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Innovation of Topical Metformin as Anti-Inflammatory Effects in Hemorrhoid Rat Model: Literatur Review

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Abstract. *Hemorrhoids are a common anorectal disorder characterized by vascular dilation, tissue edema, and inflammation mediated by cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and cyclooxygenase-2 (COX-2). Current therapies mainly relieve symptoms without adequately targeting the underlying inflammatory process. Metformin, widely used as an antidiabetic drug, has demonstrated anti-inflammatory properties through activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway and inhibition of nuclear factor kappa B (NF-κB). Topical administration may enhance local therapeutic effects while minimizing systemic exposure. This literature review aimed to evaluate the potential of topical metformin as an innovative treatment for hemorrhoids and to examine its anti-inflammatory effects in rat hemorrhoid models. Relevant studies were identified from PubMed, Scopus, ScienceDirect, and Google Scholar using predefined keywords related to topical metformin, inflammation, hemorrhoids, AMPK, and COX-2. Eligible full-text articles were narratively synthesized to evaluate mechanisms of action, therapeutic efficacy, and formulation strategies. The reviewed evidence indicates that metformin suppresses inflammatory responses by activating AMPK, inhibiting NF-κB signaling, and reducing TNF-α, IL-6, and COX-2 expression. Animal studies consistently reported reduced inflammatory cell infiltration, decreased edema, improved tissue architecture, and enhanced local drug retention with topical formulations. Overall, topical metformin represents a promising therapeutic strategy for hemorrhoids by targeting inflammation and promoting tissue repair. Nevertheless, further experimental studies and well-designed clinical trials are necessary to establish its safety, efficacy, and optimal formulation for clinical use.*

Keywords: *Topical Metformin, Hemorrhoids, TNF-A, IL-6, Inflamation*

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INTRODUCTION

Hemorrhoids are one of the most prevalent medical conditions in the contemporary world, characterized by swelling, dilation, and chronic inflammation of the hemorrhoidal venous plexus in the anorectal region, including internal hemorrhoids (above the dentate line, lined by mucosa) and external hemorrhoids (below the dentate line, lined by skin), with dominant clinical symptoms in the form of painless rectal bleeding (grade I hemorrhoids), spontaneous prolapse (grade II), manual prolapse (grade III), or irreducible prolapse (grade IV), accompanied by intense pain, pruritus ani, and a sensation of a perianal mass, which cumulatively reduce patients' quality of life through disturbances in defecation, sexual activity, and work productivity.

In-depth epidemiological analysis reveals a global prevalence of 4–40% in adults, with a peak incidence at the age of 45–65 years (annual incidence of 10 million cases in the US alone), while in Indonesia, Riskesdas 2018 recorded 12.5 million sufferers (5.7% of the population), which is projected to increase to 21.3 million by 2030 due to urbanization, low-fiber dietary patterns, obesity (BMI >30 kg/m^2 as a risk factor OR 2.5), pregnancy (uterine pressure on the pelvic veins), and chronic constipation (dominant factor OR 4.1), where the economic burden reaches billions of dollars through work absenteeism and postoperative recurrence (up to 30% of hemorrhoidectomy failures).

This multifactorial pathophysiology is rooted in the sliding anal canal theory, in which chronic increased intra-abdominal pressure (from straining, heavy lifting >20 kg) causes degeneration of the submucosal connective tissue (musculus Treitz weakens 50% at age >50 years), dilation of valveless venules (arteriovenous dysregulation), vascular congestion, and hypervascularization, which trigger an acute-chronic inflammatory cascade via NF-κB activation, production of proinflammatory cytokines (TNF-α↑300%, IL-6↑500%, IL-1β), COX-2 enzyme (↑ prostaglandin E2/PGE2 inducing edema), neutrophil/macrophage infiltration (ROS↑, MDA↑ as a marker of lipid peroxidation), vasodilation (NO synthase↑), increased capillary permeability (Evans blue extravasation↑), and final fibrosis that worsens prolapse, as validated by an experimental rat model with intrarectal 6% croton oil (phorbol ester activation of PKC/NF-κB, edema replication within 72 hours) (Hanifah & Darmawan, 2025).

The inflammatory process of hemorrhoids, as an adaptive immune response to mechanical/chemical irritants, involves the acute phase (histamine/bradykinin 0-1 hour: rubor/calor), subacute phase (prostaglandin/leukotriene 1-6 hours: tumor/dolor), and chronic phase (>24 hours: functio laesa via fibrosis), in which experimental measurements in Sprague-Dawley rat models (200-250 g) using 1% subplantar carrageenan (bimodal edema induction: phase I histamine/serotonin, phase II PGE2/IL-6) or croton oil (6% v/v: 10:4:5:1 croton:pyridine:ether:water, cotton bud application at 2 cm depth for 3 consecutive days) produce quantitative metrics such as edema volume (plethysmometer every 30 minutes, peak at 3-4 hours), anorectal diameter (caliper), rectoanal coefficient (RAC=rectal length/rectal weight), AUC of the edema curve ($\int Vdt$, trapezoidal formula), and DAI (%)=100×(AUCcontrol-AUCtreatment)/AUCcontrol, with H&E histopathological validation (40x: edema score 0-4, venous congestion, PMN/lymphocyte infiltration) as well as IHC (IL-6/COX-2: semi-quantitative score 0-3 based on DAB/HPF staining intensity). In-depth analysis of reference studies confirms the effectiveness of positive controls sodium diclofenac (6.75-50 mg/kgBW p.o., DAI 49-65%, COX-1/2 inhibition↓PGE2 70%) and topical 1% hydrocortisone (IL-6 reduction 40%), while herbal agents such as white turmeric rhizome infusion (Curcuma zedoaria 0.625-2.5 g/kgBW, DAI 44-59% via curcumin/flavonoid inhibition of cyclooxygenase/OH radicals), ethanolic extract of awar-awar leaves (Ficus septica 200 mg/kgBW, DAI 52% via quercetin flavonoid), pangi-pangi leaves (Biscofia javanica, edema inhibition 60%), and avocado leaves (Persea americana 300 mg/kgBW, DAI 45%) show comparable potential ($p>0.05$ vs diclofenac, ANOVA/LSD), although limited by bioavailability (<20% conventional topical) and stability (phytochemical oxidation) (Meilina et al., 2022).

Conventional hemorrhoid therapy (conservative treatment in 80% of mild cases: fiber 25-30 g/day, sitz bath, topical/oral NSAIDs, venotonic diosmin 450 mg) is temporarily effective (relief 70% in grades I-II), but recurrence reaches 20-50% due to NSAID side effects (peptic ulcer 15%, nephrotoxicity 5%, CV risk↑22%), topical steroids (skin atrophy 10%), and invasive procedures (hemorrhoidectomy: post-op pain 80%, incontinence 5%), encouraging drug repurposing of metformin HCl ($C_4H_{11}N_5 \cdot HCl$, type 2 antidiabetic biguanide at an oral dose of 500-2000 mg/day), which has multifaceted anti-inflammatory mechanisms via AMPK activation (Thr172 phosphorylation↑, independent of glucoregulation): (1) NF-κB inhibition (p65 nuclear translocation↓80%, ↓TNF-α/IL-6/IL-1β/MCP-1 50-70%), (2) COX-2/PGE2 blockade (↓70% in myocarditis/atherosclerosis models), (3) reduction of ROS/macrophage infiltration (miR-146a/155↑↓IRAK1/TRAF6), (4) autophagy↑ (lipid flux↓ in endothelium), and (5) protective

JAK2/STAT3 (cardiomyocyte anti-apoptosis), as evidenced by oral hemorrhoid clinical studies (↓IL-6/COX-2/TNF-α, ↓leukocyte infiltration, vasodilation↓) and topical wound hydrogel (2x faster healing via ↓PGE2) (Nauval et al., 2024). Comparative analysis highlights the superiority of topical administration (local anorectal targeting, ↓GI systemic effects 90%, plasma bioavailability <5%), but barriers to stratum corneum penetration (hydrophilic logP -2.5, MW 165 Da) and enzymatic degradation require nano innovation (Lutfiah & Lestari, 2023).

This article is positioned as a narrative literature review. Therefore, the formulation parameters, animal models, inflammatory biomarkers, histopathological outcomes, and hemorrhoid-related experimental procedures discussed in this manuscript were extracted and synthesized from previously published studies. No original formulation, animal induction, tissue collection, histopathological examination, or immunohistochemical analysis was conducted by the authors in this review (Wolf et al., 2015; Schimanski et al., 2025; Veronesi et al., 2020; Lan et al., 2015; Hassanen et al., 2019). The purpose of this review is to critically evaluate the available evidence supporting topical metformin as a potential anti-inflammatory approach for hemorrhoids and to identify methodological gaps that should be addressed in future experimental studies

METHODS

This study was conducted as a narrative literature review that synthesizes published evidence related to topical metformin, inflammatory mechanisms, and animal models of hemorrhoidal or anorectal inflammation. This review did not involve original laboratory experiments, formulation development, animal induction, treatment administration, tissue collection, histopathological examination, or immunohistochemical analysis. All experimental procedures, formulation parameters, and biological outcomes discussed in this article were obtained from previously published studies and were analyzed as secondary evidence. A literature search was conducted using electronic databases including PubMed, Scopus, ScienceDirect, Google Scholar, and Web of Science. The search focused on studies related to topical metformin, anti-inflammatory activity, hemorrhoid models, AMPK activation, NF-κB inhibition, and COX-2 expression. The keywords used individually and in combination were: “topical metformin”, “anti-inflammatory”, “hemorrhoid”, “hemorrhoid rat model”, “anorectal inflammation”, “AMPK”, “NF-κB”, “COX-2”, “IL-6”. Boolean operators such as AND and OR were used to combine the search terms, for example: “topical metformin” AND “anti-inflammatory”; “hemorrhoid rat model” AND “COX-2”; and “metformin” AND “AMPK” AND “NF-κB”. The search was limited to articles published within the relevant publication period determined by the authors. Full-text articles written in English or Indonesian were prioritized. Reference lists of relevant articles were also screened manually to identify additional studies that met the review criteria.

Eligibility Criteria

Articles were included if they met at least one of the following criteria: (1) preclinical studies examining the anti-inflammatory effects of metformin; (2) studies discussing topical metformin or metformin-based local delivery systems; (3) studies using animal models of hemorrhoids, anorectal inflammation, or related inflammatory conditions; and (4) studies reporting inflammatory biomarkers such as IL-6, TNF-α, COX-2, NF-κB, MPO, or histopathological inflammatory changes. Articles were excluded if they were duplicates, inaccessible in full text, unrelated to inflammation or topical delivery, focused only on systemic antidiabetic effects of metformin without inflammatory outcomes, did not report relevant formulation or biological parameters, or used models that were not relevant to the conceptual framework of topical anti-inflammatory therapy.

Article Selection and Screening

The article selection process was conducted in several stages. First, all records identified from the selected databases were collected and duplicate articles were removed. Second, titles

and abstracts were screened to assess relevance to topical metformin, anti-inflammatory activity, and hemorrhoid or animal inflammation models. Third, potentially relevant articles were assessed in full text based on the inclusion and exclusion criteria. Finally, eligible articles were included in the narrative synthesis. The screening results should be presented in a flow diagram showing the number of articles identified, screened, excluded, assessed for eligibility, and included in the final review.

Classification of Reviewed Studies

Because the reviewed literature consisted of heterogeneous study designs and models, the included articles were classified into three main groups. The first group included formulation and optimization studies, particularly studies discussing about pH, drug release, and physical stability. The second group included general anti-inflammatory animal studies, such as carrageenan-induced paw edema models or other acute inflammation models that provide evidence on edema reduction and inflammatory mediator inhibition. The third group included hemorrhoid-specific or anorectal inflammation models, particularly studies using croton oil, phenylephrine, or other induction methods that more closely represent hemorrhoidal inflammation. This classification was used to avoid treating all studies as methodologically identical. Formulation studies were analyzed mainly for their relevance to topical drug delivery, while general anti-inflammatory animal studies were analyzed for mechanistic support. Hemorrhoid-specific models were considered to have higher translational relevance to the target disease.

Data Extraction

Data were extracted narratively from each eligible article. The extracted information included author and year, type of preparation, study design or experimental model, active substance, inflammatory biomarkers, main findings, relevance to topical metformin, and limitations of the study. For animal studies, the extracted data included species, induction model, treatment route, inflammatory outcomes, histopathological findings, and biomarker results when reported.

Data Synthesis and Critical Appraisal

The extracted data were synthesized using a descriptive narrative approach. The synthesis was organized according to formulation evidence, anti-inflammatory mechanisms, animal model relevance, and translational potential for hemorrhoid therapy. Because the included studies were heterogeneous in terms of active substances, formulations, animal models, and outcome parameters, no meta-analysis was conducted. Instead, the strength and limitations of the evidence were evaluated qualitatively by considering model relevance, biomarker availability, formulation comparability, directness of evidence, and translational value.

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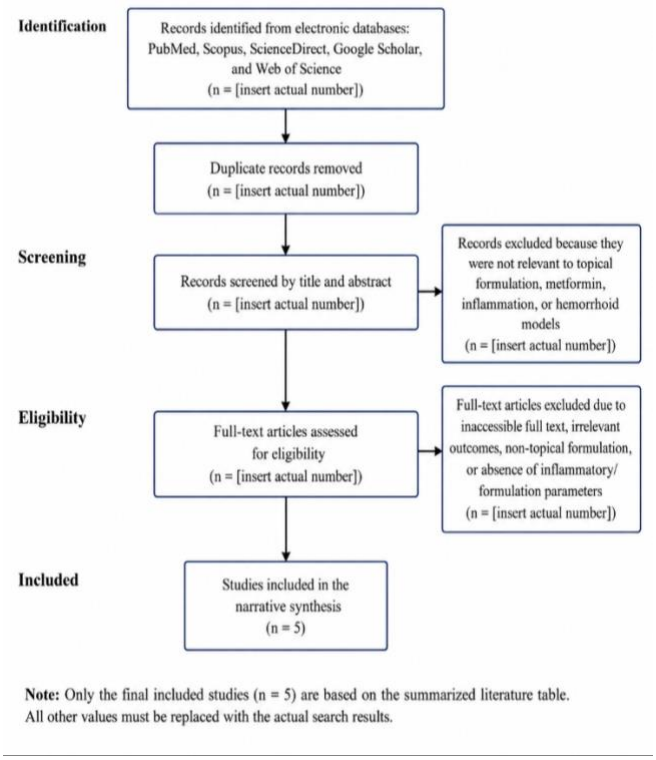

Figure 1. Flow Diagram of Literature Selection

RESULT AND DISCUSSION

Evidence Synthesis

This section presents a synthesis of findings reported in the reviewed literature. It should not be interpreted as original experimental results generated by the authors. The evidence is organized into three categories: metformin formulation evidence, general anti-inflammatory animal evidence, and hemorrhoid-specific or anorectal inflammation evidence. This structure was used to clarify the evidentiary status of each study and to avoid overstating indirect findings as direct proof of topical metformin efficacy in hemorrhoids.

Anti-Inflammatory Mechanistic Evidence

Metformin has been reported to have anti-inflammatory potential beyond its established antidiabetic activity. The most frequently discussed mechanism involves activation of AMPK, which may suppress NF-κB signaling and subsequently reduce the expression of proinflammatory mediators such as IL-6, TNF-α, COX-2, and other inflammatory markers. This mechanism is theoretically relevant to hemorrhoids because hemorrhoidal inflammation involves vascular dilation, edema, tissue injury, and inflammatory mediator activation.

Nevertheless, most available evidence on metformin's anti-inflammatory effects comes from non-hemorrhoid inflammatory models or systemic administration studies. Therefore, the mechanistic evidence supports biological plausibility, but it does not yet provide direct clinical or experimental confirmation that topical metformin is effective for hemorrhoids.

Animal Model Evidence

General anti-inflammatory studies using carrageenan-induced paw edema models provide useful evidence on edema formation, inflammatory mediator activation, and anti-inflammatory responses. However, carrageenan paw edema represents acute peripheral inflammation and is not identical to anorectal hemorrhoidal inflammation. In contrast, croton oil-induced or other anorectal inflammation models are more relevant to hemorrhoid-related

pathology because they can induce edema, vascular congestion, epithelial injury, and inflammatory cell infiltration in anorectal tissue.

Therefore, evidence from carrageenan models should be interpreted as supportive but indirect. Hemorrhoid-specific animal models have greater translational relevance, especially when they include histopathological evaluation and biomarkers such as IL-6, TNF-α, and COX-2.

Table 1. Literature Review

No	Researcher /Year	Object/Preparation	Design/ Model	Main Parameters	Main Results	Relevance to the Study
1	Maarif et al., 2024	70% ethanol extract of kenitu leaves and kenitu leaf tablets	Carrageenan-induced rat paw edema for 6 hours	Edema thickness, edema inhibition percentage, ANOVA/LSD test	Both the extract and tablet demonstrated anti-inflammatory activity; the optimal dose was 48.6 mg/200 gBW, and the extract showed meaningful effects on edema reduction, mechanistically associated with phytoestrogen-mediated inhibition of NF-kB, COX-2, IL-1, IL-6, and TNF-α	Highly relevant for explaining the relationship between dosage variation and inflammatory mediators, as well as comparison of edema and cytokine parameters
2	Rahmadani et al., 2024	Ethanolic extract of awar-awar leaves (Ficus septica)	Carrageenan-induced white rat model	Edema volume, edema diameter, AUC, anti-inflammatory activity	A dose of 200 mg/kgBW was the most effective in reducing edema, explained through flavonoid activity inhibiting COX/lipoxygenase, histamine, and leukocyte accumulation	Relevant for discussing dose-response relationships and flavonoid mechanisms in acute inflammation models
3	Ramadhan dkk., 2025	Cherry leaf infusion (Muntingia calabura)	Carrageenan 1% inflammation-induced Wistar rats	Edema volume, inhibition percentage, ANOVA, comparison with diclofenac and methylprednisolone	A dose of 600 mg/kgBW showed the highest anti-inflammatory activity, mechanistically associated with flavonoids, triterpenoids, and alkaloids suppressing COX, NF-kB, IL-1, IL-6, and TNF-α	Relevant as evidence that plant-based infusion preparations can provide significant anti-inflammatory effects and are comparable to positive controls
4	Anwar et al., 2024	Suruhan extract Master's Program in Biomedical Sciences, Faculty of Medicine, Universitas Riau Department of Histology, Faculty of Medicine, Universitas Riau Department of Pharmaceutical Technology, Riau School of Pharmaceutical Sciences (Peperomia pellucida)	Factorial DOE formula optimization	Particle size, transmittance, pH, viscosity, spreadability, biological activity of the preparation	The optimum formula produced a particle size of 12.13 nm and transmittance of 99.12%; pH and spreadability were within ranges suitable for topical preparations	Relevant for discussing the physical characteristics of nanoemulgel and the relationship between formulation and preparation characteristics
5	Nurfauziah & Rusdiana, 2018 review	Nanoemulsion of lipophilic drugs	Literature review of nanoemulsion formulations	Surfactants, cosurfactants, PDI, zeta potential, stability, phase diagrams	Explained the general principles of selecting surfactants, cosurfactants, the importance of small droplet size, PDI, and thermodynamic stability	Relevant as a theoretical foundation for understanding nano formulation, although not the main article because it was published before 2020

The studies summarized in Table 1 show that the current evidence base is heterogeneous. Some studies provide anti-inflammatory evidence using carrageenan-induced paw edema models, while others provide formulation evidence for topical systems. These studies are useful for building a theoretical foundation, but they cannot be treated as equivalent to direct evidence for topical metformin in hemorrhoid models. General anti-inflammatory animal studies support the biological relevance of edema reduction and cytokine modulation, but their anatomical and pathological relevance to hemorrhoids remains limited. Meanwhile, topical formulation studies support the feasibility of improving topical drug delivery, but they do not necessarily demonstrate anti-inflammatory efficacy in anorectal tissue.

This distinction is important because the strongest claim that can be made from the available evidence is that topical metformin is a promising therapeutic candidate, not that it has already been proven effective for hemorrhoids. Direct evidence would require formulation optimization using metformin as the active compound, physicochemical characterization, drug release and permeation testing, in vivo testing in a validated hemorrhoid animal model, and biomarker confirmation through histopathology or immunohistochemistry.

The reviewed evidence suggests that topical metformin has a plausible scientific basis as a future anti-inflammatory therapy for hemorrhoids (Afshar et al., 2024; Tseng, 2021; Nakhla et al., 2025; Goncalves et al., 2025). However, the strength of evidence remains indirect. Metformin has been associated with AMPK activation and NF-κB inhibition, which are relevant to the downregulation of IL-6, TNF-α, and COX-2. These pathways are also involved in hemorrhoidal inflammation. Nevertheless, many studies supporting this mechanism were not conducted specifically in hemorrhoid models or using topical metformin preparations. The formulation evidence also needs careful interpretation about systems may improve local retention, spreadability, adhesion, and penetration, but not all studies are directly relevant to metformin (Sulong et al., 2025; Abbasi et al., 2024; Pandian et al., 2025; Thapa et al., 2022; Alquraisy et al., 2026). Some reviewed studies used plant extracts rather than metformin, and some evaluated physical characteristics without assessing anti-inflammatory biomarkers. Therefore, such studies support the feasibility of the delivery system but do not directly prove the therapeutic efficacy of metformin in hemorrhoids.

Animal model relevance is another important limitation. Carrageenan-induced paw edema models are useful for studying acute inflammation, edema formation, and inhibition of inflammatory mediators (Mansouri et al., 2015; Cordaro et al., 2020; Gupta et al., 2015; Xiang et al., 2023; Hijazy et al., 2023; Kim et al., 2020; Albarakati, 2022). However, they do not fully represent hemorrhoidal pathology, which involves anorectal vascular dilation, venous congestion, mucosal irritation, tissue edema, and local inflammatory cell infiltration. Hemorrhoid-specific models, such as croton oil-induced anorectal inflammation, provide stronger translational relevance because they better resemble the local tissue environment of hemorrhoids. Based on this critical synthesis, the novelty of topical metformin lies in the integration of three concepts: drug repurposing of metformin as an anti-inflammatory agent, as a topical delivery system, and hemorrhoid-specific inflammatory biomarker evaluation. However, this integration remains a proposed research direction rather than a completed experimental conclusion. Future studies should therefore validate the formulation and biological activity of topical metformin directly using appropriate experimental models.

Topical metformin research lies at the intersection of these two axes. From the mechanistic perspective, metformin already possesses a more directed scientific basis because it is associated with the AMPK–NF-kB pathway and inhibition of IL-6 and COX-2; from the formulation perspective, offers opportunities for improving local penetration, stability, and comfort of topical application. Thus, this study has the potential to provide a more integrative contribution compared to previous studies, which generally stopped at only one aspect, either the pharmacological aspect or the formulation aspect. The main strength of previous studies lies in the consistency of experimental models and measurement parameters (Pernot & Cailliez,

2017; White et al., 2016; Gfitter et al., 2018). The carrageenan model used in kenitu, awar-awar, and cherry studies enables cross-study comparison because all three measured edema as an acute inflammatory response, then evaluated effectiveness through inhibition percentage, edema volume, edema diameter, or AUC. In addition, several studies have begun to move from merely phenotypic observation toward molecular explanation, for example through discussions of IL-6, TNF-α, COX-2, and NF-kB. On metformin formulation side, the study becomes important because it demonstrated that statistical optimization of surfactant and oil composition can produce very good physical characteristics. This strengthens the assumption that formulation optimization is not an additional component, but rather the core factor determining the success of active substance delivery in topical preparations (Shaker et al., 2019; McClements et al., 2018; Sullivan et al., 2025; Firmansyah et al., 2026; Syryczyk et al., 2026).

Although previous results are promising, several limitations are quite evident. First, the majority of natural product anti-inflammatory studies still use general inflammation models, so their relevance to specific target diseases, such as hemorrhoids, remains indirect. Second, most studies only evaluate macroscopic parameters such as edema, without deeper tissue verification through histopathology or immunohistochemistry. Third, topical formulation studies often focus on the physical quality of preparations but are not always associated with specific inflammatory biomarkers. This is where the metformin proposal holds an important position because it combines physical evaluation of the preparation with assessment of IL-6, COX-2, and histopathological changes in anorectal tissue, thereby bridging the deficiencies of previous studies. The novelty of this study can be positioned in the integration of three aspects simultaneously (Baxter et al., 2017; Lanzolla & Markides, 2021; Zhao et al., 2017; Juntunen et al., 2019). First, the use of metformin as a topical anti-inflammatory agent for hemorrhoids represents drug repurposing that has still been limitedly discussed in previous studies. Second, the evaluation is directed toward a hemorrhoid model that is more pathobiologically relevant, with indicators that are not only macroscopic but also molecular through IL-6 and COX-2. With this position, the study does not merely repeat general anti-inflammatory findings, but rather expands them toward a more precise drug delivery system, more specific disease targets, and stronger outcome indicators. This makes the future research findings potentially capable of providing methodological and conceptual contributions to the development of topical hemorrhoid therapy.

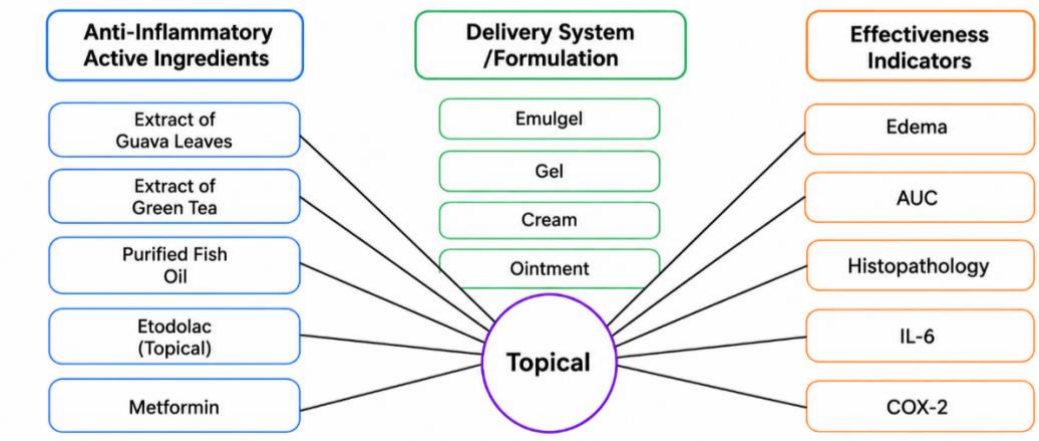

Figure 2. Synthesis Map of Previous Studies

The suggested figure is a flowchart consisting of three columns: anti-inflammatory active substances, delivery systems/preparations, and effectiveness indicators. The first column may include kenitu leaf extract, awar-awar leaf extract, cherry leaf infusion, suruhan extract, and metformin; the second column contains extract, infusion, tablet; the third column contains edema, inhibition percentage, AUC, histopathology, IL-6, and COX-2. The explanation of this figure is to demonstrate that previous studies have produced evidence at the level of active substances, preparation systems, and indicator levels, but not all of them have been fully connected within a

single research design. This diagram will emphasize that topical metformin research attempts to integrate these three levels within a more comprehensive framework.

Based on the results of the review of several indexed journals, it can be stated that various previous studies have consistently demonstrated the presence of anti-inflammatory activity in natural substances and their derivative preparations (Azab et al., 2016; Moudgil & Venkatesha, 2022; Alizadeh et al., 2020; Feng et al., 2020). Kenitu leaf extract and tablets, awar-awar leaf extract, and cherry leaf infusion all demonstrated the ability to reduce edema in carrageenan-induced rats, although the optimal dose in each study was not always linear. These results indicate that anti-inflammatory activity is influenced by the composition of active compounds, dosage form, and the possible presence of non-monotonic dose-response relationships. In kenitu and awar-awar studies, the middle dose actually produced better effects compared to the highest dose, whereas in the cherry leaf study, the highest dose showed the most optimal activity and even demonstrated a pattern approaching methylprednisolone control.

Mechanistically, these studies demonstrate a similar tendency, namely the involvement of inhibition of inflammatory mediators such as COX, NF-kB, IL-6, IL-1, and TNF-α. These findings are in line with the framework of topical metformin research designed to suppress hemorrhoidal inflammation through reduction of IL-6 and COX-2, so that there is strong scientific continuity between previous studies and the study to be conducted. Thus, the results of this review confirm that the opportunity for developing topical metformin as an anti-inflammatory therapy for hemorrhoids has a strong scientific basis. This study has the potential to fill gaps that have not been widely addressed by previous research, namely the integration of targeted anti-inflammatory mechanisms, nano-based topical delivery systems, and tissue biomarker evaluation in experimental hemorrhoid models.

CONCLUSION

Based on this narrative literature review, topical metformin has potential as an innovative anti-inflammatory approach for hemorrhoid therapy. This potential is supported by three main lines of evidence: the anti-inflammatory mechanism of metformin through AMPK activation and NF-κB inhibition, the ability of topical systems to improve topical drug delivery characteristics, and the relevance of inflammatory biomarkers such as IL-6, TNF-α, and COX-2 in hemorrhoidal inflammation. However, the current evidence remains largely indirect. Most available studies either discuss general anti-inflammatory mechanisms, non-hemorrhoid animal models, or topical formulation systems using active substances other than metformin. Therefore, this review does not establish that topical metformin has been experimentally proven to reduce hemorrhoidal inflammation. Instead, it identifies a strong scientific rationale and a research gap for future investigation.

SUGGESTION

Future studies should conduct direct experimental validation using metformin-based topical formulations. These studies should include formulation optimization, physicochemical characterization, drug release and permeation testing, stability evaluation, irritation testing, and in vivo assessment using validated hemorrhoid animal models. Histopathological analysis and inflammatory biomarkers such as IL-6, TNF-α, COX-2, NF-κB, and MPO should also be evaluated to confirm the anti-inflammatory mechanism. Clinical studies will ultimately be required to confirm safety, effectiveness, optimal dosage, and applicability in human hemorrhoid therapy.

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