

"A CRITICAL APPROACH ON THERAPEUTIC APPLICATION OF ARSENIC COMPOUNDS"

Dr. Vijaykumar B. Chavadi M.D (Ayu)

Asst. Professor

P.G Dept of Rasashastra and Bhaishajya kalpana
BVVS Ayurved Medical College and Hospital, Bagalkot-587101

E-mail: drvbc05@gmail.com

CONTENTS

- **INTRODUCTION**
- **BIOLOGICAL RESPONSES TO ARSENIC COMPOUNDS**
- **EDIBLE SOURCES OF ARSENIC**
- **PHARMACODYNAMICS**
- **PHARMACOKINETICS**
- **THERAPEUTIC APPLICATION OF ARSENIC COMPOUNDS IN DIFFERENT CONDITIONS. . .**
- **IMPORTANT YOGAS, DOSE, ANUPANA**
- **DISCUSSION**
- **CONCLUSION**
- **LIST OF REFERENCES**

INTRODUCTION

- Haratala, Manahshila & Gouripashana are the Arsenic compounds, which are mentioned in our classics.
- During Samhita kaala, in Cha.Su 1/70, Cha.Su 3/5 while explaining the Parthiva dravyas Haratala, Manahshila are mentioned.
- Also in Cha.Chi 7th chapter we can find the references of Arsenic compounds.
- In Asthanga Hridaya also we can find the references regarding Arsenic compounds.

- Arsenic combines with oxygen, chlorine and sulfur to make inorganic arsenic compounds.
- Inorganic arsenic compounds are used to preserve wood and make insecticides and weed killers.
- Arsenic in plants and animals combines with carbon and hydrogen to make organic arsenic.
- Organic arsenic is usually less harmful than inorganic arsenic.

- Arsenic is a common, naturally occurring substance in nature, it is rarely found in its pure elemental state.
- There are three inorganic forms of arsenic: red, yellow, and white.
- Red arsenic (arsenic disulfide, As_2S_2 , referred to as realgar or sandaraca)
- Yellow arsenic (arsenic trisulfide, As_2S_3 , referred to as arsenikon, aurum pigmentum, or orpiment) are toxic, chemically unstable complex sulfides.

- White arsenic (arsenic trioxide, As_2O_3) is an industrial by-product produced by roasting arsenic-containing ores (realgar) and salvaging and purifying the smoke.
- The organic arsenicals consist of an arsenic atom in its trivalent or pentavalent state linked covalently to a carbon atom.
- Compared with the inorganic forms, the organic compounds are often more stable, less toxic, and excreted more rapidly.

BIOLOGICAL RESPONSES TO ARSENIC COMPOUNDS

- Arsenic is a metalloid that generates various biological effects on cells and tissues. Depending on the specific tissue exposed and the time and degree of exposure, diverse responses can be observed.
- In humans, prolonged or high dose exposure to arsenic can have a variety of outcomes, including the development of malignancies, severe gastrointestinal toxicities, diabetes, cardiac arrhythmias and death.
- On the other hand, one of the arsenic derivative, arsenic trioxide (As_2O_3), has important antitumor properties.

- This agent is a potent inducer of antileukemic responses, and it is now approved by the Food & Drug Administration for the treatment of acute promyelocytic leukemia in humans.
- An emerging approach of interest and therapeutic potential involves efforts to target and block cellular pathways activated in a negative feedback manner during treatment of cells with As_2O_3 .
- Such an approach may ultimately provide the means to selectively enhance the suppressive effects of this agent on malignant cells and render normal resistant to tumors due to its antineoplastic properties.

EDIBLE SOURCES OF ARSENIC

ARSENIC IN FOOD

- Fish
- Chicken
- Goat meat
- Beef liver
- Potato
- Brinjal.

PHARMACODYNAMICS

- Inhaled and ingested inorganic arsenic compounds first of all enter the blood. With a half-time of two hours, inorganic arsenic is rapidly eliminated from the blood.
- The arsenic compounds are distributed, as investigations with radioactively labelled arsenic compounds showed, in all the organs investigated.

- In addition to renal elimination, biliary excretion takes place.
- Experiments showed that elimination occurs in 3 phases in man.
- About 66 % of the administered doses is renally eliminated with a half-time of 2.1 days, around 30% with 9.4 days and the rest (4 %) with of 38.4 days.

PHARMACOKINETICS

- Absorption of arsenic in inhaled airborne particles is highly dependent on the solubility and the size of particles; material that reaches the lungs will be well absorbed.
- Studies in experimental animals and humans have shown that both soluble pentavalent and trivalent arsenic compounds are rapidly and extensively absorbed from the gastrointestinal tract (over 90%); these include arsenious acid and sodium arsenite.
- Insoluble compounds such as arsenic disulphide are poorly absorbed.

- Inorganic arsenic compounds react with sulphhydryl (-SH) groups of cellular proteins, thereby inhibiting enzymes and therefore oxidative processes including pyruvate and succinate pathways.

- Arsenic metabolism is characterized by 2 main types of reactions:

1) Reduction reactions of pentavalent to trivalent arsenic,

2) Oxidative methylation reactions in which trivalent forms of arsenic are sequentially methylated to form mono-, di- and trimethylated products using *S*-adenosyl methionine (SAM) as the methyl donor and glutathione as an essential co-factor.

- Methylated products (MMA and DMA) are readily excreted in urine.

- The metabolism and disposition of inorganic arsenic may be influenced by its valence state, particularly at high dose levels.
- Studies in laboratory animals indicate that administration of trivalent arsenic, such as arsenic trioxide, results initially in higher concentrations in most tissues than does the administration of pentavalent arsenic.
- However, the trivalent form is more extensively methylated, leading to similar long-term excretion.

- Concentrations of arsenic or its metabolites in blood, hair, nails and urine may be used as biomarkers of arsenic exposure.
- Blood arsenic is a useful biomarker only in the case of acute arsenic poisoning or stable chronic high-level exposure.
- Since the elimination of arsenic takes place mainly via the kidneys, the concentration of arsenic in the urine is a good indication of recent exposure to inorganic arsenic.

**THERAPEUTIC APPLICATION
OF ARSENIC COMPOUNDS IN
DIFFERENT CONDITIONS...**

Therapeutic application of arsenic compounds in...

- **CANCER** [Acute promyelocytic leukemia (APL)]
- **MULTIPLE MYELOMA**
- **PSORIASIS**

Therapeutic application of arsenic trioxide in...
CANCER [Acute promyelocytic leukemia (APL)]

Although the precise mechanism of arsenic trioxide action is unknown, a variety of in vitro studies suggest that several mechanisms may contribute to its effectiveness in vivo.

- THESE MECHANISMS INCLUDE ...
- Induction of apoptosis,
- Partial cellular differentiation,
- Degradation of specific APL fusion transcripts,
- Antiproliferation and
- Inhibition of angiogenesis.

- Many of the studies that show specific activities for arsenic trioxide in APL have used NB4.
- NB4 is a unique cell line that carries the transcript(15;17) translocation juxtaposing the *PML* and *RARA* genes and was derived from the bone marrow of an APL patient.

Induction of Apoptosis

- Apoptosis, or programmed cell death, occurs during senescence of normal cells.
- Inhibition of this process can immortalize cells and occurs through several mechanisms including upregulation of bcl-2 activity, deletions of the retinoblastoma (*RB*) gene, *p53* mutations, and over expression of cyclin D2.

Inhibition of Angiogenesis

- Angiogenesis plays a critical role in the growth of solid tumors and may also be important for the expansion of leukemic cell populations.
- Arsenic trioxide has inhibited angiogenesis in both systems. In experimental solid tumors, a single administration of arsenic trioxide produced preferential vascular shutdown in the tumor tissue with a resultant hemorrhagic necrosis.

- This phenomenon was repeatable and without apparent toxic effects on the normal skin, muscle, or kidneys of the experimental animals.
- Studies of human umbilical vein endothelial cells treated with arsenic trioxide have revealed a series of events that may contribute to the ability of arsenic to exert antitumor activity.

- They include activation of endothelial cells, upregulation of endothelial cell adhesion molecules, prevention of capillary tubule growth and branching vessels, apoptosis of endothelial cells, and inhibition of vascular endothelial growth factor production.
- It is possible that release of vascular endothelial growth factor by the leukemic cells causes a positive feedback loop with the paracrine production of GM-CSF, IL-6, IL-7, and IL-10 by the stimulated, rapidly proliferating endothelial cells.
- (IL-Interleukin factor)

- These cytokines then provide additional growth signals to the leukemic cell population, and a vicious cycle ensues.
- The ability of arsenic trioxide to interrupt this loop may contribute to its efficacy.

Therapeutic application of arsenic trioxide in...
MULTIPLE MYELOMA

- Multiple myeloma remains an incurable malignancy with a median survival that does not exceed 3 years.
- At least one third of patients with multiple myeloma fail to respond to induction chemotherapy, and those who initially achieve remission eventually relapse and require additional therapy.

- Recent reports demonstrating the efficacy of arsenic trioxide in acute promyelocytic leukemia have prompted a revival in the clinical use of this compound.
- The achievement of clinical responses marked by molecular conversion of the malignant phenotype and remissions in patients who had failed to respond to multiple courses of conventional chemotherapy provided the impetus to explore its use in multiple myeloma.

- Properties that favor the use of arsenic trioxide are its ability to target selectively malignant cells for apoptosis through enhancement of reactive oxygen species, to induce differentiation, and to inhibit angiogenesis.
- Multiple events involved in the pathogenesis of multiple myeloma coincide with pathways targeted by arsenic trioxide, and early results have suggested that clinical responses and safety in patients are promising with advanced disease.

Arsenic-Based Antineoplastic Drugs and Their Mechanisms of Action

- Arsenic-based compounds have become accepted agents for cancer therapy providing high rates of remission of some cancers such as acute promyelocytic leukemia (APL).
- This knowledge was gained in parallel with increasing understanding and awareness of the importance of intracellular redox systems and regulation of the production of reactive oxygen species (ROS) by controlling mitochondrial function.

- Many of the targets for the arsenic-containing compounds are mitochondrial proteins involved in regulating the production of ROS.
- Inhibition of these proteins by disulfide linkage of vicinal thiol groups often leads to increased production of ROS and induction of apoptotic signaling pathways.
- Sensitivity or resistance to the actions of arsenic-containing compounds on cancer cells and normal cells depends on the levels of transport systems for their uptake or efflux from the cells as well as their redox defence mechanisms.

TARGETING OF CANCER CELLS: SELECTIVE UPTAKE AND DELIVERY INTO SPECIFIC TYPES OF CANCER CELLS

- As(III) as the anhydrous form of $\text{As}(\text{OH})_3$ received FDA approval in 2000 as a chemotherapeutic agent for the treatment of APL.
- Acute promyelocytic leukemia (APL) is associated with reciprocal and balanced chromosomal translocations always involving the retinoic acid receptor alpha (RARalpha) gene on chromosome 17 and variable partner genes on distinct chromosomes.
- RARalpha fuses to the promyelocytic leukemia (PML) gene in the majority of APL cases.

- Arsenic trioxide is particularly effective at killing APL cells and this was proposed to be the direct result of its ability to induce the relocalization and degradation of the nuclear body protein PML, as well as the degradation of PML-RARalpha in APL cells.
- In this regard, it is worth noting that Aquaglyceroporins AQP7 and AQP9 are present in normal cell types.
- Interestingly, AQP9 is primarily expressed in human lung, liver, and leukocytes and this may help explain arsenic toxicity, given that liver is one of the main organs affected.

- The fact that AQP9 provides APL cancer cell specificity with high response rates suggests that if arsenic-containing compounds could be targeted for specific delivery into cancer cells, then they would represent outstanding agents for killing these cells.
- Vicinal thiols located in key enzymes and proteins provide targets for reaction with arsenic-containing compounds, particularly organic derivatives such as phenylarsenic-containing compounds that favour intramolecular cross-linking between adjacent thiols.

- Most of the key intracellular targets for this reaction have been identified to include the main REDOX regulatory systems in the mitochondria, including thioredoxin and peroxiredoxin systems and the adenine nucleotide transporter, all of whose function is adversely affected.
- The net result is the activation of several independent pathways including ROS production to facilitate the induction of apoptosis.

Therapeutic application of arsenic trioxide in...

PSORIASIS

RASAMANIKYA (ARSENIC) AND ANGIOGENESIS

- Rasamanikya strengthens the blood vessels and Arsenic is one of the micro-nutrient of the human beings (10 to 25 micrograms/day diet intake is necessary).
- The new research work done by Barchowsky and colleagues after thorough examination and several observations proves that arsenic has good effects in living systems.
- The group has found that the growth factors stimulated by low levels of arsenic promote the formation of new micro vessels, a process called angiogenesis.
- New blood vessels are essential in providing nutrients for rebuilding or repairing tissue, a process called tissue remodeling.

cont...

- In Ekskustha (Psoriasis), there is a need of repair and remodeling skin tissue that will be done by Rasamanikya.
- The arsenic mainly absorbs in skin,Hairs,and Nails similarly their the disease Psoriasis occurs in skin,Hairs and Nails, thus the rasamanikya target the diseased area and remodelling the skin tissue thus it cures the Ekakushta (psoriasis).
- Rasamanikya induces apoptosis (Am. J. Hematol. 78:113-116, 2005.) of death skin tissue after that by angiogenesis repairing and remodelling of the skin tissue occurs.

IMPORTANT YOGAS

- Mallasindura
- Suchikabharana rasa
- Chandeshwara rasa
- Rasamanikya
- Sameerapannaga rasa
- Nityananda rasa
- Kasturibhairava rasa
- Smrutisagara rasa

Therapeutic dose

- Haratala - $1/4$ to $1/2$ ratti.
- Manahshila - $1/8$ to $1/4$ ratti.
- Gouripashana - $1/120$ to $1/30$ ratti
- **ANUPANA**

Madhu, Grutha, Dugdha.

according to the diseases anupana will change.

- **DAILY INTAKE;**
- 1/2 to 1 mg contains in food and water.

- **FATAL DOSE & FATAL PERIOD;**
- 0.1 to 0.2 mg & 1-2 days.

- **DURATION OF ADMINISTRATION;**
- In chronic diseases start with low dose, after 15 days increase the dose.

- The disease which manifest due to consumption of unpurified Haratala can be cured by the purified Haratala.

EFFECTS OF UNPURIFIED ARSENIC:

- Reduces Kaanti of body.
- Raises body temperature.
- Contracts the body parts and organs.
- Induces body pain,
- Increases Kapha-Vata,
- Produces Prameha and Kustha rogas.

ANTIDOTE:

- Use kajjali and sharakara for 3 days or use yavakshar, kushmanda for 3 days.
- These drugs act as an antidote and thus prevent its bad effects

DISCUSSION

- Compared with the inorganic forms, the organic compounds are often more stable, less toxic, and excreted more rapidly.
- The promise and therapeutic potential of arsenic and its various derivatives have been exploited for hundreds of years. Remarkably, research focused on the potential use of arsenic compounds in the treatment of human diseases remains highly promising, and it is an area of active investigation.

CONCLUSION

- Arsenic is said to be toxic in its inorganic form where as highly effective in its organic form.
- The inorganic arsenic compounds should be subjected to proper Shodana & Marana to make them fit for internal administration.
- Apart from the therapeutic applications such as... cancer [Acute promyelocytic leukemia (APL)], multiple myeloma, Psoriasis, also it can be extensively used in syphilis, Neurological conditions etc...

REFERENCES

- **Charaka samhita**
- **Asthanga Hridaya**
- **Rasaratna samuchhaya**
- **Rasatarangini**
- **Anderson, Kenneth C. MD; Boise, Lawrence H. PhD; Louie, Robert PhD; Waxman, Samuel MD**
- **www.metalloids.com**

THANK YOU