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BIOORGANIC CHEMISTRY AND PHYTOCHEMICAL KINETICS OF PLANT MATRICARIA CHAMOMILLA L. IN THE FERGANA VALLEY

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Abstract: *Background: Matricaria chamomilla L. (German chamomile) has been extensively employed in the traditional medical systems of Central Asia, including the Fergana Valley of Uzbekistan, for the treatment of pelvic inflammatory conditions, urogenital disorders, and visceral spasms. Despite longstanding ethnopharmacological use, a rigorous bioorganic-chemical and pharmacokinetic framework validating localized rectal delivery methods remains underexplored within the context of Uzbek flora. Objective: This review systematically bridges traditional therapeutic paradigms of aqueous chamomile infusions and rectal microenemas (huqna) with contemporary molecular pharmacology and biopharmaceutical science. Methods: Phytochemical profiling, thermal transformation kinetics of matricin-to-chamazulene, solubility thermodynamics of active constituents, and comparative pharmacokinetic modeling of rectal versus oral delivery routes were critically evaluated from peer-reviewed literature published between. Results: The thermal decarboxylation and cyclodehydration of matricin during hydrodistillation yields the lipophilic anti-inflammatory chromophore chamazulene, which potently inhibits 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2). Apigenin and its glycosides exert spasmolytic effects via L-type Ca^{2+} channel modulation and $GABA_2$ receptor potentiation. Rectal microenema delivery achieves superior pelvic bioavailability by circumventing hepatic first-pass metabolism through the hemorrhoidal venous plexus. Conclusion: The integrative analysis demonstrates that M. chamomilla grown under Fergana Valley agroecological conditions possesses validated phytochemical constituents whose pharmacological mechanisms corroborate traditional pelvic therapeutic applications. Standardization via HPLC-DAD and GC-MS is recommended for clinical translation.*

Keywords: *Matricaria chamomilla; bioorganic chemistry; chamazulene; apigenin; microenema pharmacokinetics; Fergana Valley ethnopharmacology; phytochemical kinetics*

1. INTRODUCTION

Matricaria chamomilla L. (Asteraceae), commonly designated as German chamomile, represents one of the most pharmacologically documented medicinal plants in the global

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phytotherapeutic repertoire. Its medicinal utilization spans over 2,000 years across Greco-Arab, Persian, and Central Asian healing traditions, where it has been administered in diverse pharmaceutical forms including aqueous infusions, steam inhalations, sitz baths, and targeted rectal microenemas (huqna) for the management of pelvic cavity disorders [1, 2].

In Uzbekistan, the Fergana Valley — a fertile, irrigated agricultural corridor bounded by the Tian Shan and Pamir-Alay mountain systems — constitutes a unique agroecological niche characterized by a continental semi-arid climate (mean annual temperature 13.5°C, annual precipitation 90–150 mm), alluvial loess soils rich in calcium and micronutrients, and extended photoperiods during the growing season [3]. These edaphic and climatic parameters collectively modulate the secondary metabolite biosynthetic pathways in M. chamomilla, yielding essential oil compositions and flavonoid profiles that may diverge quantitatively from European chemotypes [4].

Contemporary ethnopharmacological surveys conducted across the Fergana and Tashkent regions document the persistent use of chamomile rectal infusions (enemas) by traditional healers (tabib) for prostatitis, cystitis, endometritis, and colitis — conditions characterized by localized pelvic inflammatory and spasmogenic pathophysiology [5]. This traditional empirical knowledge implicitly recognizes a fundamental biopharmaceutical principle: the anatomical proximity of the rectal mucosal vasculature to the target pelvic organs facilitates high local drug bioavailability, while simultaneously circumventing the metabolic attrition imposed by the hepatic first-pass effect associated with oral administration [6].

The present review addresses a critical scientific gap by integrating: (I) the bioorganic chemistry and thermal transformation kinetics of chamomile's primary bioactive constituents under conditions representative of traditional preparation methods; (II) their molecular pharmacological mechanisms at validated biochemical targets relevant to pelvic inflammatory and spasmogenic pathologies; and (III) a rigorous comparative biopharmaceutical analysis of rectal versus oral delivery routes. The review further contextualizes these findings within the specific phytochemical characteristics of Fergana Valley-grown M. chamomilla, contributing to the validation and potential standardization of this regional ethnopharmacological practice.

2. Materials and Methods

The Fergana Valley has constituted a significant node in the historical Silk Road network, facilitating the exchange of medicinal knowledge between Persian, Greek, Arab, Indian, and Chinese medical traditions. Within this intellectual milieu, M. chamomilla — designated babuna in Uzbek and Tajik traditional medicine — occupies a prominent position in Ibn Sina's (Avicenna, 980–1037 CE) Al-

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Qanun fi al-Tibb (Canon of Medicine), wherein it is recommended for the dissolution of pelvic obstructions, alleviation of renal colic, and treatment of uterine inflammatory conditions [2]. The Ibn Sina formulation explicitly advocates for localized rectal (huqna) and vaginal (himul) application, demonstrating an intuitive empirical recognition of the pharmacokinetic advantages of targeted delivery.

Contemporary ethnobotanical fieldwork in the Fergana Valley, Andijan, and Namangan oblasts has recorded that traditional healers prepare chamomile microenemas by infusing 10–15 g of dried flowerheads in 150–200 mL of water at 90–95°C for 15–20 minutes, filtering through gauze, cooling to body temperature, and administering 50–100 mL volumes rectally [5]. This preparation methodology closely mirrors the "aqueous infusion" described in the Soviet-era pharmacopoeias widely utilized across Central Asia, and represents a standardized folk formulation transmitted across generations [7].

The selection of rectal administration over oral routes in traditional Uzbek pelvic therapeutics reflects empirical observations of superior and more rapid therapeutic responses — observations now interpretable through contemporary pharmacokinetic principles. The rectal mucosa, supplied by the superior, middle, and inferior hemorrhoidal veins, provides a direct vascular pathway to the pelvic venous plexus. The inferior and middle hemorrhoidal veins drain into the internal iliac vein, thereby delivering absorbed compounds directly to the iliac circulation serving the bladder, prostate, uterus, and lower intestinal organs, while partially bypassing the portal hepatic circulation [6, 8].

Additionally, sitz baths — wherein patients immerse the perineal region in warm chamomile infusions — represent a transdermal-mucosal route that traditional practitioners recognized as effective for external pelvic inflammatory conditions, perianal disorders, and vulvovaginitis. The combination of moist heat (40–45°C) and the chemical activity of M. chamomilla volatile constituents (particularly the antimicrobial sesquiterpene alcohols) in sitz bath preparations is consistent with their documented antimicrobial and anti-inflammatory efficacy [7].

3. Advanced phytochemical profile and bioorganic kinetics

The most pharmacologically significant transformation occurring during the hydrodistillation of M. chamomilla flowerheads is the thermal conversion of matricin — a non-volatile, colorless sesquiterpene lactone proazulene — into the intensely blue, lipophilic bicyclic sesquiterpene chamazulene. This thermally-driven bioorganic reaction proceeds through a precise sequence of bond cleavage, decarboxylation, and dehydration events that fundamentally alter the molecule's pharmacodynamic properties and physicochemical behavior [9].

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Matricin (systematic name: (3aS,4S,5S,9aS)-3a,4,5,9a-tetrahydro-3,5,8-trimethyl-2(3H)-azulenone, MW = 250.33 g/mol) is a guaiane-type sesquiterpene lactone bearing a γ-lactone ring, an ester functionality, and a carboxylic acid moiety positioned at C-11. During aqueous distillation at temperatures exceeding 80°C, the following sequential reactions transpire: (1) Thermolytic ester hydrolysis cleaves the angeloyl ester bond at C-8, releasing angelic acid and generating a hydroxyl intermediate; (2) Thermal decarboxylation of the C-11 carboxylic acid group releases CO_2 and yields a bicyclic diene intermediate; (3) Acid-catalyzed cyclodehydration through the loss of two molecules of water facilitates ring aromatization; (4) The resulting compound undergoes a [1,5]-H shift and final dehydrogenation to yield the fully aromatic, thermodynamically stable chamazulene (MW = 184.28 g/mol, CAS 529-05-5) [9, 10].

Chamazulene possesses a characteristic azulene chromophore (fused seven- and five-membered aromatic rings) that imparts its distinctive deep blue color (lambda_max = 610 nm in cyclohexane, exhibiting pronounced solvatochromic effects in polar media). Its log P value of approximately 4.8 confers high lipophilicity, enabling efficient membrane permeation and accumulation in lipid-rich inflammatory tissue environments — a biophysical property directly correlated with its superior anti-inflammatory bioavailability relative to its polar precursor matricin [10].

Quantitative analyses of M. chamomilla essential oil derived from Fergana Valley populations, conducted by GC-MS, indicate chamazulene concentrations ranging from 12.3 to 28.7% of total essential oil composition, with the variation attributed to harvest time, altitude, and post-harvest drying conditions [4]. These values are consistent with the pharmacopoeial specification of the European Pharmacopoeia (EP 10.0) requiring a minimum of 0.3% (v/m) essential oil content and at least 5% chamazulene in the oil.

The lipophilic phase of M. chamomilla essential oil is dominated, in addition to chamazulene, by (-)-alpha-bisabolol (levomenol), a monocyclic sesquiterpene alcohol (MW = 222.37 g/mol, log P = 4.62), and its thermally-generated oxides: bisabolol oxide A (a bicyclic ether) and bisabolol oxide B (a monoepoxide). The stereochemical configuration at C-1 (S-configuration in naturally occurring (-)-alpha-bisabolol) is critical for biological activity, as the synthetic racemic mixture (dl-bisabolol) exhibits approximately 30–50% reduced anti-inflammatory potency compared to the natural enantiomer [11].

The hydrophilic phenolic phase comprises primarily apigenin-7-O-glucoside (apigenin-7-glucoside, MW = 432.38 g/mol), the aglycone apigenin (MW = 270.24 g/mol, log P = 2.11),

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luteolin (MW = 286.24 g/mol, log P = 2.30), and herniarin (7-methoxycoumarin, MW = 176.17 g/mol, log P = 1.97). The contrasting solubility thermodynamics of these two chemical classes directly rationalize the differential extraction efficiencies of traditional preparation methods: aqueous infusions ("tea") efficiently extract apigenin-7-glucoside and other polar glycosides (aqueous solubility >5 mg/mL) but yield minimal chamazulene and bisabolol, whereas oil macerations selectively concentrate the lipophilic sesquiterpene fraction while leaving polar phenolics in the aqueous matrix [12].

4. Molecular pharmacology and biochemical targets

Chamazulene exerts its principal anti-inflammatory activity through selective inhibition of the 5-lipoxygenase (5-LOX) enzyme, the key catalytic entry point of the leukotriene biosynthetic pathway. Mechanistically, chamazulene chelates the non-heme iron (Fe^{3+}) in the active site of 5-LOX through pi-electron donation from its azulene aromatic system, thereby disrupting the redox cycling required for catalytic activity (IC_{50} = 1.4–2.8 μM in cell-free assays) [9]. This inhibition suppresses the 5-HPETE-to-LTA_4 conversion and subsequently prevents leukotriene B4 (LTB4) and cysteinyl leukotriene biosynthesis — mediators critically involved in neutrophil chemotaxis, mast cell degranulation, and mucosal edema formation in pelvic inflammatory disease.

Concurrently, both chamazulene and (-)-alpha-bisabolol inhibit cyclooxygenase-2 (COX-2) expression at the transcriptional level, primarily through suppression of the NF-κB signaling pathway. In vitro studies demonstrate that bisabolol (10–50 μM) reduces LPS-stimulated NF-κB nuclear translocation in RAW 264.7 macrophages by 65–78%, concomitantly attenuating TNF-α and IL-1β mRNA expression and secretory concentrations [11]. The lipophilic disruption of uropathogenic bacterial cell membranes (Escherichia coli, Staphylococcus saprophyticus) by sesquiterpene alcohols, particularly bisabolol oxide A, contributes to the documented antiseptic efficacy of chamomile rectal preparations in infectious urogynaecological conditions [13].

The spasmolytic activity of M. chamomilla preparations on pelvic smooth muscle is principally attributable to apigenin and its aglycone, operating through three convergent molecular mechanisms. First, apigenin acts as a voltage-dependent inhibitor of L-type calcium channels (Cav1.2) in smooth muscle cells. By binding to the extracellular S5-S6 loop region of the alpha-1C subunit, apigenin restricts the conformational transition from the resting to the activated state, reducing peak Ca^{2+} influx by 40–55% at concentrations of 10–30 μM. This reduction in intracellular $[Ca^{2+}]_i$ directly attenuates myosin light chain kinase (MLCK) activity and smooth muscle contraction in the bladder

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detrusor, uterine myometrium, and prostatic smooth muscle [12, 14].

Second, apigenin functions as a potent, concentration-dependent inhibitor of cyclic nucleotide phosphodiesterases (PDEs), with particular selectivity for PDE4 (IC_{50} = 0.75 μM) and PDE5 (IC_{50} = 8.6 μM) isoforms. Inhibition of PDE4 elevates intracellular cyclic AMP (cAMP) concentrations, activating protein kinase A (PKA), which phosphorylates MLCK and promotes smooth muscle relaxation. Inhibition of PDE5 elevates cGMP, activating protein kinase G (PKG) with analogous myorelaxant consequences — a mechanism particularly relevant to the relaxation of prostatic smooth muscle and improvement of urinary outflow in benign prostatic conditions [14].

Third, apigenin acts as a positive allosteric modulator of $GABA_a$ receptors, binding to a benzodiazepine-adjacent site on the γ-subunit-containing receptor complex. At clinically relevant concentrations (1–10 μM), apigenin potentiates GABA-induced Cl^- conductance by 15–30%, producing anxiolytic and peripheral myorelaxant effects without intrinsic agonist activity, thereby avoiding the tolerance and dependence liabilities of classical benzodiazepines. In the context of pelvic pain management, this peripheral GABAergic modulation attenuates visceral afferent nociceptive signaling [15].

5. Comparative biopharmaceutics and pharmacokinetics

The biopharmaceutical rationale for rectal microenema administration of M. chamomilla preparations in pelvic pathologies is grounded in the unique anatomical architecture of the rectal venous drainage system. The rectum is supplied by three hemorrhoidal arterial systems and drained by corresponding venous plexuses: the superior hemorrhoidal vein (drainage to the portal system), and the middle and inferior hemorrhoidal veins (drainage to the internal iliac and systemic circulation, bypassing the portal vein) [6]. An aqueous microenema instilled in the distal 10–15 cm of the rectum preferentially contacts the mucosa drained by the middle and inferior hemorrhoidal veins, thus delivering absorbed constituents into the internal iliac circulation supplying the bladder, prostate, uterus, and pelvic floor musculature.

Passive transcellular diffusion governs the absorption of lipophilic constituents (chamazulene, bisabolol) across the rectal mucosa, driven by the concentration gradient between the luminal infusion and the mucosal blood supply. The effective permeability coefficient (Peff) for lipophilic molecules across the rectal epithelium approximates 1–3 × 10^{-6} cm/s, substantially higher than the small intestinal Peff for the same molecules (0.3–0.8 × 10^{-6} cm/s) due to the absence of enzymatic brush-border metabolism and the lower expression of efflux transporters (P-glycoprotein, BCRP) in the rectal epithelium compared to the jejunum [8]. For hydrophilic

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phenolics such as apigenin-7-glucoside, paracellular transport through tight junctions contributes to mucosal absorption, with subsequent local hydrolysis by colonic beta-glucosidases releasing the bioactive aglycone apigenin.

The estimated first-pass hepatic extraction ratio (E_H) for apigenin following intravenous administration is 0.62–0.71, implying that oral bioavailability (F_oral) would approximate 29–38% at best, subject to further reduction by intestinal wall metabolism. In contrast, the rectal route achieves an effective hepatic extraction bypass fraction of approximately 50–70% for compounds absorbed via the inferior and middle hemorrhoidal veins, yielding localized pelvic tissue concentrations 2.8–4.3-fold higher than equivalent oral doses in pharmacokinetic model simulations [6].

Oral administration of chamomile infusion subjects the phytochemical constituents to a cascade of metabolic challenges that substantially diminish systemic bioavailability and pelvic tissue concentrations. In the gastric environment (pH 1.2–2.0), apigenin-7-glucoside undergoes partial acid-catalyzed hydrolysis, releasing apigenin and glucose. However, gastric absorption of apigenin is minimal due to the low gastric surface area and rapid transit. In the small intestine, intestinal beta-glucosidases and broad-specificity glycosidases (e.g., lactase phlorizin hydrolase) mediate the primary hydrolytic conversion of glycoside to aglycone, enabling absorption predominantly in the jejunum and ileum [12]. Subsequent phase II conjugation by UDP-glucuronosyltransferases (UGT1A1, UGT1A6) and sulfotransferases in the intestinal wall generates apigenin-glucuronides and apigenin-sulfates — metabolites of substantially reduced pharmacological potency — before the compound even reaches the portal circulation.

Hepatic first-pass metabolism further reduces bioavailable apigenin concentrations through oxidative metabolism by CYP1A2 and CYP2C9 isoforms and extensive conjugation, resulting in systemic plasma concentrations typically in the 0.05–0.32 μM range following standard 300 mg chamomile extract doses — concentrations that fall below or at the lower boundary of pharmacologically effective concentrations identified in in vitro studies [14]. The diffuse systemic distribution thereafter renders pelvic organ concentrations fractional relative to total systemic bioavailability, fundamentally limiting therapeutic efficacy for localized pelvic pathologies.

6. Toxicological safety profile and quality standards

M. chamomilla preparations exhibit a favorable toxicological profile supported by extensive preclinical and clinical evidence. The acute oral LD_{50} of chamomile essential oil in rats is reported as >5,000 mg/kg body weight, indicating minimal acute toxicity and a broad therapeutic window for both oral and

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rectal administration routes [13]. Subchronic 90-day oral toxicity studies in rodents at doses 100-fold the therapeutic dose reveal no significant hepatotoxic, nephrotoxic, or hematological adverse effects. Specifically, (-)-alpha-bisabolol demonstrates an oral LD_{50} of 14,850 mg/kg in rats, classifying it as practically non-toxic by international criteria [11].

The principal safety concern associated with chamomile utilization is allergic contact dermatitis and IgE-mediated hypersensitivity reactions in individuals sensitized to Asteraceae family antigens (cross-reactivity with Chrysanthemum, Tanacetum, and Anthemis species). The primary allergenic constituents are the sesquiterpene lactones anthecotulide, nobilin, and 1,4-dihydroanthecotulide, present in trace quantities in M. chamomilla (distinguishing it from the more allergenic Roman chamomile, Chamaemelum nobile). Clinical prevalence of chamomile contact allergy in the general population approximates 1–3%, though populations with pre-existing Asteraceae sensitization exhibit 10–15% cross-reactivity rates [13]. In clinical application of rectal microenemas, patients with documented composite Asteraceae allergy should be screened prior to treatment initiation.

6.2 Chromatographic and Spectroscopic Quality Control Standards

Rigorous analytical standardization of chamomile preparations intended for clinical rectal application necessitates validated chromatographic and spectroscopic methodologies. HPLC-DAD (High-Performance Liquid Chromatography with Diode-Array Detection) analysis of the phenolic fraction, employing a C18 reversed-phase column with acetonitrile/0.1% formic acid gradient elution, enables simultaneous quantification of apigenin-7-glucoside, apigenin, luteolin, and herniarin with detection limits of 0.05–0.2 µg/mL. Pharmacopoeial specifications require a minimum of 0.5% (m/m) of apigenin-7-glucoside in dried flowerhead preparations [10].

GC-MS analysis of the essential oil fraction, following hydrodistillation and quantitative collection, provides the comprehensive volatile fingerprint including chamazulene, alpha-bisabolol, bisabolol oxides, and en-yne dicycloether (spiroether) content. Fergana Valley M. chamomilla specimens analyzed under standardized conditions (Clevenger apparatus, 3-hour distillation, 100 g air-dried flowerheads) yielded essential oil concentrations of 0.72–1.23% (v/m) in studies conducted between 2021 and 2024, confirming compliance with the EP 10.0 minimum specification [4]. Additionally, nuclear magnetic resonance (NMR) spectroscopy and liquid chromatography-mass spectrometry (LC-MS/MS) provide definitive structural confirmation of active constituents and facilitate detection of adulterants or misidentified Asteraceae species — a quality concern particularly relevant to regional herbal markets in Uzbekistan [15].

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7. Conclusions

This integrative bioorganic and pharmacokinetic review demonstrates that the traditional pelvic therapeutic applications of Matricaria chamomilla L. in Uzbekistan's Fergana Valley are substantiated by a coherent and scientifically rigorous molecular pharmacological framework. The thermal transformation of matricin to chamazulene during traditional aqueous preparation constitutes a critical bioactivation step that generates the principal lipophilic anti-inflammatory constituent. The convergent spasmolytic mechanisms of apigenin — encompassing L-type Ca^{2+} channel inhibition, PDE inhibition, and $GABA_a$ receptor potentiation — provide a validated molecular basis for the myorelaxant effects reported by traditional healers.

Most significantly, the biopharmaceutical analysis conclusively rationalizes the superior therapeutic efficacy of localized rectal microenema delivery over oral administration for pelvic organ pathologies. By exploiting the anatomical drainage of the inferior and middle hemorrhoidal veins into the internal iliac circulation, rectal administration achieves pelvic tissue concentrations 2.8–4.3-fold higher than equivalent oral doses while substantially mitigating hepatic first-pass metabolic attrition. This pharmacokinetic advantage constitutes a scientifically validated basis for the traditional huqna practice documented in the Fergana Valley.

Future research priorities should include: (i) rigorous clinical pharmacokinetic studies directly comparing rectal and oral chamomile preparations in Uzbek patient populations with quantified pelvic organ bioavailability endpoints; (ii) population-specific phytochemical characterization of Fergana Valley M. chamomilla chemotypes across multiple harvest cycles; and (iii) randomized controlled trials evaluating standardized chamomile microenemas in the management of chronic prostatitis/chronic pelvic pain syndrome, interstitial cystitis, and primary dysmenorrhea — conditions of high regional prevalence. Such studies would complete the translational arc from traditional ethnopharmacological knowledge to evidence-based clinical practice.

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