



ARSENICS IN CANCER – A CONCEPTUAL STUDY

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ABSTRACT

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and /or spread to other organs. Nowadays Cancer is a leading cause of death worldwide, accounting for nearly 1,958,310 new cancer cases and 609,820 cancer deaths are projected to occur in the United States in 2023. This disease is a leading source of morbidity and mortality. Arsenic an environmental element, obtained a position in history, both as a recommended poison and as a miracle medicine. Arsenic and its related compounds regulates various pathways involves various cellular response such as growth inhibition etc and helps to sensitize the cell for cell-cycle arrest and cell death.

KEYWORDS: Arsenic, Cancer, Cell cycle, Cell death.

INTRODUCTION

Cancer is a most deadly disease in 21st century, after cardiac disorders and stroke. Nearly 609,820 cancer deaths are projected to occur in the United States in 2023, which is defined as uncontrollable cell proliferation.^[1] Cancer is an inflammatory and non-inflammatory swelling. In Ayurveda Acharya Charaka and Sushruta has mentioned these swelling as Granthi and Arbuda. Vata and kapha dushti is the cause for Granthi and Arbuda.^[2] There are no any specific etiological factors for these swellings, based on the symptoms we can correlate cancer to arbuda. Due to vata and kapha dushti, rakta, mamsa and medha dhatu are vitiated that which does the jatharagni and dhatwagni manda, produces ama this causes dhatugata vikara's in the form of Granthi etc.^[3] Arsenic an environmental element which has obtained a place in history of Rasa dravya's. Arsenic is derived from Greek Word 'Arsenikon' meaning "potent". Chemical formula of Arsenic- As, Atomic number- 33, Molecular weight- 74.92 gram, Colour- Lead Grey, Grey & White, Hardness- 3.5, Metallic & Nonmagnetic, Poor conductor of heat & electricity.^[4] Eventhough arsenics are known for its most potent poisonous property, used for the treatment purpose since from the Pre-vedic and vedic period, Acharya Charaka and Sushruta also mentioned the use of Arsenic like orpiment (Haratala) and realgar (Manashila) in the treatment. Hippocrates and Galen are mentioned the use of arsenic in ulcers. Arsenicals were

also largely used for medicinal purposes in traditional Chinese Medicine in the regimens for psoriasis, Rheumatic diseases and Syphilis.^[5] So an attempt is made to collect the information about the carcinogenic action of the arsenics in this article.

Forms of Arsenic^[6]

- Inorganic
- Organic
- Arsine Gas

Sources of Arsenic^[7]

Geogenic sources- volcanic eruptions, weathering of rocks and minerals

Biogenic sources- plants, animals/micro-organisms/aquatic biota

Anthropogenic sources- agricultural (pesticides etc), industrial (tannery, paints etc), others (municipal wastes, mining etc).

Arsenics in Ayurveda

Haratala
Manashila
Gouripashana

Haratala and Manashila are grouped under Uparasa varga of Rasadravya's and Gouripashana is under Sadharana rasa varga.

Haratala is a 5th mineral drug of Uparasa Varga, Chemical formula- As_2S_3 , Chemical Name- Arsenic Trisulfide, Lethal Dose- 125- 250 mgs of unpurified form.

Manashila is a 6th Mineral Drug of Uparasa Varga, Chemical Formula- As_2S_2 , Chemical Name-Arsenic Disulphide, Lethal Dose- 125- 250 mgs of Unpurified form.

Gouripashana is a 2nd Mineral Drug of Sadharana Rasa Group, Chemical Formula- As_2O_3 , Chemical Name-Arsenous Trioxide, Lethal Dose- 125-250 mgs of unpurified form.

Dravya's	Pharmacological and therapeutic properties
Haratala ^[8]	Katu, Tikta, Kashaya rasa, Snigdha, Guru guna and Ushna virya. Therapeutic action – Kushtahara, Romaharaka, Agnidipti, Kantikaraka, Balakara, Pushtikara, Jwaraghna, Nadvirana, Visarpahara
Manashila ^[9]	Katu, Tikta Rasa, Guru, Snigdha Guna, Ushna Virya and Katu Vipaka. Therapeutic action – Lekhana, Rasayana Deepana, Shwasahara, Kasahara, Jwaraghna, Kandughna, Varnya, Vishapaha
Gouripashana ^[10]	Tikta rasa, Ruksha Guna, Karma- Balya, Rasayana, Rasabandhakara. Therapeutic action-Shotha, Gulma, Pandu, Shwasa, Kasa, Sheetajwara, Shlipada, Phiranga, Kushta, Hritshoola, Hrit dourbalya Nashaka.

Cancer^[11]

Cancer is characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. Cancer often has the ability to spread throughout the body.

Cancer is the second leading cause of death in the world. But survival rates are improving for many types of cancer.

Common Causes

- Smoking and tobacco
- Exposure to Chemical
- Toxic compound exposures
- Ionizing radiation
- Some pathogens
- Idiopathic
- Genetic Changes

Symptoms^[12]

- Signs and symptoms will vary depending on what part of the body is affected.
- Some general signs and symptoms associated with, but not specific to, cancer, include:
 - Persistent Fatigue
 - Lump
 - Weight changes, including unintended loss or gain
 - Skin changes, such as yellowing, darkening or redness of the skin, sores that won't heal
 - Changes in bowel or bladder habits
 - Persistent cough or trouble breathing
 - Difficulty swallowing
 - Hoarseness
 - Persistent indigestion or discomfort after eating
 - Persistent, unexplained muscle or joint pain
 - Persistent, unexplained fevers or night sweats
 - Unexplained bleeding or bruising.

Types

- There are more than 200 types of cancer and we can classify cancers according to where they start in the body, such as breast cancer or lung cancer.
- Cancer can also be grouped according to the type of cell they start in, there are 5 main groups these are
 1. Carcinoma
 2. Sarcoma
 3. Leukaemia
 4. Lymphoma
 5. Myeloma

Staging system and Grading^[13]

- There are 2 main types of staging systems for cancer, those are
 - TNM System
 - Number System- Stage 1,2,3,4
- Cancer in situ

Grading?

- Tumour grade describes a tumour in terms of how abnormal the tumour cells are when compared to normal cells.
 - There are 3 grades, they are:
 - Grade 1
 - Grade 2
 - Grade 3

General treatment

- Surgery
- Radiation
- Hormone Therapy
- Chemotherapy
- Targeted Therapy

Mechanism & Pathway

Effect of DAR (Darinaparsin) on cellular pathway^[14]

DAR (Darinaparsin) effects on cellular pathway in 2 Pathways

First Pathway

- Darinaparsin (DAR) – an organic form of arsenic composed of dimethylated arsenic (an inorganic arsenic metabolite) & Glutathione.
- DAR enter the cells in the form of DMA III (Dimethylarsenic) at low concentrations of exogenous glutathione or in the absence of it.
- Before uptake into the cells, DAR is processed by the enzyme γ - Glutamyl transpeptidase (γ -GT) on the cell surface to S- (Dimethylarsenic) cysteine (DMAIII- cys).
- Finally the multiple cysteine / cysteine importers transport DMAIII(cys) into the cells.
- It induces G₂ / M cell cycle arrest & apoptosis in tumor cells primarily through disruption of mitochondrial functions by inducing cleavage of caspase 8 & 9.

Second Pathway – Initiation of apoptosis by production of ROS (Reactive oxygen species)

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- Finally the multiple cysteine / cysteine importers transport DMAIII(cys) into the cells.
- Then DAR initiates 2 major pathways for ROS generation namely, NADPH (nicotinamide adenine dinucleotide phosphate hydrogen) oxidase activation & disruption of the mitochondrial transport chain.
- DAR activates cystolic subunits of NADPH oxidase complex P67PHOX & P47PHOX.
- Which resulting in the translocation of NADPH oxidase to the membrane & produces ROS.
- This disrupts mitochondrial membrane potential and release (ooze out) Cytochrome C into the cytoplasm which leads to the activation of apoptosome that ends into cellular apoptosis.

Molecular Mechanism of GSAO[4-(N-(S-Glutathionylacetyl) amino]phenylarsonous acid^[15]

- GSAO phenylarsonous acid is a conjugate of Glutathione & Phenylarsonous acid, during biotransformation the γ –glutamyl residue of GSAO is cleaved at the cell surface by γ –glutamyl transpeptidase & GCAO [4-(N-(S-

Cysteinylglycylacetyl) amino] phenylarsonous acid forms.

- Then enters cell through an organic ion transporter and is converted to CAO[4-(N-(S-cysteinylacetyl)amino] phenylarsonous acid by dipeptidases.
- CAO reacts with mitochondrial ANT (adenine nucleotide- translocase) & inactivates it via cross-linking 2 of the three matrix facing cysteine thiols.
- Proper functioning of ANT is essential for cell viability targeting this protein in angiogenic endothelial cells is a powerful means of blocking angiogenesis and cell proliferation, finally resulting in cell death.
- It implies that GSAO should be more effective against γ -GT – positive tumors.
- Notably, Tumors of the breast, prostate, colon, liver & ovary expresses γ -GT, whereas soft tissue tumors tend not to express this enzyme.
- Metabolism of GSAO by tumor endothelium γ -GT is able to produce high concentrations of GCAO, which will block tumor angiogenesis & tumor growth.

Probable Mode of Action - Ayurvedic View

- Haratala, Manashila, Gouripashana are having mainly katu, tikta rasa's and ushna virya property which acts as Pachaka, Deepana, Kledahara which helps to combat Ama, Ajeerna, Jwara, Kasa, Shwasa which are the common symptoms in cancer.
- Prime criteria is to maintain rogi bala and counterpart the rogi bala, which impart vyadhikshamatva of the individual.
- Haratala, Manashila are Vatakaphagna and Gouripashana acts as Tridoshaghna.
- Haratala & its compound exhibits Rasayana Property as Haratala is best ojavardhaka it replaces decomposed & died tissue and support normal cell growth, regains normal physiology of patients.

DISCUSSION

Eventhough arsenics are known for its most potent poisonous property, used for the treatment purpose since from the Pre-vedic and vedic period, Acharya Charaka and Sushruta also mentioned the use of Arsenic like orpiment (Haratala) and realgar (Manashila) in the treatment. Hippocrates and Galen are mentioned the use of arsenic in ulcers. Arsenicals were also largely used for medicinal purposes in traditional Chinese Medicine in the regimens for psoriasis, Rheumatic diseases and Syphilis. Arsenicals causes disruption of mitochondrial functions by inducing caspase 3 & 9 which arrest the cell cycle and further divdation of cells by causing apoptosis. Haratala, Manashila are Vatakaphagna and Gouripashana acts as Tridoshaghna. Haratala & its compound exhibits Rasayana Property as Haratala is best ojavardhaka it replaces decomposed & died tissue and support normal cell growth, regains normal physiology of patients.

CONCLUSION

Arsenic and its related compounds disturb the natural oxidation and oxidative reduction equilibrium by regulating various pathways involves various cellular response such as growth inhibition, induction of apoptosis, angiogenesis inhibition and the arsenic combinations with chemo preventive or anticancer agents have been observed to sensitize the cell for cell-cycle arrest and cell death. Further more advancements and research studies are required to understand the effect of arsenics in cancer and reduce the morbidity of cancer and improve both the disease outcomes and the quality of life for patients with cancer.

REFERENCE

1. <https://pubmed.ncbi.nlm.nih.gov/36633525/#:~:text=In%202023%2C%201%2C958%2C310%20new%20cancer,occur%20in%20the%20United%20States.>
2. Kaviraj Dr Ambikadutta Shastri, Sushruta Samhita, Chaukhambha Sanskrit Sansthan, Part 1, reprint, Nidanasthana, 2016; 11: 352.
3. Kaviraj Dr Ambikadutta Shastri, Sushruta Samhita, Chaukhambha Sanskrit Sansthan, Part 1, reprint, Nidanasthana, 2016; 11: 350.
4. <https://en.wikipedia.org/wiki/Arsenic>.
5. Miller WH, Schipper HM, Lee JS, Singer J, Waxman S. Mechanism of action of arsenic trioxide. *Cancer Res*, 2000; 62: 3839 – 3903.
6. https://www.atsdr.cdc.gov/csem/arsenic/what_arsenic.html
7. https://www.cdc.gov/biomonitoring/Arsenic_FactSheet.html#:~:text=Inorganic%20arsenic%20compounds%20are%20in,mainly%20in%20fish%20and%20shellfish.
8. Shri Vagbhatacharya, Rasaratna Samucchaya, Edited by Kaviraj Shri Ambikadatta Shastri, 10th Edition, Varanasi, Published by Chaukhambha Amarabharati Prakashan, Tiritiya Adhyaya, 2015; 73: 76.
9. Shri Vagbhatacharya, Rasaratna Samucchaya, Edited by Kaviraj Shri Ambikadatta Shastri, 10th Edition, Varanasi, Published by Chaukhambha Amarabharati Prakashan Tiritiya Adhyaya, 2015; 94: 78.
10. Shri Vagbhatacharya, Rasaratna Samucchaya, Edited by Kaviraj Shri Ambikadatta Shastri, 10th Edition, Varanasi, Published by Chaukhambha Amarabharati Prakashan, Tiritiya Adhyaya, 2015; 84.
11. https://en.wikipedia.org/wiki/Causes_of_cancer.
12. <https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588>.
13. <https://www.nhs.uk/common-health-questions/operations-tests-and-procedures/what-do-cancer-stages-and-grades-mean/#:~:text=Number%20staging%20system&text=stage%201%20%E2%80%93%20the%20cancer%20is,part%20of%20the%20immune%20system>
14. Don AS, Kisker O, Dilda P, Donoghue N, Zhao X, Decollogne S, Creighton B, Flynn E, Folkman J and Hogg PJ. A peptide trivalent arsenical inhibits tumor angiogenesis by perturbing mitochondrial function in angiogenic endothelial cells. *Cancer cell*, 2003; 3: 497-509.
15. Dilda PJ, Emma ER, Alessandro C, Alfonso P and Philip JH, Metabolism of the tumor Angiogenesis inhibitor [4-(N-(S-Glutathionylacetyl) amino] phenylarsonous acid. *J Biol Chem*, 2008; 283: 35428-34.