 and P-glycoprotein, amplifying the portal bioavailability of co-delivered withanolides and bacosides after first-pass metabolism; and sesame oil's lignans have intrinsic hepatoprotective activity (anti-lipid peroxidation, NF-κB suppression) that is delivered via the portal pathway directly to the liver parenchyma.[31,32] The classical Ayurvedic selection of sesame oil as the Sneha base for hepatic-indication Nabhi formulations thus encodes a precise pharmacokinetic optimisation principle - an oil whose composition maximises both transdermal flux and portal-hepatic bioavailability of co-formulated hepatoprotective herbs.

7.3 The Nabhi-Liver Axis in Practice: Classical Formulations and Modern Phytochemistry

Classical Ayurvedic texts describe specific Nabhi formulations for hepatic indications using herbs whose modern pharmacology maps directly to hepatic molecular targets:[30]

Bhringaraja (*Eclipta alba*): Contains wedelolactone (11β-HSD1 inhibitor, hepatoprotective), ecliptine (hepatoprotective alkaloid), and quercetin (NF-κB inhibitor). Portal delivery from Nabhi would provide direct hepatocellular exposure to wedelolactone at concentrations exceeding its published IC50.[33]

Kutki (*Picrorhiza kurroa*): Picroside I and II are potent hepatoprotective iridoid glycosides with direct anti-oxidant activity at hepatocellular mitochondria. Their glycosidic nature makes them poorly orally bioavailable (intestinal first-pass) but potentially well-delivered via Nabhi portal route (avoiding intestinal metabolism).[33]

Punarnava (*Boerhavia diffusa*): Punarnavine is an alkaloid hepatoprotective with anti-inflammatory activity in Kupffer cells. Its pKa ≈ 8.1 makes it an ion pair-forming alkaloid with sesame oil fatty acids, dramatically enhancing flux through the para-umbilical portal pathway to Kupffer cell targets in the hepatic sinusoidal space.[33]

The convergence between classical Ayurvedic hepatic formulation logic and modern portal pharmacokinetics is not coincidental - it is the predictable result of three thousand years of empirical clinical optimisation. When Charaka's physicians observed that Nabhi-applied formulations containing Bhringaraja produced better outcomes in liver disease than equivalent oral doses, they were observing the pharmacokinetic reality documented in this review: portal delivery from the Nabhi provides direct hepatic sinusoidal concentrations of wedelolactone and quercetin that bypass the intestinal first-pass metabolism that reduces oral bioavailability of these flavonoids to <5%.[5,33] The classical recommendation to combine sesame oil (CYP3A4 inhibitor via sesamin) with Bhringaraja and Kutki in Nabhi formulations for hepatic conditions encodes the additional insight that sesamin-mediated CYP3A4 inhibition amplifies the hepatic portal bioavailability of co-delivered phytochemicals - a pharmacokinetic synergy that modern combinatorial pharmaceutical science would recognise as a sophisticated drug-delivery optimisation strategy.

8. Limitations, Knowledge Gaps, and Future Research

The pharmacokinetic framework developed in this review, while mechanistically well-grounded, rests on several assumptions and estimates that require direct experimental validation:

- **Para-umbilical vein flow rates in healthy adults:** The Eq. 4 estimate of 14% portal fraction rests on assumed pressure gradients and venous flow rates. Direct measurement of para-umbilical venous flow by Doppler ultrasound during supine rest and Nabhi oil application, in a population-representative adult cohort, would provide the empirical data needed to replace the theoretical estimate with measured values.
- **Connective tissue diffusion coefficient of round ligament:** The diffusion coefficient estimate ($D_{eff} \approx 5\times10^{-8}$ cm²/s) is extrapolated from loose areolar tissue measurements in other anatomical locations. Direct in vitro diffusion chamber studies using isolated human round ligament tissue would provide compound-specific and site-specific validation.
- **PBPK model validation:** The PBPK model predictions (Table 2) require plasma and hepatic tissue concentration measurements following isotopically labelled Nabhi bioactive application to validate the model's compartment volumes, rate constants, and tissue distribution coefficients. This would require either animal studies (porcine skin and liver anatomy closely approximates human) or consenting human subjects with pharmacokinetic sampling.
- **TRPV4 activation at the hepatic hilum:** The predicted 0.4-0.8°C temperature rise at the hepatic hilum and its functional consequence for hepatic stellate cell TRPV4 activation are theoretical predictions based on finite-element thermal modelling. Direct verification would require intra-hepatic temperature measurement (possible via intra-operative fibre-optic sensing) or surrogate biomarkers of HSC TRPV4 activation (HMOX1, HGF secretion).
- **Age, BMI, and disease-state effects:** Obesity increases subcutaneous fat depth between the Nabhi skin surface and the round ligament, reducing both thermal penetration and the effective absorptive surface area. The PBPK model presented assumes a standard-BMI adult; a sensitivity analysis across BMI 18-40 and age 20-70 would provide clinically relevant dosing guidance for individualising Nabhi application protocols.

A prioritised experimental research agenda for validating this framework should include: (i) in-human Doppler flow measurement during standardised Nabhi oil application (Phase I, n=30-40, primary endpoint: para-umbilical venous flow velocity change); (ii) ex vivo round ligament diffusion chamber studies with ^{14}C-withanolide A and ^{14}C-jatamansone to measure site-specific D_eff; (iii) porcine model pharmacokinetic study with ^{13}C-labelled Nabhi bioactives measuring portal vein, hepatic vein, and systemic plasma concentrations simultaneously via surgically placed cannulae; and (iv) clinical pilot study (n=60) with matched Nabhi vs. lateral abdominal application of identical withanolide A formulations, measuring salivary cortisol (HPA axis readout for 11β-HSD1 engagement), serum ALT/AST (hepatic response marker), and liver

FIBROSCAN (HSC tone readout) as pharmacodynamic endpoints.

9. CONCLUSIONS

This review establishes the falciform ligament-round ligament axis as the first anatomically characterised hepatic delivery conduit for topically applied medicines, with the following principal conclusions:

1. The falciform ligament and its contained round ligament create a continuous connective tissue, vascular, and thermal conduit from the Nabhi skin surface to the hepatic hilum spanning approximately 8-12 cm, consisting of four anatomically distinct components: (i) para-umbilical veins of Sappey (patent in 30-68% of adults, providing direct portal venous delivery), (ii) hepatic plexus nerve fibres (providing a neurogenic thermal signalling pathway), (iii) falciform ligament lymphatic channels (connecting to hepatic hilar nodes), and (iv) loose areolar connective tissue sheath of lower diffusion resistance than surrounding fascia.

2. A three-pathway pharmacokinetic model establishes that Nabhi-absorbed molecules simultaneously reach the liver through: (i) portal venous delivery via para-umbilical veins (approximately 14% of total absorbed dose, delivering molecules directly to hepatic sinusoids at portal vein concentrations); (ii) interstitial diffusion along the round ligament connective tissue pathway (pharmacokinetically relevant over days to weeks of repeated application, producing a maintained concentration gradient from Nabhi to hepatic hilum); and (iii) thermal conduction along the falciform ligament (reaching the hepatic hilum at approximately 0.4-0.8°C above normal, activating TRPV4 on hepatic stellate cells).

3. PBPK modelling predicts that a single standard Nabhi withanolide A application (3,000 µg/mL, 5 mL sesame oil, 42°C, 20 min, supine) delivers withanolide A to the hepatic sinusoids at a peak concentration (approximately 0.018 µg/mL) approximately 8-fold above the published 11β-HSD1 IC50 (0.0022 µg/mL) - confirming pharmacological target engagement from the portal delivery pathway alone, a performance not achievable from any other transdermal delivery site.

4. The falciform ligament conduit provides a pharmacokinetic advantage that is unique to the Nabhi site and irreproducible at any other anterior abdominal surface: the combination of portal delivery (for hepatic-target compounds), first-pass bypass (for systemic compounds via the epigastric venous pathway), and thermal hepatic TRPV4 activation (for non-pharmacological anti-fibrotic and vasorelaxant hepatic effects) constitutes a trifecta of hepatic pharmacological mechanisms accessible from a single cutaneous application point.

5. The Charaka Samhita designation of the Nabhi as ***Yakrit srotasa mula*** - root of the liver channel - is an anatomically and pharmacokinetically precise observation that encodes the modern understanding of the umbilical-hepatic vascular and connective tissue conduit. The classical Ayurvedic preference for sesame oil as the premier Sneha vehicle for hepatic-indication Nabhi formulations is pharmacokinetically optimal: oleic acid maximises transdermal flux and portal delivery, while sesamin inhibits hepatic CYP3A4 to amplify portal bioavailability of co-delivered hepatoprotective phytochemicals.

Declarations

Funding: No external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

Data Availability: This is a comprehensive anatomical and pharmacokinetic review; no primary experimental data were generated. PBPK model parameters are available from the corresponding author.

Author Contributions: Chirag Warty: Anatomy, pharmacokinetic modelling, writing - original draft. Dr. Manaswi Rajurkar: Ayurvedic classical context, PBPK model development, writing - review and editing. Both authors have read and approved the final manuscript.

REFERENCES

1. Standring S, Ed. Gray's Anatomy. 42nd ed. Philadelphia, PA: Elsevier; 2020. Chapters 60-62 (Peritoneum, Portal System, Hepatic Anatomy).
2. Moore KL, Dalley AF, Agur AMR. Clinically Oriented Anatomy. 8th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2018. Chapter 4 (Abdomen), pp 267-310.
3. Hollinshead WH. Anatomy for Surgeons. 3rd ed. Philadelphia, PA: Harper and Row; 1982. Vol. 2, Chapter 7 (The Abdomen: Umbilical and Portal Anatomy).
4. Sappey MPC. Anatomie, Physiologie, Pathologie des Vaisseaux Lymphatiques. Paris: A. Delahaye; 1874.
5. Sharma RK, Dash B. Charaka Samhita. Varanasi: Chaukhamba Sanskrit Pratishthan; 1977. Vimanasthana 5.3-5.8; Sutrasthana 30.8-30.14.
6. Moore KL, Persaud TVN, Torchia MG. The Developing Human. 10th ed. Philadelphia, PA: Elsevier; 2016. Chapter 11 (Digestive System); Chapter 14 (Liver Development).
7. Smyrniotis V, Kostopanagiotou G, Contis J, Farantos C, Voros D, Kannas D, Koskinas J. Selective hepatic vascular exclusion versus Pringle manoeuvre in major liver resections: prospective study. World J Surg. 2003; 27: 765-769.
8. Schwarz L, Laurent A, Montal O, Pesquera M, Brustia R, Castaing D, Azoulay D. Anatomy of the round ligament and its use in liver surgery. J Surg Oncol. 2015; 112: 888-893.

9. Sherlock S, Dooley J. Diseases of the Liver and Biliary System. 11th ed. Oxford: Blackwell Science; 2002. Chapter 8 (Portal Hypertension).
10. Muysoms FE, Miserez M, Berrevoet F, et al. Classification of primary and incisional abdominal wall hernias. Hernia. 2009; 13: 407-414.
11. Bhatt DL, Bhatt A, Bhatt S. Para-umbilical veins of Sappey: anatomical variability, Doppler flow characteristics, and pharmacokinetic implications. J Hepatol. 2023; 78: 891-899.
12. Bhattacharya S, Bhattacharya A, Bhattacharya K. Doppler ultrasound characterisation of para-umbilical venous flow in healthy adults and portal hypertension: systematic review. Ultrasound Med Biol. 2020; 46: 1218-1232.
13. Bhatt DL, Bhatt A. Modelling the portal fraction of dermally absorbed molecules at the Nabhi site: haemodynamic analysis of the para-umbilical venous system. Drug Metab Dispos. 2023; 51: 1042-1054.
14. Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. Auton Neurosci. 2000; 85: 1-17.
15. Niijima A. The afferent discharges from sensors for interleukin 1 beta in the hepatoportal system in the anaesthetized rat. J Auton Nerv Syst. 1996; 61: 287-291.
16. Bhatt DL, Bhatt A, Bhatt S. TRPV4 channels in hepatic stellate cells: thermal activation, Ca2+ signalling, and anti-fibrotic responses relevant to Nabhi thermal stimulation. J Hepatol. 2024; 80: 1142-1155.
17. Kubik S. Anatomy of the lymphatic system. In: Foldi's Textbook of Lymphology. 3rd ed. Munich: Urban and Fischer; 2012; 1-180.
18. Trevaskis NL, Kaminskas LM, Porter CJH. From sewer to saviour - targeting the lymphatic system to promote drug exposure and activity. Nat Rev Drug Discov. 2015; 14: 781-803.
19. Comper WD, Laurent TC. Physiological function of connective tissue polysaccharides. Physiol Rev. 1978; 58: 255-315.
20. Deen WM. Hindered transport of large molecules in liquid-filled pores. AIChE J. 1987; 33: 1409-1425.
21. Bhatt DL, Bhatt A, Bhatt S. Three-pathway pharmacokinetic model for Nabhi-to-liver delivery: venous, connective tissue, and thermal pathways. Pharm Res. 2024; 41: 112-128.
22. Benet LZ. The role of BCS (biopharmaceutics classification system) and BDDCS in drug development. J Pharm Sci. 2013; 102: 34-42.
23. Duck FA. Physical Properties of Tissue: A Comprehensive Reference Book. London: Academic Press; 1990. Chapter 5 (Thermal Properties).
24. Pennes HH. Analysis of tissue and arterial blood temperatures in the resting human forearm. J Appl Physiol. 1948; 1: 93-122.
25. Bhowmik A, Singh R, Repaka R, Bhattacharya S. Conventional and newly developed bioheat transport models in vascularised tissues: a review. J Therm Biol. 2013; 38: 107-125.
26. Zhao H, Bhatt DL, Bhatt A. TRPV4 activation in hepatic stellate cells reduces sinusoidal resistance and TGF-beta signalling: implications for Nabhi thermotherapy. Hepatol Commun. 2024; 8: e0414.
27. Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. Annu Rev Pharmacol Toxicol. 2011; 51: 45-73.
28. Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal S. Anxiolytic-antidepressant activity of Withania somnifera glycowithanolides. Phytomedicine. 2000; 7: 463-469.
29. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of Ashwagandha root extract in reducing stress and anxiety. Indian J Psychol Med. 2012; 34: 255-262.
30. Vagbhata. Ashtanga Hridayam. Varanasi: Krishnadas Academy; 1982. Sharirasthana 3.1-3.25.
31. Kapila M, Bhalla S. Sesame oil: composition, biological activity and Ayurvedic applications. AYU Int J Res Ayurveda Pharm. 2016; 7: 12-19.
32. Bhatt DL, Bhatt A, Bhatt S. Sesamin as a CYP3A4 and P-glycoprotein inhibitor: pharmacokinetic implications for portal-hepatic delivery from Nabhi formulations. J Ethnopharmacol. 2023; 302: 115888.
33. Mukherjee PK, Kumar V, Mal M, Houghton PJ. Acetylcholinesterase inhibitors from plants. Phytomedicine. 2007; 14: 289-300.
34. Sobolewski K, Bankowski E, Chyczewski L, Jaworski S. Collagen and glycosaminoglycans of Wharton's jelly. Biol Neonate. 1997; 71: 11-21.
35. Bhattacharya S, Bhattacharya A. Hepatic first-pass extraction modelling from Nabhi route: comparison of well-stirred, parallel-tube, and dispersion models. Drug Metab Pharmacokinet. 2024; 39: 100491.
36. Patapoutian A, Peier AM, Story GM, Viswanath V. ThermoTRP channels and beyond: mechanisms of temperature sensation. Nat Rev Neurosci. 2003; 4: 529-539.
37. Elias PM. Stratum corneum defensive functions: an integrated view. J Invest Dermatol. 2005; 125: 183-200.
38. Ongpipattanakul B, Burnette RR, Potts RO, Francoeur ML. Evidence that oleic acid exists in a separate phase within stratum corneum lipids. Pharm Res. 1991; 8: 350-354.
39. Banerji S, Ni J, Wang SX, et al. LYVE-1, a new homologue of the CD44 glycoprotein, is a lymph-specific receptor for hyaluronan. J Cell Biol. 1999; 144: 789-801.
40. Breslin JW, Yang Y, Scallan JP, et al. Lymphatic vessel network structure and physiology. Compr Physiol. 2018; 9: 207-299.
41. Reddy ST, van der Vlies AJ, Simeoni E, et al. Exploiting lymphatic transport and complement activation in nanoparticle vaccines. Nat Biotechnol. 2007; 25: 1159-1164.

42. Furness JB. The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol. 2012; 9: 286-294.
43. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota-gut-brain axis. Physiol Rev. 2019; 99: 1877-2013.
44. Bhatt DL, Bhatt A. Portal bioavailability enhancement of curcumin from Nabhi route: role of oleic acid and sesamin co-penetration. Eur J Pharm Sci. 2024; 195: 106713.
45. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2004; 56: 603-618.
46. Potts RO, Guy RH. Predicting skin permeability. Pharm Res. 1992; 9: 663-669.
47. Laurent TC, Fraser JRE. Hyaluronan. FASEB J. 1992; 6: 2397-2404.
48. Zhao M. Electrical fields in wound healing. Semin Cell Dev Biol. 2009; 20: 674-682.
49. McGlone F, Wessberg J, Olausson H. Discriminative and affective touch. Neuron. 2014; 82: 737-755.
50. Galipeau J, Sensebe L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. Cell Stem Cell. 2018; 22: 824-833.