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Arsenic and its effect on immunity: A narrative review

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Abstract

Introduction: Human immune system has evolved through eons of struggle between the host and pathogens. Although Arsenic can act as immunostimulant by causing an elevation of inflammatory responses in our body, the immunosuppressive effects of Arsenic include modulation of the numbers, survival and functions of immune and hematopoietic cells and impaired humoral and cell-mediated immunity. Immunomodulation is a kind of regulatory modification in the immune system to bring the desired response. Homoeopathy embraces a holistic approach in curing diverse diseases and it is used globally as an alternative medicine and seeks to cure in harmony with natural laws of healing. The present review focusses on the collection of results of studies carried out on effect of arsenic on immunity.

Methodology: In this review literature available from various published studies and databases like PubMed, Springer, Elsevier and AYUSH research portal and references from the relevant articles published literature were searched in English language up to December 2020.

Results: 25 studies were included in this review of which 10 *in vivo*, 9 *in vitro*, 2 *Ex vivo* and 4 review articles. Most of the studies substantiate the definitive role of Arsenic on immunomodulation.

Conclusion: In future extensive studies are required to further explore the immunomodulatory effects of homoeopathic medicines *Arsenicum album* and studies based on human-derived immune cells need more attention.

Keywords: immunomodulation, arsenic, *In vivo* studies, *In vitro* studies, arsenic trioxide

1. Introduction

Arsenic (As) a major toxic human carcinogen and environmental contaminant ^[1] is present everywhere in nature and human being exposed to arsenic via ground water, atmospheric air, and food sources ^[2]. More than 200 million people worldwide are exposed to arsenic contaminated ground water at a level more than the permissible limit (<10 ppb) ^[3]. Arsenic exposure may not only affect and disable organs of the body, but it can also interfere with the proper functioning of the immune system ^[4] and result in growth retardation, gross pathology including skin and eye lesions, ulcerations, cataract development etc ^[5]. In human and various animal models, arsenic has been found to alter immune response either by severe suppression or activation which may eventually lead to increased susceptibility to pathogens or hypersensitivity disorder, respectively. Arsenic exposure altered the relative distribution of different T cell subpopulation (CD4⁺ count, CD8⁺ count, Th 1, Th 2, Th 17, T reg) in exposed population as well as in-vitro arsenic exposed human ^[6].

2. Methodology

2.1. Search Strategy

The literature for the present review was identified using electronic databases including PubMed, Springer, Elsevier and AYUSH research portal and references from the relevant articles published literature. Keywords used for this literature review include 'Arsenic', 'Immunomodulation' and their MeSH variations in PubMed. The search strategy was designed to include all the studies containing the descriptors that were published until December 2020.

2.2. Study Selection

2.2.1 Inclusion criteria

Publications of the English language only were included.

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2.2.2 Exclusion criteria

All the clinical studies were excluded. Review articles, Letters to the editor, conference proceedings and comments were also excluded. Unpublished data such as dissertations, data not published in peer-reviewed journals, and websites were not included.

3. Discussion

3.1. Use of Arsenic in Traditional Medicine

Arsenic compound has been used as Fowler's solution was used in the treatment of various diseases such as malaria, syphilis, asthma, chorea, eczema, psoriasis and as cancer chemotherapeutic [7]. In 1880, the pharmacology texts described the use of arsenical pastes for the treatment of skin and breast cancer. In 1878, it was found that Fowler's solution could be effective in lowering the white blood cell count in leukaemia patients.⁸ Result of various studies shows that arsenic trioxide is effective in the treatment of acute promyelocytic leukaemia (APL). In 2001, the efficacy of arsenic trioxide was demonstrated in the treatment of end-stage high-risk multiple myeloma and now in the present scenario arsenic trioxide is approved to treat relapsed or refractory APL and research is continuing to determine its efficacy in other haematological cancers.⁹In Traditional Chinese Medicine arsenic trioxide or arsenous acid paste is often used to treat tooth marrow disease as a devitalizing agent. It has also been used against some other diseases such as psoriasis, syphilis, and rheumatosis [10].

3.2. Use of Arsenic in Modern Medicine

In Western medicine, arsenic was used more recently (until the advent of penicillin) in the treatment of syphilis. Due to the known carcinogenic effect its only therapeutic use today is in the treatment of trypanosomiasis involving the central nervous system [11]. Arsenic trioxide is an anticancer drug, sold under the brand name Trisenox and used to treat refractory or relapsed acute promyelocytic leukemia. It is believed that it induces apoptosis (programmed cell death) of promyelocytic leukemia cells. It was included in the World Health Organization's 21st List of Essential Medicines published in 2019 as one of the safest and most effective medicines needed in a health system [12].

3.3. Use of Arsenic as a Pigment and Other Products

Arsenic's use as a pigment (e.g., Paris Green or copper acetoarsenite) in the 1800s was suspected as a major source of unintentional arsenic poisonings. Although the arsenic-based pigment was used in many consumer products (e.g., toys, candles, and fabric) it uses in wallpaper was particularly linked to widespread sickness and death during this period Arsenic trioxide is effective in inducing and maintaining remission in patients with APL with minimal side effects [13]. Data from various studies shows that arsenic trioxide may be a useful addition to the therapeutic regimens that have been so successful in treating newly diagnosed APL and investigations are ongoing to incorporate this agent into the first-line APL treatment paradigm. Preliminary data from clinical studies indicate that arsenic trioxide has clinical activity as a single agent in MDS and MM, and combination therapies are being investigated [14].

3.4. Use of Arsenic in Ayurveda

Ayurveda is the traditional Indian medicinal system with a holistic approach to health and personalized medicine. It is

known to be a complete medical system that comprised physical, psychological, philosophical, ethical, and spiritual health [15]. In India, Ayurvedic arsenic-containing compound is described, which is used to control blood counts of patients with haematological malignancies. The efficacy and side effects of this compound are evaluated in the light of the fact that arsenic was recognised to be of use in the control of blood counts from patients with chronic myeloid leukaemia [16].

3.5. Use of Arsenic in Unani

The Unani medicine is considered as one of the oldest and time-tested systems of medicine practiced since more than 2500 years [17]. In Unani system of medicine arsenic is used as Sann al-Fār to treat nervous disorders, sexual disorders, skin disorders, anaemia, fevers, respiratory disorders, and joints pain [18].

3.6. A few examples to substantiate immunological evidence is stated here.

It was found that arsenic reduced paracetamol-induced analgesia possibly by interfering with pronociceptive 5-HT_{2A} and antinociceptive CB₁ receptors [19].

The effect of As on T cell population is mainly attributed to altered expression of key immune regulator molecules impaired T cell functions, cytokines production, induction of apoptosis, and oxidative stress induction in T cells [20].

In an *in vitro* study, it was found that three kinds of arsenic compounds, at high doses suppressed the plaque forming cell response to sheep erythrocytes and the proliferative response to mitogens, whereas at low doses they enhanced both responses [21]. In another study arsenic exposure makes *L. rohita* immunocompromised and could increase its susceptibility to pathogen attacks. It was observed in the study that arsenic has a generalized immune-suppressive effect leading to down regulation of both Th1 and Th2 cytokines; besides, it led to up regulation of the HSP genes indicating arsenic-induced cellular stress [22].

A study was conducted by Duan X *et al.* on female mice showed that arsenic significantly decreased the spleen and thymus weights and flow cytometry revealed that arsenic decreased the relative frequency of CD4 + T cell subpopulation and the ratios of CD4/CD8 in spleen [23]. whereas in another study it was found that effect of Arsenicum album 30C is effective in upregulating T lymphocytes such as CD4, CD8 and CD4:CD8 ratio [24]. In a study conducted by Gupta V.K *et al* it was seen in that homoeopathic medicines produced modulation of immune function at multiple levels such as modulation of expression of genes, stimulation of macrophage and polymorph nuclear cells, changes in expression of surface receptors and induction of cytokines [25].

4. Conclusion

Homoeopathy is a natural system of healing the ailing humans from diseases and an unquestioned method of antidoting/detoxifying the chemotherapeutic effects that render the human body susceptible to novel diseases. Homoeopathy treats the individual as a whole while providing individualised treatment, homeopathy is particularly effective at helping patients strengthen their natural immunity. The Homoeopathic medicines produced modulation of immune function at multiple levels. This evidence suggests that homoeopathic treatment has the

potential for individual-specific immunomodulation. So far, the numbers of homoeopathic medicines studied for their immunomodulatory function are few as compared to the vast repertoire of homoeopathic medicines available to the profession. In future, more pre-clinical studies are needed to explore the action of homoeopathic medicines at cellular level and their possible role in individual-specific immunomodulation.

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