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Review Article

A Review on Synergy of Visha-Upavisha through its ADME Profiling and Pharmacological Validation

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ABSTRACT

Ayurveda, with its profound pharmaco-toxicological wisdom, describes *Visha* and *Upavisha* as potent substances that, despite their inherent toxicity, possess significant therapeutic potential when subjected to proper purification and formulation protocols. In recent years, the integration of traditional knowledge with modern biomedical science has enabled a renewed evaluation of these agents through ADME (Absorption, Distribution, Metabolism, and Excretion) profiling and pharmacological validation. This review highlights the emerging scientific understanding of these substances, focusing on their synergistic roles when combined with other herbs or minerals. It underscores the critical importance of detoxification processes in reducing toxicity and enhancing pharmacological efficacy, particularly by influencing the ADME characteristics of these compounds. Recent pharmacological studies employing advanced analytical techniques such as LC-MS/MS, molecular docking, and in vitro cytotoxicity assays validate their roles in diverse therapeutic domains, including immunomodulation, anticancer activity, antimicrobial effects, and inflammatory disorders. This work primarily aims to elucidate how inherently toxic drugs (*Visadravyas, Rasaoushadhis*), after undergoing accurate purification can act along with Herbal drugs (*Kasthoushadhi*) specifically on targeted sites to deliver desired therapeutic outcomes through their active constituents. Moreover, it emphasizes the judicious use of these drugs, advocating for strict adherence to traditional detoxification and dosing protocols to maximize benefits while minimizing risks, thereby ensuring their safe and effective incorporation into contemporary integrative medicine.

Keywords: *Visha-Upavisha*, Pharmaceutical validation, Therapeutic application, ADME Profiling.

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INTRODUCTION

In the realm of Ayurvedic pharmaceutics, *Visha* (poisonous substances) and *Upavisha* (semi-poisonous substances) hold a paradoxical yet critical position revered not merely as toxic agents but as powerful therapeutic tools when processed correctly. Classical texts elaborate extensively on their purification (*Shodhana*) and controlled therapeutic applications. In recent years, modern pharmacological science has shown renewed interest in these substances, especially in light of advanced analytical tools such as ADME profiling (Absorption, Distribution, Metabolism, and Excretion), which help elucidate their behavior within biological systems. Contemporary research underscores the concept of synergy in traditional formulations the idea that combinations of herbs, including *Visha-Upavisha* components, may exert enhanced therapeutic effects or reduced toxicity compared to isolated constituents. Through integrative pharmacology, scientists are beginning to map the mechanistic pathways of these substances, bridging traditional knowledge with molecular-level understanding. Modern tools such as in silico docking, LC-MS/MS, and pharmacokinetic modeling are increasingly employed to validate their therapeutic potential, especially in chronic inflammatory conditions, cancer, pain management, and antimicrobial resistance. By revisiting these potent agents through the lens of ADME science and pharmacological validation, this review aims to highlight the modern rationale behind ancient wisdom, focusing on the therapeutic synergy of *Visha-Upavisha* and the safety frameworks required for their responsible use.

METHODOLOGY

The data for the review has been gathered from the classical *Ayurveda* texts of *Charaka Samhita, Sushruta Samhita, Ashtanga Hridayam, Ashtanga Sangraha; Nighantus* (lexicons), and the Ayurvedic Formulary of India (AFI). Additional references from *Rasatarangini, Rasaratna Samuccaya*, *Rasa Hridaya Tantra*, and other Rasasastra literature were used to understand various formulations which involved *Visha-Upavisha* along with certain *Kastoushadhi* (herbal *churna*), its dosage, *Anupana* and their respective *Roga Avastha* (Table 1). The contemporary

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and pharmacological review has been dealt from textbooks of forensic and toxicological texts along with biomedical medicine and the peer reviewed scientific research journals available on Google Scholar, PubMed, Elsevier, Scopus, and alike relevant databases using keywords like Visha-Upavisha AND Ayurveda, Pharmacological chemistry AND Biological activities, Phytochemical AND Therapeutic actions. Further, each Visha-Upavisha in the formulations were evaluated to known and understand the active constituents and their Characteristic actions in treating the conditions by synergism. As the study is based exclusively on textual and literature-based sources, involving no direct human or animal experimentation, ethical approval was not applicable.

RESULTS

Table 1: Showing the formulations of *visa-upavisa* along with its *Bhavana Dravya*, Dosage, *Anupana* and Indications.

Formulation	Ingredients	Bhavana dravya	Dosage	Anupana	Indications
Pancamrta rasa	Shuddha Vatsanabha Shuddha Parada Shuddha Gandhaka Maricha Churna Shuddha Tankana.	Jala	1 Ratti (125mg)	*Punarnava swarasa* *Ardraka swarasa.*	All types of Shirasula All types of Shotha Pinasa Galagraha Nasika roga Kantha roga Kaphaja roga.
Amrta rasayana	Shuddha Vatsanabha Kantaloha Bhasma Abhraka Bhasma Swarna-makshika Bhasma Swarna sindura Rajata Bhasma Vanga Bhasma Khadira sara Shunth churna.	Ghrtakumari swarasa	2 Ratti (250 mgs)	*Ghrita* *Sarkara* *Madhu.*	Deepana Brmhana Bala vruddhi karaka Kasa Shwasa Ksaya roga Atisara Grahani Agnimandya Rakta vikrutijanya Twak roga Kustha roga Oja vruddhikaraka Dharana & Smarana shakti Vrushya.
Hinguleshwara rasa	Shuddha Vatsanabha Pippali Churna.	Jala	½ Ratti (62 mg)	-	Amavata Teevra, vatika and Nava Jwara.
Jaya vati	Shuddha Vatsanabha Haridra Churna Shunthi Churna Maricha Churna Pippali Churna Vidanga Churna Nimbatwak Churna Musta churna Jayatimula Churna.	Jala	2 Ratti (250 mg)	*Rakta chandana Kashaya* *Balamula Kasaya* *Musta, Indra yava & Shunthi Kasaya* *Parpata Kashaya.*	Raktapitta Suryavarta, Ardhavabhedaka Grahani roga Pittaja Jwara.
Kaphaketu rasa	Shuddha Vatsanabha Pippali Churna Shuddha Tankana Shankha Bhasma.	Ardraka swarasa	½ Ratti (62 mg)	*Ardraka Swarasa* *Madhu.*	Kasa Gala Vikara Pratamaka Shwasa Pratishyaya (Vataja & Kapahaja) Nava Jwara.

Visaprabha vartika	Shuddha vatsanabha Shuddha Manashila Shankha Churna Samudraphena Saidhava lavana Pippali Churna Haritaki Churna Lodhra CHurna Haridra Churna Karanja Beeja Majja Vrukshamala Maricha Churna Manjistha Churna Rakta Chandana Churna.	Aja Dugdha	Used in Varti (wick) form as Anjana.	-	Netra Shukla Netra Mamsa Netra Arma Netra pilla roga.
Anandabhairava rasa	Shuddha Vatsanabha Pippali Churna Maricha Churna Shuddha Tankana Shuddha Hingula.	Jala	½ Ratti (62 mg)	-	Pravahika Puyameha Jwaratisara Ajirna sula Kapha-vataja Pravahika Atisara due to teevra Jwara.
Sivatandava rasa	Shuddha vatsanabha Rasa Sindura Shuddha Haratala Shuddha parada Maricha Churna.	Jala	1 Ratti (125 mg)	-	Sannipataja Jwara.
Visa (vatsanabha) rasayana	Shuddha Vatsanabha Rasa-sindura Shuddha Hingula Rajata Bhasma Tamra Bhasma Shunthi Churna Maricha Churna Pippali Churna Twak Churna Ela Churna Tejapatra Churna Nagakesara Churna Chitraka mula Churna.	Jala	2 Ratti (250 mgs)	-	Vrushya Varnya Attains Divya dristhi & Girgha kaya Yakrit - Pleeha Roga Adhmana Udara sula Anaha Ajirna.
Navajivana rasa	Shuddha Kucala Churna Loha Bhasma Rasa-sindura Shunthi churna Maricha churna Pippali churna.	Ardraka swarasa	1 Ratti (125 mg)	-	Udara shola Deepana-Pachana Adhmana Vibandha Atisara Ardhavabhedaka Manasika srama.

Agnitundi vati	Shuddha vatsanabha Shweta jeeraka Haritaki Bibhitaki Amalaki Shuddha Parada Shuddha Gandhaka Vidanga Churna Sauvarcala lavana Samudra lavana Shuddha Tankana Saindhava Lavana Sarja kshara Yava Kshara Citraka mula Ajamoda churna Shuddha kupilu.	Jambira Nimbu Swarasa	2 Ratti (250 mg)	*Ushna jala* *Nimbu swarasa*	Deepana-Pachana Agnimandya Arsha roga Atisara Kati sula.
Laksmivilasa rasa	Shuddha kucala churna Shuddha Tankana Maricha churna Loha Bhasma Shuddha Gandhaka Shuddha Parada	Ardraka Swarasa, Satavari Swarasa, Bhumyamalaki Swarasa & Bhringaraja Swarasa	1 Ratti (125 mg)		Bala-Varna karaka Kshina retas Vrushya Durbalata Agnimandya Rakta sanjanana
Sulanirmulana rasa	Shunthi churna Maricha churna Pippali churna Shuddha Gandhaka Shankha Bhasma Saidhava Lavana Rasa-sindura Jeeraka Churna Amlavetasa churna Shuddha kucala churna.	Ardraka Swarasa.	1 Ratti (125 mg)		Deepana-Pachana Agnimandya Atisara Grahani Visuchika Bala-varna karaka Vrushya Gulma Udara sula.
Suptivatari rasa	Shuddha kucala churna Samagandhaka kajjali Trayushana (Shunthi, Maricha, Pippali).	Nirgundi Swarasa, Palasa bija kasaya.	2 Ratti (250 mg)		Supta vata
Sarameyavisahara yoga	Shuddha Vishatinduka.	-	-	-	Kukkuravisha (Rabies Dog Bite).
Visatinduka taila	Shuddha kucala beeja Tila Taila Jala.	-	External Application	-	Vatavyadhi (Pakshagata).
Vedanantaka rasa	Shuddha Ahiphena Yamani Ghanasara Rasa-sindura.	Vijaya (Bhanga) patra Swarasa.	2 Ratti (250 mg)	-	Vedana nashaka.
Nidrodaya rasa	Shuddha Ahiphena Vamsa locana churna Rasa-sindura Amalaki churna.	Vijaya (Bhanga) patra Swarasa.	2 Ratti (250 mg)	-	Sukha swapna karaka.

Sindurabhusana rasa	Shuddha Ahiphena Swarna Bhasma Karpura Rasa-sindura Sukshma ela churna Vamsalocana churna.	Musta Kwatha	2 Ratti (250 mg)	-	Atisara
Harsodaya vati	Shuddha Ahiphena Kasturi churna Karpura Maricha Churna Rasa-sindura Jatiphala churna Javitri churna Kesara churna Shuddha Hingula churna.	Vijaya (Bhanga) patra Swarasa	2 Ratti (250 mg)	*Nagavalli patra* (Betal leaves) During administration of this formulation Rogi has to intake Mahisha dugdha along with cream Madhura rasa ahara to be taken which are prepared out of masha.	Bala-Varna karaka Virya sthambana Jeerna shakti prada.
Ahiphenasava	Shuddha Ahiphena Mrtasanjivani sura.	-	5 to 15 drops is general dosage.	Jala	Karna sula Danta sula Asthi-Bhagna ruja Asthi chyuti Aneka Vedana shamaka Atisara Visuchika.
Mangalodaya vati	Shuddha Ahiphena Karpura.	Jala	1 Ratti (125mg)	-	Sannipataja Jwara Anidra.
Vedanantaka malahara	Siktha Taila Shuddha Ahiphena Sindura.	-	External Application	-	Vedana shamaka Guda ankura
Jalodarari rasa	Tamra Bhasma Pippali churna Shuddha Parada Shuddha Gandhaka Maricha churna Haridra churna Shuddha Jayapala.	Trivrt Kwatha	1 - 2 Ratti (125 -250 mg)	Jala	Jalodara Roga
Jwarari rasa	Shuddha Hingula Pippali churna Shunthi Churna Maricha churna Shuddha Tankana Shuddha Vatsanabha Amalaki churna Shuddha Jayapala.	Ardraka Swarasa	1 Ratti (125 mg)	-	Nava jwara
Anjanabhairava rasa	Shuddha parada Shuddha Gandhaka Pippali churna Shuddha Tankana Shuddha Jayapala.	Nimbu Swarasa	External application as Anjana.	-	Sannipataja Jwara

Vrscikavisahara pralepa	Shuddha Jayapala.	Jala	External application as Pralepa.	-	Vrscika damsa vat Vedana.
Pralapantaka rasa	Shuddha Dhattura beeja churna Shuddha parada Shuddha Gandhaka Trikatu churna Shuddha Tankana.	Nimbu Swarasa	1 Ratti (125 mg)	-	Deepana-Pachana Agnimandya Roga.
Unmadagajankusa rasa	Shuddha Dhattura beeja churna Shuddha Parada Shuddha Gandhaka Vanga Bhasma Rajata Bhasma.	Kumari Swarasa	1 Ratti (125 mg)	-	Unmada All type of jwara.
Granthosotha-nivarika varti	Dhattura phala Kucala beeja Krishna jiraka churna Kumari ghana Mocarasa.	Snuhi patra swarasa	External application in the form of wick	-	Granthi sotha
Madanodaya modaka	Javitri churna Jatiphala churna Jatamamsi churna Lavanga churna Karpura churna Kumkum kesara Sukshma ela churna Twak churna Shunthi churna Maricha churna Pippali churna Vanga Bhasma Abhraka Bhasma Loha Bhasma Rasasindura Satavari churna Gokshura churna Draksa kalka Karkatasrngi churna Balamula churna Kapikachu beeja churna Kustha churna Viddhadaru bija churna Shuddha vijaya Sarkara.	Jala	1 modaka = 12 gm	Dugdha+ sarkara+ ela churna.	Brmhana Kama uttejaka (Good for sexual vigour & virility).
Trailokyavijaya vati	Vijaya satva Vamsalocana churna.	Jala	1 Ratti (125 mg)	-	Pralapa Unmada Vrkka sotha Sula Rajayakshma Swapna dosha Atisara roga.

Trailokya-sammohana rasa	Shuddha Vijaya Shuddha Hingula Rasa-sindura Karpura Lavanga churna Abhraka Bhasma Gokshura beeja churna Kapikacchu bija churna Karkatasrngi churna.	Bhanga swarasa, Satavari Swarasa	1 vati (375 mg)	-	Klaibya Harshotsaha karaka Dhruti-Smriti karaka
Gunjadya taila (prathama)	Shuddha gunja beeja kalka Tila Taila Bhringaraja patra swarasa.	-	External Application.	-	Kandu Kustha Darunaka All types of Vataja sula.
Gunjadya taila (dwitiya)	Shuddha gunja beeja kalka Shuddha gunja mula kalka Tila Taila Jala.	-	External Application	-	Gandamala (Reduces pain & inflammation) Gunja leaves are triturated with required quantity of Eranda taila, tied in a cloth and tied on effected area as poultice for various kinds of ruja & sotha Taila paka with 4parts of Gunja patra swarasa & 1part tila taila used for abhyanga Wet/Dry Gunja chewed daily which is helpful in swarabheda.
Gunjajivana rasa	Shuddha gunja beeja Rasa-sindura Shuddha vijaya patra.	Jala	2 Ratti (250mgs) For administration 1 Ratti pill (125mg) is used.		Balakaraka Madanodeepana (Sexual desire).
Gunjabhadra rasa	Shuddha gunja beeja curna Jayanthi Nimba beeja majja Shuddha parada Shuddha gandhaka.	Kakamachi swarasa, Jaya Swarasa, Dhattura patra swarasa, Nimbu swarasa.	2 Ratti (250 mgs)		Urusthambha roga.
Bhallataka rasayana	Shunthi churna Vidanga churna Loha Bhasma Shuddha bhallataka.	-	1 - 3 Ratti (125-375 mgs).	*Madhu* *Ghrita*	Rakta vruddhikaraka Balavardhaka Navayouvana Lavanya janana shakti yukta Rasayana
Karaviradya taila	Karavira twak kwatha Tila taila Vidanga kalka Chitrakamula kalka Gomutra.	-	External Application.	-	Kushtha Roga (Skin Ailments).
Kshara vartika	Daruharidra Snuhi kshara Arka kshara.	-	External Application in the form of Varti (wick).	-	Bhagandara Nadivrana.

Kshara- sutra	Snuhi kshara Haridra curna.	-	External Application in the form of Sutra (Thread).	-	Arsha Bhagandara.

DISCUSSION

Contemporary Pharmacological Insights on ADME of *VATSANABHA* (Aconitum ferox Wall.)

Modern pharmacology (Pharmacodynamics & Pharmacokinetics) approaches *Vatsanabha* primarily through the lens of its active principle, aconitine, a potent neurotoxin and cardiotoxin. Aconitine interacts with voltage-gated sodium channels, causing prolonged depolarization of nerve and muscle tissues, leading to symptoms like paresthesia, bradycardia, hypotension, or even fatal arrhythmias in high doses. The ADME characteristics of aconitine are crucial for understanding both its therapeutic and toxicological effects (Sun *et al*., 2009).

Absorption

Aconitine is rapidly absorbed from the gastrointestinal tract following oral administration. Because it is lipophilic in nature, it enters the systemic circulation quickly and has a high bioavailability. However, toxicity emerges quickly as a result of incorrect processing or overdosing.

Distribution

After absorption, aconitine is widely distributed throughout the bloodstream, particularly accumulating in well-perfused organs such as the liver, kidneys, heart, and brain. It crosses the Blood-Brain Barrier (BBB), which explains its impact on the central nervous system (Mi *et al*., 2021; Tao *et al*., 2021; Yang *et al*., 2013).

Metabolism

Aconitine gets processed extensively in the hepatocytes, mostly by cytochrome P450 enzyme-mediated hydrolysis and demethylation activities. However, metabolism diminishes toxicity, it can still result in active metabolites, which is why adequate dosage and monitoring are critical (He, *et al* 2019).

Excretion

Aconitine and its metabolites are primarily excreted via the renal route (urine), with very minimal amount of it gets excreted in bile. The elimination half-life of aconitine varies but is generally between 3 to 10 hr, depending on liver and kidney function (Gao *et al*., 2022; Qasem et al., 2022).

Contemporary Pharmacological Insights on ADME of *VISHATINDUKA* (*Strychnos nux-vomica* L.)

Strychnine and brucine are the two main alkaloids found in *Strychnos nux-vomica*, based on contemporary pharmacological (pharmacodynamics & pharmacokinetics) research. These stimulants of the Central Nervous System (CNS) have a confined therapeutic potential. Strychnine is well known for its potent actions as a spinal cord glycine receptor antagonist, which cause uncontrolled excitatory neurotransmission and cause muscle spasms and convulsions.

Absorption

After oral consumption, strychnine is quickly absorbed from the gastrointestinal tract. Typically, peak plasma concentrations happen in one to 2 hr. Its permeability via biological membranes is facilitated by its high lipid solubility (Xiang *et al*., 2023; Chen *et al*., 2014).

Distribution

Following absorption, strychnine efficiently penetrates the blood-brain barrier and circulates freely throughout the body, including the central nervous system. Additionally, it accumulates up in organs such as the kidneys, spleen, and liver (Patel *et al*., 2017).

Metabolism

The cytochrome P450 enzyme system is principally responsible for the demethylation that occurs during strychnine's hepatic metabolism. In general, metabolites are less harmful, although they might still have pharmacological effects (Perumal B *et al*.,).

Excretion

The renal system is the main excretion route. Some of the parent chemical is eliminated unaltered, while the remainder is eliminated as metabolites. Depending on liver function and other characteristics, strychnine's elimination half-life is predicted to be 10-14 hr (Maji *et al*., 2017).

Contemporary Pharmacological Insights on ADME of *AHIPHENA* (*Papaver somniferum* L.)

Papaver somniferum, commonly known as the opium poppy, produces a dried latex known as *Ahiphena* in Ayurvedic texts and raw opium in modern pharmacology. This latex contains a complex mixture of over 20 alkaloids, the most pharmacologically significant being morphine, codeine, and thebaine. These compounds are classified as opioid alkaloids due to their action

on opioid receptors in the central nervous system. The ADME profile of these alkaloids determines their clinical use, therapeutic effectiveness, and toxicity.

Absorption

Morphine, the principal active component of *Ahiphena*, is well absorbed when taken orally, although it suffers from low oral bioavailability (20-30%) due to first-pass hepatic metabolism (Christrup, 1997). Peak plasma concentrations are typically reached within 30-60 min after oral administration. Parenteral routes (intravenous, intramuscular, subcutaneous) bypass first-pass metabolism and provide rapid onset of action.

Codeine is also absorbed orally and is partially converted into morphine in the liver via the enzyme CYP2D6.

Thebaine, unlike morphine and codeine, is not used directly for analgesia but serves as a precursor for semi-synthetic opioids like oxycodone (Patel *et al*., 2017).

Distribution

Once absorbed, morphine is widely distributed throughout the body. It is moderately lipophilic, allowing it to cross the blood-brain barrier, although more slowly than synthetic opioids like fentanyl. Morphine has a Volume of distribution (Vd) of approximately 3-5 L/kg, and about 30-35% is bound to plasma proteins.

Distribution occurs to highly perfused organs such as the brain, liver, lungs, kidneys, and spleen, with primary effects observed in the Central Nervous System (CNS) due to binding at mu-opioid receptors, which mediate analgesia, sedation, and euphoria (Christrup *et al*., 1997).

Metabolism

Morphine undergoes extensive hepatic metabolism via Phase II conjugation, primarily by the enzyme UGT2B7, forming:

Morphine-3-Glucuronide (M3G): Lacks analgesic effects and may cause neurotoxic side effects such as agitation or seizures.

Morphine-6-Glucuronide (M6G): Potent analgesic with higher affinity for opioid receptors than morphine itself.

These metabolites are hydrophilic and do not easily cross the blood-brain barrier, although M6G does so more effectively in patients with impaired renal function, potentially leading to prolonged opioid effects and toxicity (Smith *et al*., 2000).

Excretion

Morphine and its metabolites are primarily excreted via the kidneys. Around 90% of a dose is eliminated in the urine, mostly in the form of M3G and M6G, with small amounts of unchanged morphine. The elimination half-life of morphine is approximately 2-3 hr, although the duration of analgesia can last 4-6 hr depend on the route and dose. In patients with renal impairment, accumulation of active metabolites like M6G can lead to toxicity (Lotsch & Geisskinger *et al*., 2001).

Contemporary Pharmacological Insights on ADME of *JAYAPALA* (*Croton tiglium* L.)

Absorption

Croton tiglium seeds contain phorbol esters, which are lipophilic compounds. These compounds are known to be absorbed through the gastrointestinal tract, but their absorption can be influenced by various factors, including the presence of other substances and the method of administration. The traditional Ayurvedic detoxification process, *Shodhana*, often involves the use of cow's milk, which may aid in reducing the toxicity of these compounds and potentially influence their absorption (Glare *et al*., 1991).

Distribution

Once absorbed, the phorbol esters in Croton tiglium are distributed throughout the body. Due to their lipophilic nature, they can readily cross cell membranes and may accumulate in various tissues. The distribution is also influenced by the method of administration and the presence of other substances that may alter the pharmacokinetics of these compounds (Glare *et al*., 1991; Acharya *et al*., 2018).

Metabolism

The metabolism of phorbol esters involves enzymatic processes that can modify their structure and activity. These metabolic pathways can influence the potency and duration of action of the compounds. However, the specific enzymes involved and the detailed metabolic pathways require further research to be fully understood (Acharya *et al*., 2018; Pillai *et al*., 1999).

Excretion

The excretion of phorbol esters and their metabolites primarily occurs through the liver and kidneys. The rate of excretion can be influenced by various factors, including the individual's metabolic rate and the presence of other substances that may affect the elimination processes (Pillai *et al*., 1999).

Contemporary Pharmacological Insights on ADME of DATURA (*Datura metel* L.)

Absorption

The bioactive substances in *D. metel* are absorbed through the gastrointestinal tract when taken orally. The presence of lipophilic alkaloids makes it easier for them to pass through cell membranes and reach the circulation of the blood. On the contrary, an array of factors, including as the preparation process and the presence of additional elements that may impact pH and gastrointestinal motility, might affect the efficiency of absorption (Alam *et al*., 2021).

Distribution

Due to their ability to pass through the Blood-Brain Barrier (BBB), the alkaloids circulated throughout the body once they are in systemic circulation, with an affinity for tissues like the central nervous system. The plant's fundamental anticholinergic attributes, which, when taken in excess, can cause signs like delirium and hallucinations, are based on this distribution. Additionally, elements like tissue affinity and plasma protein binding affect the distribution (Taye *et al*., 2023; Alam *et al*., 2021).

Metabolism

The therapeutic components of *D. metel* are mostly absorbed in the liver, where they go through enzymatic changes. Both active and inactive metabolites may be produced as an outcome of these metabolic processes, and they might impact the plant's overall pharmacological effects and toxicity profile. To completely comprehend the metabolic destiny of these molecules, further information of specific enzymes involved and the pathways they follow require further elucidation to fully understand the metabolic fate of these compounds (Xia *et al*., 2019).

Excretion

The elimination of *D. metel's* alkaloids and their metabolites predominantly occurs through renal excretion. Factors such as urine pH and renal function can significantly influence the rate and extent of excretion. Alterations in these factors may lead to prolonged retention of the compounds in the body, increasing the risk of toxicity (Xia *et al*., 2019; Alam *et al*., 2021; Murugan *et al*.,).

Contemporary Pharmacological Insights on ADME of *BHANGA/VIJAYA* (*Cannabis sativa* L.)

Cannabis sativa, commonly known as Bhanga in Ayurveda, is a plant renowned for its psychoactive and therapeutic properties, primarily attributed to its major cannabinoids-Δ^9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD). Understanding the pharmacokinetics-Absorption, Distribution, Metabolism, and Excretion (ADME)-of these compounds is crucial for their clinical application and safety.

Absorption

The bioavailability and onset of action of cannabinoids are significantly influenced by the route of administration:

Inhalation (smoking or vaping): This method allows cannabinoids to rapidly enter the bloodstream through the lungs, with peak plasma concentrations achieved within 3 to 10 minutes. The bioavailability for THC via inhalation ranges from 10% to 35%, and for CBD, it is approximately 31% (Arabian journal of chemistry, 2022).

Oral ingestion: When consumed orally, cannabinoids undergo first-pass metabolism in the liver, leading to a significant reduction in bioavailability. THC's oral bioavailability is between 4% and 12%, while CBD's is about 6%. Peak plasma concentrations are typically reached within 1 to 2 hr post-ingestion (Trono *et al*., 2024).

Other routes: Rectal administration of THC has shown a bioavailability of approximately 13.5%, offering an alternative for patients who cannot tolerate oral or inhalation methods.

Distribution

Cannabinoids are highly lipophilic, leading to their extensive distribution in fatty tissues.

Volume of Distribution (Vd): The Vd for THC is estimated at 3.4 L/kg following inhalation, indicating widespread distribution (Ankit *et al*., 2025; Chayasirisobhon *et al*., 2020).

Tissue affinity: THC and CBD rapidly distribute into well-vascularized organs such as the brain, lungs, liver, and heart. Due to their lipophilicity, they also accumulate in adipose tissue, from which they are slowly released over time.

Placental and breast milk transfer: Both THC and CBD can cross the placenta and are excreted in human breast milk, raising concerns regarding fetal and neonatal exposure.

Metabolism

The liver plays a central role in the metabolism of cannabinoids:

Cytochrome P450 enzymes: THC is primarily metabolized by CYP2C9, CYP2C19, and CYP3A4 enzymes to form 11-hydroxy-THC (11-OH-THC), a potent psychoactive metabolite, which is further converted to 11-nor-9-carboxy-THC (THC-COOH), an inactive metabolite.

CBD metabolism: CBD is metabolized by CYP2C19 and CYP3A4 enzymes to produce 7-hydroxy-CBD and 7-carboxy-CBD, which are then excreted in the feces and, to a lesser extent, in urine (Trono *et al*., 2024).

Metabolic variability: Genetic polymorphisms in CYP450 enzymes can lead to variability in cannabinoid metabolism, affecting drug efficacy and safety.

Elimination

The elimination of cannabinoids involves both renal and fecal excretion:

Half-life: The plasma half-life of THC ranges from 1 to 3 days in occasional users and extends to 5 to 13 days in chronic users due to accumulation in fat tissues.

Excretion pathways: Approximately 65% of THC metabolites are excreted via feces, and about 20% through urine.

Chronic use implications: In chronic users, cannabinoids may be detectable in the body for extended periods, influencing drug testing outcomes and potential therapeutic applications (Yadav *et al*., 2023).

Contemporary Pharmacological Insights on ADME of *GUNJA* (*Abrus precatorius* L.)

Abrus precatorius, commonly known as Gunja or rosary pea, is a plant native to India and parts of tropical Asia. It has been traditionally used in Ayurvedic medicine for various ailments, including sore throat, cough, bronchitis, jaundice, hepatitis, abdominal pain, contraception, tumor, abortion, malaria, and more. However, the seeds of this plant contain abrin, a potent toxin that can be fatal if ingested. Therefore, understanding the pharmacokinetics-Absorption, Distribution, Metabolism, and Excretion (ADME)-of its compounds is crucial for evaluating its therapeutic potential and safety (Garniya *et al*., 2014).

Absorption

The bioavailability of compounds from *A. precatorius* varies depending on the route of administration and the specific compound:

Intravenous administration: Studies have shown that after intravenous administration, the greatest fraction of the dose is distributed to the liver, followed by blood, lungs, spleen, kidney, and heart. This suggests that compounds from *A. precatorius* are rapidly absorbed into the systemic circulation when administered parenterally (Qian *et al*.,).

Oral administration: The absorption of compounds from *A. precatorius* following oral administration is less well-documented. However, due to the presence of toxic compounds like abrin, oral ingestion is not recommended without proper processing and dosage control (Qian *et al*.,).

Distribution

After absorption, the distribution of compounds from A. precatorius is influenced by their lipophilicity and molecular size:

Abrin: As a high molecular weight protein (approximately 65 kDa), abrin has limited gastrointestinal absorption. However, once absorbed, it is widely distributed throughout the body. Experimental studies in mice have shown that the greatest fraction of intravenously administered abrin is distributed to the liver, followed by blood, lungs, spleen, kidney, and heart (Qian *et al*.,).

Other compounds: Phytochemical analyses have identified various bioactive compounds in *A. precatorius*, including alkaloids, flavonoids, triterpenoids, saponins, and polyphenols. The distribution of these compounds in the body is not well-documented and requires further research (Reddy *et al*., 2014).

Metabolism

The metabolism of compounds from *A. precatorius* involves enzymatic transformations that can activate or deactivate their pharmacological activities:

Abrin: Once absorbed, abrin is metabolized in the liver. It is a ribosome-inactivating protein that inhibits protein synthesis by depurinating the adenine residue of the 28S rRNA of the ribosome. This leads to cell death and contributes to its toxicity.

Other compounds: The metabolic pathways of other bioactive compounds in *A. precatorius* have not been extensively studied. However, compounds such as abrusin, abrisapogenol J, and precatorine have been identified as active constituents with potential therapeutic effects. Further research is needed to elucidate their metabolic pathways.

Excretion

The elimination of compounds from *A. precatorius* occurs through various routes:

Abrin: The excretion of abrin and its metabolites has not been well-documented. Given its high molecular weight and proteinaceous nature, it is likely that abrin is primarily eliminated through the liver and kidneys.

Other compounds: The excretion pathways of other bioactive compounds in *A. precatorius* are not well-understood. Studies on the pharmacokinetics of these compounds are limited, and more research is needed to determine their elimination routes (Kopustinskiene *et al*., 2022; Bhakta & Das *et al*., 2020).

Contemporary Pharmacological Insights on ADME of *BHALLATAKA* (*Semecarpus anacardium* L.f.)

Semecarpus anacardium, commonly known as *Bhallataka*, is a plant renowned in traditional medicine for its diverse therapeutic properties. However, its potent bioactivity necessitates a comprehensive understanding of its pharmacokinetics Absorption, Distribution, Metabolism, and Excretion (ADME)-to ensure safe and effective use.

Absorption

The bioavailability of *Bhallataka's* active compounds is influenced by their chemical nature and the method of administration:

Oral Administration: Studies have demonstrated that oral administration of *Bhallataka* extracts can significantly reduce blood glucose levels in diabetic rat models. For instance, an ethanolic extract administered at 100 mg/kg body weight resulted in a notable decrease in blood glucose levels in normoglycemic rats (Aseervatham *et al*., 2010).

Intraperitoneal Administration: In certain studies, *Bhallataka* extracts have been administered via intraperitoneal injection,

which may alter the pharmacokinetic profile compared to oral administration.

These findings suggest that *Bhallataka's* active constituents are absorbed into the systemic circulation, though the extent of absorption can vary based on the administration route.

Distribution

Once absorbed, the distribution of *Bhallataka's* bioactive compounds is influenced by their lipophilicity and molecular size:

Phytochemical Constituents: *Bhallataka* contains various bioactive compounds, including flavonoids, tannins, alkaloids, phenolic compounds, and saponins. The distribution of these compounds in the body is not well-documented and requires further research (Khan *et al*., 2012).

The distribution of *Bhallataka's* compounds is likely to tissues involved in its therapeutic effects, such as the liver, kidneys, and pancreas, though specific data is limited.

Metabolism

The metabolism of *Bhallataka's* active compounds involves enzymatic transformations that can activate or deactivate their pharmacological activities:

- Biotransformation Enzymes: Oral administration of *Bhallataka* nut extract has been found to induce phase I and phase II biotransformation enzymes in the liver, suggesting that its compounds undergo hepatic metabolism.
- Antioxidant Activity: *Bhallataka* extracts have demonstrated antioxidant properties, which may influence the metabolism of other compounds and contribute to its therapeutic effects.

These findings indicate that *Bhallataka's* compounds are metabolized in the liver, potentially via cytochrome P450 enzymes, though specific metabolic pathways require further elucidation (Premalatha *et al*., 2000).

Excretion

The elimination of *Bhallataka's* metabolites primarily occurs through the urinary and fecal routes:

- Renal Excretion: Given the hydrophilic nature of many of *Bhallataka's* metabolites, renal excretion is likely a primary route of elimination.
- Fecal Excretion: Some metabolites may be excreted via the bile into the feces, especially those that are more lipophilic.

Specific data on the excretion of *Bhallataka's* metabolites is limited and warrants further investigation.

Contemporary Pharmacological Insights on ADME of *KARAVIRA* (*Nerium indicum* Mill.)

Nerium indicum, commonly known as *Karvira* or Indian oleander, is a highly toxic plant containing cardiac glycosides like oleandrin and neriine. Despite its toxicity, it has been studied for various pharmacological effects, especially in traditional medicine. Understanding its ADME (Absorption, Distribution, Metabolism, and Excretion) is critical for assessing its therapeutic potential and safety.

Absorption

Oral Absorption: Oleandrin, the primary bioactive compound, shows relatively good oral bioavailability but with a narrow therapeutic index. It is lipophilic, allowing it to be absorbed through the gastrointestinal tract efficiently. However, this absorption can lead to systemic toxicity if not carefully done.

Alternative Routes: Topical or localized use reduces systemic absorption, minimizing toxicity.

Distribution

- Tissue Distribution: Oleandrin and related glycosides rapidly distribute throughout the body, with a high affinity for cardiac tissue due to their mechanism of action on the Na^+/K^+-ATPase pump.
- Blood-Brain Barrier: Limited data suggests that oleandrin may cross the blood-brain barrier, potentially explaining neurological toxicity in poisoning cases.

Metabolism

- Hepatic Metabolism: Oleandrin undergoes metabolism mainly in the liver via phase I and phase II enzymatic processes, including oxidation and conjugation. This biotransformation alters its pharmacological activity and toxicity.
- Metabolites: Some metabolites retain cardiac glycoside activity, which may contribute to prolonged effects or toxicity.

Excretion

- Renal and Biliary Excretion: Oleandrin and its metabolites are excreted primarily via urine and bile. Renal clearance plays a key role, but enterohepatic recirculation can prolong the elimination half-life.
- Half-life: The elimination half-life of oleandrin is relatively long (several hours), contributing to cumulative toxicity risks with repeated exposure (Semalty *et al*., 2010; Dey *et al*., 2015).

Contemporary Pharmacological Insights on ADME of *LANGALI* (*Gloriosa superba* L.)

Gloriosa superba, commonly known as *Langali* or flame lily, is a medicinal plant with significant bioactive compounds, primarily colchicine and related alkaloids. These constituents impart potent therapeutic effects, especially as anti-inflammatory, anticancer, and antimitotic agents. However, their high toxicity necessitates a thorough understanding of the pharmacokinetics (ADME) for safe and effective use (Ashokkumar *et al*., 2015).

Absorption

- Oral Absorption: Colchicine, the primary active alkaloid of Gloriosa superba, is rapidly absorbed from the gastrointestinal tract upon oral administration. It demonstrates moderate to good bioavailability (approximately 45-50%).
- Influence of Food and pH: Absorption can be affected by food intake and gastrointestinal pH, with faster absorption in fasting states.
- Toxicity Concerns: Due to its narrow therapeutic index, even small variations in absorption can lead to toxicity.
- Distribution Wide Tissue Distribution: Colchicine distributes extensively throughout the body, concentrating in leukocytes, kidneys, liver, spleen, and gastrointestinal tract.
- Plasma Protein Binding: It exhibits moderate plasma protein binding (~40%), which influences its free active form in circulation.
- Volume of Distribution (Vd): The relatively large Vd (~5-8 L/kg) reflects its widespread tissue penetration.
- Crosses Placenta and Blood-Brain Barrier: Colchicine can cross the placenta and blood-brain barrier, contributing to toxicity risks in pregnancy and CNS (Dey *et al*., 2015; Leung *et al*., 2015).

Metabolism

- Hepatic Metabolism: Colchicine is extensively metabolized in the liver via cytochrome P450 enzymes, primarily CYP3A4, through demethylation.
- First-pass Effect: Significant first-pass metabolism reduces systemic bioavailability.
- Metabolites: Metabolites have minimal pharmacological activity; however, metabolic rate variations (e.g., due to CYP3A4 inhibitors) can increase colchicine toxicity.

Excretion

- Biliary and Renal Excretion: Colchicine and its metabolites are eliminated through biliary secretion into feces (~80%) and renal excretion (~10-20%).
- Enterohepatic Recycling: The drug undergoes enterohepatic recycling, prolonging its half-life and effects.
- Elimination Half-life: The elimination half-life ranges from 20 to 40 hours, supporting the potential for accumulation with repeated dosing (Sabouraud *et al*., 1992; Angelidis *et al*., 2018).

LIMITATIONS

The present study is constrained by several notable limitations. A primary concern is the limited availability of comprehensive ADME (Absorption, Distribution, Metabolism, and Excretion) data for many *Visha* and *Upavisha dravyas*, as systematic pharmacokinetic profiling remains largely unexplored. Moreover, most pharmacological validations are derived from in vitro experiments or animal models, with minimal clinical studies conducted on human subjects, thereby limiting the translational potential of these findings. Another significant challenge lies in the heterogeneous interpretations of classical Ayurvedic texts, which can lead to inconsistency and subjectivity when defining the synergistic actions of these substances. Additionally, there is a lack of standardization in the preparation of herbal formulations, including variations in raw material quality and purification (Shodhana) methods, which may affect both pharmacological outcomes and ADME characteristics. Although modern tools such as molecular docking and network pharmacology have been introduced, in-depth molecular-level mechanisms underlying synergy are still insufficiently addressed. The intrinsic toxicity of *Visha* and *Upavisha dravyas* also presents a difficulty in accurately determining their therapeutic windows, particularly when used in combination. Furthermore, the conceptual gap between Ayurvedic terminologies such as *Virya, Prabhava*, and *Anupana* and modern pharmacological language creates challenges in correlating traditional concepts with contemporary science. The absence of systems biology approaches in most studies limits the holistic understanding of synergistic interactions. Additionally, there may be an inherent selection bias in the reviewed literature, as studies with negative or inconclusive outcomes are often underreported. Lastly, regulatory and ethical barriers restrict the experimental and clinical evaluation of these inherently toxic substances, further narrowing the scope for scientific validation.

CONCLUSION

The convergence of Ayurvedic toxicology with modern pharmacological methodologies offers a fertile ground for drug discovery and therapeutic innovation. The re-evaluation of *Visha* and *Upavisha* once feared for their toxicity reveals their profound

potential when understood through scientific lenses like ADME profiling and pharmacodynamic studies. Contemporary insights affirm the synergistic benefits of these substances when incorporated into polyherbal or mineral-herbal formulations, with enhanced bioavailability, targeted action, and reduced adverse effects. However, this synergy is highly dependent on traditional detoxification methods (*Shodhana*), precise dosing, and formulation protocols areas where modern standardization is still evolving. A balanced approach that integrates Ayurvedic principles with current biotechnological tools can pave the way for safe, effective, and evidence-backed use of these traditionally significant substances. Thus, the journey from poison to potent drug reflects not only the depth of traditional wisdom but also the potential for future therapeutic breakthroughs when ancient practices meet modern science.

ABBREVIATIONS

ADME: Absorption, Distribution, Metabolism, and Excretion; **AFI:** Ayurvedic Formulary of India; **BBB:** Blood–Brain Barrier; **CNS:** Central Nervous System; **CYP450:** Cytochrome P450 enzyme system; **CYP2D6:** Cytochrome P450 2D6 enzyme; **CYP3A4:** Cytochrome P450 3A4 enzyme; **CYP2C9:** Cytochrome P450 2C9 enzyme; **CYP2C19:** Cytochrome P450 2C19 enzyme; **CBD:** Cannabidiol; **THC:** Δ^9-Tetrahydrocannabinol; **LC-MS/MS:** Liquid Chromatography–Tandem Mass Spectrometry; **UGT2B7:** Uridine 5′-diphospho-glucuronosyltransferase 2B7; **M3G:** Morphine-3-glucuronide; **M6G:** Morphine-6-glucuronide; **Vd:** Volume of Distribution; **Na^+/K^+-ATPase:** Sodium-Potassium Adenosine Triphosphatase pump; **hr:** Hour; **mg:** Milligram; **kg:** Kilogram; **L:** Liter; **%:** Percentage.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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