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"ARSENIC-CONTAINING AYURVEDIC FORMULATIONS AND ARSENIC TRIOXIDE IN ACUTE PROMYELOCYTIC LEUKAEMIA: AN INTEGRATIVE REVIEW"

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ABSTRACT

Background: Arsenic compounds are among the most toxic substances used in medicine, yet arsenic trioxide is now a curative first-line drug for acute promyelocytic leukaemia (APL), and an oral realgar-based formula from traditional Chinese medicine has matched it in a randomised trial. Ayurveda uses several arsenic minerals, notably *Haratala* (orpiment), *Manahshila* (realgar) and *Gauri pashana* or *Somala* (arsenic trioxide), in formulations such as *Rasamanikya* and *Malla sindura*. **Objective:** To bring together the modern pharmacology of arsenic in APL and the evidence on Ayurvedic arsenical formulations, and to identify what would be needed to evaluate the latter as cancer therapies. **Methods:** An integrative narrative review of clinical and mechanistic literature on arsenic trioxide and oral arsenic sulphide in APL, and of pharmaceutical, analytical, toxicological and clinical studies of Ayurvedic arsenicals. **Results:** Arsenic trioxide induces degradation of the PML-RARα oncoprotein and, combined with all-trans retinoic acid, cures most patients with standard-risk APL. Oral tetra-arsenic tetra-sulphide was non-inferior to intravenous arsenic trioxide in a multicentre randomised trial. Ayurvedic arsenicals have been standardised pharmaceutically; *Rasamanikya*, for example, contains about 55% arsenic. However, no clinical or preclinical study of an Ayurvedic arsenical in APL was identified, and case reports document chronic arsenic poisoning after long-term use of Ayurvedic medicines. **Conclusion:** The APL story shows that a traditional arsenical can become an evidence-based therapy, but only through characterisation, mechanistic work and controlled trials. Ayurvedic arsenicals have not yet been tested on this path, and their use in cancer outside research settings is not supported.

KEYWORDS: Arsenic; *Haratala*; *Manahshila*; *Rasamanikya*; *Malla sindura*; Arsenic trioxide; Acute promyelocytic leukaemia; Realgar

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INTRODUCTION

Arsenic has a long and paradoxical history in medicine. It was used in many traditional systems, including Ayurveda, Chinese and Greek medicine, and in the nineteenth century as Fowler's solution, before being largely abandoned because of its toxicity. Inorganic arsenic is classified as a human carcinogen[1]. Yet in the 1990s, arsenic trioxide (As_2O_3), first used in China on the basis of traditional practice, was shown to induce remission in acute promyelocytic leukaemia (APL)[2]. Today, arsenic trioxide combined with all-trans retinoic acid (ATRA) is standard first-line therapy for APL and cures most patients without conventional chemotherapy[3].

Ayurveda uses arsenic minerals in *Rasa Shastra*. *Haratala* (orpiment, As_2S_3), *Manahshila* (realgar, As_4S_4) and *Gauri pashana* or *Somala* (arsenic trioxide) are classed among the *uparasa* and *sadharana rasa* groups and are used, after *shodhana*, in formulations such as *Rasamanikya*, *Talasindura*, *Malla sindura* and *Sameera pannaga rasa*, mainly for skin diseases, respiratory disorders, fevers and chronic conditions[4,5]. The success of arsenic in APL has prompted suggestions that Ayurvedic arsenicals may have anticancer value. This review brings the two bodies of evidence together.

METHODS OF THE REVIEW

This is an integrative narrative review. Literature on arsenic trioxide and oral arsenic sulphide in APL, and on Ayurvedic arsenical formulations, was identified through PubMed, PubMed Central, Crossref-indexed records, Europe PMC and journal archives, using the terms arsenic trioxide, realgar, tetra-arsenic tetra-sulphide, acute promyelocytic leukaemia, *Haratala*, *Manahshila*, *Rasamanikya*, *Malla sindura*, *Somala* and arsenic poisoning. Landmark clinical trials and mechanistic reviews were included for the modern evidence, and pharmaceutical, toxicological and clinical studies for the Ayurvedic evidence.

ARSENIC IN ACUTE PROMYELOCYTIC LEUKAEMIA

1. Clinical evidence

APL is characterised by the t(15;17) translocation, which produces the PML-RARα fusion oncoprotein and blocks myeloid differentiation. Early Chinese studies showed that intravenous arsenic trioxide induced complete remission in relapsed APL[2]. In India, single-agent arsenic trioxide was used as first-line therapy with durable long-term results, an approach particularly relevant to resource-limited settings[6]. In a European randomised trial in standard-risk APL, ATRA plus arsenic trioxide was at least as effective as ATRA plus chemotherapy, with less haematological toxicity, and became a new standard of care[3].

2. Oral arsenic sulphide from traditional medicine

The most relevant precedent for Ayurveda comes from China. The Realgar-Indigo naturalis formula, an oral traditional preparation containing tetra-arsenic tetra-sulphide (realgar), was compared with intravenous arsenic trioxide as first-line treatment for APL in a multicentre randomised controlled trial and was found to be non-inferior[7]. This trial demonstrated that an orally administered arsenic sulphide from a traditional formula can match a purified intravenous arsenic drug when its arsenic content is standardised and it is tested in an appropriately designed trial. The safety of realgar- and cinnabar-containing traditional Chinese medicines has also been reviewed[8].

3. Mechanism

Arsenic trioxide binds directly to cysteine residues in the PML moiety of PML-RARα, triggering its oligomerisation, SUMOylation and proteasomal degradation, which releases the differentiation block and eliminates leukaemia-initiating cells[9,10]. This mechanism explains the remarkable specificity of arsenic for APL. It also means that efficacy in APL cannot be extrapolated to other cancers, in which the same target is absent.

AYURVEDIC ARSENICAL FORMULATIONS

1. The minerals and their processing

Table 1. Arsenic minerals used in *Rasa Shastra* and representative formulations

Ayurvedic name	Mineral and formula	Representative formulations	Classical uses (summary)
Haratala	Orpiment, As_2S_3	*Rasamanikya*, *Talasindura*, *Talakeshwara rasa*	Skin diseases (*kushtha*), respiratory disorders, fevers
Manahshila	Realgar, As_4S_4	Compound formulations for respiratory and skin conditions	Cough, dyspnoea, skin diseases

Gauri pashana / *Somala*	Arsenic trioxide, As_2O_3	*Malla sindura*, *Sameera pannaga rasa*	Respiratory disorders, fevers, chronic conditions

Arsenic minerals are purified by boiling or soaking in media such as lime water, ash-water extracts or herbal juices, and then processed by sublimation, roasting or *kupipaka*. The most detailed process study concerns *Rasamanikya*, made from purified *Haratala*. Six methods were compared, including sealed and open earthen vessels, mica sheets, a blow lamp and *kupipaka*. Arsenic content was about 58% in raw and purified *Haratala* and about 55% in *Rasamanikya* prepared by *kupipaka*, which the authors preferred for quality, economy and reproducibility; in *kupipaka*, melting was observed at about 359 °C and product formation at about 450 °C[11]. *Malla sindura*, which combines arsenic trioxide with mercury and sulphur in a *kupipakva* process, has also been prepared and characterised[12].

2. What these formulations are chemically

These figures emphasise that Ayurvedic arsenicals are not trace-arsenic medicines: *Rasamanikya* is more than half arsenic by weight. At the same time, the chemical form differs from arsenic trioxide. Orpiment and realgar are sulphides with low aqueous solubility, whereas arsenic trioxide is more soluble and readily absorbed. As with mercuric sulphide, solubility and bioavailability rather than total arsenic determine both efficacy and toxicity[13]. Whether *shodhana* and *kupipaka* change the oxidation state, phase or solubility of the arsenic has not been studied systematically with modern speciation methods.

3. Evidence of efficacy

No preclinical or clinical study of an Ayurvedic arsenical in APL or other leukaemias was identified in this review. Clinical studies of *Rasamanikya* have mainly concerned skin diseases. Commonly cited doses of *Rasamanikya* are in the range of a few tens of milligrams per day. At about 55% arsenic, even 20 mg of *Rasamanikya* contains about 11 mg of arsenic. For comparison, the usual intravenous dose of arsenic trioxide in APL is about 0.15 mg/kg/day, roughly 9 mg of arsenic trioxide (about 7 mg of arsenic) for a 60 kg adult. The fraction absorbed from poorly soluble sulphides is likely to be much lower than from intravenous arsenic trioxide, but the comparison shows that Ayurvedic arsenicals contain pharmacologically relevant amounts of arsenic, which is a reason both for interest and for caution.

4. Evidence of harm

Chronic arsenic poisoning after long-term use of Ayurvedic medicines is well documented. In one report, three patients who had taken Ayurvedic preparations for 4 months to 9 years, for eczematous dermatitis, diabetes and vitiligo, had blood arsenic levels of 93–330 µg/L (reference below 23 µg/L) and elevated hair arsenic in two cases. All three developed toxicity, including skin changes and neuropathy; they improved after stopping the medicine and chelation, but neuropathy persisted in two[14]. Market surveys have detected arsenic in a proportion of Ayurvedic products, including products not intended to contain it[15,16], and one commercial *Suvarna bhasma* contained 5.4 wt% arsenic[17]. Chronic arsenic exposure is associated with skin lesions, peripheral neuropathy, cardiovascular disease and cancer[1]. These risks are particularly relevant for skin conditions such as psoriasis and vitiligo, for which arsenicals are traditionally used for long periods.

INTEGRATIVE PERSPECTIVE

Table 2. Comparison of arsenic trioxide in APL and Ayurvedic arsenical formulations

Aspect	Arsenic trioxide / oral realgar in APL	Ayurvedic arsenicals
Chemical form	Purified As_2O_3 (intravenous) or standardised As_4S_4 formula (oral)	As_2S_3, As_4S_4 or As_2O_3 after traditional processing, often with mercury or herbs
Arsenic content	Exactly defined	Defined in some process studies (about 55% in *Rasamanikya*); rarely on labels
Indication	APL with PML-RARα, confirmed molecularly	Broad, mainly skin, respiratory and chronic conditions
Mechanism	Direct targeting of PML-RARα	Not studied
Clinical evidence	Multiple randomised trials	Small studies in non-cancer indications
Monitoring	ECG for QT prolongation, electrolytes, differentiation syndrome	Rarely monitored

The APL experience offers three lessons for *Rasa Shastra*. First, a traditional arsenical can become a validated drug, but only after standardisation of arsenic content, identification of a specific target disease and mechanism, and randomised trials[7,10]. Second, efficacy in APL depends on a specific molecular target and cannot be extended to cancer in general. Third, even in the best-controlled setting, arsenic therapy requires monitoring for QT prolongation, electrolyte disturbance and differentiation syndrome. Ayurvedic arsenicals used for months or years without monitoring fall far short of this standard.

A RESEARCH PATHWAY

A credible programme to evaluate Ayurvedic arsenicals would include:

- **Characterisation and speciation.** Phase identification, total arsenic, arsenic speciation and dissolution in simulated gastrointestinal fluids for *Rasamanikya*, *Talasindura* and *Malla sindura*.
- **In vitro testing in APL models.** Testing in APL cell lines carrying PML-RARα, with arsenic trioxide as a positive control, to see whether the Ayurvedic preparations degrade PML-RARα at achievable concentrations.
- **Pharmacokinetics.** Blood and urinary arsenic and speciation after oral dosing in animals and, if justified, in carefully monitored humans.
- **Toxicology.** Repeated-dose studies with cardiac, hepatic, renal and neurological end-points.
- **Clinical trials.** Only after the above, and within oncology settings, trials modelled on the realgar formula studies.

IMPLICATIONS FOR PRACTICE

Until such evidence exists, Ayurvedic arsenicals should not be used to treat leukaemia or other cancers outside research protocols. In their traditional indications, their arsenic content should be stated, the duration of use should be limited, and patients on long-term therapy should be monitored, for example with blood or urinary arsenic and clinical examination for skin and neurological signs. Clinicians should also be aware that patients with APL or other cancers may be taking Ayurvedic preparations that contain arsenic or mercury, which may interact with or add to the toxicity of conventional arsenic therapy.

CONCLUSION

Arsenic trioxide and oral realgar formulations have transformed the treatment of acute promyelocytic leukaemia, showing that a traditional arsenical can become an evidence-based cancer therapy. Ayurvedic arsenicals such as *Rasamanikya* and *Malla sindura* contain large proportions of arsenic, have been standardised pharmaceutically, and are associated with documented cases of chronic arsenic poisoning, but they have not been tested in APL or other cancers. A staged research programme, from speciation and mechanism to controlled trials, is needed before any anticancer claim can be made.

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