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Review Article

Pharmacological and Pharmaceutic Insights into Aphthous Ulcer and Diuretic Therapies: A 25-Year Review of Natural and Synthetic Agents, Clinical Outcomes, and Formulation Strategies (2000–2025)

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ABSTRACT

This review offers an extensive overview of developments from 2000 to 2025 in the pharmacological and pharmaceutical management of aphthous ulcers and diuretic therapy. It examines both synthetic and natural treatment options, assessing their mechanisms of action, therapeutic effectiveness, clinical data, and formulation techniques. In the case of aphthous ulcers, the paper outlines and contrasts various interventions, including corticosteroids, antimicrobials, immune modulators, and a diverse range of herbal alternatives. Simultaneously, the review delves into the physiological and pharmacodynamic principles of diuresis, discussing all primary diuretic classes, their specific sites of action within the nephron, and associated side effects. Detailed comparative tables enhance the discussion by evaluating the safety, mechanisms, and clinical applications of both synthetic and herbal agents. Overall, this dual-focused analysis highlights the growing importance of herbal medicine and promotes integrated treatment strategies to improve patient outcomes.

INTRODUCTION

Recurrent aphthous ulcers (RAUs), also known as recurrent aphthous stomatitis, are the most frequently encountered form of oral ulceration. These lesions typically present as shallow, round to oval sores, characterized by a yellowish-white pseudomembranous centre surrounded by a distinct erythematous halo. Their size can range

from less than 1 mm to over 1 cm. Epidemiological data suggest that RAUs affect approximately 20% of the general population in the United States, with prevalence rates varying significantly—from as low as 5% in hospitalized individuals to as high as 60% among professional student populations. [1, 2] Population-level studies suggest that recurrent aphthous ulcers (RAU) affect about 0.85% of adults and 1.5% of children and adolescents.

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However, because RAU tends to occur in episodes and may resolve without medical attention, the actual number of people experiencing these ulcers is likely higher than reported. [3] Research indicates that recurrent aphthous ulcers (RAU) tend to be more frequent in certain groups of adults. They are more commonly seen in women, individuals younger than 40, those with lighter skin tones, nonsmokers, and people from higher socioeconomic backgrounds. [4] Diuresis is the process by which the kidneys produce increased amounts of urine, a vital function that helps regulate the body's fluid levels, maintain electrolyte balance, and control blood pressure. This natural mechanism can be activated by a range of factors—including physiological signals, medications, and certain health conditions. Through diuresis, the body eliminates excess fluids, metabolic waste, and key electrolytes such as sodium and potassium, playing a fundamental role in renal health and overall homeostasis. There are various forms of diuresis, including osmotic, water, pressure-related, and drug-induced types. Among these, diuresis prompted by pharmacological agents—especially diuretics—has become a cornerstone in the clinical management of conditions like hypertension, heart failure, nephrotic syndrome, and chronic kidney disease (CKD). These medications harness the body's natural excretory mechanisms to achieve therapeutic goals, making them indispensable in both acute and chronic care settings. [5] Diuretic therapies are widely utilized across the globe, playing a critical role in managing various chronic health conditions. As the global population continues to age and the prevalence of hypertension, diabetes, and heart failure rises, diuretics have become one of the most commonly prescribed drug classes. In the United States, for example, findings from the National Health and Nutrition Examination Survey (NHANES) reveal that more than 30% of adults diagnosed with

hypertension rely on diuretics to help control their blood pressure—underscoring their essential place in modern clinical practice. [6]

Aphthous Ulcers

o Pathophysiology and Aetiology

Although the clinical presentation of recurrent aphthous ulcers (RAU) is well recognized, their exact cause remains uncertain and is often considered idiopathic. However, immune-related mechanisms are believed to play a significant role in RAU development. Notably, approximately one-third of individuals with RAU report a positive family history, suggesting a possible genetic component. Supporting this, studies have identified a higher prevalence of certain human leukocyte antigen (HLA) types—specifically A2, A11, B12, and DR2—among affected individuals. Additionally, genetic predisposition may be linked to the inheritance of specific alleles of inflammatory cytokines, including interleukin-1 (IL-1-51) and interleukin-6 (IL-6-174). [7] Cell-mediated immunity and the formation of immune complexes are implicated in the pathogenesis of recurrent aphthous ulcers (RAU). An increased presence of gamma delta ($\gamma\delta$) T cells further indicates a potential role for antibody-dependent cell-mediated cytotoxicity in RAU. These T cells are known to secrete tumor necrosis factor-alpha (TNF- α), a pivotal pro-inflammatory cytokine that orchestrates the initiation and amplification of the inflammatory cascade, primarily through its effects on endothelial cell activation and neutrophil chemotaxis. Accordingly, pharmacological agents that inhibit endogenous TNF- α synthesis—such as thalidomide, pentoxifylline, and levamisole—may offer therapeutic benefit by attenuating the inflammatory processes underlying RAU. [8, 9] An increased in plasma IL-2 level has been seen in the active stage of RAU[7]. Interleukin-10, a



cytokine known for promoting epithelial cell growth during the healing process, has been found at reduced levels in cases of RAU. This deficiency may contribute to slower re-epithelialization and extended healing times, potentially explaining the persistent nature of these lesions. [10, 11] In addition to cell-mediated immune changes, B cells may also play a role in RAU through antibody-dependent cytotoxicity and immune complex formation. While circulating immune complexes are rarely detected, immune deposits are often found in lesion biopsies—particularly in the stratum spinosum—along with signs of leukocytoclastic or immune complex vasculitis and nonspecific deposits of immunoglobulins and complement proteins. [12, 13] RAU can be triggered by various chemicals and medications, including NSAIDs, nicorandil (used for heart conditions), beta-blockers, ACE inhibitors, and antiarrhythmic drugs. [14, 15] Sodium lauryl sulphate, a common detergent in oral care products, may trigger mouth ulcers resembling RAU. However, the exact cause of RAU remains unclear, and no definitive treatment exists. [4]

Aphthous ulcers, commonly known as “canker sores,” are well-defined, oval or round lesions that recur in the mouth. They typically feature a painful white or yellowish centre covered by a pseudo membrane, surrounded by a red, inflamed halo. In some cases, they may begin as small red spots or raised bumps, which soon evolve into the characteristic ulcer. For ulcers that persist longer, the yellow pseudo membrane may be replaced by a greyish layer. These sores can significantly interfere with eating, speaking, and overall comfort, often preceded by a burning or tingling sensation in the affected area. Aphthous ulcers most frequently affect non-keratinized, movable parts of the oral mucosa. In order of decreasing occurrence, they are found on the inner lips (labial mucosa), inside the cheeks (buccal mucosa), the underside and sides of the tongue, the floor of the mouth, the soft palate, and occasionally, the oropharynx. [3] RAU are typically categorized into three types—minor, major, and herpetiform—based on factors such as their size, how long they last, and whether they leave scars after healing. [16]

○ Classification and Clinical Features

Table 1: Types of Aphthous Ulcers

Characteristic	Minor aphthae (Mikulicz aphthae)	Major aphthae (Sutton disease)	Herpetiform aphthae
Prevalence	Represent 75–85% of recurrent aphthous ulcers (RAU)	Less common than minor aphthae	Rarest form of RAU
Size	Less than 1.0 cm in diameter. (Usually 1 to 5 ulcers)	Typically, larger than 1.0 cm	Pinhead-sized (1–3 mm). Typically, 10 to 100 small ulcers
Duration	Last for 10–14 days	2–6 weeks	7–10 days
Healing	Heal spontaneously without scarring	Heals with scarring	Usually without scarring
Common site	Buccal mucosa, labial mucosa, ventral tongue, soft palate, vestibules	Lips, soft palate, tonsillar fauces, pharynx	Any area of the oral mucosa
Impact	Self-limiting but frequently recurrent	Painful; can interfere with speech and eating	Extremely painful

Recurrence Pattern	Variable; some patients experience continuous cycles of ulcer formation	Frequent; may be persistent or overlapping in some patients	Frequent; may mimic herpetic stomatitis
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○ **Treatment Strategies**

The choice of treatment for RAU depends on several factors, including the diagnosis, how the condition presents clinically, its severity, and whether there are any lesions outside the mouth. The main goals of treatment are to manage pain, reduce inflammation, lower the chances of the ulcers coming back, and help the ulcers heal by

softening their edges. It’s also important to educate patients about the non-threatening but recurring nature of RAU and to emphasize the role of stress management and avoiding local trauma—like accidentally biting the inside of the cheek—in preventing flare-ups. [7]

a. Synthetic Drugs

Table 2: Synthetic drugs [17-27]

Therapeutic Category	Drug/Agent	Form	Usage/Effect	Side Effects / Notes
Local Anaesthetics	Lidocaine 2%	Viscous solution, spray	Topical pain relief	—
	Polidocanol	Adhesive dental paste	Local anesthesia	—
	Benzocaine	Lozenges, rinse (combo with cetylpyridinium chloride)	Topical relief	—
	Tetracaine + Polidocanol	Pump spray	Combination topical anesthetic	—
	Benzocaine + Cetylpyridinium Chloride	Mouth rinse	Combined anesthetic and antiseptic	—
Antimicrobial Agents	Tetracycline	Antibiotic solution	Reduces ulcer size, duration, pain	Dysgeusia, candidiasis, angular cheilitis
	Chlorhexidine Gluconate	Mouthrinse	Antibacterial, mixed efficacy	Bitter taste, brown staining
	Triclosan	Toothpaste/mouth rinse	Antibacterial, anti-inflammatory	—
Topical Glucocorticoids	Triamcinolone Acetonide	Orabase, elixir, injectable	Reduces inflammation	Oral candidiasis, minor systemic effects
	Clobetasol Propionate 0.05%	Topical	Potent corticosteroid	—
	Fluocinonide 0.05%	Topical	Potent corticosteroid	—
	Hydrocortisone 0.3%	Mouthrinse	Anti-inflammatory	Burning, altered taste

	Dexamethasone 0.5 mg/5mL	Elixir	Swish and spit	Risk if swallowed
Anti-inflammatory Agents	Amlexanox 5% (Aphthasol®)	Paste	Inhibits inflammatory mediators	No effect on recurrence
	Prostaglandin E2	Topical gel (0.3 mg)	Prevents aphthae in short-term use	—
	Sucralfate	5 mL, oral suspension	Forms protective barrier	—
Systemic Treatments	Prednisone	Oral	1 mg/kg/day, taper in 1–2 weeks	Depression, HPA suppression, osteoporosis
	Colchicine	Oral, 1–2 mg/day	Reduces ulcer number/duration	GI upset, headache, contraindicated in pregnancy
	Dapsone	Oral, 100–150 mg/day	Effective for complex aphthosis	Hemolysis, methemoglobinemia, agranulocytosis
	Clofazimine	Oral, 100 mg daily / q.o.d.	Up to 44% ulcer remission	Hepatitis, bowel obstruction, pregnancy category C
	Levamisole	Oral	Reduces pain, ulcer count	Nausea, dysgeusia, flu-like symptoms
Anti-TNF-α Agents	Thalidomide	Oral, 50–200 mg/day	Major aphthae, HIV patients	Neuropathy, pregnancy category X
	Pentoxifylline	Oral, 400 mg TID	36–63% effective	Arrhythmia, needs renal function monitoring
	Infliximab	IV, 5 mg/kg	Rapid healing of lesions	Highly effective, systemic immunosuppression
	Etanercept	SubQ, 25 mg twice weekly	Works for oral aphthae	TB reactivation, lymphoma risk, pregnancy category B

b. Natural (Herbal) Approaches

A natural treatment refers to a substance that occurs naturally as a secondary metabolite and may have potential clinical benefits. These compounds are typically derived from living organisms such as fungi, bacteria, plants, or animals.[28] Natural remedies are widely

recognized as valuable sources for developing and producing agents with anti-inflammatory, pain-relieving, antimicrobial, and immune-boosting properties.[29] Medications used to treat RAU are usually prepared in topical forms such as gels, mouthwashes, pastes, or adhesive patches applied directly to the affected area.[20]

Table 3: Herbal Drugs [28-49]

Natural Agent	Botanical Name	Key Constituents	Medicinal Properties	Clinical Findings
Turmeric	Curcuma longa	Curcumin	Analgesic, Antioxidant, Antiseptic, Antibacterial, Anti-inflammatory, Immunomodulatory	Comparable to triamcinolone; better than placebo and slightly better than honey in reducing lesion size and pain.



Aloe Vera	Aloe barbadensis	Anthraquinones, vitamins, folic acid, choline, amino acids, minerals	Anti-inflammatory, Antiviral, Antiseptic, Moisturizing, Healing	Effective in reducing pain, ulcer size, and healing time; better than CHX gel; comparable but slightly less effective than triamcinolone; better than myrrh.
Licorice	Glycyrrhiza glabra	Glycyrrhizin, glabridin, licochalcone A, licoricidin, licorisoflavan A	Anti-inflammatory, Soothing	90% ulcer size reduction; effective in reducing pain intensity and healing time.
Echinacea	Echinacea purpurea	Alkaloids, Polysaccharides, Chicoric acid	Immunomodulatory, Anti-inflammatory	Reduced lesions and pain; effects similar to prednisolone and colchicine but slightly less pronounced.
Honey	-	Sugars, polyphenols, antioxidants	Regeneration, Anti-inflammatory, Antibacterial	Effective like salicylate and corticosteroids; honey ice cubes reduced mucositis in children.
Propolis (Bee Glue)	-	Flavonoids, polyphenols	Antimicrobial, Anti-inflammatory, Wound healing, Immunostimulant	Reduced ulcer size and pain, prevented recurrences; superior to placebo and sesame-based formula.
Lady Mantle	Alchemilla vulgaris	Tannins, flavonoids	Healing, Anti-inflammatory	Aphtarine gel effective in healing ulcers in 3 days; no adverse effects.
Guava	Psidium guajava	Flavonoids	Antioxidant, Anti-inflammatory, Astringent	Guava leaf gel and mouthwash effective in reducing pain and promoting healing.
Chamomile	Matricaria chamomilla	Terpenoids, Flavonoids	Analgesic, Anti-inflammatory	Reduced pain and burning in RAS; no adverse effects.
Ginger	Zingiber officinale	Gingerols, Shogaols	Anti-inflammatory	Bioadhesive film relieved pain; no significant difference in ulcer size or healing time vs placebo.
Triphala	E. officinalis, T. bellirica, T. chebula	Tannins, Phenolic compounds	Antioxidant, Anti-ulcer, Antifungal, Antiplaque	Forms protective biofilm; with honey helps heal aphthous ulcers.
Neem	Azadirachta indica	Nimbidin, Nimbin, Nimbolide, Azadirachtin, Gallic acid, Catechins	Antibacterial, Anti-inflammatory	Used in Haridradi Tail; effective in relieving RAS symptoms.

Diuresis

Diuresis is the process by which the kidneys produce and expel greater amounts of urine, serving as a key mechanism for regulating the body's fluid levels, electrolyte balance, and blood pressure. This response can occur naturally—for

example, following high fluid intake—or it can be triggered intentionally through the administration of diuretics, which are drugs designed to promote the excretion of water and dissolved substances by the kidneys. [50] Diuretic compounds are widely utilized therapeutic agents in the management of



numerous medical conditions across the globe. While all diuretics share the common mechanism of inhibiting sodium (Na⁺) reabsorption within the renal tubules, they vary significantly in their chemical structures and modes of action. These differences influence the specific ion transport pathways they target within the nephron. As a result, each class of diuretics exerts its effects at distinct sites along the nephron, and because the extent of sodium reabsorption varies across these segments, this variability ultimately shapes their natriuretic potency, pharmacodynamic profiles, and clinical applications. [51,52] Owing to their distinct pharmacological profiles, different classes of diuretics are applied variably across a range of common and less frequent clinical conditions. Loop diuretics, in particular, are generally preferred as first-line agents for managing fluid overload associated with oedematous states such as heart failure, nephrotic syndrome, and liver cirrhosis. They also play a key role in controlling blood pressure and fluid volume in individuals with advanced stages of chronic kidney disease (CKD). [51]

○ **Physiology of Diuresis**

❖ **Glomerular Filtration**

Urine formation begins at the glomerulus, where plasma is filtered to produce a protein-free ultrafiltrate. The glomerular filtration rate (GFR)—a measure of how much filtrate is generated per unit time—plays a central role in regulating urine output. [53]

❖ **Tubular Reabsorption and Secretion**

As the filtrate passes through different segments of the nephron, its composition is modified through selective reabsorption and secretion:

Proximal Tubule: Approximately 65% of sodium and water, along with essential nutrients such as glucose, amino acids, and bicarbonate, are reabsorbed in this segment. [54]

Loop of Henle: Particularly in the thick ascending limb, active reabsorption of sodium, potassium, and chloride establishes a hyperosmotic environment in the renal medulla, a critical step in enabling water reabsorption in later nephron segments.

Distal Tubule and Collecting Duct: These segments fine-tune fluid and electrolyte balance, primarily under hormonal control. Aldosterone promotes sodium reabsorption, while antidiuretic hormone (ADH) regulates water permeability via aquaporin channels. [55]

❖ **Hormonal Regulation**

Hormones exert powerful effects on diuretic processes:

Antidiuretic Hormone (ADH) enhances water reabsorption in the collecting ducts by promoting the insertion of aquaporin-2 water channels into the apical membrane.

Aldosterone acts on the distal nephron to increase sodium reabsorption and potassium excretion, contributing to fluid retention. [56]

○ **Classification Of Diuretics**

Table 4: Types of Diuretics

Type	Site Of Action	Mechanism Of Action	Clinical Uses	Adverse Effects
Carbonic Anhydrase Inhibitors	Proximal convoluted tubule	Inhibit carbonic anhydrase enzyme, leading to decreased	Management of glaucoma, treatment of metabolic alkalosis,	May cause metabolic acidosis,



		reabsorption of bicarbonate and sodium, resulting in increased diuresis.	prophylaxis for acute mountain sickness, and urinary alkalization.	hypokalemia, renal stone formation, and hypersensitivity reactions.
Loop Diuretics	Thick ascending limb of the loop of Henle	Block the Na ⁺ -K ⁺ -2Cl ⁻ symporter, leading to significant excretion of sodium, chloride, and water; also increase calcium and magnesium excretion.	Treatment of edema associated with heart failure, liver cirrhosis, and renal disease; management of hypertension and hypercalcemia.	Potential for hypokalemia, hyponatremia, hypocalcemia, ototoxicity, dehydration, and hypotension.
Thiazide Diuretics	Distal convoluted tubule	Inhibit the Na ⁺ -Cl ⁻ symporter, reducing sodium and chloride reabsorption, leading to moderate diuresis and decreased calcium excretion.	First-line treatment for hypertension; also used for edema in heart failure, nephrolithiasis due to hypercalciuria, and nephrogenic diabetes insipidus.	Can cause hypokalemia, hyperuricemia, hyperglycemia, hyponatremia, and sexual dysfunction.
Potassium-Sparing Diuretics	Collecting ducts and late distal tubule	Either antagonize aldosterone receptors (e.g., spironolactone) or directly inhibit epithelial sodium channels (e.g., amiloride), leading to sodium excretion while conserving potassium.	Used in combination with other diuretics to prevent hypokalemia; treatment of hyperaldosteronism, heart failure, and resistant hypertension.	Risk of hyperkalemia; spironolactone may cause gynecomastia, menstrual irregularities, and impotence.
Osmotic Diuretics	Proximal tubule and descending limb of Henle	Increase the osmolarity of the filtrate, preventing water reabsorption and promoting diuresis; do not interfere with electrolyte transport mechanisms.	Reduction of intracranial and intraocular pressure; prophylaxis and treatment of acute renal failure; promotion of toxin excretion.	May lead to dehydration, electrolyte imbalances, and in some cases, pulmonary edema due to increased plasma volume.

Herbal Diuretic

Table 5: Herbal Diuretics

Plant Name	Extract Type / Dose	Observed Diuretic Effect
Mangifera indica	Aqueous, ethanol, ethyl acetate (250 mg/kg)	Aqueous extract had highest Na ⁺ /K ⁺ ratio and best diuretic effect. Compared with furosemide and mannitol. [57]



Mimosa pudica	Aqueous extract (100, 200, 400 mg/kg)	Significant increase in urine output and electrolyte excretion at 100 mg/kg. No further effect at higher doses. [58]
Lepidium sativum	Aqueous and methanolic extracts	Significant diuretic activity; methanol extract had potassium-conserving effect. Comparable to hydrochlorothiazide. [59]
Achyranthes aspera	Methanolic extract	Increased renal clearance of Na ⁺ , K ⁺ , Cl ⁻ ; effect lower than furosemide. [60]
Bixa orellana	Methanolic extract	Increased urine volume and excretion of Na ⁺ , K ⁺ , Cl ⁻ . [61]
Euphorbia thymifolia	Ethanol extract and fractions	Significant diuretic effect compared with furosemide. [62]
Taraxacum officinale	Aqueous leaf extract (2 g/kg)	Diuretic effect comparable to furosemide; potassium-rich profile may replenish lost K ⁺ . [63]
Allium sativum	Purified fractions (i.v.)	Biphasic natriuretic effect; inhibits Na ⁺ -K ⁺ -ATPase; no effect on blood pressure. [64]
Senna septemtrionalis	Ethanol extract (100 mg/kg)	2.67-fold increase in urine; 5.6-fold (Na ⁺) and 7.2-fold (K ⁺) excretion; linked to prostaglandins and NO pathway. [65]
Halosarcia indica	Aqueous extract (400 mg/kg)	Diuretic effect comparable to furosemide; time-dependent urine volume increase. [66]
Lagopsis supina	Aqueous soluble fraction	Acute and prolonged diuresis; RAAS pathway inhibition; downregulation of aquaporins AQP1–3. [67]
Kalanchoe pinnata	Ethyl acetate fraction (50 & 100 mg/kg)	Significant Na ⁺ , K ⁺ , and Cl ⁻ excretion at 100 mg/kg; rich in flavonoids and polyphenols. [68]
Desmostachya bipinnata	Hydroalcoholic extract (250 & 500 mg/kg)	Dose-dependent diuretic activity, maximal at 500 mg/kg; increases Na ⁺ , K ⁺ , Cl ⁻ excretion; comparable to furosemide. [69]
Petroselinum crispum	Ethanol extract, essential oil	Significant 24-hr urine output; inhibits Na ⁺ -K ⁺ pump; rich in flavonoids and apiole. [70]
Cicer arietinum	Methanol extract (200 & 400 mg/kg)	Delayed diuretic effect (12–24 hrs); increases urine volume; mechanism likely linked to RAAS and vasodilation. [71]
Alismatis rhizoma	Ethanol extract	Diuretic effect via Na ⁺ -Cl ⁻ co-transporter inhibition; similar to thiazide-like action (neoflumen). [72,73]
Opuntia ficus-indica	Aqueous extract & cladode gel	Increased urine, Na ⁺ , K ⁺ excretion; similar to loop diuretic furosemide. [74]
Citrullus lanatus	Ethanol pulp extract	Increased urinary Na ⁺ and Cl ⁻ excretion; decreased serum Cl ⁻ ; rich in steroidal compounds with natriuretic properties. [75]

Comparative Analysis of Herbal And Synthetic Drugs

Feature	Synthetic Drugs	Herbal Drugs
Mode of Action	Specific target with known pharmacological pathways	Broad, synergistic actions on multiple physiological systems
Safety Profile	Higher rate of adverse effects and hospital admissions (approx. 8% in USA); 100,000 deaths/year	Generally considered safer; deaths or hospitalizations rare and mostly due to misidentification or misuse
Mechanistic Understanding	Well-studied, based on clinical pharmacology	Less understood; often relies on traditional use and holistic approach
Side Effects	Common, often traded off for therapeutic benefit	Rare, usually described as “contraindications” rather than side effects
Therapeutic Scope	Targets specific symptoms or pathologies	Supports body’s healing processes, holistic healing
Complexity of Composition	Single or limited active compound(s)	Contains complex mixtures; polysaccharides, tannins, flavonoids, etc.
Drug Interactions	Well-documented; monitored in practice	Interactions may occur, especially with pharmaceuticals; need clinical oversight
Toxicity Risks	Known and quantified risks; requires dose management	Potential risks from misidentification, contamination, or inappropriate use
Examples of Toxic Agents	NSAIDs, chemotherapeutics, etc.	Aconitum spp., Atropa belladonna, Digitalis spp. (if misused)
Suitability in Pregnancy	Risk-based usage; some are contraindicated	Generally discouraged unless proven safe; evidence of teratogenicity is rare
Scientific Validation	Clinical trials, randomized controlled studies	Increasing use of clinical trials, but often challenged by complexity of herbal extracts
Regulatory Oversight	Stringent regulations and standardization	Less standardized; quality depends on source and practitioner
Antioxidant Activity	Rarely emphasized	Strong antioxidant activity; protective in cancer, diabetes, CVD, Alzheimer’s

Challenges And Future Perspectives

The future of therapeutic strategies for aphthous ulcers and diuresis lies in the integration of synthetic and herbal medicines to harness synergistic benefits while minimizing adverse effects. One promising avenue is the development of integrative therapies that combine conventional pharmaceuticals with plant-based agents to improve efficacy and reduce toxicity. Simultaneously, advancements in drug delivery—particularly the use of nanoscale systems such as

proliposomes, bioadhesive films, and buccal patches—can enable targeted, sustained release and improved patient compliance. Personalized medicine is another vital frontier, where pharmacogenomic tools may help tailor therapies based on individual genetic profiles, especially in recurrent aphthous stomatitis and chronic kidney disease, which exhibit significant patient variability in drug response. Despite the therapeutic potential of numerous herbal agents such as *Curcuma longa*, *Aloe vera*, and *Psidium guajava*, there remains a significant research gap:



the lack of robust, large-scale randomized controlled trials to confirm their safety and effectiveness. Furthermore, the herbal medicine sector continues to face challenges related to inconsistent quality, inadequate standardization, and insufficient regulatory oversight. Addressing these gaps requires a global initiative for harmonized guidelines on production, quality assurance, and safety evaluation. On the mechanistic front, more in-depth studies are needed to elucidate how herbal and synthetic compounds exert their effects—particularly through pathways involving cytokine modulation, TNF- α inhibition, and aquaporin expression. Finally, translating these advancements into practical healthcare solutions will demand improvements in the commercial scalability, shelf-life, and global market acceptability of herbal formulations. These efforts must be supported by modern pharmaceutical technologies and strong regulatory frameworks to bridge the gap between traditional remedies and modern therapeutic standards.

CONCLUSION

Over the past 25 years, therapeutic paradigms for recurrent aphthous ulcers (RAU) and diuretic-associated pathologies have undergone substantial transformation, underpinned by advances in pharmacological sciences and an increasing emphasis on integrative healthcare. This review systematically evaluated the mechanistic pathways, clinical efficacy, safety considerations, and formulation technologies associated with both synthetic and phytotherapeutic agents, underscoring the emerging relevance of evidence-based integrative treatment models. In the management of RAU, synthetic pharmacological agents—including topical and systemic corticosteroids, immunomodulators, and antimicrobial compounds—remain central due to

their well-defined mechanisms and rapid symptom control. However, these agents are often constrained by their adverse effect profiles, resistance development, and limited effectiveness in recurrent or idiopathic cases. In contrast, botanical therapeutics such as *Curcuma longa*, *Aloe vera*, *Glycyrrhiza glabra*, and *Echinacea purpurea* have demonstrated significant anti-inflammatory, antimicrobial, and epithelial regenerative effects across various preclinical and clinical studies. These phytoconstituents, owing to their pleiotropic actions, modulate multiple targets within the inflammatory and wound-healing cascades, offering a broader therapeutic window with favorable safety margins. Similarly, synthetic diuretics—including loop diuretics, thiazides, and aldosterone antagonists—continue to be indispensable in the pharmacotherapy of hypertension, heart failure, and fluid overload conditions. Despite their efficacy, these agents necessitate careful monitoring due to risks such as electrolyte imbalance, nephrotoxicity, and endocrine disruptions. Herbal diuretics, including extracts from *Taraxacum officinale*, *Mangifera indica*, *Mimosa pudica*, and *Desmostachya bipinnata*, have emerged as safer alternatives, exerting their effects through mechanisms such as modulation of renal ion transporters, aquaporin regulation, and suppression of the renin-angiotensin-aldosterone system (RAAS). The findings of this review reinforce the potential of integrative pharmacotherapy—where conventional and phytopharmaceutical agents are co-utilized to enhance therapeutic outcomes while mitigating adverse effects. However, several translational barriers remain. These include the paucity of well-powered, randomized clinical trials on herbal agents, lack of standardized extraction and formulation protocols, and limited mechanistic elucidation at the molecular level. Regulatory harmonization and quality assurance remain pressing needs. Future directions should



focus on the development of advanced drug delivery systems such as proliposomes, mucoadhesive films, and nanoparticulate carriers to optimize the bioavailability and therapeutic index of herbal drugs. Additionally, incorporation of pharmacogenomic data can enable personalized, targeted interventions. Collectively, these strategies hold promise for establishing scientifically robust, patient-centric models of care that integrate traditional and modern therapeutic systems.

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