



**Review Article**

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## Arsenic in the management of leukemia: An Ayurvedic perspective

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### ABSTRACT

*Gauripasan, Harital and Manhasila* are important classical Ayurvedic arsenic containing minerals found in *Rasashastra* (Indian Alchemy). Though there are no direct references about the role of these minerals in treating leukemia but there are several references of the above minerals in combating blood disorders, infection and anemia which can occur secondary to leukemia. This review discusses the probable role of this arsenic based Ayurvedic compounds in the management of leukemia, its study from ancient classics supporting its therapeutic efficacy and also to draw a comparison among the effectiveness in between several arsenic containing mineral groups in Ayurveda.

**Keywords:** Leukemia, Ayurveda, Arsenic.

### INTRODUCTION

In modern medicine, leukemia is classified into chronic lymphocytic leukemia, chronic myeloid leukemia, acute lymphocytic (Lymphoblastic) leukemia and acute myeloid leukemia (AML).

AML affects myeloid cells and grows quickly and affects for more than 13,000 new cases of leukemia each year and it occurs in both adults and children. In APL, there is an abnormal accumulation of immature granulocytes called promyelocytes<sup>[1]</sup>. The disease is unique from other forms of AML in its responsiveness to all *trans* retinoic acid (group of natural and synthetic derivatives of vitamin A)<sup>[2, 3]</sup>. However, APL cells develop resistance to retinoic acid treatment. Compounds containing arsenic can induce clinical remission in patients with APL, including those who have relapsed after retinoic acid treatment, by inducing apoptosis (programmed cell death) of the leukemia cells<sup>[4, 5]</sup>. But all this drug used or administered are from modern background. In Ayurveda the arsenic containing minerals are documented in several *latrochemical* books of yesteryear and there are several references of this arsenic containing compounds in the treatment of symptoms that arise when a patient is suffering from leukemia. These ancient references are validated in the modern school of thoughts and that's why US-FDA has approved Arsenic trioxide as the standard treatment for relapsed APL. This proves the authenticity of using a poisonous mineral like arsenic in the treatment of dreadful disease like leukemia. But the toxicity of this arsenic compounds are too much to level them as free from side-effect, the ayurvedic way of preparing *bhasmas* of this arsenic containing mineral may be an answer to reduce the toxicity and to alter the bioavailability of this minerals due to nano size formation of the *bhasmas* after calcinations<sup>[6]</sup>.

### Acute promyelocytic Leukemia and Ayurveda

According to some scholars, the modern day leukemia may be correlated with *Rakta arbuda / Rakta pitta* since the symptoms are much related with leukemia<sup>[7]</sup>. Leukemic cells rapidly accumulate in bone marrow cavity replacing most of the normal cells and thus resulting in anemia, hemorrhage and infection. Later on leukemia cells get circulate into the blood. Ayurvedic literature has no direct reference for the diagnosis of leukemia or its sub classification, but indirect references are available with their treatment. In *Vagbhatta's Astanga Hridayam*, it is stated that *Tato alpo rakta medasko nihsarah*<sup>[8]</sup>. Here '*Raktameda*' refers to bone marrow, it is cleared from the above that any pathogenesis of the bone marrow may lead to anemia; this may be associated with leukemia.

In the field of Ayurveda most of the credit for the development, prognosis and diagnosis of APL goes to *Vaidya Chandra prakash* and *Vaidya Balendu Prakash*. Under the guidance of *Vd. Chandra Prakash* a remarkable recovery for a 10 year old boy from APL was documented in the year 1982. Later beneficial effect was observed in five other cases by *Vd. Balendu Prakash* from 1987 to 1996<sup>[9]</sup>. *Vd. Balendu Prakash*

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also successfully treated patients with undifferentiated Acute Myeloid leukemia with patented *Navajeevan*, Prak-20, Valipani and traditional drugs like *Kamadudha ras*<sup>[10]</sup>.

### Arsenic and Ayurveda

There are a vast number of Ayurvedic preparations that contains arsenic. The toxic level of arsenic is carefully manipulated with strict dosage form during administration. *Charaka* had once said; “*Yogadapi visam tikshnam uttam bhesajyam Bhawt bhesajam chapi duryuktam tikshnam sampadhate visam*”<sup>[11]</sup> which means with proper preparation a highly poisonous substance can become an excellent medicine.

There are several references of arsenic containing minerals in Indian Alchemy books like *Ayurveda Prakasha*, *Rasendra churamani*, *Rasatarangini*, *Rasendra Sara Sangraha* etc. Three main arsenic containing minerals (table-1) in Ayurveda are *Harital*, *Manhasila* and *Gouripasan*<sup>[12]</sup>.

According to the Ayurvedic classical literature there are several references that these compounds may be used in disorders of the blood. Regarding *Manhasila*, it is mentioned in *Ayurved Prakash*<sup>[13]</sup>, that “*Manhasilatyadi lekhami lekhamakari, dhatunmalan va dehasya visosyolekhanche yathlekhanam tadyatha kshaudram nirmusanam vacha yvah. Iti sesham subodham*” Whereas regarding *Harital* it is mentioned in classical texts, *Rasendra churamani*<sup>[14]</sup>, that, “*Sleshmatavavrakthavuthnuthkevalam cha khalu pushpahrishrih*”.

All the above Sanskrit *slokas* signifies the importance of arsenic compounds in blood disorders.

Patients suffering from APL have low immunity and hence they suffer from intermittent fever, thus resembling the symptoms of *visam jwara*.

In *Rasatarangini* also, regarding *Harital* it is written that “*Bimalam talakam snigdyā vuthjwarbinashanam. Twachya kushthadisaman kathito ch rasayanam*”<sup>[15]</sup>, it causes remission of high fever due to infection, it is a great immunomodulator and helps in formation of new red blood corpuscles and hence very useful in erythropoiesis and ultimately fights severe anemia.

It is also mentioned in *Rasatarangini* regarding *Manhasila* that “*...Kash swashhara vutupadrava nasini*”<sup>[16]</sup> Where as in *Rasendrachuramani* it is written that “*Satwatmika vutvishagni agnimandya kanduti kothchayaharini ch*”<sup>[17]</sup> Here *vutupadrava* means infection. We know that in leukemia due to unavailability of proper healthy white blood corpuscles, body is frequently prone to infection. Hence *Manhasila* have germicidal property according to the above verse and it fights infection, it is also a good medicament for high fever.

Regarding *Gouripasan*, it is mentioned in *Rasatarangini* that,

**“Agnimandyaharvisham jwarnashan  
kantiprada param jirna pandu rog nishudana”**<sup>[18]</sup>

From the above sloke it is clear that *Gouripasan* has direct influence over *pandu* (anemia) and high fever (*Visham jwar*).

Furthur more *Harital* is purified by *swedan* (~boiling) in *Benincasa hispida*<sup>[19]</sup> and *Manhasila* is purified by *bhavana* (~drying through trituration) in *Zinziber officinalis*<sup>[20]</sup> juice, respectively.

Studies have showed that there Induction of apoptosis by phenol compound, [8]-shogaol, 6 gingerol (found in *Zinziber officinalis*) via reactive oxygen species generation, glutathione depletion, caspase activation and mitochondrial membrane potential changes in human leukemia cells<sup>[21]</sup>. While Cucurmosin which is an active compound in *Benincasa hispida*, recently has been proved that it is a kind of

Ribosome inactivating protein (RIP), and has high rate of cell apoptosis<sup>[22]</sup>, hence purification by the above agents may enhance the synergistic effect of *Harital* and *Manhasila* in cellular apoptosis for the treatment of leukemia.

**Table 1**

Ayurvedic name	English name	Chemical formula
<i>Harital</i>	Orpiment	As <sub>2</sub> S <sub>3</sub>
<i>Manhasila</i>	Realgar	As <sub>2</sub> S <sub>2</sub>
<i>Gouripasana</i>	White Arsenic	As <sub>2</sub> O <sub>3</sub>

*Harital*, *Manhasila* and *Gouripasana* with their English counterpart and chemical formula.

### Arsenic trioxide in modern medicine

As<sub>2</sub>O<sub>3</sub> is currently being evaluated for treatment of relapsed / refractory (APL). As<sub>2</sub>O<sub>3</sub> is indicated for induction of remission and consolidation in patients with acute promyelocytic leukemia (APL) who are refractory to, or have relapsed from retinoid and anthracycline chemotherapy, and whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression.

Arsenic trioxide is registered under US-FDA in the year of 2000, as a standard treatment of relapse (APL). It is sold in the injection form and is supplied as a sterile, clear, colorless solution in 10 ml glass, single-use ampoules, by the drug manufacturers.

The mechanism of action of Arsenic trioxide is not completely understood. Arsenic trioxide causes morphological changes and DNA fragmentation characteristic of apoptosis in human promyelocytic leukemia cells lines like NB4 or HL-60 *in vitro*. Arsenic trioxide also causes damage or degradation of the fusion protein PML/RAR-alpha<sup>[23]</sup>.

### Bioavailability of *Harital* and *Manhasila* with respect to arsenic trioxide

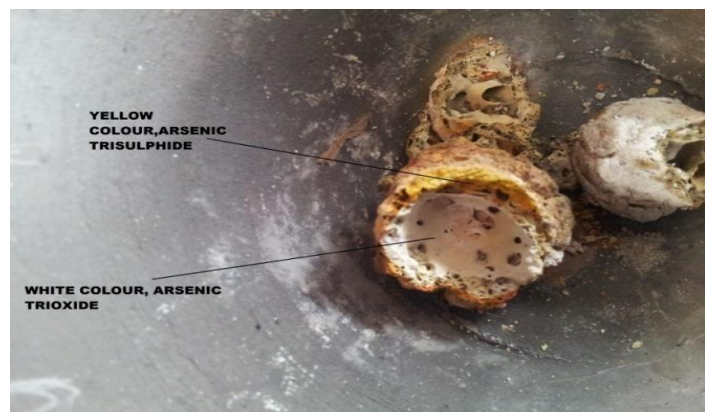
Arsenic trioxide is highly toxic compared to orpiment and realgar. Acute toxicity of arsenic trioxide is the major concern in the use of this agent to against malignancies. The clinical doses of arsenic trioxide (5-10 mg i.v.) could induce cardiac injury, such as QT prolongation, arrhythmias, and in extreme cases, cardiac arrest<sup>[24, 25, 26]</sup>. Other adverse effects include skin lesions, gastrointestinal symptoms, neuropathy and liver dysfunction are reported with long-term arsenic trioxide use<sup>[27, 28]</sup>. It is generally assumed that the severity of poisoning is related to the total amount of poison ingested, and assessment of health risk associated with arsenic exposure from human ingestion of traditional medicines has typically taken this tactic. However, in many cases, a significant portion of some forms of mineral arsenicals are poorly absorbed into the body and would be unavailable to cause systemic damage. The disposition of these arsenicals in the body depends on various key factors including solubility, absorption, distribution and excretion. Absorbed arsenic from *Harital* or *Manhasila* does appear in the blood, but with much less distribution to the tissues due to poor absorption. The bioavailability is a critical determinant of efficacy and toxicity of arsenical compounds. Thus, it is not surprising that *Harital* and *Manhasila* have quite different toxicological profiles from arsenic trioxide.

### Bhasmikaran process and potency

Ayurvedic *bhasmas* are popular as well as controversial worldwide. During *bhasmikaran* (calcination) process under high heat, sulphur gets vaporized from sulphur containing arsenic minerals and sulphide of arsenic forms trioxide of arsenic that is As<sub>2</sub>O<sub>3</sub><sup>[29,30]</sup>, and thus may

validate the usefulness of *bhasmikaran* process for sulphur containing arsenic minerals like *Harital*, in the blood disorders like leukemia. After *bhasmikaran* process the yellow coloured *Harital* is partly converted to white coloured *Gouripasan* after application of heat through the process of calcinations. The white portion (refer to Figure number 1) is arsenic trioxide, that is formed after calcinations of *Harital*.

As after *bhasmikaran* process, both *Harital* and *Manhasila* get converted to arsenic trioxide, the results of cellular apoptosis will follow the same profile of that of arsenic trioxide.



**Figure 1:** After calcination, yellow coloured *Harital* (arsenic trisulphide) forms white coloured *Gouripasan*(arsenic trioxide).

## DISCUSSION AND CONCLUSION

Acharya Charaka judiciously said that,

**“Vikaranama kushalo na jihavihat kadachana  
Nahi sarva vikaranam namatosti dhruvah sthiti”<sup>[31]</sup>**

which means a physician should not feel shy, if he could not name the disease. He should treat after analyzing the pathogenesis of the disease rather feeling shyness. Similarly though there is no direct reference of Leukemia in Ayurveda, but still diagnosis can proceed after analyzing the pathogenesis. Thus we see there are several references in ancient Ayurvedic classical literature about the use of arsenic in blood disorders and modern science prove the fact. Ayurvedic *bhasmas* of *Harital* or *Manhasila* may be a good answer for the infamous low bioavailability of this two compounds, because it makes the minerals more bio-compatible due to its increased surface area due to sub nano structure formation after *bhasmikaran* process and also their close resemblance to arsenic trioxide.

The review made a humble attempt to highlight the scientific aptitude of ancient protocols that are documented in ancient texts of Ayurveda and Rasashastra, the constant apathy towards indigenous system of medicine made our mind deprived of the scientific facts that are hidden in our classical texts. The review effectively points out the potential of arsenic containing ayurvedic minerals in the cellular apoptosis for the treatment of leukemia. The invention of Arsenic trioxide as a treatment of APL in modern medicaments, only support our rich scientific heritage. Furthermore *bhasmikaran* process may enhance the bioavailability of the drug and hence potentiate its action. There is a huge scope of the cellular apoptosis property of arsenic containing drugs in combating leukemia. Further research is welcomed in the case of *Harital* and *Manhasila* in respect to arsenic trioxide, because their toxicological profile is far better than arsenic trioxide.

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**Conflict of interest** – None declared.

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