Arsenic in the management of leukemia: An Ayurvedic perspective

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ABSTRACT

Gauripason, 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. 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). 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. But all this drug used or administered are from modern background. In Ayurveda the arsenic containing minerals are documented in several Ayurvedic literature has no direct reference for the diagnosis of leukemia or its sub classification, but indirect references are available with their treatment. In Iatrochemical 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 asfree 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.

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. 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 Voghbotto’s Astanga Hridayam, it is stated that Toto alpo rakta medasko nihsarah. 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 Vaidya Balendu Prakash from 1987 to 1996. Vd. Balendu Prakash
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; “Yadgadapi visam tikshnam uttam bhesajam Bhawt bhesajam chapī duryuktena tikshnam sampadhte visam”[11], 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 Prakash, Rasendra churamanī, Rasatarangini, Rasendra Sara Sangrahā etc. Three main arsenic containing minerals (table-1) in Ayurveda are Harital, Manhasila and Gouripasana[12].

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 Ayurveda Prakash[13] that “Manhasila tratata yadi lekhanī lekhamarkaṇī, dhautumala va dehasya visoṣyolekhanche yathlekhanam tadyaṭa kṣaḍārama nirmanaṃ vacha yvaḥ. Iti sesham subdhoḥ” whereas regarding Harital it is mentioned in classical texts, Rasendra churamanī[14], that, “Sleshmavatavisraktavuthnukethvalam ka chhalu pushpahrstrīḥ”. After 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 jwarā. In Rasatarangini also, regarding Harital it is written that “Bimalam talakam snigdha vuthvārwaḥīnasmā. Twachya kusthasadasmā kathito ch rasyaṃ”[15], 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 Manahsila that “...Kash swashhara vutupadrava nasinī[16]”. Where as in Rasendrarachuramani it is written that “Satwamitra vutvisvahinī agnimandya kandutī kothciḥ ch rasyaṃ”[17]. 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 Gouripasana, it is mentioned in Rasatarangini that, “Agnimandyaarvisham jwarānashan kantiprada param jirna pandu rog nishudānāḥ”[18].

From the above sloke it is clear that Gouripasana has direct influence over pandu (anemia) and high fever (Visham jwar). Further more Harital is purified by swad (<boiling> in Benincasa hispida[19] and Manhasila is purified by bhavana (<drying through trituration> in Ziziber officinalis[20]) juice, respectively.

Studies have showed that there induction of apoptosis by phenol compound, [8]-shogaol, 6 gingerol (found in Ziziber officinalis) via reactive oxygen species generation, glutathione depletion, caspase activation and mitochondrial membrane potential changes in human leukemia cells[21]. 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[22], 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

<table>
<thead>
<tr>
<th>Ayurvedic name</th>
<th>English name</th>
<th>Chemical formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harital</td>
<td>Orpiment</td>
<td>As₂S₃</td>
</tr>
<tr>
<td>Manhasila</td>
<td>Realgar</td>
<td>As₂S₃</td>
</tr>
<tr>
<td>Gouripasana</td>
<td>White Arsenic</td>
<td>As₂O₃</td>
</tr>
</tbody>
</table>

Harital, Manhasilaand Gouripasana with their English counterpart and chemical formula.

Arsenic trioxide in modern medicine

As₂O₃ is currently being evaluated for treatment of relapsed / refractory (APL). As₂O₃ 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[23].

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[24, 25, 26]. Other adverse effects include skin lesions, gastrointestinal symptoms, neuropathy and liver dysfunction are reported with long-term arsenic trioxide use[27, 28]. 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 arsenuclals are poorly absorbed into the body and would be unavailable to cause systemic damage. The dosing 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 As₂O₃[29,30], 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 kushala na jihovihat kadachana
Nahi sarva vikaranam namatosti dhruvah shhitw”

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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