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Down-regulation of RdRp complex and activated immune response due to increased arsenic level leads to decreased corona virus replication

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ABSTRACT

Corona virus is pandemic and responsible for more than 5.6 million deaths. It was observed that its severity was reported in varied ways in different countries and even in different states of India. This variation was critically evaluated in the area with high contamination of Arsenic (As) to understand the arsenic toxicity and Covid epidemiology and associated health effects in the human population. It was reported that the area with low arsenic contamination has a very high incidence rate of Corona infection in the world. Even in the Indian scenario, high As-contaminated states like West Bengal, Jharkhand and Bihar, the incidence rate is 1.994%, 1.114% and 0.661%, respectively. In contrast, states with the least arsenic contamination have a very high corona incidence rate like 6.308, 17.289 and 4.351, respectively. It was evident that Arsenic inhibits the RdRp complex, which leads to the inhibition of viral genome replication. The PAMP associated pathway was activated by Arsenic and effectively bound with viral spike proteins leading to effective clearance of virus through activation of TNF alpha and IL-1. It finally leads to increased production of IgE, IgG and IGA. Arsenic also enhances inflammatory response against the virus through increased production of cytokine. The high arsenic level also induces apoptosis in viral infected cells through Bax/Bak pathway. It activates cytochrome-c and caspase-3 activity, inducing apoptosis in viral infected cells through PARP activation in the nucleus. These combined findings suggest that high arsenic contamination causes replication inhibition, activates an inflammatory response, increases antibody production, and finally leads to apoptosis through the mitochondrial pathway. People residing in arsenic hit areas are at a very low threat of corona infection.

Introduction

Corona is a disease pandemic in present decade is caused by SARS-CoV-2 virus, till date more than 370 million cases of confirmed disease is reported and more than 5.6 million deaths reported globally due to corona virus disease (WHO, 2022). But the incidence rates and death rates are widely different in different countries. To understand the heavy metal toxicity and viral diseases epidemiology in Arsenic affected areas, large data on Arsenic and covid-19 infections revealed very interesting observations that low covid incidence rates in Arsenic hit countries, whereas high in arsenic non-contaminated countries. In the countries polluted with a high concentration of Arsenic like India, China, Bangladesh, Pakistan and Vietnam, the incidence rate of the virus is very low, i.e. 3.029, 0.008, 1.107, 0.654 and 2.358%, respectively (Mcarthur, 2019) (Table 1). These countries are reported with high arsenic contamination areas (Brammer and Ravenscroft, 2009). These countries are highly populated instead of that very low incidence of corona virus infection are reported from these countries despite the high contagious nature of the virus. While on the other hand, many countries have a very high rate of infection and mortality, like the USA, Italy, Denmark and the UK, which has a very low level of groundwater arsenic contamination (Table 2).

In the Indian scenario, the same trends were observed in groundwater arsenic contamination and the incidence of corona virus infection. Many states of India has high arsenic contamination, like West Bengal, Bihar, Jharkhand, Utter Pradesh and Assam (Ghosh and Singh, 2009).

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Table 1
Showing incidence of COVID cases in Arsenic hit areas worldwide.

S. No.	Country	Population	Confirmed case	Mortality	Incidence rate (%)
1	Bangladesh	16,46,89,383	1,824,180	28,461	1.1076
2.	India	1,38,00,04,385	41,803,318	4,98,983	3.0292
3.	China	1,43,93,23,776	1,20,232	4,849	0.0083
4.	Pakistan	22,05,23,615	14,42,263	29,372	0.6540
5.	Vietnam	9,73,38 579	22,95,494	37,777	2.3582

Table 2
Showing incidence of COVID cases in non-arsenic hit areas worldwide.

S. No.	Country	Population	Confirmed case	Mortality	Incidence rate (%)
1	USA	33,10,02,651	7,51,66,794	8,90,008	22.7088
2.	Italy	6,04,61,826	1,12,35,745	1,47,320	18.5832
3.	United Kingdom	6,78,86,011	1,73,98,336	1,56,880	25.6287
4.	Germany	8,37,83,942	1,04,74,992	1,18,339	12.5023
5.	Denmark	57,92,202	18,10,658	3,765	31.2602

Based on ICMR data, it was evident that these states have a very low incidence rate of corona virus infection despite a very dense population in these states (Table 3). While the states which are least exposed to groundwater arsenic contamination, like Kerala, Maharashtra, Gujarat and Tamilnadu, showed a very high incidence of corona virus cases. The total confirmed corona cases were highest in Maharashtra, followed by Kerala, Tamil Nadu, and Delhi. Since the outbreak of COVID-19 in India, Maharashtra and Kerala had the highest number of confirmed cases (Table 4). This finding suggests that groundwater arsenic contamination and corona virus infection are similar in the Indian and Global scenarios.

The incidence of COVID in different countries of the world in arsenic hit areas is 1.431±0.554, while in the arsenic non-hit country was 22.14 ±3.172. The incidence of COVID infection in Arsenic hit states of India was 1.330 ±0.268, while the incidence rate in non-Arsenic hit states is 8.099 ± 2.585 (Fig 1).

Role of Arsenic in viral replication

Viral replication pattern closely interrelate with chronic arsenic exposure due to its immunotoxic nature (Amouzougan et al., 2020), whereas *in silico* docking analysis showed antiviral effect of arsenic compound in inhibiting SARS-CoV-2 viral proteins (Chowdhury et al., 2021). The immune system gets significantly weakened due to the Arsenic exposure, leading to highly impaired response to influenza virus infection increase morbidity (Kozul et al., 2009). This indicates that water contaminated with arsenic causes increases influenza A virus susceptibility (H1N1).

Arsenic trioxide (ATO) is shown to impair the *in-vitro* replication of several viruses. Therefore, it is a potent antiviral agent. ATO inhibits Hepatitis C Virus replication (Kuroki et al., 2009). Arsenic Trioxide can also inhibit coxsackie virus replication (Molin et al., 2010) and Epstein-Barr Virus replication (Yin et al., 2017). ATO even inhibits Epstein-Barr Virus lytic genes expression and causes death in Epstein-Barr Virus infected cells (Yin et al., 2017).

Table 3
Showing incidence of COVID cases in arsenic hit areas of India.

S. No.	State	Population	Confirmed case	Mortality	Incidence rate (%)
1	West Bengal	9,96,09,303	20,02,169	20,723	1.9944
2.	Jharkhand	3,85,93,948	4,30,296	5,308	1.1149
3.	Bihar	12,47,99,926	8,26,079	12,230	0.6619
4.	Uttar Pradesh	23,78,82,725	20,34,456	23,277	0.8552
5.	Assam	3,56,07,039	7,19,939	6,518	2.0219

Table 4
Showing incidence of COVID cases in non-arsenic hit areas of India.

S. No.	State	Population	Confirmed case	Mortality	Incidence rate (%)
1	Maharashtra	12,31,44,223	77,68,800	1,42,859	6.3087
2.	Kerala	3,56,99,443	61,72,432	56,701	17.2899
3.	Tamil Nadu	7,78,41,267	33,87,322	37,666	4.3515
4.	Delhi	1,87,10,922	18,38,647	25,932	9.8265
5.	Odisha	4,63,56,334	12,59,405	8,666	2.7167

Mechanism of replication inhibition in Corona Virus in high Arsenic concentration

Ministry of AYUSH has suggested using Arsenicum album for its potential effect against corona infection, due to which there is a huge demand for Arsenicum album - 30 in COVID-19 treatment (Parikh and Parikh, 2020). *In silico* studies on arsenical derivative, Darinaparsin, have revealed its strong binding affinity to RNA based RNA polymerase and proteases of SARSCoV-2. Darinaparsin binds to RdRp's catalytic domain of D618 residue region of motif A, which is conserved among most viral polymerases. In silico studies showed that Darinaparsin docks with receptor proteins such as nsp9 (non-structural protein9) and nsp15, where darinaparsin inhibits the protein's active site (Chowdhury et al., 2021). Another Arsenic based drug, di-phenyl phenoxy roxarsone has been an effective virus-mitigation molecule. It can cause cessation of the replication of the virus by binding to RNA dependent RNA polymerase (Chowdhury et al., 2020). Even the incidence rate of COVID-19 indicates the protective role of Arsenic in COVID. The states with the heavy burden of Arsenic contamination are experiencing fewer COVID cases and less mortality due to disease.

It was observed that coxsackievirus B3 (CVB3) infection caused reduction in arsenic concentration in the infected organ (Molin et al., 2009a). while this reduction is co-rellated with redistribution of arsenic due to infection caused changes in mitochondrial metabolism and their role in viral replication is not known in detailes. Treatment with As2O3 results in higher arsenic uptake in mice infected with CVB3 than non infected mice, it was observed in both target infected organ and in other tissues (Molin et al, 2009b). Studies on arsenic and viral replication suggests that Arsenic play crucial role in viral replication mechanism and directly affect the infection outcome, it can stimulate viral replication process in both beneficial and harmful manner. Different metabolite of arsenic such as arsenic trioxide showed impaired replication in herpes simplex virus-1, foot and mouth disease virus and hepatitis C virus (Kuroki et al.,2009; Burkham et al., 2001; Hwang et al., 2004). While, many *In Vitro* studies showed that arsenic plays stimulatory effect in viral replication (Turelli et al., 2001; Berthoux et al., 2003 and Kozul et al., 2009). However change in mode of arsenic administration, concentration of arsenic (Gainer and Pry, 1972) and the types of cells used (Sebastian et al., 2006) are responsible for variable replication potential in virus due to arsenic administration.

Therapeutic impact of Arsenic

Arsenic trioxide were also used in treatment of acute promyelocytic leukaemia, which causes chromosomal translocation through alpha fusion protein called oncogenic PML-retinoic acid receptor (Shen et al., 1997; Soignet et al., 1998; Zhang et al, 1996). Arsenic trioxide causes degradation of PML-retinoic acid receptor through complete remission (Zhu et al., 1997). The PML tumour suppressor protein mediates formation of PML nuclear body (PML-NB) . PML-NB is also called PML oncogenic determinants, these are degraded by DNA viruses infection, such as herpes simplex virus type 1, human cytomegalovirus and Epstein

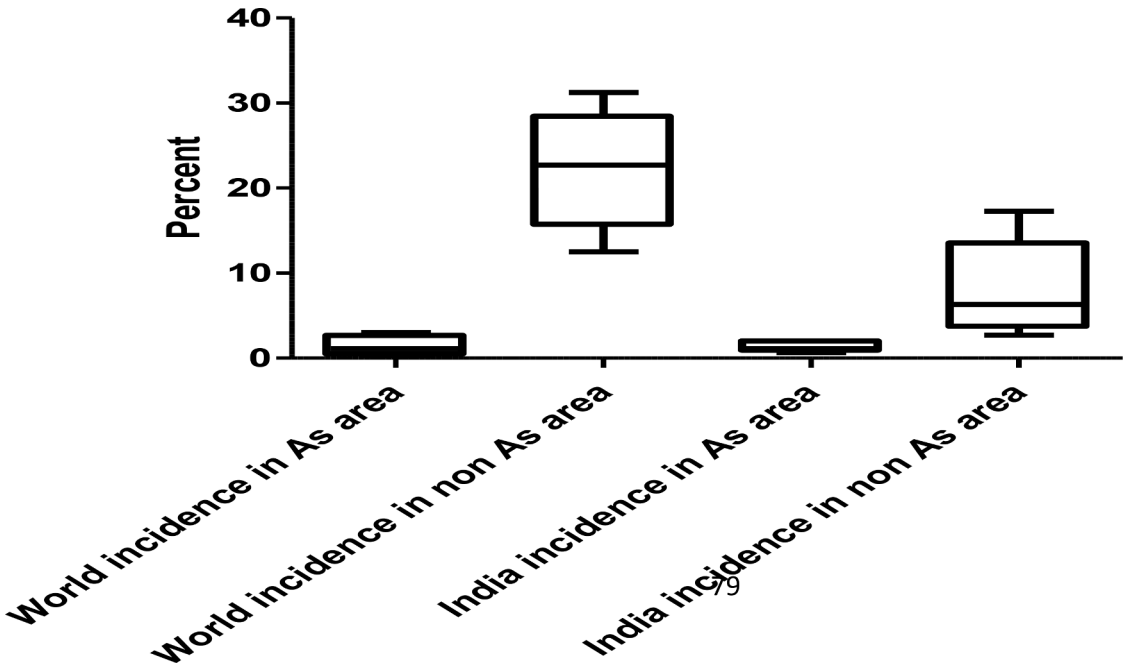

Fig. 1. Incidence of Covid positive cases in an arsenic hit and non-arsenic hit areas worldwide and India (WHO-2022 (WHO. (2022). COVID-19 Weekly Epidemiological Update. February.) and COVID-19 cases in India, 2022(website: www.covid19india.org)

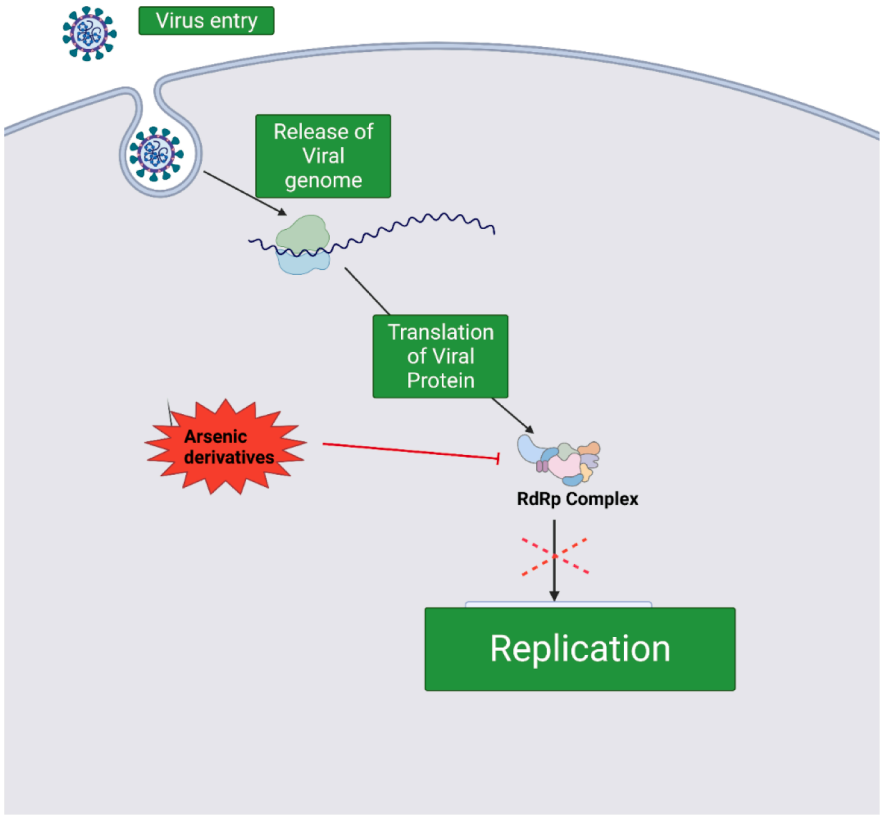

Figure 2. Arsenic bind to RNA polymerase of corona virus and cause cessation of the replication of the virus, which leads to non-expression of infection in the infected cell. Multiple copies of the viral genome are not formed in this stage, leading to replication inhibition.

Barr virus (Everett and Chelbi, 2007). The administration of ATO results in PML-NB disruption and degradation PML protein (Zhu et al, 1997). In this way arsenic trioxide become usefull for understanding the PML-NB functions, includes apoptosis, stress response, cell growth, and viral multiplication. Indeed, ATO also showed increased retroviral infectivities including HIV-1 and murine leukaemia virus infectivity, but its mechanism are still not well understood (Berthoux et al, 2003; Berthoux et al., 2004; Pion et al., 2007; Keckesova et al., 2004, Saenz et al., 2005; Sayah et al.,2004; Turelli et al., 2001). ATO were also showed inhibitory effect on HCV subgenomic replicon RNA replication (Hwang

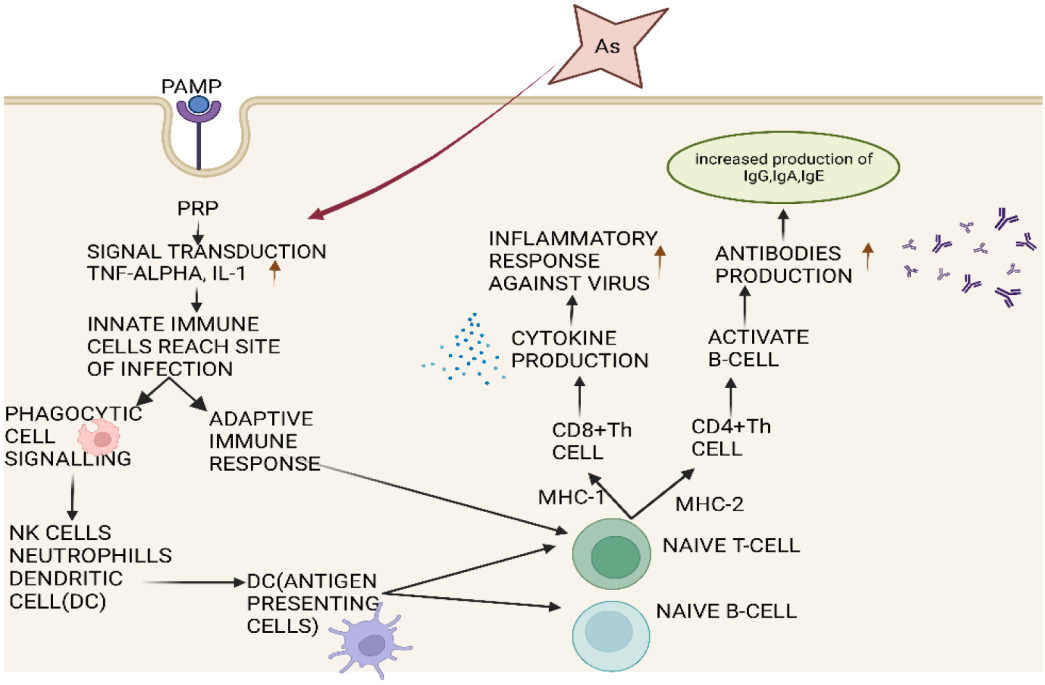

Fig. 3. Showing up-regulation of the immune response through activated PAMP in a high level of arsenic exposure.

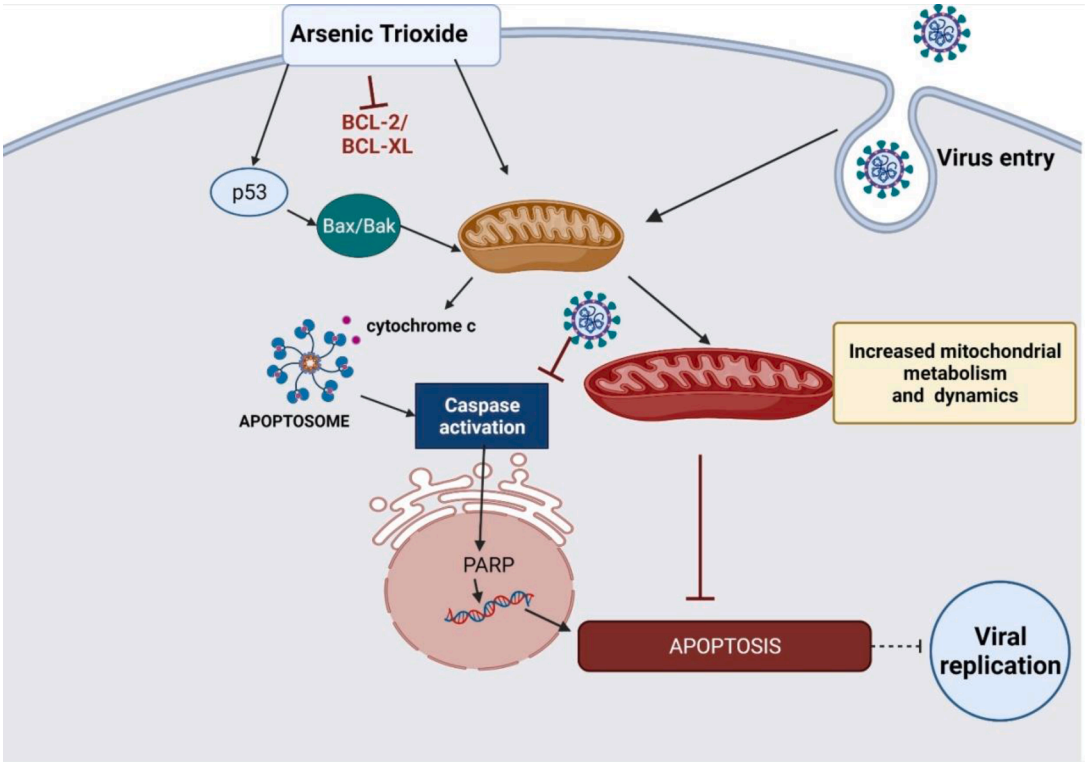

Fig. 4. Mechanism of arsenic intervention in cellular apoptosis and inhibition of viral replication and their infection.

et al., 2004). While mechanism of HCV RNA replication is clearly understood.

Hyper activated Immune system due to high concentration of arsenic play vital role in the inhibition of virus

Influenza virus require host immune system for infection and replication (Duan and Thomas, 2016). However, the viral replication depends on specific adaptive immune response of virus (Chiu and Openshaw, 2015). This reaction involves CD8+ T cells, CD4+ T cells and antibodies. Viral proteins are neutralized by antibody and it participates in clearance of viral material with other immune system cells (Murin et al, 2019); CD4+ T cells helps in antibody and B cells production, as well as it also stimulates CD8+ T cells proliferation (Luckheeram et al, 2012);

CD8+ T cells is directly responsible for viral clearance through cytokine production and cytolysis which finally induces inflammatory responses against the virus (Rosendahl Huber et al, 2014). These finding showed that how arsenic acts on influenza infection in host cells and how it influences viral replication are well understood. Due to which inorganic arsenic is known as very good immunomodulatory agent (Zhou et al, 2006; Nayak et al, 2007; Lemarie et al, 2006; Hernandez-Castro et al, 2009; Andrew et al, 2008). When inorganic arsenic was administered in moderate dose of 100ppb it caused increased CD8+ T cells in comparision to non administered groups. While CD4+ T cells showed no difference after seven days of post-infection period (Kozul et al, 2009).

Total number of lymphocytes was not affected on arsenic exposed group. Which showed increased CD8+ T cells due to arsenic exposure leads to reduced potential of viral clearance. It was also evident that there was no change in cytokine level in seven days arsenic administered group on different types of interleukin, TNFα, M-CSF, MIP-2, and MIP-1β. There was high increase in lung cell number in aesenic exposed group in comparision to non administered group. Many researchers found that in arsenic exposed group cytokine production was highly reduced. Researchers found that moderate arsenic exposed mice showed higher viral titer inpost infection period of one week compared to the controls. Higher neutrophils number were observed in bronchoalveolar lavage fluid collected from seven days arsenic exposed group. These finding suggests that arsenic exposure in developmental stages may alters inflammatory response against early life influenza virus infection (Ramsey et al, 2013). Arsenic increases granulocyte macrophage colony stimulating factor (GMCSF) in children while arsenic also reduces secretion and proliferation of IL-2, peripheral blood mononuclear cells, CD4+ T cell, CD8+ cell and the CD4+/CD8+ T cell ratio in children (Soto-Peña et al, 2006). In chronic inflammation GM-CSF may increase many folds (Zhan et al, 2012), while reduced CD4+/CD8+ ratio leads to immunosuppression (Wikby et al, 1998; Hernberg et al, 1998), which causes reduced immune responses on influenza virus infection because CD4+ T cells play crucial role in activation of virus-specific CD8+ T cell (Rosendahl Huber et al, 2014). Arsenic exposures also showed varied impact on different sex. Vegal et al. (2004) reported that on high dose of arsenic exposure T lymphocytes and PBMCs showed least proliferation in female in comparision to male (Vega et al, 2004). Vega et al, observed that Arsenic showed high toxic effect on CD4+ T cells in comparision to CD8+ T cells in women. It was found that at dose of 1 ppb CD4+ T cells proliferation were reduced, while at same dose CD8+ T cells does not show any effect (Vega et al, 2004). Due to these reason arsenic showed varied immunological response in men and women. It was evident from previous study that arsenic alters influenza virus infection, transmission, and treatment outcomes. Different species of influenza virus showed varied response. Kozul et al., found that in arsenic exposed group there is no significant difference in CD4+ and CD8+ T cells. While CD8+ T cells were increased after influenza infection in same group of mice (Kozul et al, 2009). Soto-Peña et al. reported that in arsenic exposed children there were reduced CD4+ T cell but no change in CD8+ T cells was observed (Soto-Peña et al, 2006). Arsenic possesses ability to reduce T cells, and it has ability to fight against influenza virus, but that directly dependent on species of influenza virus.T cells behaves differently with different species.

Arsenic alters the expression of critical immune regulators, induces apoptosis, oxidative stress, and inflammation in circulating PBMC, impairs lymphocyte activation and macrophage function, and modifies cellular and humoral immunity, all of which have an impact on both innate and adaptive immune defences (Dangleben et al., 2013). The production of reactive oxygen species (ROS), modification of redox-sensitive signalling pathways controlling gene expression, induction of DNA damage, epigenetic effects (DNA methylation and histone modifications), and inhibition of the inflammasome are just a few of the molecular mechanisms by which arsenic impairs immune cell functions (Bellamri et al., 2018). Arsenic inhibits inflammasome activity and causes IL-1 production in human macrophages (Howrylak and Nakahira, 2017) and this is how it may reduce chronic inflammation in serious inflammasome-mediated diseases including COVID. Arsenic also enhances the production of pro-inflammatory cytokines like IL-6, IL-8, and TNF- and make people more susceptible to inflammatory illnesses (Prasad and Sinha, 2017).

Pathogen recognition receptors (PRRs) on recognize virus and its component as pathogen-associated molecule patterns (PAMPs) on host cells. After recognition it will activate production of cytokines, interleukin and TNF through activated cell signalling pathways. Their activation will lead to innate immune cells to the infection site and amplify the signaltransduction pathway to induce phagocytic cell and activates adaptive immune system. When Influenza A virus causes lung epithelial cells infection, dendrite cells (cDCs) move to the lymph node and activates naive B and T cells (Liao, 2020). Then naive T cells will be either activated as CD4+ T helper (Th) or influenza A virus specific CD8+ cytotoxic T lymphocyte cells (CTL) leading to activation and binding with major histocompatibility complex (Van de Sandt et al., 2012). CD4+ T cells then activates B cells and leading to transformation into plasmablasts, this is the plasmoblast which produces influenza A virus specific antibodies. CTLs induces apoptosis in virus-infected cells by using perforin and granzyme, leads to formation of pores in the target cell membrane (Chen et al., 2018). Inorganic Arsenic are well known for their properties in altering immune response. While chronic exposure arsenic exposure caused high level of serun Immunoglobulin like IgA, IgG, and IgE (Islam et al., 2007). At very low doses arsenic increases cytokines, including IL-8, IL-6, and TNF- α, which are known as pro-inflammatory cytokines, it leads to increases susceptibility in different inflammatory diseases (Prasad and Sinha, 2017).

Inhibition of viral replication due to Arsenic-induces apoptosis

Single-stranded RNA viruses activates oxidative phosphorilation in mitochondria to generate high amount of ATP and mitochondrial metabolites which are required for replication of virus and virion assembly (Gatti et al., 2020). SAR-CoV-2 alters cellular metabolism by taking over their hosts' cellular machinery to replicate themselves. One frequent approach is repressing apoptosis and controlling the immune system to prevent anti-viral programmes (Nunn et al., 2020). The delayed apoptosis of host cells benefits coronavirus replication and worsens the infection early. So, if apoptosis is induced early in the infection, it can be a good strategy for inhibiting virus replication and limiting the number of viruses(Ivanisenko et al., 2020). ATO induces apoptosis in many human cancer including colonic, breast, and pancreatic cancer cells through Caspase activation (Wang et al., 2011). Arsenic trioxide directly affects component of apoptosis in gradual manner on pro- apoptotic proteins, anti-apoptotic proteins and caspaces. Caspases are apoptotic mediators. ATO promotes apoptosis via the mitochondrial route. Bax depolarizes the mitochondrial membrane potential, allowing cytochrome c to be released; after that outer membrane becomes permeable. Cytochrome c binds to procaspase-3 and activates it, resulting in their cleavage and formation of caspase-3, inducing apoptosis, and preventing viral replication (Stevens et al., 2017).

Arsenic trioxide induces ROS activity and DNA damage, leading to G0/G1 extension in skin fibroblasts through the ATM-ATR-associated Chk pathway (Chayapong et al, 2017). Deciphering the molecular events during arsenic induced transcription signal cascade activation in cellular conditions (Madhyastha et al., 2018). The replication inhibition is also reported by Charan et al. 2012. According to Chatran et al, 2012, arsenic oxide at 10 and 12 ppm concentration completely inhibited the viral multiplication in the host strain is an indication of virucidal nature of metal oxides. Arsenic trioxide prevents the Hepatitis C virus from replicating (Kuroki et al., 2009). Coxsackie virus and Epstein-Barr virus replication can both be slowed down by arsenic trioxide (Molin et al., 2010; Yin et al., 2017).

Conclusion

It was clear from global and Indian data that the corona incidence rate was very low in Arsenic exposed areas while cases were drastically high in the non-arsenic-contaminated area. It was evident that Arsenic inhibits RdRp complex, which leads to inhibition of viral genome replication. The PAMP associated pathway was activated by Arsenic and effectively bound with viral spike proteins leading to effective clearance of virus through activation of TNF alpha and IL-1. It causes increased production of antibodies and enhances inflammatory response against the virus. High arsenic level induces apoptosis in viral infected cells through Bax/Bak pathway. It activates cytochrome-c and caspase-3 activity, which finally induce apoptosis in the infected viral cell through PARP activation in the nucleus. Hence, arsenic exposure to the human body activates an inflammatory response, increases antibody production, leads to apoptosis through the mitochondrial pathway, and inhibits viral replication in the cells. So, Arsenicum alum-30 was initially used to treat corona cases, but it was not practised for long due to a lack of scientific support. Now, evidence from many studies suggests that Arsenic derived chemicals effectively protect against RNA virus replication. Therefore, people residing in arsenic hit areas are at a very low threat of corona infection; however, it should be further investigated given the level of arsenic exposure, covid severity, covid virion copy exposure, nutritional status, and co-morbidity with other chronic diseases.

CRediT authorship contribution statement

Ranjit Kumar: Conceptualization, Writing – original draft, Writing – review & editing. **Disha Chauhan:** Software, Writing – original draft. **Geetika Saini:** Formal analysis, Writing – review & editing. **Rakesh Kumar:** Writing – review & editing. **Sunil Kumar:** Writing – review & editing. **Dixit Sharma:** Formal analysis. **Munish Sharma:** Writing – original draft. **Vijay Kumar Bharti:** Writing – review & editing. **Arun Kumar:** Writing – original draft. **Ashok Ghosh:** Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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