Journal of Advanced Zoology

*ISSN: 0253-7214*
*Volume **44** Issue **S-6 Year 2023** Page **1605:1610***

# Arsenic As a Therapy in Cancer: A Short Review

**Sabarni Sarkar[1], Pritha Pal[2*]**

*[1]Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal, W.B., India.*
*[2*]Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, West Bengal, W.B., India.*

**Corresponding author's E-mail: prithap@svu.ac.in*

***Article History***

Received: 28 Sept 2023
Revised: 21 Oct 2023
Accepted: 02 Nov 2023



***Abstract***

*Acute myeloid leukemia (AML) is a cancer of the blood and bone marrow in which the bone marrow produces immature white blood cells, called myeloblasts. AML (acute myeloid leukemia) prevents these myeloblasts from developing into mature, healthy blood cells, as a result they accumulate and crowd out other healthy cells, such as red blood cells, white blood cells, and platelets. Sometimes acute myeloid leukemia(AML) can also spread to other organs, such as the brain, spinal cord, liver, or spleen. Without prompt treatment, AML can be life-threatening. There has been 2–3 cases per 100,000 people annually. Compared to women, men are more likely to experience it. acute myeloid leukemia(AML) makes up roughly 3% of all malignancies, with a median age of 32 years, according to the population-based Cancer Registry for Delhi. Among the various drugs for treatment of leukemia arsenic has been one of the most effective in treating it. Arsenic has been known as poison over 4000years.Long-term exposure to as has led to various adverse effects on health, but after the discovery of chemo therapeutic properties of As the understanding has been changed from poison to drug. Arsenic trioxide (ATO) is the most active antileukemia agent in treatment of acute promyelocytic leukemia(APL). Arsenic trioxide (ATO) cause degradation of PML RAR alpha promoting differentiation. Not only this but also arsenic induces apoptosis via mitochondrial caspase or formation of reactive oxygen species (ROS) and deleting GSH content of cell. This article focuses on the therapeutic effect of arsenic on acute myeloid leukemia.*

**Keywords:** *Acute Myeloid Leukemia, Arsenic Trioxide, PML RAR Alpha, Reactive Oxygen Species*

## 1. Introduction

Arsenic is the 20th most prevalent element in the crust of the planet. It is the 33rd element on the periodic table, found everywhere in organic or inorganic forms; pure metallic arsenic is far less common. There are 5 valence states of arsenic: 0 (arsenic), V (arsenate), III (arsenite), I (arsonium metal), and III (arsine). Natural sources of inorganic arsenic include soils and sedimentary rocks such minerals and ores that include copper or lead. It frequently coexists with other elements, most notably oxygen, chlorine, and sulphur. There are three different types of inorganic arsenic: red arsenic ($As_4S_4$, also known as realgar), yellow arsenic ($As_2S_3$, commonly known as orpiment), and white arsenic (arsenic trioxide, ATO; As2O3). (Chenet al., 2011)

Although long term exposure to arsenic has various adverse health impacts, the contradictory nature of arsenic also saves lives. In balanced translocation known as t (15;17) (q22; q12-21) that causes the fusion of the retinoic acid receptor alpha (RARA) and promyelocytic leukaemia (PML) genes causes acute promyelocytic leukemia(APL). In the majority of these instances, molecular investigation identifies an underlying PML-RARA fusion transcript that resulted from cytogenetically obscure or difficult insertion events.(Yilmazetal., 2021) the production of the fusion protein PML—RARA, which prevents normal promyelocytic cells from differentiating and encourages the growth of leukaemia cells.PML.RARA degradation is encouraged by arsenic trioxide, which is now regarded as "the most effective anti-leukemic agent in treatment of APL(acute promyelocytic leukemia) patients."(Meijuanetal., 2014).Using ATO(arsenic trioxide) and all-*trans* retinoic acid(ATRA) together has the potential to "replace conventional approaches for most, if not all, patients in the very near

future." Over the past ten years, ATO (arsenic trioxide) has gained widespread recognition, and evidence of more ATO (arsenic trioxide) applications—from those with relapsed APL to those who have just been diagnosed—has increased. (Rao et al., 2013)

## 2. Materials And Methods

The information for this review was obtained by searching in PubMed Central, Google Scholar and Google for published research work on therapeutic effect of arsenic in cancer. No language other than English was used for writing this review.

## 3. Results and Discussion

***Negative Health Impact Of Arsenic:*** Arsenic is an established class I human carcinogen declared by the International Agency of Research on Cancer. Ingestion of arsenic is associated with different types of cancer like in skin, kidney, liver, liver, prostate, lung etc.The toxicity propagated by arsenic involves different aspects of cellular damages via the processes of generation of ROS with oxidative stress, alteration of DNA-repair presses with genotoxicity /carcinogenicity and mitochondrial and cytoskeletal damages (Medda et al., 2021).Arsenic exposure in humans occurs mostly from ingesting water, air, food, exposure in work environments, and other environmental sources. Arsenic is frequently found in seafood, particularly in organic forms Chronic or long-term exposure to arsenic is also associated with extremely adverse health consequences like such as dermatitis, heart conditions, chronic bronchitis, immune system complications, diabetes, liver damage, kidney failure, peripheral neuropathy, and other detrimental hematological effects, reproductive complications, and other Illnesses. In actuality, arsenic damages nearly all essential human body organs that have been destroyed or are malfunctioning. (Khairulet al., 2017). For living things, arsenic species that are inorganic are often more hazardous than those that are organic, and arsenite is typically more toxic than arsenate. Trivalent arsenic is hazardous because it has a strong affinity for sulfhydryl groups on biomolecules like glutathione and lipoic acid as well as cysteinyl residues on several proteins and enzymes. Arsenic binds to sulfhydryl groups and increases the activity of enzymes and genes associated to glutathione. Because enzymes including glutathione reductase, glutathione peroxidase, thioredoxin reductase, and thioredoxin peroxidase are inhibited by the production of As III-sulfur bonds, they have a number of negative impacts. Reactive oxygen species (ROS) are produced as a result of arsenic exposure because all of these enzymes control cellular redox status by offering antioxidant defence. (Rao et al., 2013)

### Effect of Arsenic on Leukemia

***Arsenic Trioxide with all-trans retinoic acid (ATRA):***Acute promyelocytic leukemia(APL), the M3 subtype of acute myeloid leukemia (AML M3), is distinguished by the buildup of aberrant promyelocytes in blood and bone marrow, the presence of fibrinogenopenia and disseminated intravascularcoagulation, and the particular chromosomal translocation t(15;17)(q22;q21).The promyelocytic leukemia (PML) RAR fusion protein, which is the primary initiator of APL leukemogenesis, is produced when the t(15;17) fuses the retinoic acid receptor (RAR) gene on chromosome 17 to the promyelocytic leukemia (PML) gene on chromosome 15q.The initial ray of hope is provided by chemotherapy (anthracyclines), but all-trans retinoic acid (ATRA), which causes the final differentiation of APL cells, has a complete remission (CR) rate of 90%. APL is seldom cured by ATRA alone; however, a large number of cures were made possible by ATRA combined with anthracyclines. Patients with APL who have relapsed or are resistant to treatment are more likely to survive longer because of arsenic trioxide (ATO). Additionally, the combination of ATRA and ATO together not only significantly improves the clearing of the PML-RAR transcript but also raises the 5-year overall survival (OS) rate to 91.7%. The PML-RAR fusion protein is catabolized by both ATRA and ATO in the same manner. (Chen et al., 2011)

***PML RAR degradation by arsenic trioxide (ATO):*** Arsenic trioxide (ATO) has been found to directly attach to the PML portion of the PML-RARαfusion protein, enhancing the ubiquitination and destruction of the fusion protein via the ubiquitin proteasome pathway. To the best of our knowledge, ATO directly binds to the C-C motif of the B2 domain of PML, causing the oxidation of these residues and eventually leading to the formation of intramolecular disulfide bonds. Additionally, by increasing the SUMO-conjugating enzyme UBC9's affinity for the PML RING domain, SUMOylation of PML may be induced. The PML/PML-RARα is then polyubiquitinated by the SUMO-dependent ubiquitin E3 ligase RNF4 and reorganized from a diffuse or micro speckled nuclear pool into the matrix-related structure of macromolecules known as PML-NBsand then destroyed by the proteasome. The proteasomes, ubiquitin, and RNF4 that the SUMOylated PML recruits may combine the ubiquitination, SUMOylation, and degradation processes. ATO causes PML to oligomerize as a consequence, which improves its interaction with the SUMO-conjugating enzyme UBC9. This leads to more SUMOylation and destruction via the ubiquitin proteasome pathway. Combining these effects, ATO therapy causes

the DNA-binding PML-RARα co-repressor complex to become inactive. This opens a channel for co-activator complexes and causes an up-regulation of target genes that help induce granulocytic differentiation and cell death in APL cells. (Liu et al., 2021)

***Action of arsenic via ROS generation:***There is substantial evidence that arsenic administration can start a variety of ROS production in vascular endothelial cells, peripheral human leukocytes, vascular smooth muscle cells, and chronic lymphocytic leukemia cells, however the mechanism is yet unknown. ROS may change DNA structure by insertion, deletion, and other mutations.When arsenic-induced ROS cause these kinds of events in tumour suppressor genes, cancer may result. Arsenic-induced ROS may participate in the Fenton reaction, causing lipid peroxidation, when iron chelators (Fe 2+) are present. Glutathione levels were reduced and rat brain lipids were oxidised after chronic arsenic exposure (300 g/L). In addition to ROS-mediated cellular signaling, arsenic may also impactnuclearsignaling and cell cycle regulatory factors to govern the differentiation/proliferation balance through p53 activation. (Medda et al., 2021). Treatments that alter ROS levels may also influence tumours since tumour cells are extremely sensitive to the stress response to ROS. Arsenic trioxide causes cell death by stimulating the production of ROS, mitochondrial aggregation, Bax oligomerization, dissipation of membrane potential, and mitochondrial membrane collapse. These processes are followed by the release of apoptotic factors and the caspase cascade. Both the A172 and T98G cell lines were exposed to 50 M arsenic trioxide, and elevated ROS levels were seen in both. But in these T98G cells, there was no mitochondrial aggregation nor membrane potential dissipation nor Bax oligomerization. T98G cells' mitochondria may be less reactive and sensitive to oxidative stress, making them resistant to arsenic trioxide's induction of mitochondrial mediated apoptosis.Due to the associated rise in intracellular ROS generation, arsenic trioxide therapy results in DNA double-strand breaks. This causes hTERT to get phosphorylated, move from the nucleus to the cytoplasm, and become dysfunctional, which causes apoptosis, cell cycle arrest, and other biological abnormalities. (Fang et al., 2020)

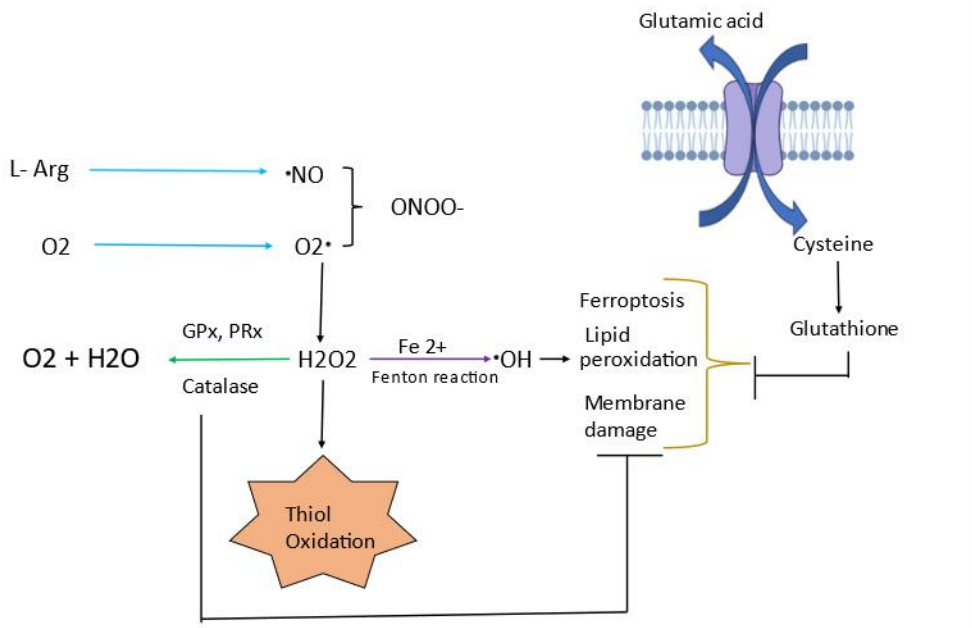


Fig1: Reactive oxygen species produced by arsenic and their interactions. (Medda et al., 2021)

***Cell cycle arrest by arsenic:*** Arsenic has been found to cause cell arrest at the G1 or G2-M phase, however the exact chemical mechanism is unknown. According to certain investigations, arsenic trioxide changed the stability of cyclin-cdk complexes in human cancer cell lines. According to some data, arsenic can cause cell cycle arrest if Rb protein hypophosphorylation occurs and cdc25 B/C phosphatases are reduced by the suppression of cdk2/6 and cdc2 related kinases. Cell cycle arrest caused by arsenic poisoning has been linked to the main signalling system known as the p53 pathway. P53 accumulation happens as a result of p53 activation by the elevated levels of mdm2 (murine double minute-2) and p21 when arsenic breaks DNA strands. It makes sure that the cell cycle stops in the G2M phase. Analysis of the phosphorylation of p53's serine 15 location revealed that it is specifically phosphorylated by ATM, a protein kinase that is connected to PI3 kinase and is involved in the arsenic-related induction process. The GADD45 checkpoint protein, which is present at this stage, was also discovered to be involved in the cell-cycle arrest during the G2M phase. Western blot study of lung

epithelial cells (LEC) treated with sodium arsenite at various doses revealed that GADD4 expression was present only at higher concentrations of arsenite and missing at lower values. (Medda et al., 2021)

***Interrelation of GSH with Arsenic Treatment: According*** to study, the amount of GSH that cells have will have an impact on the arsenic treatment's effectiveness. Both in vitro and in vivo studies have established a link between intracellular GSH levels and cytotoxicity. When GSH levels above a certain concentration, arsenic trioxide failed to trigger apoptosis in NB4 cell lines (an acute promyelocytic leukemia cell line). In APL cells stimulated by ATO showed that by controlling the GSH level, it was feasible to change the sensitivity. (Meijuan et al., 2014)

***Role of $As_2O_3$ in inhibition of NFκB:*** NF-κβ is a heterodimer made up of the p65 and p50 subunits that remains inactive in the cytoplasm by adhering to one of its inhibitors (p100, p105, or I). NF-, a stress-responsive fast transcription factor, functions in cellular settings in a variety of ways, including intracellular signalling, cell-cell contact, main pathogenic signal change initiating or progressing carcinogenesis, etc. (Medda et al., 2021).NFκB is a transcriptional factor that aids in cell survival and plays a crucial part in many cancer cells. The integrity of the IKK is required for the activation of NFκB; following phosphorylation by the IKK, the inhibitory protein I-B releases NFκB for translocation to the nucleus. As2O3 has been found to bind to cysteine-179 in the enzyme catalytic subunit's activation loop, inhibiting IKK. Although cysteine 179 does not share a space with another cysteine in the IKK primary structure, it has been hypothesised that another cysteine may pass a critical distance from cysteine 179 during polypeptide chain folding or during dimerization of the catalytic subunits, creating a high-affinity target for arsenite. (Emadi et al., 2010)

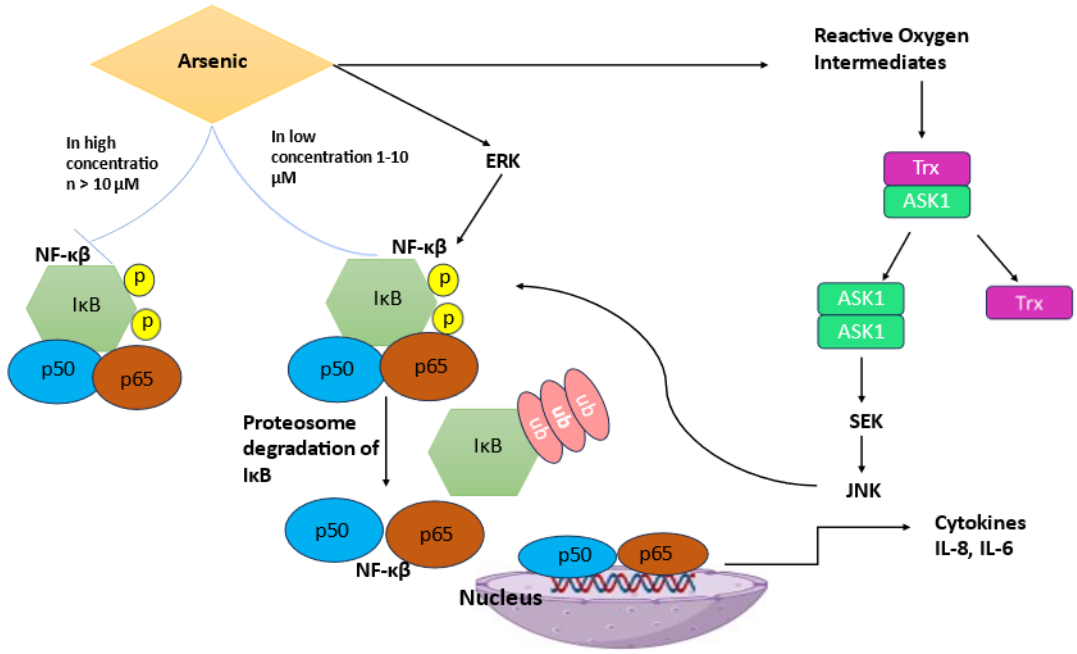


Fig 2: Activation and Inhibition of NFκB at various concentration of Arsenic (Medda et al., 2021)

***ETosis(death with release of extracellular traps) by Arsenic trioxide(ATO):*** Recent research has shown that APL cells go through a new type of autophagic cell killing process termed ETosis, which involves the interplay of the cytoskeleton, histone citrullination, superoxide production, and autophagy [98]. Through mammalian target of rapamycin (mTOR)-dependent autophagy, which is in part regulated by reactive oxygen species (ROS), arsenic trioxide (ATO) causes ETosis. According to research findings, (ATO) targets leukemia initiating cells (LICs) primarily through ETosis, but it also exerts anti-leukemic effects indirectly through ETosis. More research has revealed that mTOR-mediated autophagy and Nox-dependent ROS production are required for ETosis caused by ATO.Additionally, research has shown that mTOR facilitates ATO-induced ETosis, which results in decreased activity of LICs, suggesting that ETosis facilitates the loss of LICs in APL cells.Collectively, ATO triggers autophagy-induced cell death in a range of tumor cells and destroys PML-RARα protein in APL cells via the mTOR pathway. According to findings from earlier studies, one of the hypothesized ways by which ATO influences cellular activity is oxidative production. This process appears to facilitate ATO-induced ETosis and control autophagy. (Liu et al., 2021). According to recent studies, JNK kinase plays a significant role in $As_2O_3$driven apoptosis. Additionally, $As_2O_3$has the ability to downregulate bcl-2, bcl-xl, and mcl-1 while upregulate pro-apoptotic proteins such bax, bad, bmf, and bim. It has been proven that $As_2O_3$ made cancer cells more susceptible to apoptosis caused by death receptors. Evidence

suggested that $As_2O_3$sensitized human glioma cells by upregulating DR5 through TRAIL-induced apoptosis. Members of the TNFR family are also known as death receptors and cause apoptosis. Caspases and death receptors are connected via adaptor proteins. Death receptors commonly contain a death effectors domain (DED), a death domain (DD), and a caspase recruited domain (CARD), and when these domains are involved, both initiator and effector caspases are activated, which causes apoptosis. (Liu et al., 2021)

**Treatment of Other Malignancies**

***Multiple Myeloma:*** At pharmacological (micromolar) doses, As2O3 prevented the growth of MM cell lines in preclinical experiments.When bone marrow mononuclear cells from MM patients were treated with As2O3, it specifically caused myeloma cells to undergo apoptosis while preserving the majority of myeloid cells.

***Myelodysplastic syndromes (MDSs):*** Several in vitro investigations have shown that MDS cells exposed to As2O3 undergo apoptosis. Increased oxidative stress is present in MDS cells64, which might enhance their susceptibility to As2O3.

Several studies on adult T-cell leukemia-lymphoma (ATL) and AML using human T-cell lymphotropic virus type I (HTLV-I) have shown encouraging outcomes.A number of solid tumors, such as bladder cancer, glioma, breast cancer, hepatocellular carcinoma (HCC), esophageal cancer, germ cell tumors, liver cancer, lung cancer, and melanoma are being studied as potential candidates for therapy with As2O3 (www. clinicaltrials.gov). In a small number of patients with HCC, melanoma, and renal cell carcinoma, little clinical efficacy as a single agent has been documented; however, when combined with chemotherapy, As2O3 has showed promising potential in osteosarcoma and Ewing sarcoma. (Emadi et al., 2010)

## 4. Conclusion

The processes of As and its compounds in treating illnesses continue to be complicated and varied, and their numerous paths offer fresh motivation for the therapy of Acute promyelocytic leukemia (APL) and other malignancies. An Arsenic trioxide (ATO) is an FDA-approved medication used as the first-line therapy for APL and exhibits remarkable therapeutic promise by promoting differentiation and death in APL cells through the breakdown of PML-RARα. Additionally, ATO can directly attach to PML/PML-RARαin APL cells and destroy them, or it can do so indirectly by affecting the mitochondria and ROS generation, or apoptosis by cellular pathway. On the other hand, various mechanisms have been proposed for how as could cause cancer, including As-induced oxidative stress, As-inhibited DNA repair, As-induced micronuclei, aberrations of the chromosomes and the production of epigenetic modifications. (Liu et al., 2021) ATO is presently recognized as the preferred therapy option for APL that has relapsed. ATO treatment offers the benefit of having significantly reduced toxicity as compared to an ATRA-plus-chemotherapy-based salvage regimen (Lengfelder et al., 2012). More exploration and research on arsenic is going on as various data has corroborated the efficiency of arsenic in treating not only PML but also other malignancies.

**Conflict of Interest:** There is no conflict of interest related to the study.

**Author contributions:** Acquisition and interpretation of data is done by Sabarni Sarkar. Conception, design and revising of the article are done by Dr. Pritha Pal.

**Acknowledgement:** I would like to express my special thanks of gratitude to the higher dignitaries of Swami Vivekananda University for allowing me to carry out the study.

**References:**

Chen, S. J., Zhou, G. B., Zhang, X. W., Mao, J. H., de Thé, H., & Chen, Z. (2011). From an old remedy to a magic bullet: molecular mechanisms underlying the therapeutic effects of arsenic in fighting leukemia. Blood, The Journal of the American Society of Hematology, 117(24), 6425-6437.

Emadi, A., & Gore, S. D. (2010). Arsenic trioxide—an old drug rediscovered. Blood reviews, 24(4-5), 191-199.

Khairul, I., Wang, Q. Q., Jiang, Y. H., Wang, C., & Naranmandura, H. (2017). Metabolism, toxicity and anticancer activities of arsenic compounds. Oncotarget, 8(14), 23905.

Lengfelder, E., Hofmann, W. K., & Nowak, D. (2012). Impact of arsenic trioxide in the treatment of acute promyelocytic leukemia. Leukemia, 26(3), 433-442.

Liu, G., Song, Y., Li, C., Liu, R., Chen, Y., Yu, L., ... & Liu, Y. (2021). Arsenic compounds: the wide application and mechanisms applied in acute promyelocytic leukemia and carcinogenic toxicology. European Journal of Medicinal Chemistry, 221, 113519.

Medda, N., De, S. K., & Maiti, S. (2021). Different mechanisms of arsenic related signaling in cellular proliferation, apoptosis and neo-plastic transformation. Ecotoxicology and Environmental Safety, 208, 111752.

Rao, Y., Li, R., & Zhang, D. (2013). A drug from poison: how the therapeutic effect of arsenic trioxide on acute promyelocytic leukemia was discovered. Science China Life Sciences, 56, 495-502.

Sui, M., Zhang, Z., & Zhou, J. (2014). Inhibition factors of arsenic trioxide therapeutic effects in patients with acute promyelocytic leukemia. Chinese Medical Journal, 127(19), 3503-3506.

Yilmaz, M., Kantarjian, H., & Ravandi, F. (2021). Acute promyelocytic leukemia current treatment algorithms. Blood cancer journal, 11(6), 123.