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# VISHA-DRAVYA DUAL PHARMACODYNAMICS A NOVEL INTEGRATIVE FRAMEWORK CORRELATING AGADTANTRA AND DRAVYAGUNA THROUGH THE LENS OF XENOBIOTIC HORMESIS AND PHYTOCHEMICAL DOSE-RESPONSE MODULATION

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## ABSTRACT

**Background:** Classical Ayurvedic scholarship has long maintained a conceptual tension between Agadtantra - the science of toxins, antidotes, and poisons - and Dravyaguna - the science of drug properties and pharmacodynamics. Many substances catalogued as Visha (toxic) in Agadtantra texts are simultaneously listed as therapeutically potent Dravyas in Dravyaguna literature, yet no systematic framework has articulated the mechanistic basis for this dual pharmacological identity. The phenomenon of hormesis - whereby sub-toxic doses of xenobiotics elicit adaptive, beneficial biological responses - offers a compelling modern correlate to this classical paradox.

**Aim:** To construct an original integrative framework - termed Visha-Dravya Dual Pharmacodynamics (VDDP) - that formally correlates the Agadtantra concept of Upavisha (sub-lethal toxins) with the Dravyaguna concept of Vipaka-mediated dose-response modulation, and to validate this framework through phytochemical and toxicological evidence from indexed biomedical literature.

**Methods:** A structured conceptual synthesis was performed integrating classical Ayurvedic texts - primarily Charaka Samhita, Sushruta Samhita, Ashtanga Hridayam, and Rasatarangini

- with peer-reviewed pharmacological studies indexed in PubMed and Scopus (2000–2024). Substances appearing as Upavisha in Agadtantra taxonomies and simultaneously listed as medicinal Dravyas were selected for cross-analysis. Key parameters included Vipaka (post-digestive transformation), Prabhava (idiosyncratic pharmacological action), and xenobiotic hormesis thresholds documented in modern toxicology.

**Results:** Eleven Upavisha substances - including Vatsanabha (Aconitum ferox), Ahiphena (Papaver somniferum), Dhattura (Datura metel), Langali (Gloriosa superba), and Jayapala (Croton tiglium) - demonstrate mechanistically coherent dual pharmacological profiles. Classical Shodhana (purification) procedures correspond to toxicokinetic modifications that suppress peak plasma concentrations of alkaloids while preserving sub-threshold bioactive fractions. Vipaka transformations align with hepatic Phase I/II metabolic processing, and Prabhava actions correspond to hormetin-mediated stress-response pathways including Nrf2 activation and heat-shock protein upregulation.

**Conclusion:** The VDDP framework resolves a persistent conceptual lacuna in classical Ayurvedic pharmacology and offers a translatable model for evidence-informed re-evaluation of Upavisha-containing formulations. Shodhana emerges not merely as a ritual detoxification but as a dose-engineering process with precise xenobiotic pharmacokinetic implications.

**KEYWORDS:** *Agadtantra, Dravyaguna, Upavisha, Visha-Dravya Dual Pharmacodynamics, Xenobiotic Hormesis, Shodhana, Vatsanabha, Vipaka, Prabhava, Dose-Response Modulation.*

## 1. INTRODUCTION

The intersection of Agadtantra (*विषविज्ञान*) and Dravyaguna (*द्रव्यगुण विज्ञान*) represents one of the most intellectually fertile, yet undertheorized, domains within classical Ayurvedic scholarship. Agadtantra, enumerated as one of the eight canonical branches (*Ashtanga*) of Ayurveda, concerns itself primarily with the taxonomy of poisons (*Visha*), their pathophysiological mechanisms (*Visha-Vegam*), antidotal therapies (*Agada*), and forensic considerations. Dravyaguna, by contrast, occupies itself with the pharmacological attributes - Rasa (taste), Guna (qualities), Virya (potency), Vipaka (post-digestive effect), and Prabhava (specific action) - of substances deployed therapeutically.

A profound taxonomic paradox permeates the classical literature: numerous substances catalogued within Agadtantra as inherently toxic - particularly the class designated *Upavisha* (sub-poisons or conditionally toxic substances) - appear simultaneously as valued medicinal

agents in Dravyaguna treatises and formulary texts such as the *Rasatarangini*, *Sharangadhara Samhita*, and *Bhavaprakasha Nighantu*.[1,2] Vatsanabha (*Aconitum ferox* Wall. ex Ser.), arguably the most studied of the Upavisha, is simultaneously the most potent cardiotoxin in the Ayurvedic pharmacopoeia and an ingredient in classical cardiovascular and analgesic formulations.[3] This pharmacological duality - toxicity and therapeutics residing within the same substance - has resisted systematic explanation within either purely classical or purely biomedical frameworks.

The Charaka Samhita articulates a foundational epistemological principle that underpins this duality:

*"हितं द्रव्यं प्रयोक्तव्यं मात्राकालौ विचिन्त्य च।*

*अहितं हि विषं प्रोक्तं हितं अमृतसमं मतम्॥"*

**Charaka Samhita, Sutrasthana, 26/13**

Translation: "A substance prescribed appropriately with due consideration of quantity and time is medicine; what is harmful is called poison, while what is beneficial is considered nectar." This verse encodes an ancient recognition that toxicity and therapeutics are not categorical properties of substances but emergent properties of dose, context, and biological state - a position that resonates strikingly with the modern concept of xenobiotic hormesis.[4]

Hormesis - derived from the Greek *hórmēsis* meaning "to set in motion" - describes a biphasic dose-response phenomenon wherein low doses of an agent that is toxic at high doses stimulate adaptive, often beneficial, biological responses.[5] Pioneered in modern toxicology by Calabrese and Baldwin[6] and subsequently validated across thousands of pharmacological studies, hormesis provides a mechanistic vocabulary through which the Upavisha paradox can be formally analyzed. The present article constructs a novel integrative framework - designated Visha-Dravya Dual Pharmacodynamics (VDDP) - that systematically correlates Agadtantra's Upavisha taxonomy with Dravyaguna's dose-response architecture, and grounds both within contemporary phytopharmacological and toxicokinetic evidence.

No prior publication has proposed a formal mechanistic framework explicitly linking the Agadtantra classification of Upavisha with Dravyaguna dose-response principles through the lens of xenobiotic hormesis. Existing reviews either examine Vatsanabha or other Upavisha as isolated pharmacological case studies [7,8] or address Shodhana as a purification procedure without connecting it to modern toxicokinetic dose-engineering concepts.[9] The VDDP framework, presented here for the first time, attempts to address this gap comprehensively.

## 2. Conceptual Methodology

This article employs a structured conceptual synthesis methodology, combining textual analysis of classical Ayurvedic primary sources with systematic review of indexed pharmacological literature. The study design comprised four sequential phases:

***Phase 1: Classical Text Analysis***

Primary Ayurvedic texts consulted include the *Charaka Samhita* (with Chakrapanidatta's commentary *Ayurveda Dipika*), *Sushruta Samhita* (with Dalhana's *Nibandhasangraha* commentary), *Ashtanga Hridayam* of Vagbhata, *Rasatarangini* by Sadananda Sharma, *Bhavaprakasha Nighantu*, and the *Dhanvantari Nighantu*. Relevant Agadtantra chapters (*Kalpasthana* of Charaka, *Kalpasthana* of Sushruta) and Dravyaguna sections (*Sutrasthana*, *Dravyadiguna* chapters) were analyzed for classifications, properties, and pharmaceutical instructions pertaining to Upavisha substances. [1,2,10]

***Phase 2: Substance Selection Criteria***

Upavisha substances were selected for cross-analysis against the following inclusion criteria: (a) explicit listing in Agadtantra chapters as toxic or sub-toxic; (b) simultaneous listing as a therapeutic Dravya with documented Guna-Karma (properties and actions); (c) post-Shodhana use in at least one classical formulation from recognized Samhitas or Nighantus; and (d) availability of peer-reviewed pharmacological and toxicological data in PubMed- or Scopus-indexed journals published between 2000 and 2024. Eleven substances met all four criteria and formed the analytical corpus of this study.

***Phase 3: Biomedical Literature Review***

A systematic search of PubMed and Scopus was conducted between March and September 2024 using the following MeSH terms and keywords in combination: "Aconitum alkaloids", "hormesis dose-response", "Datura alkaloids toxicology", "Gloriosa superba colchicine", "Croton tiglium phorbol esters", "Shodhana purification pharmacokinetics", "xenobiotic biotransformation Nrf2", "herbal toxin therapeutic window". Boolean operators (AND, OR) were applied to refine retrieval. Only studies providing quantitative dose-response data or mechanistic pathway evidence were retained for synthesis.

***Phase 4: Framework Construction***

Correlation mapping was performed across three levels: (a) taxonomic-conceptual - aligning Agadtantra classifications with xenobiotic categories; (b) mechanistic - mapping Vipaka transformations onto Phase I/II hepatic biotransformation; and (c) pharmacodynamic - correlating Prabhava actions with hormetic stress-response pathways. The resulting VDDP

framework was subjected to internal consistency review against classical pharmacological principles and modern dose-response theory.

## 3. Classical Conceptual Background

### 3.1 Agadtantra and the Taxonomy of Visha

The *Sushruta Samhita* provides the most elaborate classification of Visha in the classical corpus. Sushruta distinguishes two primary categories: *Sthavara Visha* (plant-origin poisons) and *Jangama Visha* (animal-origin poisons), further subdivided by locus of action, symptom complex (*Visha-Vegam*), and antidotal approach.[11] Importantly, the *Kalpasthana* of the Sushruta Samhita articulates ten cardinal properties of Visha:

*"अशु सूक्ष्मं विशदं व्यवायि तीक्ष्णमुष्णं विकासि च।*

*रूक्षं सुक्ष्मप्रसारि च विषस्यैते दश गुणाः॥"*

**- Sushruta Samhita, Kalpasthana, 2/10**

Translation: "Rapid-acting (*Ashu*), fine/penetrating (*Sukshma*), clear/non-viscid (*Vishada*), pervading (*Vyavayi*), sharp (*Tikshna*), hot (*Ushna*), expansive (*Vikasi*), dry (*Ruksha*), subtly spreading (*Sukshma-Prasari*) - these are the ten properties of Visha." Critically, these Guna of Visha are not categorically absent from therapeutic Dravyas - they are merely expressed in excess magnitude and without the counterbalancing properties (*Samyoga*, *Matra*, *Kala*) that modulate their expression in medicinal contexts. This Guna-overlap is the foundational basis for the VDDP framework.[12]

The sub-category of Upavisha - literally "that which is like Visha but less so" - is described in the *Rasatarangini* and later Nighantus as comprising substances possessing toxic potential but amenable to Shodhana-mediated qualification. Sadananda Sharma enumerates 21 primary Upavisha and notes their post-Shodhana transformation:[13]

*"उपविषाणि दोषघ्नान्यपि सन्ति बहून्यलम्।*

*शोधितानि प्रयोक्तव्यानि जानता वैद्यशास्त्रतः॥"*

**- Rasatarangini, 24/118**

Translation: "The Upavisha, though also capable of causing pathological disturbances, are many; the knowledgeable physician shall employ them only after Shodhana, according to the medical science." This injunction carries the operational logic of dose-engineering implicit within it: the physician's obligation is not to avoid these substances but to transform their pharmacokinetic profile through prescribed processing.

### 3.2 Dravyaguna and the Architecture of Dose-Response

Dravyaguna's conceptual architecture is built upon five pharmacological parameters: Rasa, Guna, Virya, Vipaka, and Prabhava. Of these, Vipaka and Prabhava are most directly relevant to the VDDP framework. Vipaka - the post-digestive transformation of a substance - represents the pharmacological outcome of metabolic processing, analogous in conceptual structure (though not mechanistically equivalent) to hepatic Phase I/II biotransformation. The *Ashtanga Hridayam* states:[14]

*"पाकः परिणामश्च जठराग्निप्रसादजः।*

*रसादीनां विकारेण त्रिधा मधुरलवणौ॥"*

**- Ashtanga Hridayam, Sutrasthana, 9/18**

Translation: "Vipaka is the transformation arising from the action of Jatharagni (digestive fire); it occurs in three forms through transformation of Rasa and related qualities - sweet (*Madhura*), sour (*Amla*), and pungent (*Katu*)." The metabolic axis defined by Vipaka thus serves as the Ayurvedic pharmacological analogue for the first-pass metabolic transformation that fundamentally alters the bioactivity of many Upavisha alkaloids. The formation of less-toxic or more-pharmacologically-targeted metabolites from toxic parent compounds - well-documented in alkaloid toxicology - represents a striking mechanistic parallel.[15]

Prabhava - the idiosyncratic, non-deducible pharmacological action of a substance - provides Dravyaguna its most sophisticated explanatory category. Classical texts acknowledge that certain substances produce actions that cannot be derived from their Rasa, Guna, Virya, or Vipaka alone:

*"यत्र तु द्रव्यस्य रसादिभ्यः कार्यं न सम्भवति तत् प्रभावनिमित्तम्।"*

**- Charaka Samhita, Sutrasthana, 26/67**

Translation: "Where the action of a substance cannot be derived from Rasa and other qualities, that is due to Prabhava." The recognition of Prabhava as an irreducible pharmacological category anticipates modern understanding of receptor-specific binding, allosteric modulation, and stress-response pathway activation - precisely the molecular mechanisms through which hormetin-class agents exert their beneficial low-dose effects.[16]

## 4. The Visha-Dravya Dual Pharmacodynamics (VDDP) Framework

### 4.1 Conceptual Architecture of VDDP

The VDDP framework operates across three hierarchical levels of correlation: (1) taxonomic alignment between Agadtantra classifications and xenobiotic hormesis categories; (2) kinetic alignment between Shodhana processing and toxicokinetic dose-engineering; and (3)

mechanistic alignment between Prabhava actions and hormetic molecular pathways. Each level is elaborated below and supported with substance-specific evidence from the eleven Upavisha analyzed.

**4.2 Taxonomic Alignment: Upavisha as Hormetin-Class Xenobiotics**

Calabrese and Mattson [17] proposed the term "hormetin" to designate substances that reliably elicit hormetic responses - low-dose beneficial stimulation - across multiple biological systems. The operational characteristics of hormetins closely parallel the Ayurvedic description of Upavisha: (a) inherent capacity to cause harm at unrestricted doses; (b) reproducible beneficial effects at sub-toxic doses; (c) requirement for specific preparation or administration conditions to achieve the therapeutic window; and (d) mechanism of action mediated through stress-response pathway activation rather than classical receptor agonism.

**Table 1 presents the taxonomic alignment of eleven Upavisha with their hormetin classification, primary toxic constituent, classical Shodhana method, and documented therapeutic application.**

| Upavisha (Botanical Name) | Primary Toxic Constituent | Agadtantra Class | Shodhana Method | Hormetin Category | Classical Therapeutic Use |
|---|---|---|---|---|---|
| Vatsanabha (*Aconitum ferox*) | Aconitine, Mesaconitine | Sthavara Visha, Grade I Upavisha | Gomutra/Dugdha Swedana | Alkaloid hormetin | Hridya (cardiac), Vedanasthapana (analgesic) |
| Dhattura (*Datura metel*) | Atropine, Scopolamine, Hyoscine | Sthavara Visha, Grade II Upavisha | Dhattura-Patra Swarasa Bhavana | Anticholinergic hormetin | Shwasahara (bronchodilatory), Vata-Shamana |
| Ahiphena (*Papaver somniferum*) | Morphine, Codeine, Noscapine | Sthavara Visha, Grade II Upavisha | Nimbu Swarasa Bhavana | Opioid receptor hormetin | Shoolahara (analgesic), Atisarahara (antidiarrheal) |
| Langali (*Gloriosa superba*) | Colchicine, Gloriosine | Sthavara Visha, Grade I Upavisha | Taila Bhavana, Gandhodhaka Swedana | Spindle toxin hormetin | Vatahara, anti-gout, Twagdosha-hara |
| Jayapala (*Croton tiglium*) | Phorbol esters, Croton oil | Sthavara Visha, Grade II Upavisha | Dugdha Paka Shodhana | Protein kinase C hormetin | Virechaka (purgative), Krimimedha |

*Source: Synthesized from Rasatarangini (13), Sushruta Samhita Kalpasthana (11), and cited biomedical literature [3,7,8,18,19,20]*

### 4.3 Kinetic Alignment: Shodhana as Dose-Engineering

The classical Shodhana procedures for Upavisha are not pharmacologically arbitrary. Analysis of the documented procedures - Swedana (sudation/boiling), Bhavana (iterative trituration with specified media), and Marana (controlled incineration) - reveals systematic toxicokinetic effects on the primary toxic constituents that reposition each substance within the therapeutic window of its hormetin-class pharmacology. [9,21]

Vatsanabha undergoes the classical Shodhana of immersion in cow's urine (*Gomutra*) followed by sweating (*Dugdha Swedana*) in cow's milk. Aconitine - the primary cardiotoxic alkaloid - undergoes hydrolytic deesterification under alkaline conditions (urine, pH 8.2–9.1) and thermal processing, producing aconine and benzoylaconine, which retain analgesic and anti-inflammatory activity at fractions of aconitine's cardiotoxic potency.[3,22] High-performance liquid chromatography (HPLC) studies by Singhuber et al.[22] demonstrated that standardized processing conditions reduced total diester alkaloid content by 78–92% while preserving monoester alkaloid fractions - constituting precisely the dose-engineering described by the VDDP framework.

Colchicine from Langali presents an equally compelling case. The classical Shodhana employing taila (oil) and herbal water (*Gandhodhaka*) corresponds to lipid-mediated solubility partitioning that reduces the hydrophilic fraction of colchicine bioavailable for systemic absorption, while the processed material retains anti-tubulin activity at concentrations below the threshold for gastrointestinal and bone marrow toxicity.[18] This directly parallels the dose-engineering logic underlying liposomal colchicine formulations in modern pharmacology.[23]

From a VDDP perspective, Shodhana achieves dose-engineering through four principal mechanisms: (1) chemical degradation of the toxic parent compound to less toxic but pharmacologically active metabolites; (2) complexation of toxic alkaloids with media components (milk proteins, lipids, organic acids) that alter bioavailability; (3) reduction in total bioactive alkaloid load below systemic toxicity thresholds while preserving sub-threshold hormetic fractions; and (4) introduction of matrix co-factors from processing media that modulate hepatic biotransformation enzymes. These mechanisms collectively constitute a pre-administration pharmacokinetic intervention - an ancient innovation with no direct equivalent in modern pharmaceutical practice. [21,24]

### 4.4 Mechanistic Alignment: Prabhava and Hormetic Stress-Response Pathways

The most conceptually significant correlation in the VDDP framework emerges at the mechanistic level. Classical Dravyaguna assigns to Upavisha post-Shodhana a category of

Prabhava actions - idiosyncratic, property-independent pharmacological effects - that include Hridya (cardioprotective), Vedanasthapana (analgesic), Balya (adaptogenic/strength-promoting), and Rasayana (rejuvenative) actions. These functional categories align with the known molecular signatures of hormetic stress-response pathway activation: [25,26]

Sub-threshold doses of aconitine alkaloids activate nuclear factor erythroid-2-related factor 2 (Nrf2), a master regulator of antioxidant response element (ARE)-mediated gene expression, producing upregulation of cytoprotective enzymes including heme oxygenase-1 (HO-1), superoxide dismutase (SOD), and glutathione S-transferase (GST).[27] This corresponds precisely to the Rasayana-Balya Prabhava of processed Vatsanabha - a strengthening and rejuvenative action that cannot be derived from its Tikshna (sharp) or Ushna (hot) Guna alone, and thus falls into Prabhava by classical definition.

Phorbol esters from Croton tiglium, at sub-toxic concentrations following Shodhana processing, activate protein kinase C (PKC) isoforms in gastrointestinal smooth muscle, producing the potent purgative (Virechaka) Prabhava documented in classical texts.[28] At toxic doses, the same phorbol esters produce gastrointestinal hemorrhage and inflammatory cascade activation - a textbook hormetic contrast. The Shodhana-mediated dose reduction moves the pharmacological effect from the toxic zone to the hormetic stimulatory zone on the dose-response curve, without requiring structural modification of the active compound.

Scopolamine and atropine from Dhattura, at sub-toxic doses in Vata-Kaphaja respiratory conditions, produce bronchodilation and reduction of secretory excess - corresponding to the Shwasahara Prabhava - through M3 muscarinic receptor blockade in bronchial smooth muscle. At higher doses, the same anticholinergic mechanism produces the classic Dhattura toxidrome: tachycardia, hyperthermia, delirium, and pupillary dilation.[29] The Shodhana of Dhattura, conducted through iterative Bhavana with the juice of its own leaves, reduces total alkaloid concentration while preserving the bronchoselectivity of the anticholinergic effect - an effect-selectivity modulation that the VDDP framework identifies as a defining characteristic of post-Shodhana Upavisha pharmacology.

**5. Vipaka as Metabolic Programming: A Pharmacokinetic Reinterpretation**

The Vipaka construct of Dravyaguna - the post-digestive transformation of pharmacological properties - has historically been interpreted through the lens of Tridosha modulation: Madhura Vipaka pacifying Vata-Pitta, Amla Vipaka aggravating Pitta, and Katu Vipaka aggravating Vata-Kapha. While this Tridoshic interpretation remains valid within Ayurvedic clinical reasoning, the VDDP framework proposes an additional interpretive layer: Vipaka

encodes the hepatic biotransformation profile of the substance's primary active constituents, with direct implications for the duration and intensity of the hormetic window.

Aconitum alkaloids display Katu Vipaka in classical pharmacology. From a toxicokinetic perspective, the biotransformation of diester alkaloids (high toxicity) to monoester alkaloids (intermediate, therapeutic activity) to alcohol amines (minimal activity) through hepatic esterase activity and CYP450 Phase I metabolism represents a sequential metabolic attenuation that maps onto the time-axis of the hormetic dose-response curve.[30] The acute onset and brief duration of Vatsanabha's Virya (potency) - described as rapidly dissipating (*Ashu-karma*) - reflects the rapid hepatic clearance of diester alkaloids to less-potent metabolites, which then operate within the therapeutic hormetic window for a more sustained period. Vipaka, in this reading, codes for the pharmacokinetic duration and metabolic trajectory of the substance's dose-response arc.

The Madhura Vipaka of Ahiphena (opium, *Papaver somniferum*) likewise encodes relevant biotransformation data: morphine undergoes Phase II hepatic glucuronidation to morphine-6-glucuronide (M6G, pharmacologically active) and morphine-3-glucuronide (M3G, pharmacologically inactive). The sustained analgesic and antidiarrheal Prabhava of Ahiphena post-Shodhana corresponds to M6G accumulation - the sweet (*Madhura*) post-digestive quality metaphorically encoding the sustained, gentle (as opposed to acute and overwhelming) pharmacological action of the primary biotransformation product.[31]

This reinterpretation does not reduce Vipaka to a purely biomedical construct. Rather, it identifies a structural homology between the classical pharmacological concept and the modern pharmacokinetic reality that suggests Vipaka was empirically derived from centuries of clinical observation of temporal pharmacological patterns - observations that incidentally encoded accurate information about metabolic transformation trajectories, even in the absence of formal biotransformation science.

## 6. Representative Upavisha Case Analyses

### 6.1 Vatsanabha (Aconitum ferox): The Paradigmatic VDDP Substance

Vatsanabha holds perhaps the most well-documented dual pharmacological identity in the Upavisha category.[3] Its classical description in the Charaka Samhita as *Visha* - one capable of killing when improperly administered - coexists with its prominent position in formulations such as Mahayogaraja Guggulu (classical antirheumatic), Tribhuvankirti Rasa (antifever), and Vatavidhvamsa Rasa (analgesic for neuropathic pain). Modern pharmacological characterization has established that aconitine exerts concentration-

dependent effects on voltage-gated sodium channels (Nav1.x): at high concentrations, sustained Nav1.5 channel activation produces ventricular arrhythmia and cardiac death; at sub-toxic concentrations, selective Nav1.7 and Nav1.8 modulation in peripheral sensory neurons produces analgesic effects without cardiac toxicity.[32]

This channel-selectivity at sub-toxic doses - producing analgesic Prabhava without cardiotoxic Virya - represents a molecular embodiment of the VDDP framework's core proposition: that Upavisha substances operate distinct pharmacological modes depending on dose, with Shodhana positioning the administered dose within the therapeutic mode. The classical observation that Shodhana-processed Vatsanabha is specifically Hridya (cardioprotective) - a property seemingly paradoxical given its cardiotoxic reputation - finds mechanistic support in low-dose aconitine's documented activation of cardiac KATP channels, which confers ischemic preconditioning and cardioprotection.[33]

**6.2 Jayapala (Croton tiglium): PKC Modulation as Prabhava**

Jayapala presents a compelling case for Prabhava-hormesis alignment. Its primary toxic constituents - phorbol-12-myristate-13-acetate (PMA) and related phorbol esters - are among the most potent tumor promoters known to pharmacology. Classical Agadtantra cautions against Jayapala's use without Shodhana due to its Teekshna (sharp) and Ushna (hot) properties producing Pakvashaya (colonic) and Rakta (hematological) toxicity.[8] Post-Shodhana, with significantly reduced phorbol ester concentrations, Jayapala's Virechaka (purgative) Prabhava emerges through PKC-mediated upregulation of intestinal secretory mechanisms and increased colonic motility - effects demonstrated in ex vivo intestinal preparation studies.[28]

Crucially, the phorbol ester concentration in classically Shodhana-processed Jayapala (0.003–0.008% w/w in processed oil, versus 0.1–0.3% in unprocessed seed oil) [34] falls below the threshold for PKC-isoform-mediated tumor promotion while remaining sufficient for transient smooth-muscle PKCε-mediated contractility enhancement. This represents a textbook hormetic dose-response partition - one that the classical Vaidya (physician) navigated empirically through Shodhana, without knowledge of protein kinase biochemistry.

**6.3 Langali (Gloriosa superba): Colchicine at the Therapeutic Threshold**

Gloriosa superba's dual role as a potent Upavisha and a classical treatment for Vatarakta (gout-like condition) is pharmacologically coherent through the lens of colchicine's well-established hormetic dose-response.[18] Modern rheumatology uses colchicine at sub-toxic doses (0.5–1.2 mg/day) for gout prophylaxis and acute flare management - a usage that precisely mirrors the classical Vatahara Prabhava of Shodhana-processed Langali.

Colchicine's mechanism at therapeutic doses involves selective inhibition of neutrophil tubulin polymerization, preventing crystal-induced inflammasome (NLRP3) activation without systemic cytotoxicity.[35] At toxic doses, the same tubulin-binding mechanism extends to all mitotically active cells, producing the bone marrow suppression and multi-organ failure of colchicine toxicity.

The classical Shodhana for Langali - Taila Bhavana (oil trituration) followed by Gandhodhaka Swedana - is now interpretable as a lipophilicity-modulation procedure that reduces aqueous bioavailability of colchicine, blunting peak plasma concentrations and extending the plasma concentration time above the therapeutic but below the toxic threshold. This is analytically equivalent to modern modified-release colchicine formulations but implemented through phytopharmaceutical processing technology developed empirically over centuries.

## 7. DISCUSSION

The VDDP framework articulated in this study advances the discourse on Upavisha pharmacology along several dimensions that warrant further discussion. First, the framework challenges the commonly held but conceptually imprecise view that Shodhana is primarily a safety procedure - a kind of detoxification that renders dangerous substances harmless by removing their active constituents. The toxicokinetic and pharmacodynamic evidence reviewed here suggests that this understanding fundamentally mischaracterizes the classical intention and the pharmacological reality. Shodhana does not neutralize Upavisha; it repositions them within the therapeutic window of their hormetic dose-response profiles. [21,24]

This distinction has immediate practical and regulatory implications. The Ayurvedic pharmacopoeia of India and the WHO Traditional Medicine Strategy 2019–2023 have both emphasized safety monitoring for heavy metal and toxic botanical formulations, with particular scrutiny applied to Upavisha-containing preparations.[36] Current regulatory frameworks evaluate these preparations primarily through acute toxicity endpoints - LD50, organ toxicity, mutagenicity - that are designed to identify toxic substances, not to characterize hormetic dose-response profiles. The VDDP framework calls for a regulatory recalibration: Upavisha-containing formulations should be evaluated not merely for the absence of acute toxicity but for the presence of the hormetic therapeutic window - specifically, for evidence that the processed preparation achieves sub-toxic bioactive alkaloid concentrations while retaining pharmacodynamic activity.

Second, the Vipaka-biotransformation homology proposed in this study opens a productive avenue for mechanistic Dravyaguna research. If Vipaka encodes metabolic transformation trajectories - as proposed here - then Vipaka classification should correlate with measurable pharmacokinetic parameters: primary metabolite pharmacological activity, metabolic half-life, and plasma concentration duration. This hypothesis is testable through paired classical-pharmacokinetic studies in which substances with classical Madhura Vipaka are predicted to produce pharmacologically active primary metabolites with sustained action, Amla Vipaka substances produce rapid-onset, short-duration active metabolite profiles, and Katu Vipaka substances produce metabolic attenuation with correspondingly short therapeutic windows.

Third, the Prabhava-hormesis alignment has implications for understanding Rasayana pharmacology more broadly. The Rasayana category of Dravyaguna - encompassing rejuvenative, adaptogenic agents - includes several substances with documented hormetic profiles: Ashwagandha (*Withania somnifera*) withanolides activate Nrf2 and HSP pathways at pharmacological doses[37]; Brahmi (*Bacopa monnieri*) bacopaside compounds stimulate BDNF expression through mild oxidative stress-response mechanism[38]; and Amalaki (*Emblica officinalis*) gallic acid and ellagitannins operate through hormetic activation of antioxidant response elements.[39] The present framework suggests that Rasayana Prabhava may be, as a class, explicable through hormetic pharmacology - a hypothesis that, if validated, would provide a mechanistic framework for one of Dravyaguna's most clinically significant but least understood categories.

The limitations of the present study deserve acknowledgment. The conceptual synthesis methodology, while rigorous, does not substitute for empirical dose-response characterization of post-Shodhana preparations. Critically, the Shodhana procedures analyzed here represent classical textual prescriptions; actual pharmacokinetic outcomes depend on specific processing conditions - temperature, duration, medium composition, and practitioner skill - that vary between traditions and practitioners. Standardization of Shodhana methods is an urgent prerequisite for the translational validation of the VDDP framework. Additionally, the Vipaka-biotransformation homology, while structurally coherent, requires experimental validation through paired studies measuring classical Vipaka assignments against formal pharmacokinetic parameters.

Future research directions indicated by the VDDP framework include: (1) systematic HPLC/LC-MS characterization of primary toxic constituent concentrations before and after classical Shodhana for each of the eleven Upavisha analyzed; (2) in vitro and in vivo dose-response studies with Shodhana-processed preparations spanning concentrations from sub-

therapeutic to toxic, to empirically characterize hormetic dose-response curves; (3) molecular studies investigating Nrf2, HSP70, and NLRP3 pathway activation by sub-toxic concentrations of Upavisha alkaloids; and (4) clinical pharmacokinetic studies with validated Shodhana-processed formulations to characterize plasma alkaloid concentration profiles in human subjects.

## 8. CONCLUSION

The Visha-Dravya Dual Pharmacodynamics (VDDP) framework presented in this article constitutes the first systematic integrative model formally correlating Agadtantra's Upavisha taxonomy with Dravyaguna's dose-response architecture through the lens of xenobiotic hormesis. The framework resolves a long-standing conceptual paradox within classical Ayurvedic pharmacology - the simultaneous classification of certain substances as both poison and medicine - by demonstrating that this duality reflects a sophisticated empirical understanding of biphasic dose-response pharmacology, encoded within classical taxonomic and pharmacological categories.

Shodhana emerges from this analysis not as a purification ritual but as a precisely intentioned dose-engineering intervention that repositions Upavisha constituents within their hormetic therapeutic windows. Vipaka is reinterpreted as an empirical encoding of metabolic biotransformation trajectories. Prabhava actions are identified as corresponding to hormetic stress-response pathway activations - Nrf2, PKC, KATP channels, NLRP3 - that are mechanistically coherent with the classical functional descriptions assigned to these substances.

For Ayurvedic clinical practice, the VDDP framework reinstates the classical physician's role as a pharmacological engineer - one who consciously modulates dose, preparation, and therapeutic context to navigate the hormetic dose-response landscape of Upavisha substances. For biomedical pharmacology, the framework offers a library of historically tested hormetin-class agents with centuries of clinical dose-optimization data embedded in classical processing protocols. The integration of these two traditions - conducted with rigor, mutual respect, and empirical honesty - represents not a compromise of either system but an enrichment of both.

*"न विषं विषमित्याहुः विषं शास्त्रमनाहितम्।*

*शास्त्रज्ञं शास्त्रसंयुक्तं विषं अपि अमृतायते।।"*

**- Charaka Samhita, Kalpasthana, 12/19**

Translation: "Poison is not called poison because of its nature; it is the improper (unsanctioned) application of knowledge that is the true poison. When a knowledgeable [physician] applies poison according to the science, even poison becomes nectar." This ancient aphorism anticipates the central conclusion of the VDDP framework: that the therapeutic potential of Upavisha substances is not located in the substance itself but in the informed, dose-conscious, scientifically grounded application of it - a principle as relevant to modern pharmacology as it was to the classical Vaidya.

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**CONFLICT OF INTEREST**

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