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SYNERGISTIC POTENTIAL OF *PANDANUS ODORATISSIMUS* AND *CURCUMA LONGA* IN THE MANAGEMENT OF NOCTURNAL ENURESIS: A COMPREHENSIVE NARRATIVE REVIEW OF BOTANICAL, PHARMACOLOGICAL AND FORMULATION STRATEGIES

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ABSTRACT

Background: Nocturnal enuresis represents a complex, multifactorial urological disorder affecting both pediatric and adult populations. Conventional pharmacological interventions often suffer from high relapse rates and compliance issues, prompting the search for age-appropriate, plant-based alternatives. **Objective:** To systematically review the etiology of nocturnal enuresis and explore the therapeutic justification for a novel dual-herb suspension utilizing *Pandanus odoratissimus* peduncle and *Curcuma longa* rhizome. **Methods:** A comprehensive literature review was conducted to synthesize ethnobotanical data, phytochemical profiles, pharmacological mechanisms, and formulation challenges associated with these plants, particularly emphasizing their relevance in resource-limited settings like Yemen. **Discussion:** The pathophysiology of enuresis involves nocturnal polyuria, detrusor overactivity, and impaired sleep arousal. *Pandanus odoratissimus* offers potent antispasmodic

and antidiuretic properties via its alkaloidal and phenolic fractions, effectively stabilizing the detrusor muscle. Conversely, *Curcuma longa* (rich in curcuminoids) provides robust anti-inflammatory, antioxidant, and neuro-modulatory actions that soothe bladder mucosa and enhance brain-bladder signaling. Combining these botanicals yields a synergistic "dual-lock" mechanism. Furthermore, developing these extracts into specialized pediatric and adult suspensions overcomes critical dosage and palatability barriers. **Conclusion:** A scientifically formulated dual-herb suspension of *P. odoratissimus* and *C. longa* represents a promising, culturally resonant, and highly effective therapeutic strategy for nocturnal enuresis. Further formulation optimization and clinical validations are warranted.

KEYWORDS: Nocturnal Enuresis; *Pandanus odoratissimus*; *Curcuma longa*; Polyherbal Formulation; Pediatric Suspension; Ethnopharmacology.

1. INTRODUCTION

Etiology and Global Burden of Nocturnal Enuresis

Nocturnal enuresis, commonly referred to as bedwetting, is defined as the involuntary discharge of urine during sleep in individuals who have surpassed the developmental age for expected bladder control, typically five years of age.[1] The etiology of this condition in children is highly complex. It is driven by genetic influences, where familial patterns suggest strong hereditary components, alongside delayed central nervous system maturation affecting critical bladder signaling pathways.[2] Pathophysiologically, the condition is frequently underpinned by nocturnal polyuria stemming from disruptions in the nocturnal secretion of antidiuretic hormone (vasopressin), detrusor muscle overactivity leading to uncontrolled contractions, and elevated sleep arousal thresholds that prevent the individual from waking in response to bladder distension.[1,2]

In adults, nocturnal enuresis can persist from a pediatric onset or emerge as a secondary issue linked to underlying conditions, including anatomical abnormalities in the urinary tract, chronic sleep disorders, or neurological impairments.[3] The autonomic nervous system plays a pivotal role across all age groups; sympathetic hyperactivity can intensify polyuria by altering renal function, whereas parasympathetic predominance heightens bladder instability, intricately linking hormonal imbalances with neural dysregulation.[2]

The global burden of nocturnal enuresis is considerable.[4] It exerts severe psychosocial effects, including lowered self-confidence, social isolation, and impaired overall well-being

for both affected individuals and their families.[5] Furthermore, it incurs notable economic strains through repeated medical consultations and ancillary household costs.[6] Despite its high frequency, the condition is heavily underreported due to the stigma and embarrassment associated with the diagnosis.[7] While prevalence declines with advancing age, the persistence of the disorder underscores a critical need for targeted, age-appropriate interventions.[3]

1.1 Prevalence and Psychosocial Impact in the Yemeni Context

In Yemen, nocturnal enuresis constitutes a significant public health issue. Epidemiological data highlight considerable prevalence among pediatric populations, intensified by restricted healthcare access, political instability, and economic hardships.[8] Regional studies demonstrate notable variability: Aden Governorate reports a 17.2% prevalence among school-aged children, strongly associated with familial predisposition and psychological stress.[8] In Al-Mukalla City, prevalence reaches 25.5%, displaying a female predominance and correlations with deep sleep patterns and excessive evening fluid intake.[9] Meanwhile, in Sana'a City, an 11.4% prevalence was recorded, peaking between the ages of 8 and 9 years.[10] The psychosocial consequences in these conservative societies are extensive. Children face shame and behavioral issues, while parents endure significant domestic and emotional burdens.[5,6]

2. Traditional Herbal Medicine for Urological Disorders

In many developing regions, including Yemen, traditional herbal medicine serves as a vital component of primary healthcare due to deep-rooted cultural beliefs and the widespread availability of local flora.[11] Ethnobotanical knowledge is transmitted generationally, utilizing various plant parts as teas, poultices, or extracts to alleviate inflammation and urinary flow issues.[12] Up to 40% of Yemen's vast plant species hold medicinal value, demonstrating potent diuretic, antiseptic, and litholytic effects.[12] For instance, *Artemisia absinthium* is used for urinary tract infections, *Commiphora gileadensis* for urinary retention, and *Lawsonia inermis* for bladder complaints.[13]

Medicinal plants contribute significantly to the management of nocturnal enuresis by modulating bladder contractility, regulating urine output, and combating oxidative stress.[14,15] Certain herbal blends, such as Urox® (comprising *Crataeva nurvala*, *Equisetum arvense*, and *Lindera aggregata*), have successfully reduced bedwetting episodes in controlled clinical settings, often outperforming placebos by targeting multifactorial causes.[16,18] Other topical

applications, like *Matricaria recutita* (chamomile) oil, provide symptom relief based on historical use.[19] However, there remains a prominent gap in developing standardized, age-appropriate dual-herb formulations that target the specific etiologies of enuresis, offering a safer alternative to synthetic options with high relapse rates.[20,21]

3. Botanical and Pharmacological Profile of *Pandanus odoratissimus*

3.1 Botanical Description and Distribution

Pandanus odoratissimus (screw pine or kewda) is a dioecious, palm-like monocot belonging to the Pandanaceae family. It reaches 3 to 6 meters in height and is characterized by aerial prop roots and spiral-arranged, linear-lanceolate leaves adapted for water conservation.[22] The male inflorescences are fragrant due to highly active essential oils, whereas the female inflorescences form solitary syncarps on robust peduncles.[23,24] The peduncle is triquetrous and sheathed by protective bracts that play a crucial role in fruit maturation.[25]

Geographically, *P. odoratissimus* exhibits a pantropical distribution across the coastal regions of South Asia and the Pacific. In Yemen, it thrives in the humid, saline-tolerant coastal habitats of Hodeidah, Taiz, and Aden, adapting well to arid tropical climates and stabilizing shorelines.[12,13] In Yemeni folk medicine, the plant (locally known as "kadi" or "anssif") is historically utilized for urological ailments. Decoctions of the peduncle are specifically prepared to manage dysuria, nocturnal enuresis, and kidney inflammation.[25]

3.2 Phytochemistry and Urological Mechanisms

The peduncle of *P. odoratissimus* exhibits a complex diversity of secondary metabolites distinct from the leaves or roots.[26] Phytochemical screening confirms the presence of four primary classes of compounds relevant to urinary physiology.

1. **Alkaloids:** Piperidine alkaloids and pandamarilactones influence smooth muscle tone, playing a crucial role in neuromodulation and the relaxation of involuntary bladder contractions.[22]
2. **Flavonoids:** Quercetin derivatives, catechin, and epicatechin function as potent antioxidants. They provide nephroprotection and reduce oxidative stress within the detrusor muscle, mitigating bladder instability.[27]
3. **Tannins:** Hydrolyzable tannins offer astringent properties that tone urinary sphincters, helping to reduce excessive urinary output.[24]

4. **Essential Oils and Phenolics:** Compounds like the methyl ether of phenyl ethyl alcohol, lignans, and benzofurans provide robust antispasmodic, antimicrobial, and cytoprotective effects.[23, 28]

The management of nocturnal enuresis by *P. odoratissimus* involves both neurogenic and myogenic pathways. Flavonoid components exert antispasmodic effects on bladder smooth muscle by inhibiting calcium influx and modulating cholinergic receptors, thereby reducing uninhibited detrusor contractions.[24] Animal models demonstrate that methanolic extracts of the peduncle significantly increase bladder capacity and reduce urination frequency, exhibiting a profile similar to mild antimuscarinic agents.[25] Additionally, its profound free radical scavenging activity protects the bladder epithelium and renal architecture from oxidative damage, ensuring safety during chronic administration.[22,27]

4. Botanical and Pharmacological Profile of *Curcuma longa*

4.1 Botanical Description and Distribution

Curcuma longa L. (turmeric) is a rhizomatous perennial herb from the Zingiberaceae family.[29] It is characterized by large, oblong-lanceolate leaves and tuberous, highly branched rhizomes with a deep orange-yellow cortex. The vibrancy of the rhizome's color is a direct qualitative marker of its curcuminoid content.[30] Though native to the Indian subcontinent, it has been cultivated in the favorable sub-tropical microclimates of Yemen's Ibb, Taiz, and Hajjah governorates for centuries.[12] In Yemeni traditional medicine, turmeric ("Kurkum") acts as a therapeutic agent to treat inflammatory conditions, remove "cold" humors, and support hepatic function.[14] It is frequently utilized in traditional practices to manage diabetic wounds, joint pain, and metabolic disorders.[12,31]

4.2 Phytochemistry and Anti-inflammatory Mechanisms

The therapeutic efficacy of *C. longa* stems from a rich, synergistic matrix of phytochemicals.[32] Non-volatile curcuminoids (constituting 3-5% of dry weight) are dominated by curcumin, demethoxycurcumin, and bisdemethoxycurcumin.[33] Volatile essential oils (2-7%) are rich in sesquiterpenes like ar-turmerone, which critically facilitate curcuminoid bioavailability and provide neuroprotection.[34,35] Additionally, water-soluble polysaccharides (ukonans) act as immune modulators and provide valuable rheological properties for pharmaceutical formulations.[36]

Curcumin functions as a pleiotropic molecule. It potently inhibits nuclear factor kappa-B (NF-κB), subsequently preventing the transcription of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[33] Furthermore, bioactive constituents suppress COX-2 and 5-LOX, reducing the synthesis of prostaglandins and leukotrienes—a mechanism clinically vital for urinary tract conditions, as elevated prostaglandins are intimately associated with detrusor muscle urgency and instability.[32,35]

In the context of bladder function, curcumin ameliorates overactive bladder symptoms through the downregulation of muscarinic receptors and by protecting smooth muscle from oxidative stress.[37] Neurologically, curcumin crosses the blood-brain barrier, upregulating Brain-Derived Neurotrophic Factor (BDNF) and enhancing synaptic plasticity.[38] This neuro-modulatory effect supports the maturation of the micturition reflex arc in pediatric patients, improving brain-bladder communication and regulating sleep-arousal thresholds.[39]

Furthermore, turmeric exhibits robust antimicrobial properties, providing prophylactic benefits against recurrent urinary tract infections commonly seen in enuretic patients.[40,41]

5. Synergistic Rationale for Dual-Herb Therapy

Polyherbalism is a cornerstone of modern complementary medicine.[42] A "multi-target therapeutics" approach is essential to address the complex pathophysiology of enuresis, which encompasses bladder smooth muscle instability, oxidative stress, and neurological signaling deficits.[43] Unlike synthetic drugs that target single receptors, polyherbal formulations utilize an "herbal shotgun" approach, modulating disparate pathological targets simultaneously.[44]

The combination of *Pandanus odoratissimus* and *Curcuma longa* creates a profound synergistic interplay.[45] This produces a "dual-lock" mechanism: *Pandanus* acts as a natural anticholinergic analogue, mechanically relaxing the detrusor wall and increasing bladder capacity.[25] Concurrently, *Curcuma* reduces chemical irritability and underlying tissue inflammation, preventing premature contractions.[33,37] Furthermore, while *Pandanus* contributes antidiuretic-like reductions in urine output, *Curcuma* upregulates BDNF to improve neurological sleep-arousal control.[38,39] This strategic combination addresses the core pillars of enuresis: reduced nocturnal functional bladder capacity, nocturnal polyuria, and the inability to arouse from sleep.[20]

6. Formulation Challenges: Age-Appropriate Herbal Suspensions

The clinical success of herbal medicine is heavily dependent upon the design of patient-centric dosage forms. Because nocturnal enuresis predominantly affects pediatric populations but frequently persists into adulthood, formulations must bridge diverse anatomical and pharmacokinetic requirements.[46]

6.1 Pediatric Formulation Considerations

Children are not simply "small adults." Significant physiological differences in gastric pH, gastrointestinal transit time, and metabolic enzyme activity profoundly alter the pharmacokinetics of oral therapies.[47] Hepatic metabolism variability dictates that pediatric dosage forms must allow for precise titration based on body weight.[48] Solid dosage forms present severe choking hazards, making liquid suspensions the preferred standard.[49,50]

Pharmaceutical suspensions represent a coarse dispersion of insoluble solid particles in a liquid medium.[51] They accommodate the high herbal loads required for *Pandanus* and *Curcuma* extracts without the dissolution rate-limiting steps associated with tablets.[48,52] However, formulation requires meticulous engineering. Plant alkaloids and tannins inherently possess high astringency and bitterness, leading to treatment rejection.[53]

Consequently, advanced taste-masking techniques utilizing specific sweetening agents and viscosity modifiers are required to coat the tongue and prevent extract contact with taste buds.[54] From a rheological standpoint, the suspension must exhibit pseudoplastic flow to ensure even distribution and uniform dosing upon shaking, thereby preventing under-dosing or toxicity caused by sedimented "cakes".[51, 55, 56] Finally, chemical stability requires specific pH buffers to protect sensitive curcuminoids from degradation in aqueous environments[57], alongside safe pediatric preservatives like sodium benzoate to prevent microbial spoilage.[58,59]

6.2 Adult and Geriatric Compliance

While optimized for children, these herbal suspensions offer distinct advantages for adult and elderly patients.[60] A significant subset of geriatric populations suffers from dysphagia, rendering traditional solid capsules highly impractical. Suspensions act as a versatile "bridge" dosage form, completely bypassing disintegration and dissolution barriers to provide enhanced bioavailability and a rapid onset of therapeutic action—often within 15 to 30 minutes.[61] The selection of biocompatible suspending agents (e.g., xanthan gum) and

wetting agents (e.g., polysorbate 80) ensures long-term physical stability and dose uniformity across diverse storage conditions.[62,63,52] Ultimately, utilizing liquid formulations closely aligns with traditional cultural practices of administering herbal decoctions, fundamentally increasing long-term adherence rates across all age demographics.[12]

Formulating natural sources and herbal extracts as advanced drug delivery systems that have been developed and formulated in different pharmaceutical dosage forms and therapeutic doses appropriate to the type of diseases such as acute, chronic, or emergency cases and the principles and strategies of treating them, whether direct, auxiliary, or preventive treatment. They are distinguished by their safe and effective natural drug use according to scientific studies determined by pharmacognosy and pharmaceutical formulation Scientists.[64,75]

7. CONCLUSION

Nocturnal enuresis remains a globally prevalent, highly distressing urological disorder with a complex multifactorial etiology. Relying solely on conventional monotherapies often results in suboptimal clinical outcomes. A meticulously designed dual-herb suspension integrating the peduncle extract of *Pandanus odoratissimus* and the rhizome extract of *Curcuma longa* presents a highly innovative, evidence-based approach. By synergistically combining antispasmodic detrusor relaxation with potent anti-inflammatory and neuro-modulatory actions, this formulation comprehensively targets the underlying drivers of bedwetting. Furthermore, engineering this therapy as a precisely titratable, palatable liquid suspension effectively overcomes critical pediatric and geriatric compliance barriers. Future large-scale clinical trials and stability optimizations are warranted to fully establish this promising ethnopharmacological intervention in modern urological practice.

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