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REVIEW ARTICLE

Extra-Oral Receptors in *Bidalaka*: Eyelid Delivery Mechanisms of *Tikta Rasa* Herbs

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ABSTRACT

Bidalaka, a classical Ayurvedic periocular therapy involving medicated paste application over closed eyelids, has been employed for centuries in managing anterior segment conditions, principally inflammation. Classical texts attribute its efficacy to *Tikta rasa* (bitter-tasting) herbs possessing *Shothahara* (anti-inflammatory) and *Kandughna* (anti-pruritic) properties. This review proposes a receptor-mediated pharmacological framework in which *Bidalaka*'s therapeutic action is, at least in part, mediated through activation of extra-oral bitter taste receptors (TAS2Rs) on periocular keratinocytes and resident immune cells via G protein-coupled receptor signaling. The eyelid's exceptionally thin cutaneous barrier confers superior drug permeability, while keratinocyte-expressed TAS2Rs – including TAS2R38 and TAS2R14 – coupled with α-gustducin, activate phospholipase Cβ2-mediated calcium signaling, barrier reinforcement through p38 mitogen-activated protein kinase/peroxisome proliferator-activated receptor gamma pathways, and suppression of mast cell degranulation, histamine, prostaglandin D_2, tumor necrosis factor-alpha, and chemokine release upon bitter agonist stimulation. The shared microvascular and lymphatic anatomy between the eyelid and palpebral conjunctiva further facilitates transdermal-to-ocular drug translocation. This convergence of eyelid anatomy, TAS2R biology, and periocular vascular architecture provides a coherent molecular rationale for *Bidalaka*'s efficacy, supporting both standardization of Ayurvedic ophthalmic therapies and development of novel transdermal ophthalmic drug delivery platforms.

1. INTRODUCTION

Within *Shalakya Tantra*, the specialized branch of Ayurvedic ophthalmology, management of ocular disease relies on targeted, localized therapeutic modalities collectively termed *Kriyakalpas*. Among these, *Bidalaka* is classically defined as the topical application of a finely levigated medicinal paste (*Lepa*) over the exterior surface of closed eyelids, carefully sparing the ciliary margin to prevent mechanical irritation of the globe. According to the *Charaka Samhita*, *Bidalaka* is specifically indicated during the acute inflammatory stage (*Amavastha*) of *Netrarogas* (ocular diseases), positioning it among first-line *Kriyakalpa* modalities in anterior segment management.[1,2]

Periocular application of these formulations is indicated for inflammatory pathologies affecting the conjunctiva, cornea, and broader ocular surface. By utilizing the vascularized and permeable eyelid skin as a therapeutic interface, *Bidalaka* aims to counteract localized edema, hyperemia, and inflammatory exudates without direct instillation into the conjunctival sac.[2]

The pharmacological activity of *Bidalaka* formulations is intrinsically associated with botanical ingredients predominantly characterized by *Tikta rasa* (bitter taste). In Ayurvedic pharmacology, *Tikta rasa* is associated with *Shothahara* (anti-inflammatory) and *Kandughna* (anti-pruritic) properties. Topical application of these bitter-dominant herbs – rich in alkaloids, glycosides, and terpenoids – is proposed to reduce localized vascular engorgement and alleviate the pruritus and swelling accompanying anterior segment inflammation. Key bitter principles in classical *Bidalaka* botanicals include amarogentin (a secoiridoid glycoside and potent taste receptors (TAS2R) agonist from *Swertia chirata*), berberine (an isoquinoline alkaloid from *Berberis aristata*), and nimbin (a terpenoid limonoid from *Azadirachta indica*). The receptor-level mechanisms by which these compounds applied to the cutaneous surface mitigate deeper ocular inflammation have, until recently, remained unexplored in contemporary biomedicine.[3,4]

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A significant development in G protein-coupled receptor (GPCR) biology has provided a framework for examining these traditional practices. Bitter taste receptors – designated as TAS2Rs – were historically considered restricted to the gustatory epithelium, functioning solely as a dietary warning system against toxic plant alkaloids. Contemporary pharmacological research has established that functionally active, extra-oral TAS2Rs are expressed across diverse human tissues. Molecular and histological studies have confirmed that these chemosensory receptors are present on human epidermal keratinocytes and on tissue-resident immune cells, including mast cells and macrophages.[5-8]

This evidence indicates that the skin functions not merely as a passive structural barrier, but as a chemosensory interface capable of responding directly to applied botanical compounds. This review proposes that the therapeutic efficacy of *Bidalaka* is, at least in part, mediated through activation of extra-oral TAS2Rs on periocular keratinocytes and resident immune cells, providing a receptor-level mechanism that aligns classical Ayurvedic pharmacology with contemporary GPCR biology. This intersection offers a framework for validating traditional Ayurvedic ocular therapies and informing the development of future transdermal ophthalmic drug delivery systems.

2. MATERIALS AND METHODS

The present study was designed as a proposes to explain a receptor-mediated pharmacological framework in which *Bidalaka*'s therapeutic action is, at least in part, mediated through activation of extra-oral bitter TAS2Rs on periocular keratinocytes and resident immune cells via GPCR signaling. The study aimed to synthesize classical textual knowledge with contemporary scientific literature to understand their role in promoting holistic health.

2.1. Study Design

This work adopted a qualitative literature-based review approach.

2.2. Anatomical and Physiological Advantages of the Eyelid for Drug Delivery

2.2.1. The Epidermal barrier

Successful transdermal drug delivery depends on penetration of the stratum corneum, which constitutes the principal physical barrier to percutaneous absorption. The eyelid skin is anatomically distinct from other cutaneous sites: It is the thinnest cutaneous surface in the body, with a total skin thickness of approximately 0.5 mm.[9] Histomorphological analyses demonstrate that the eyelid stratum corneum comprises significantly fewer cell layers – averaging 8 ± 2 – relative to standard dermal sites, such as the abdomen, which averages 14 ± 4 layers.[9]

The lipid composition of this barrier is similarly specialized. Nile red staining and confocal laser scanning microscopy demonstrate that the eyelid stratum corneum possesses a markedly lower neutral lipid content relative to abdominal skin.[9] As tightly packed lipid matrices constitute the primary resistance to percutaneous xenobiotic absorption, this reduced lipid density renders the eyelid an exceptionally permeable site for topical drug delivery.

2.2.2. Permeability dynamics

The reduced lipid architecture of the eyelid translates directly into enhanced permeability. This structural laxity is evidenced by low electrical impedance, consistent with a physically weaker diffusion barrier relative to other cutaneous sites. The eyelid accordingly exhibits high transepidermal water loss, reflecting a relaxed epidermal state that favors both outward moisture loss and inward percutaneous penetration.[9]

Experimental models confirm that permeability coefficients are significantly higher through eyelid skin. Permeability for diclofenac sodium and tranilast was approximately 6-fold and 11-fold greater, respectively, through the eyelid compared to abdominal skin, irrespective of molecular lipophilicity.[9] For complex botanical pastes, this enhanced permeability suggests that the spectrum of active phytochemicals – from water-soluble glycosides to lipid-soluble terpenoids – may simultaneously and efficiently diffuse across the eyelid epidermis.

2.2.3. The periocular–conjunctival bridge

Once therapeutic compounds traverse the eyelid epidermal barrier, the anatomical proximity of the external eyelid skin to the palpebral conjunctiva provides a unique physiological advantage for targeted ocular therapy. The two structures share a contiguous network of microvascular arcades and lymphatic drainage pathways. Active phytochemicals partitioning through the eyelid stratum corneum are taken up by this shared cutaneous microcirculation just beneath the basal epidermis.

In vivo absorption studies using fluorescent model compounds – including Rhodamine B and fluorescein sodium – applied to the eyelid surface demonstrated progressive migration into the underlying conjunctival tissue, as confirmed by confocal laser scanning microscopy.[9] This periocular transdermal route has also been shown to maintain sustained drug concentrations at the ocular surface,[10] circumventing the rapid elimination mechanisms – reflex blinking, tear turnover, and nasolacrimal drainage – that limit conventional topical eye drop bioavailability to below 5–10%.[11]

2.3. Expression of Extra-Oral TAS2RS in the Periocular Region

2.3.1. Receptors on structural cells: Keratinocytes

The structural integrity of the eyelid is maintained by epidermal keratinocytes, forming the primary cellular barrier protecting underlying ocular tissues. Immunohistochemical and molecular analyses have demonstrated that these cells possess chemosensory capabilities through the expression of functional extra-oral bitter TAS2Rs.

Functional expression of TAS2R1 and TAS2R38 has been demonstrated in human HaCaT keratinocytes and primary keratinocyte cultures by immunofluorescence and calcium flux assays.[5] Functional TAS2R14 expression in human epidermal keratinocytes has been independently confirmed, with receptor-mediated intracellular signaling demonstrated upon bitter ligand application.[6] TAS2R expression profiles in skin exhibit inter-individual variability. A comprehensive messenger Ribonucleic Acid (mRNA) expression study profiling 25 TAS2R transcripts in human skin biopsies identified TAS2R10, TAS2R19, and TAS2R30 as the most consistently expressed subtypes, while TAS2R1 showed no detectable mRNA expression in that dataset.[7] This discrepancy between protein-level detection in cell lines and mRNA-level analysis of tissue biopsies warrants further investigation with tissue-specific methodologies. For the purposes of this review, TAS2R38 and TAS2R14 are considered the best-supported keratinocyte subtypes, while TAS2R1 expression requires independent corroboration.

These extra-oral receptors in keratinocytes co-localize with α-gustducin, the G-protein subunit required for intracellular

transduction of bitter taste signals.[5] The presence of this complete signaling machinery confirms that periocular keratinocytes are equipped to detect and process the bitter phytochemicals applied topically during *Bidalaka* therapy, translating applied botanical chemistry into a defined intracellular signal.

Intracellular TAS2R expression has also been identified in keratinocytes, where receptor activation was found to regulate the ABCB1 efflux transporter, suggesting that TAS2R engagement may influence cellular handling of xenobiotics beyond surface receptor signaling.[12]

2.3.2. Receptors on immune cells: Mast cells and macrophages

Beneath the epidermal layer, the periocular dermis is populated with tissue-resident immune cells that orchestrate local inflammatory cascades. Immunological profiling has demonstrated that these cells express extra-oral bitter TAS2Rs capable of modulating their immunological behavior.

TAS2R profiling of human cord blood-derived mast cells (CBMCs), which share key phenotypic characteristics with tissue mast cells, has identified functional expression of multiple TAS2R subtypes, with TAS2R4 as the most abundantly expressed, followed by TAS2R3, TAS2R5, TAS2R10, TAS2R13, TAS2R14, TAS2R19, TAS2R20, and TAS2R46.[8] This profiling was performed in a cord blood-derived and respiratory disease context; whether cutaneous mast cells within the periocular dermis express an equivalent receptor repertoire remains to be characterized in dedicated studies.

Human macrophages similarly express a broad TAS2R repertoire. Transcription of all 16 tested TAS2R subtypes has been demonstrated in lung-resident macrophages, with TAS2R agonists shown to significantly suppress lipopolysaccharide induced tumor necrosis factor-alpha (TNF-α), CCL3, and CXCL8 production.[13] TAS2R46 expression has additionally been confirmed in monocyte-derived macrophages, where activation was associated with protection against oxidative stress.[14] While these findings derive from pulmonary and circulating macrophages, their extrapolation to periocular dermal macrophages – while anatomically plausible – requires tissue-specific confirmation.

This receptor repertoire on local immune cells establishes a molecular target for the *Tikta rasa* compounds present in *Bidalaka* formulations, proposing a receptor-mediated route for therapeutic intervention without the need for systemic drug absorption.

2.4. Pharmacodynamics: Tikta Rasa as Natural TAS2R Agonists

2.4.1. Phytochemical engagement

The therapeutic efficacy of *Tikta rasa* in Ayurvedic pharmacology is attributed to bioactive phytochemicals predominantly comprising alkaloids, glycosides, and terpenoids. When a finely levigated *Bidalaka* paste is applied topically, these bitter principles dissolve and penetrate the eyelid's stratum corneum – a process favored by its reduced lipid matrix and enhanced permeability. Upon traversing this barrier, the botanical compounds encounter the underlying keratinocytes and resident immune cells expressing functional TAS2Rs.

Natural plant molecules can act as direct agonists for extra-oral TAS2Rs. Specifically, amarogentin – a secoiridoid glycoside present in *Swertia chirata* and *Gentiana lutea*, both recognized *Tikta rasa* herbs – has been shown to directly bind and activate TAS2R38 in human keratinocytes, triggering a defined intracellular calcium response.[5] Thymol has been demonstrated to act as a functional TAS2R14 agonist in keratinocytes, confirming that structurally diverse bitter phytochemicals can engage keratinocyte TAS2Rs through receptor-mediated mechanisms.[6] The *Tikta rasa* phytochemistry of *Bidalaka* formulations is thereby proposed to translate topical botanical chemistry into a targeted cellular signal within the periocular tissue.

2.4.2. Epidermal fortification

The binding of bitter phytochemicals to epidermal TAS2Rs initiates an intracellular signaling cascade that reinforces the periocular epidermal barrier. In human keratinocytes, TAS2R activation triggers an intracellular calcium influx via phospholipase Cβ2 (PLCβ2)-mediated IP3 generation. This calcium signal promotes terminal differentiation of keratinocytes, with significant upregulation of the barrier proteins keratin 10, involucrin, and transglutaminase 1.[5]

Bitter TAS2R stimulation by *Gentiana lutea* extract has further been shown to promote lipid synthesis through activation of p38 mitogen-activated protein kinase (p38 MAPK) and peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathways. This drives upregulation of ceramide synthase 3, resulting in enhanced synthesis of very long-chain ceramides, free fatty acids, and triglycerides – key components of the functional stratum corneum lipid matrix. Both effects were abrogated by the p38 MAPK inhibitor SB203580 and the PPARγ antagonist GW9962, confirming pathway specificity.[4]

For periocular applications, where underlying ocular tissues are sensitive to inflammatory stimulation, these barrier-reinforcing effects were not accompanied by induction of pro-inflammatory mediator release in the experimental models.[5] This profile – barrier repair without concurrent inflammation – is a critical pharmacological characteristic for any therapeutic applied in proximity to the ocular surface. The bitter principles inherent in *Bidalaka* formulations are therefore proposed to actively optimize the eyelid stratum corneum lipid matrix, potentially creating a more stable transdermal vehicle for sustained delivery of therapeutic compounds to the underlying ocular tissues.

2.5. The Localized Anti-inflammatory Mechanism

2.5.1. The Intracellular signaling cascade

The proposed transdermal anti-inflammatory activity of *Bidalaka* therapy is rooted in the intracellular signaling events initiated upon bitter phytochemical engagement with periocular TAS2Rs. The binding of bitter ligands to TAS2Rs initiates a canonical GPCR cascade, as characterized in multiple tissue types.[10,11] Upon ligand engagement, the TAS2R undergoes a conformational change, inducing dissociation of the heterotrimeric G-protein complex. The liberated Gβγ subunit subsequently activates PLCβ2, which hydrolyses membrane phosphatidylinositol 4,5-bisphosphate to generate inositol 1,4,5-trisphosphate (IP3). IP3 binds to receptors on the endoplasmic reticulum, triggering calcium release into the cytoplasm.[10] This intracellular calcium rise serves as the primary second messenger mediating the downstream biological effects of TAS2R activation.

2.5.2. Proposed mast cell and macrophage immunomodulation

Within the vascularized periocular dermis, TAS2R-induced intracellular calcium is proposed to function as an immunological modulatory signal in tissue-resident immune cells. Evidence from CBMC models demonstrates that bitter agonist engagement of TAS2Rs on these cells inhibits IgE-dependent activation, suppressing the release of histamine and prostaglandin D_2 (PGD_2) – primary vasodilatory and pro-inflammatory mediators.[8] These findings, while derived from CBMCs in an asthma context, provide the primary published evidence for TAS2R-mediated immunomodulation in mast-cell-type immune cells.

TAS2R activation in macrophage models has been shown to suppress de novo synthesis and secretion of TNF-α, alongside significant reductions in CCL3 and CXCL8 production.[13] These suppressive effects were mediated through a pathway consistent with PLC/calcium signaling, supporting the mechanistic coherence of the proposed cascade across immune cell types.

2.5.3. Silencing the keratinocyte inflammatory amplifier

Under pathological conditions, the initial release of histamine and TNF-α from local dermal mast cells and macrophages acts as a paracrine signal driving overlying epidermal keratinocytes into a secondary inflammatory amplifier role. Once stimulated by these mediators, keratinocytes characteristically secrete interleukin-8 (IL-8/CXCL8) – a potent chemokine responsible for neutrophil and T-cell recruitment – and matrix metalloproteinase-1 (MMP-1), an interstitial collagenase that degrades fibrillar collagens within the periocular extracellular matrix, facilitating immune cell transmigration into the inflamed tissue.

Experimental data from keratinocyte models demonstrate that TAS2R agonist stimulation directly reduces the expression and release of both IL-8 and MMP-1.[5,6] This suppressive effect is proposed to arise from two concurrent mechanisms: Upstream inhibition of TNF-α and histamine release deprives keratinocytes of their inflammatory paracrine trigger, while direct TAS2R engagement on the keratinocytes themselves provides a concurrent suppressive intracellular signal. By interrupting this secondary amplification loop, the herbal application may attenuate the localized cytokine environment before it propagates into the vascular arcades feeding the conjunctiva and anterior chamber.

2.6. Proposed Resolution of Ocular Surface Pathologies via Bidalaka

While each individual mechanistic component described in this section is supported by published peer-reviewed evidence, the integrated model linking topical TAS2R activation at the periocular skin to the resolution of ocular surface pathology represents a coherent pharmacological hypothesis. The individual components – TAS2R expression in keratinocytes and immune cells, mast cell immunomodulation, and eyelid-to-conjunctival drug translocation – have each been independently validated in relevant experimental systems. Their functional integration in the specific context of eyelid skin drug delivery and anterior segment disease requires dedicated preclinical and clinical investigation.

2.6.1. Translating skin physiology to ocular healing

The proposed clinical efficacy of *Bidalaka* rests on the anatomical intimacy between the eyelid skin and the ocular surface. The external eyelid skin and the underlying palpebral conjunctiva are linked by a contiguous microvascular network and shared lymphatic drainage pathways.[9] The immunological microenvironment of the eyelid dermis is therefore proposed to exert a direct influence on the inflammatory state of the contiguous conjunctiva. By engaging TAS2Rs on cutaneous mast cells and keratinocytes, *Tikta rasa* compounds may suppress the production of pro-inflammatory cytokines and chemokines within the eyelid, potentially reducing their availability to the ocular surface through shared vascular and lymphatic channels.

2.6.2. Proposed reduction of conjunctival vasodilation (hyperemia)

In acute ocular inflammation, IgE-receptor-mediated histamine release from periocular mast cells is a primary driver of localized vasodilation and conjunctival hyperemia. By potentially activating TAS2Rs to inhibit IgE-dependent mast cell degranulation,[8] the bitter plant ligands in *Bidalaka* formulations may reduce histamine release within the periocular microenvironment. Without this vasodilatory stimulus, the contiguous capillary arcades shared by the eyelid and conjunctiva would be expected to return passively to resting tone, potentially reducing conjunctival hyperemia.

2.6.3. Proposed resolution of chemosis (periorbital edema)

Inflammatory prostaglandins and histamine increase vascular permeability, driving fluid exudation from capillaries into the interstitial spaces of the conjunctiva and eyelid – the clinical correlate of chemosis. By suppressing the synthesis of PGD_2 and related prostanoids through TAS2R-mediated signaling,[8] the therapy is proposed to contribute to the restoration of normal endothelial paracellular permeability, thereby limiting the exudation responsible for periorbital swelling and chemosis. This mechanism is consistent with the classical *Shothahara* (anti-inflammatory) property attributed to *Tikta rasa* in Ayurvedic pharmacology.

2.6.4. Proposed attenuation of leukocyte recruitment

The infiltration of destructive immune cells represents a critical phase of anterior segment pathology. TNF-α and IL-8 serve as potent chemotactic signals recruiting neutrophils and T-cells to sites of tissue damage. By potentially blocking TNF-α synthesis in macrophages and mast cells,[8,13] and subsequently suppressing IL-8 and MMP-1 release from overlying keratinocytes,[5,6] the botanical application may attenuate this chemotactic gradient within the periocular microenvironment. This cascade, if validated, would represent a receptor-mediated mechanism by which *Bidalaka* may reduce immune cell recruitment into the anterior chamber, protecting delicate ocular structures from immune-mediated degradation.

Limited clinical observation supports the broader therapeutic potential of this approach. A case study documenting significant clinical resolution of seborrhoeic blepharitis following application of *Punarnava* (*Boerhavia diffusa*) *Bidalaka*,[2] providing an initial clinical data point warranting validation in controlled trials.

3. DISCUSSION

3.1. Future Directions and Clinical Perspectives

3.1.1. Mechanism-based standardization of bidalaka

Identification of extra-oral TAS2Rs as potential biological targets for *Tikta rasa* provides a framework for pharmacological standardization of traditional *Bidalaka* therapies. Historically, Ayurvedic formulations have been characterized based on organoleptic properties and broad physicochemical profiles. Understanding the GPCR-mediated pharmacodynamics described in this review permits a shift toward mechanism-based quality control.

Future research should systematically characterize the TAS2R agonist profiles of classical *Bidalaka* botanicals. Classical formulations employ herbs rich in established TAS2R-active bitter principles – including *Nimba* (*Azadirachta indica*; nimbin, terpenoids), *Daruharidra* (*Berberis aristata*; berberine), *Haridra* (*Curcuma longa*; curcumin), and *Swertia chirata* (amarogentin, swertiamarin) – providing a tractable set of compounds for systematic receptor-binding profiling. By quantifying active bitter ligand concentrations and correlating them with TAS2R activation potency, researchers can establish precise biological markers for quality control, ensuring that herbal pastes achieve the receptor engagement required for their proposed immunomodulatory activity.

3.1.2. Advancing transdermal ophthalmic delivery

The physiological characteristics of the eyelid documented in Section 2 offer a compelling basis for modernizing ocular drug delivery. Conventional ophthalmic eye drops achieve a bioavailability below 5–10%, due to robust ocular defense mechanisms – reflex blinking, rapid tear turnover, and nasolacrimal drainage.[15] This pharmacokinetic limitation necessitates frequent instillation, reducing patient compliance.

The anatomical rationale of *Bidalaka* provides a scientific basis for developing modernized periocular patch delivery systems. By leveraging the eyelid's thin stratum corneum and low neutral lipid matrix, sustained-release transdermal platforms – such as hydrogels, liposomal patches, or bioadhesive films – can be engineered to deliver a controlled supply of active compounds over extended periods. Preclinical models have demonstrated sustained ocular drug distribution following eyelid-applied formulations, with prolonged tranilast distribution confirmed in ocular tissues after topical eyelid application, providing proof-of-concept for this delivery strategy. These systems offer the additional advantage of active therapeutic delivery during sleep, overcoming the pharmacokinetic limitations of conventional liquid eye drops.

3.1.3. Research priorities and limitations

Several research gaps must be addressed before the mechanistic model proposed in this review can be considered validated. First, the TAS2R expression profile of cutaneous periocular mast cells – as distinct from CBMCs models – requires direct histological and molecular characterization. Second, the pharmacokinetic profile of bitter phytochemicals from classical *Bidalaka* botanicals through human eyelid skin requires formal permeation studies. Third, the proposed model requires testing in purpose-designed animal models of ocular surface inflammation in which periocular TAS2R activation can be pharmacologically confirmed. Controlled clinical trials comparing *Bidalaka* with active comparators in defined ocular surface pathologies are an essential step toward evidence-based integration of this therapy into mainstream ophthalmic practice.

4. CONCLUSION

This review presents a pharmacological framework for the Ayurvedic periocular therapy *Bidalaka*, grounded in contemporary GPCR biology and eyelid skin pharmacology. The convergence of several lines of evidence – the exceptionally permeable barrier of the eyelid skin, the demonstrated expression of functional extra-oral TAS2Rs on human keratinocytes and immune cells, the established anti-inflammatory signaling consequences of TAS2R activation, and the shared periocular-conjunctival vascular anatomy – provides a coherent mechanistic rationale for the therapeutic properties attributed to *Tikta rasa* in classical Ayurvedic texts.

The integrated model proposed here – connecting topical periocular TAS2R activation to the resolution of ocular surface pathology – represents a hypothesis supported by convergent independent evidence rather than a directly validated clinical mechanism. The individual components are each independently supported in the literature; their functional integration in the specific context of eyelid skin drug delivery and anterior segment disease requires dedicated investigation.

This framework carries dual translational significance: It offers a molecular basis for the validation and standardization of traditional *Bidalaka* formulations, and positions the eyelid as an underexplored but pharmacologically rational site for next-generation transdermal ophthalmic drug delivery. Future research bridging Ayurvedic pharmacognosy, GPCR pharmacology, and clinical ophthalmology has the potential to yield both mechanistic insights and clinically applicable innovations.

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6. AUTHORS' CONTRIBUTIONS

All authors give equal contribution in making of this manuscript.

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8. ETHICAL APPROVALS

Ethical approval was not required for this study as it was a review article with data obtained through a literature search.

9. CONFLICT OF INTERESTS

The authors declare no conflicts of interest regarding the publication of this paper.

10. DATA AVAILABILITY STATEMENT

The data analyzed in this review were obtained from publicly available sources, including peer-reviewed articles, observational studies, and surveys accessible through databases.

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