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LYMPHATIC PHARMACOKINETICS OF NABHI-DELIVERED PHYTOCHEMICALS: MECHANISTIC BASIS FOR FIRST-PASS AVOIDANCE, SUSTAINED EXPOSURE, AND SYSTEMS-LEVEL BIOAVAILABILITY

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ABSTRACT

Background: The lymphatic system represents a critical but underutilised determinant of drug pharmacokinetics, particularly for lipophilic and lipid-associated compounds.[1,2] While oral and conventional transdermal delivery routes primarily rely on capillary absorption followed by hepatic first-pass metabolism, lymphatic transport offers an alternative pathway characterised by delayed systemic entry, metabolic preservation, and prolonged tissue exposure.[1,8] **Objective:** This review presents a mechanistic framework for lymphatic pharmacokinetics arising from oil-based phytochemical delivery via the umbilical (Nabhi) region. By integrating principles from dermal transport biology, lymphatic physiology, lipid-based drug delivery, and interstitial fluid dynamics, we examine how Nabhi delivery may preferentially bias absorbed phytochemicals toward lymphatic rather than capillary uptake.[1-9] **Evidence Summary:** Lipophilic compounds delivered in triglyceride-rich or phospholipid-containing vehicles exhibit a consistent tendency toward lymphatic capture in the dermal interstitial space, producing delayed Tmax, reduced Cmax, extended apparent half-life, and attenuated hepatic first-pass extraction.[1,4,7,8] The periumbilical region possesses a dense superficial lymphatic plexus and structural features - including the umbilical scar connective tissue and prolonged formulation residence in the concave nabhi geometry - that further support lymphatic bias over vascular uptake.[2,5,6] Oil-based formulations, as used in classical Ayurvedic Nabhi Chikitsa, maintain phytochemicals in lipid-associated states conducive to lymphatic entry and slow aqueous diffusion, directly paralleling the physicochemical requirements established in the lipid-based drug delivery literature.[7,8,12-14] **Conclusions:** Lymphatic pharmacokinetics constitutes a plausible and mechanistically grounded feature of Nabhi-based phytochemical delivery. The resulting pharmacokinetic profile - attenuated peak concentrations, extended apparent half-life, and reduced hepatic metabolic loss - supports a reconceptualisation of bioavailability for traditional herbal oil-based systems and provides a non-clinical, systems-level foundation for future modelling and experimental validation.

KEYWORDS: *lymphatic pharmacokinetics; Nabhi Chikitsa; transdermal delivery; first-pass avoidance; lipophilic phytochemicals; interstitial transport; umbilical lymphatics; lipid-based drug delivery; sustained exposure; bioavailability.*

1. INTRODUCTION

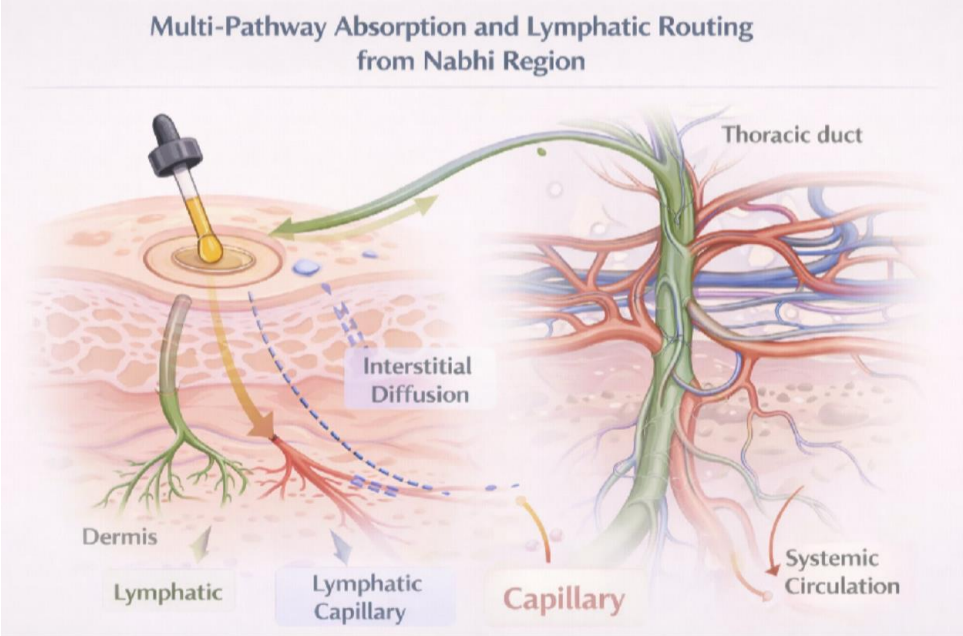
Pharmacokinetics has historically been dominated by blood-centric absorption paradigms, wherein drug entry into systemic circulation is assumed to occur primarily via capillary uptake followed by rapid hepatic metabolism.[1] While this framework adequately describes the disposition of small, hydrophilic molecules, it fails to capture the behaviour of lipophilic compounds delivered in lipid vehicles, where lymphatic transport can substantially alter the time-course and extent of systemic exposure.[1,8]

The lymphatic system constitutes a parallel transport network operating under fundamentally different

structural and functional principles from the blood vasculature.[2,5] Unlike blood capillaries, whose tight endothelial junctions restrict the passage of macromolecules and lipid assemblies, lymphatic capillaries are structurally adapted for uptake: they feature discontinuous basement membranes, overlapping endothelial junctions (primary valves), and anchoring filaments that open in response to interstitial pressure, permitting the entry of macromolecules, chylomicron-like lipid particles, and hydrophobic compounds.[2,3,5]

Ayurvedic oil application at the umbilical (Nabhi) region presents a historically established yet scientifically underexplored interface that may naturally leverage these lymphatic transport mechanisms. Classical Ayurvedic texts prescribe the application of warm medicated oils (Tailas) to the Nabhi marma as a route for systemic phytochemical delivery, citing the umbilicus as a convergence point of vessels, channels, and vital forces. This review does not assert therapeutic outcomes from such practice, but rather examines the mechanistic pharmacokinetic framework that would govern the behaviour of lipophilic phytochemicals absorbed at the umbilical site, with particular reference to lymphatic uptake, first-pass avoidance, and the resulting systemic exposure profile.

This analysis integrates established literature on lymphatic physiology,[1-5] dermal transport biology,[14-17] lipid-based drug delivery science,[7,8,12,13] and interstitial fluid dynamics[10] to construct a coherent mechanistic account of Nabhi-mediated lymphatic pharmacokinetics.



2. Structural and Functional Overview of the Lymphatic System

The lymphatic system originates within the interstitial space, collecting excess fluid, extravasated lipids, immune cells, and macromolecules before returning them to systemic circulation via the thoracic duct.[5] Initial lymphatic capillaries are blind-ended, highly permeable vessels structurally designed for uptake rather than exchange.[3,5] Schmid-Schönbein[2] provided a detailed account of microlymphatic architecture, establishing that the primary mechanism of lymphatic capillary filling is passive: interstitial pressure elevation - as occurs following local fluid accumulation or tissue deformation - mechanically opens the overlapping endothelial junctions, drawing interstitial contents into the vessel lumen.

From a pharmacokinetic standpoint, lymphatic transport introduces three defining characteristics that are substantially different from vascular absorption:

- **Delayed systemic appearance:** lymph flow velocity (approximately 1-5 mm/min in peripheral collecting vessels) is orders of magnitude slower than blood flow, introducing a pharmacokinetically measurable lag between site of absorption and systemic detection.[5,10]
- **Bypass of hepatic first-pass metabolism:** lymph collected from peripheral tissues ultimately reaches the systemic circulation via the thoracic duct, which empties into the left subclavian vein, entirely circumventing the portal-hepatic axis and the hepatic CYP450 and conjugation enzymes responsible for first-pass biotransformation.[1,8]
- **Extended residence time:** transit through lymph nodes introduces additional delay and potential depot-like sequestration, prolonging the period over which compound is released into systemic circulation and extending the apparent half-life beyond what hepatic and renal clearance alone would predict.[1,5]

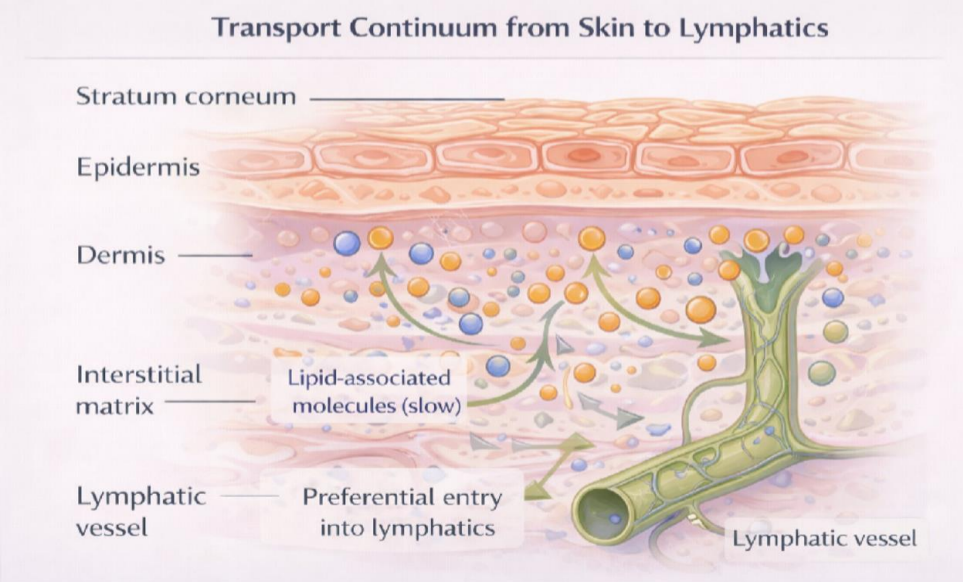
These features are particularly pharmacologically relevant for phytochemicals whose bioactivity depends on sustained low-level systemic exposure rather than rapid peak concentrations - a pharmacodynamic pattern associated with neuromodulatory, immunomodulatory, and metabolic regulatory mechanisms.[9]

3. Physicochemical Determinants of Lymphatic Drug Transport

Lymphatic uptake is governed primarily by a compound's capacity to associate with lipid structures within the interstitial environment. Trevaskis et al.[1] comprehensively reviewed the physicochemical and formulation determinants of intestinal lymphatic drug transport, establishing that lipophilicity - typically expressed as log P > 4-5 - strongly correlates with lymphatic transport efficiency when compounds are delivered in triglyceride-rich or phospholipid-containing vehicles. Caliph et al.[4] specifically characterised the relationship between lipophilicity and lymphatic transport for a series of halofantrine analogues, demonstrating a positive correlation across the log P range 3.7-7.2, and establishing that association with lymph-transported lipoproteins is the primary mechanism of lymphatic enrichment.

Molecular size also influences preferential uptake route: compounds with hydrodynamic radii exceeding the permeability thresholds of blood capillary walls are more likely to enter lymphatic vessels, whose structural permeability is substantially higher.[2,3] Many bioactive phytochemicals - including boswellic acids, sesquiterpene lactones, phytosterols, diterpenoids, and triterpenoid saponins - naturally occupy the physicochemical niche of lipophilicity and molecular weight that favours lymphatic over vascular uptake,[1,4]

Importantly, Ayurvedic oils function not merely as solvents but as transport mediators. Charman[12] reviewed the role of lipids in oral drug delivery and established that the physicochemical state of a compound in a lipid vehicle - specifically whether it is dissolved in triglycerides, partitioned into phospholipid bilayers, or co-associated with endogenous lipoproteins - determines its post-absorption fate at the dermal-vascular-lymphatic interface. Porter et al.[8] extended this framework to show that lipid-based drug delivery systems substantially increase the fraction of administered dose entering lymphatic transport relative to aqueous formulations of the same compound.



4. Dermal-Interstitial-Lymphatic Continuum

Following transdermal penetration through the stratum corneum - the primary rate-limiting barrier to percutaneous absorption[16,17] - absorbed molecules enter the dermal interstitial space. The dermis is a dynamic compartment governed by hydrostatic and oncotic pressure gradients between plasma, interstitial fluid, and lymph, and by the composition and hydraulic conductivity of the extracellular matrix.[10] Wiig and Swartz[10] provided a comprehensive physiological analysis of interstitial fluid formation and lymphatic drainage, establishing that net interstitial fluid movement is directed toward lymphatic capillaries under normal conditions and is further biased toward lymphatic uptake when lipid-associated solutes increase the oncotic pressure of interstitial fluid.

The dermal-lymphatic interface thus represents a selective gateway between two competing absorption routes. Compounds that remain lipid-associated, exhibit slow aqueous diffusivity, or have physicochemical properties that reduce their affinity for blood capillary fenestrations are preferentially captured by the open junctions of lymphatic endothelium.[15.10] This selectivity is mechanistically analogous to the intestinal lymphatic bias described for orally administered lipophilic drugs in long-chain triglyceride vehicles, where chylomicron

association in enterocytes is the key determinant of lymphatic enrichment.[7,8]

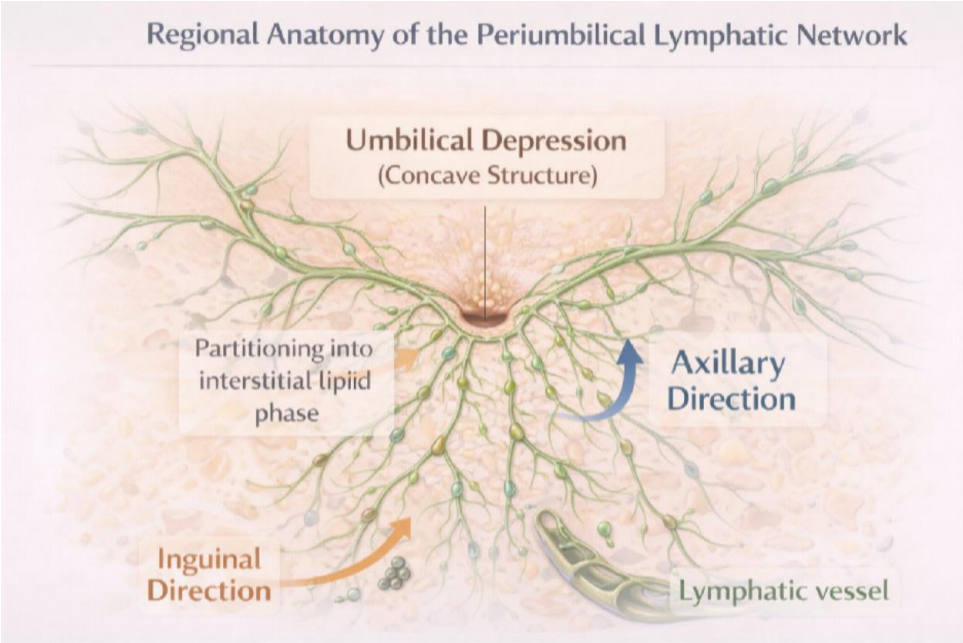
This continuum explains why identical phytochemical molecules may exhibit substantially divergent pharmacokinetic profiles depending on formulation vehicle, application site, and local interstitial conditions. The same compound administered in an aqueous vehicle will be predominantly absorbed via blood capillaries, while the same compound in a lipid vehicle applied to a lymphatic-rich site - such as the periumbilical region - will be proportionally more likely to enter lymphatic vessels, producing the characteristic lymphatic pharmacokinetic profile described in Section 8.[1,4,8]

5. Regional Lymphatic Architecture of the Umbilical Area

Anatomical studies of the anterior abdominal wall demonstrate that the periumbilical region contains a dense superficial lymphatic plexus connected to deeper abdominal lymphatic networks.[6] The periumbilical superficial lymphatics drain bilaterally to the inguinal and axillary lymph node groups via the Sappey lines - watershed lymphatic boundaries traversing the umbilical level - before rejoining the deep abdominal and thoracic collecting vessels en route to the thoracic duct.[6]

The umbilical scar itself represents a site of connective tissue convergence, with vertically oriented fibrous tracts extending from the dermis through the subcutaneous tissue toward the umbilical fascia. This structural architecture has two pharmacokinetically relevant consequences: first, the dense fibrous tissue creates preferential channels for interstitial fluid flow in the cephalocaudal and transverse directions, directing absorbed phytochemicals toward lymphatic openings; second, the reduced tortuosity of the periumbilical interstitial matrix relative to adjacent fat-containing subcutaneous tissue may decrease aqueous diffusion barriers, maintaining higher local phytochemical concentrations at the lymphatic interface.[5,6,10]

Additionally, the concave geometry of the nabhi naturally supports prolonged formulation residence time at the application site: oil applied within the umbilical recess is retained by capillary forces and geometric containment for substantially longer than oil applied to flat abdominal skin. This extended contact duration increases the cumulative absorbed dose and further favours the kinetically slower lymphatic pathway over rapid capillary absorption, as lymphatic entry requires a longer interstitial residence period to allow lipid-particle association.[1,5]



6. Role of Oil-Based Formulations in Enhancing Lymphatic Bias

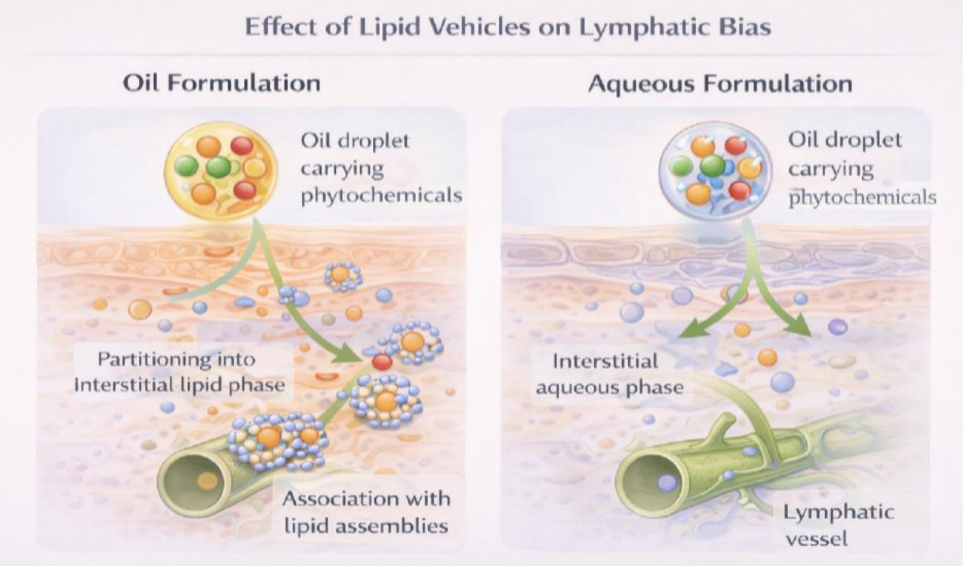
Lipid vehicles are central to lymphatic drug delivery strategies across multiple administration routes. In oral systems, the digestion of long-chain triglycerides by pancreatic lipase produces monoglycerides and fatty acids that are re-esterified within enterocytes into triglycerides, packaged into chylomicrons, and secreted into the intestinal lacteals - a process well characterised by Charman and Stella[7] and more recently reviewed by Pouton.[13] While dermal delivery lacks enterocyte involvement and chylomicron formation, analogous principles govern the fate of lipid-associated compounds in the dermal interstitial space: compounds dissolved in triglyceride or phospholipid vehicles partition into interstitial lipid assemblies that are preferentially taken up by lymphatic capillaries over blood capillaries.[1,7,8]

Ayurvedic oils used in Nabhi Chikitsa - principally sesame oil (Tila Taila), castor oil (Eranda Taila), and various medicated Tailas - exert several convergent

pharmacokinetic effects that collectively enhance lymphatic bias:

- **Stratum corneum lipid fluidity enhancement:** oleic acid (C18:1), present at 38-42% w/w in sesame oil and 52-61% in neem oil, disrupts the orthorhombic crystalline packing of stratum corneum ceramide-cholesterol bilayers by intercalating into lamellar lipid domains, increasing diffusivity (D) for co-delivered lipophilic compounds.[14,15]
- **Sustained high local drug concentration:** the lipid vehicle maintains phytochemicals at saturation or near-saturation concentrations in the dermis for longer periods than aqueous vehicles, sustaining the thermodynamic driving force for interstitial diffusion and lymphatic association.[8,12]
- **Preservation of lipid-associated state:** phytochemicals dissolved in a triglyceride vehicle remain associated with lipid droplets or micelles in the interstitial space, maintaining the physicochemical state most conducive to lymphatic endothelial uptake.[1,4,8]
- **Slowed aqueous diffusion:** the high viscosity and low aqueous miscibility of Ayurvedic oil vehicles retard the diffusion of phytochemicals from the application site into the aqueous phases of the interstitium that communicate with blood capillaries, kinetically favouring the slower but structurally accessible lymphatic route.[5,12]

Collectively, these properties shift the absorbed fraction of phytochemicals toward lymphatic rather than vascular uptake, and the magnitude of this shift is expected to increase with log P, vehicle lipid chain length, and application temperature - the last of these being relevant to the Ayurvedic specification of warm (Ushna Virya) oil application.[1,4,8,14]



7. Avoidance of Hepatic First-Pass Metabolism

One of the most pharmacokinetically significant implications of lymphatic transport is circumvention of hepatic first-pass metabolism. Compounds entering systemic circulation via the thoracic duct - which empties into the left subclavian vein - initially bypass the portal-hepatic axis entirely, resulting in a higher fraction of unmetabolised parent compound reaching the systemic circulation relative to the same compound absorbed via portal-capillary routes.[1,8]

Trevaskis et al.[1] documented this first-pass bypass effect for multiple lipophilic drugs and established that the magnitude of the hepatic extraction ratio reduction achieved by lymphatic routing is proportional to the compound's intrinsic hepatic clearance: highly extracted compounds (hepatic extraction ratio $E_H > 0.6$) benefit most substantially from lymphatic routing, as portal absorption of such compounds results in near-complete first-pass loss, whereas lymphatic absorption preserves the parent compound.

For phytochemicals with extensive hepatic biotransformation - which often results in reduced bioactivity, altered receptor binding profiles, or loss of the parent compound's specific pharmacological action - the lymphatic pathway may preserve functional integrity and prolong signalling activity.[1,8] This is particularly relevant for sesquiterpene lactones, triterpenoids, and steroidal phytochemicals that undergo rapid CYP3A4-mediated oxidation, glucuronidation, or sulphation when delivered via portal absorption routes.[8]

Porter et al.[8] reviewed the relationship between lipid formulation composition and lymphatic transport across a series of lipophilic drugs with varying hepatic extraction ratios, providing quantitative evidence that long-chain triglyceride formulations produced substantially higher systemic exposures (2-8-fold higher

AUC for high-extraction compounds) compared to aqueous or medium-chain triglyceride vehicles for the same compounds - a difference attributable primarily to first-pass avoidance via lymphatic routing.

8. Pharmacokinetic Profiles Characteristic of Lymphatic Transport

The pharmacokinetic literature on lymphatically transported compounds consistently identifies a characteristic concentration-time profile that differs qualitatively from blood-capillary absorbed compounds.[1,4,5,8,9] Based on this established body of evidence, the following pharmacokinetic features are recognised as signatures of lymphatic absorption:

Delayed Tmax: lymphatically absorbed compounds consistently demonstrate later time-to-peak-concentration than capillary-absorbed compounds due to the slower lymph flow velocity, transit through lymph node chains, and the length of the thoracic duct before entry into the subclavian vein.[1,5] This delay has been quantified in multiple in vivo lymph cannulation studies in animals, where lipophilic drugs in long-chain triglyceride vehicles showed Tmax values 2-4-fold longer than the same compounds in aqueous vehicles.[4,8]

Reduced Cmax: the gradual release of compound from the lymphatic depot results in a flattened concentration-time profile with a substantially lower peak plasma concentration relative to the same dose absorbed via capillary routes.[1,8] From a pharmacological safety perspective, this Cmax reduction minimizes the risk of peak-concentration-dependent adverse effects and receptor desensitisation - relevant to phytochemicals acting on saturable receptor targets.[9]

Extended apparent half-life: lymph node transit and the diffuse, distributed nature of lymphatic tissue create depot-like behaviour, whereby the compound is slowly and continuously released into systemic circulation over an extended period. This manifests as a prolonged terminal phase in the concentration-time curve beyond what hepatic and renal clearance rates alone would predict.[1,5,9]

Flattened concentration-time curve: the integrated consequence of delayed Tmax, reduced Cmax, and extended half-life is a broad, flat exposure profile.[1,4,9] Gabrielsson and Weiner[9] describe this profile as characteristic of slow absorption with depot-release kinetics and discuss its pharmacodynamic implications for compounds whose efficacy is governed by time above a threshold concentration rather than by peak concentration.

Such profiles align mechanistically with neuromodulatory, immunomodulatory, and metabolic regulatory applications - pharmacological domains in which continuous low-level receptor occupancy or sustained ligand availability produces greater efficacy than transient high-concentration stimulation.[9]

9. Implications for Pharmacokinetic Modelling

Standard one- or two-compartment pharmacokinetic models inadequately represent lymphatic transport because they assume instantaneous or first-order absorption directly from the application site into systemic circulation, omitting the intermediate physiological compartments through which lymphatically transported compounds must transit.[9]

Adequate modelling of Nabhi-based lymphatic delivery requires at minimum the inclusion of four interconnected compartments:

- A dermal depot compartment, representing phytochemical dissolved or suspended in the oil vehicle within the stratum corneum and superficial dermis, governed by a permeability coefficient (Kp) reflecting the Potts-Guy relationship for the specific molecule-vehicle combination.[16]
- An interstitial diffusion compartment, representing the time-dependent redistribution of absorbed phytochemical within the dermal extracellular matrix, governed by the diffusion coefficient in tissue water and the partitioning between lipid assemblies and aqueous interstitial fluid.[10]
- A lymphatic transport compartment, characterised by a slow, first-order transfer rate constant reflecting lymph flow velocity and the surface-area-to-volume ratio of lymphatic capillaries at the application site.[1,5]
- Delayed systemic entry kinetics, reflecting thoracic duct transit time and the physiological lag between peripheral lymphatic absorption and subclavian vein entry.[1,5]

Such models can be parameterised using published non-clinical values: lymph flow rates in human skin lymphatics (approximately 1-10 µL/h/cm²), dermal diffusion coefficients for lipophilic compounds (10^{-8} to 10^{-6} cm²/s), and Kp values from transdermal permeability databases. The resulting models can generate quantitative predictions of Cmax, Tmax, AUC, and apparent half-life for specific phytochemical-oil formulation combinations, forming a testable computational framework for experimental validation.[5,9,16]

10. Systems-Level and Translational Implications

Lymphatic pharmacokinetics has implications extending beyond drug concentration metrics. The lymphatic system interfaces directly with immune surveillance machinery: lymph nodes are sites of antigen presentation, T-cell priming, and cytokine secretion, and compounds transiting through lymph nodes are exposed to - and may interact with - the full repertoire of innate and adaptive immune effectors.[11] Tammela and Alitalo[11] reviewed the molecular mechanisms of lymphangiogenesis and the role of lymphatic vessels in immune cell trafficking and inflammatory signalling, establishing a mechanistic basis for the proposition that lymphatically delivered compounds may influence immune regulation through

anatomically specific exposure patterns distinct from those achievable by systemic administration.

For Nabhi-delivered phytochemicals, this lymphatic-immune interface is mechanistically relevant because several classical Nabhi Chikitsa formulations contain immunomodulatory compounds - including withanolides (Ashwagandha), bacosides (Brahmi), and neem limonoids - that have demonstrated effects on T-cell activation, macrophage polarisation, and cytokine profiles in preclinical studies. If these compounds are preferentially routed through mesenteric and inguinal lymph nodes following periumbilical absorption, they encounter immune cells in a different kinetic and concentration context than would be the case following oral or intravenous administration.[1,8,11]

More broadly, this analysis supports a shift from dose-centric thinking toward exposure-centric and systems-biology-informed frameworks for evaluating the pharmacological activity of traditional herbal formulations. Rather than assessing phytochemical efficacy solely by peak plasma concentration or oral bioavailability - metrics designed for small-molecule pharmaceuticals - lymphatic routing suggests that the relevant pharmacokinetic parameters are exposure duration, tissue distribution pattern, lymph node concentration, and the temporal relationship between systemic appearance and immune-neuroendocrine signalling events.[1,9]

11. CONCLUSIONS

This review establishes lymphatic pharmacokinetics as a plausible and mechanistically grounded feature of Nabhi-based phytochemical delivery. By integrating established literature on lipid-based drug delivery science, regional lymphatic anatomy, and interstitial transport dynamics, a coherent pharmacokinetic framework emerges: oil-based phytochemical formulations applied to the periumbilical region encounter a structurally favourable lymphatic drainage environment, and their lipophilic physicochemical properties further bias the partition of absorbed compound toward lymphatic rather than capillary uptake.[1-10]

The pharmacokinetic consequences - delayed Tmax, reduced Cmax, extended apparent half-life, and hepatic first-pass avoidance - are consistent with the characterised behaviour of lipophilic compounds in long-chain triglyceride vehicles across multiple in vivo lymphatic transport studies and computational frameworks in the established literature.[1,4,5,8,9] These features produce exposure profiles particularly suited to pharmacological targets that respond to sustained low-level ligand presence rather than acute high-concentration stimulation.

The mechanistic account presented here is non-clinical and theoretical. It identifies a framework and a set of testable hypotheses - regarding Tmax, lymph-to-plasma concentration ratios, first-pass avoidance fractions, and lymph node concentrations - that future experimental studies employing cannulated lymph duct animal models, ex vivo dermal absorption and lymphatic transport assays, and ultimately pharmacokinetic clinical studies will be required to validate or refute.[1,4,8,9]

Declarations

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Author Contributions: Chirag Warty: conceptualisation, lymphatic pharmacokinetics framework, interstitial transport analysis, primary manuscript drafting, and all revisions. Dr. Manaswi Rajurkar: Ayurvedic classical context, clinical Nabhi Chikitsa framework, writing - review and editing. Both authors read and approved the final manuscript.

Data Availability: This is a mechanistic narrative review. No primary experimental data were generated. All pharmacokinetic parameters cited are from published literature as referenced.

Ethics Statement: This review does not involve human subjects, animal experiments, or unpublished clinical data. No ethics committee approval was required.

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