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Original Review Article

Evolution of Arsenic as a Toxic and Therapeutic agent through ages- A Scientometric Study

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Abstract

Introduction: Arsenic is enormously toxic in chronic as well as in acute manifestations and this fact has been established in different works of literature. Arsenic gets inside the body by skin absorption, ingestion, and inhalation, then dispersed into different organs. **Methodology:** The objective of the study is to do a comparative study based on different research publications on Arsenic toxicity and its therapeutic uses. For retrieval of arsenic-related articles, the Scopus database was used and the results were presented in form of bibliometric tables. The articles which were published in the duration of 14 years from January 2008 to October 2021 were taken for this study. Total 7606 documents were retrieved from the SCOPUS database in which 6330 documents supported therapeutic nature and 1276 supporting toxic nature of Arsenic. Maximum documents on therapeutic uses of Arsenic (9.54 %) are published in the year 2020. **Conclusion:** Arsenic has been a source of constant fascination and has influenced the human psyche since time immemorial, owing to Arsenic's ability to act both as a therapeutic and toxic agent. A critical study of the publications on Arsenic can open new vistas in Arsenic research.

1. Introduction

Arsenic is commonly known as "The King of Poison", has influenced human affairs, for ages, owing both to its toxic as well as therapeutic potential. It has been a preferred homicidal poison, as it satisfies almost all the criteria required of a homicidal poison. It is cheap, odorless, tasteless, and easily available.

It is undetectable in food and drink and simulates food poisoning (cholera) in its acute

clinical manifestation. These characteristics of Arsenic often cause considerable difficulty during diagnosis of death from Arsenic poisoning, giving ample time for the poisoner to escape in the ensuing confusion surrounding such deaths from Arsenic poisoning. History is replete with instances, where Arsenic has been used as a potent homicidal poison to kill rulers to usurp the throne and to kill rulers to usurp the throne and to kill wealthy

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individuals to grab their riches. Arsenic, apart from being a potent homicidal poison, also has the potential to be used in chemical warfare. In the year 1918, the respiratory irritant and vesicant properties of organic Arsenicals like Adamsite and Lewisite, have been a subject of intense research by the Army of United States, to develop them as potential Chemical Weapons, to be used in chemical warfare. However, they were never used in actual war. Both these arsenical compounds are still listed by the Center for Disease Control and Prevention (CDC) as potential bioterrorism agents.^{1, 2, 3}

Arsenic is also a skin, lung, and bladder carcinogen, along with being a potent toxin for liver and brain tissues.^{4,5,6} Though Arsenic has a fearsome reputation as a homicidal poison, it still enjoys a respectable position in the history of Medicine, especially in the treatment of Trypanosomiasis and Syphilis. In the year 1909, Paul Enrich and Sahachiro Hata discovered "Salvarsan" – an organic compound of Arsenic, which could be used for treating Syphilis.⁷
⁸ An inorganic compound of Arsenic – Arsenic

trioxide, is currently allowed for treatment purposes in refractory acute promyelocytic leukemia.⁹

The objective of the study is to evaluate Arsenic as a toxic and therapeutic agent through the ages and to do a comparative study based on different research publications on Arsenic.

2. Methodology

For retrieval of arsenic-related articles, the Scopus database was used and the results were presented in form of bibliometric tables. For maximizing accuracy, the search query was manually changed using terms related to the article. Arsenic-related articles published in the period of 14 years i.e. from January 2008 to October 2021 were collected and different parameters were compared in our study.

Analysis of data recovered from different kinds of literature

In this retrospective study, a total number of 7606 articles were retrieved from the SCOPUS database.

Table 1: Year-wise distribution of published document related to Arsenic poisoning and therapeutic use

Year	Arsenic Therapeutics	% age of total documents	Arsenic Poisoning	% age of total documents	Total document
2008	442	6.98	72	5.64	514
2009	335	5.29	78	6.11	413
2010	396	6.26	81	6.35	477
2011	432	6.82	77	6.03	509
2012	423	6.68	97	7.60	520
2013	426	6.73	84	6.58	510
2014	431	6.81	101	7.92	532
2015	449	7.09	99	7.76	548
2016	428	6.76	96	7.52	524
2017	448	7.08	115	9.01	563
2018	494	7.80	95	7.45	589
2019	483	7.63	74	5.80	557
2020	604	9.54	116	9.09	720
2021	539	8.52	91	7.13	630
Grand Total	6330	100.00	1276	100.00	7606

Table 2: Type of documents published during these 14 years

Document type	Arsenic Therapeutics	% age of total documents	Arsenic Poisoning	% age of total documents	Total document
Article	4351	68.74	858	67.24	5209
Review	1542	24.36	216	16.93	1758
Book Chapter	229	3.62	115	9.01	344
Short Survey	34	0.54	11	0.86	45
Note	32	0.51	12	0.94	44
Editorial	33	0.52	8	0.63	41
Conference Paper	66	1.04	34	2.66	100
Book	12	0.19	14	1.10	26
Letter	31	0.49	8	0.63	39
Grand total	6330	100.00	1276	100.00	7606

In this comparative study, it is found that though Arsenic is a strong poison, it is also used for therapeutic purposes. This study reveals that out of 7606 documents, 6330 documents are published on Arsenic therapeutics and 1276 documents are relating to Arsenic poison (table 1).

The highest number of documents on Arsenic therapeutics is published in the year 2020 i.e. 9.54 % of total documents collected related to therapeutic use and 9.09% of total documents about toxic effects are published on Arsenic poisoning again in the year 2020 which is the highest number in a single year.

Table 2 indicates different documents published on Arsenic poison and Arsenic therapeutic effects and indexed in the SCOPUS database from 2008 to 2021. It is found that 4351 (57.20 %) of total documents (7606) are original research articles on Arsenic therapeutic whereas 11.28 % of total documents are original research articles on Arsenic poison. Out of the total of 7606 documents, 6330 documents are related to Arsenic therapeutic, and 1276 are about Arsenic poison.

The researchers are from different corners of the globe who have published articles on Arsenic. It is found that the United States of America is on top with 2057 documents followed by China and India with 1778 and 864 documents respectively (**Table 3**).

Table 3: Affiliation of authors into different countries

Sl. No	Name of Country	Arsenic Therapeutics	Arsenic Poison	Total
1	United States	1701	356	2057
2	China	1569	209	1778
3	India	706	158	864
4	Italy	325	50	375
5	France	218	37	255
6	Germany	239	57	296
7	Japan	251	36	287
8	United Kingdom	220	66	286
9	Canada	210	48	258
10	Iran	226	24	250

The study of Arsenic literature reveals that around 96 % of total documents during this period (2008 to 2021) are published in the English language whereas about 4 % of documents are published in other languages like Chinese, French, Spanish, Polish, German, and Japanese (**table 4**).

Table 4: Distribution of documents in different languages

Language	Arsenic Therapeutics	Arsenic Poison	Total	% age
English	6132	1218	7350	96.24
Chinese	132	22	154	2.02
French	15	11	26	0.34
Spanish	14	9	23	0.30

Polish	11	8	19	0.25
German	11	3	14	0.18
Japanese	6	2	8	0.10
Persian, Russian & Turkish	12	5	17	0.22
Czech, Portuguese	6	3	9	0.12
Italian, Malay	4	2	6	0.08
Bulgarian, Greek, Hungarian, Serbian, Slovenian, Ukrainian	6	5	11	0.14
Total	6349	1288	7637	100.00

3. Discussion

3.1 Arsenic as poison

The poisonous effects of Arsenic have been well-known to man for ages. Philosophers of the ancient world, notably Hippocrates (370 B.C.), Theophrastus of Erebus (4th century B.C.), and Pliny the Elder (1st century B.C.), had deep insights into the noxious properties of Arsenic. A vivid description of abdominal colic and similar abdominal discomfort, in miner of metals, has been presented by these philosophers in their scholarly works.¹⁰ The Greek physician Pedanius Dioscorides, creator of the historical pharmacopeia "De Materia Medica", has described the use of Arsenic in 55 B.C., by the Roman Emperor Nero, to kill his brother Tiberius, to consolidate his position as the Roman Emperor.^{11,12} In the Medieval Era, arsenic became very infamous as an ideal homicidal poison. Arsenic was used with increasing frequency, to eliminate persons of the decision-making class in the Medieval Era and the period of Renaissance in Europe.⁷ The practice of killing one's rival with Arsenic poisoning, became so rampant in Renaissance Europe, that two families of the time The Medicis and The Borgias cultivated the "Art of Poisoning" and got contracts to kill one's troublesome neighbors and potential rivals by using the subtle art of poisoning, with Arsenic.¹³ In the middle of the 17th century, cosmetics having Arsenic content, were prepared and sold under the name "Aqua Toffana" by an Italian lady "GluliaToffana". These cosmetics were sold with appropriate instructions on their method of application on the intended victim.^{12,14} In France during the 17th century, white Arsenic (Arsenic Trioxide) came to be known as "Poudre de succession" or the "Inheritance Powder".¹¹ Till about 1850, Arsenic continued to be used in high profile murder cases, and one of the famous cases was a political assassination of Napoleon Bonaparte in the year 1851.¹³ According to some works of literature inorganic Arsenic present in

groundwater and some foods, higher than the normal limit is a well-known carcinogen and toxicant.^{15,16}

3.2 Development of Analytical Tests to Detect Arsenic

The fact that Arsenic could be put to criminal use with impunity, for so long, was because no reliable tests were available to detect arsenic inside the body, even though initial tests to detect Arsenic was developed in the mid-18th century.

A breakthrough for the detection of Arsenic, came in the year 1832, when James Marsh, a British Chemist developed an analytical method to demonstrate reliable evidence of "Visible Arsenic" to Juries.¹³ The Marsh test for Arsenic, which involved, treating the suspected sample in a glass apparatus with Zinc and Sulfuric acid and heating, which would cause collection of a silvery-black substance on the cold ceramic vessel, which was not only specific to arsenic but also as minute as 0.02 mg of arsenic could be detected.^{17,18} In the year 1840, the Marsh test was used for the first time when Marie LaFarge of France was trialed for the murder of her husband by the use of arsenic in his food.¹³ These historic incidents of murder using Arsenic, though appeals to the gloomy interest of the common man, the murders, never the less provide important insights for advancement of knowledge of Arsenic toxicology. The study of such poisonings indicates the acute effects and target organs in death due to arsenic. These murder cases that were affected by Arsenic poisoning, also helped in developing the analytical methods for arsenic in different biological samples and other media, leading to a better understanding of arsenic metabolism.

3.3 Arsenic in Therapeutics

Though Arsenic is very infamous as a toxic agent in the annals of Medicine, it is also used as an effective therapeutic agent through the ages. It is perhaps because of the inherent toxic nature of Arsenic, certain ailments have been treated by Arsenic. In about 2000 B. C. E, a paste of Arsenic was used for the treatment of ulcers and abscesses by Hippocrates, known as the father of Medicine.^{19,20,21,22} Other great physicians like Aristotle and Paracelsus also knew of Arsenic's use as a therapeutic agent.^{13,23} Paracelsus was a pioneer in advocating the use of Arsenic for treatment and prepared a balsam using white Arsenic, which was used for the treatment of anthrax, wounds, carbuncles, buboes, and other ulcers.^{12,24} Traditionally it has been used by the Chinese as a medicine as far back as 200 B. C. E.

According to the Chinese concept, a poison in the body can be neutralized by using another poison.²⁵ Ayurvedic herbal medicines, originated in India, too contained Lead, Mercury, and Arsenic, and the notion was the "essence of five planets" can help in the preparation of mineral elixir which could offer long-lasting life.^{7,26} A detailed documentation of the use of Arsenic in Medicine started in the latter half of the Eighteenth Century. In 1786 Thomas Fowler discovered Fowler's solution, consisting of 1 percent Potassium Arsenide solution and it was used for the treatment of different diseases like Syphilis, Psoriasis, Chorea, Eczema, Asthma, and Malaria.^{25,27} In 1809, Fowler's solution also called "Liquor Mineralis" was accepted in the London Pharmacopeia. In the year 1878, it was found that Fowler's solution helps in decreasing the number of white cells in Chronic Myeloid Leukemia and was used to treat leukemia until the 20th century, that chemotherapy and radiotherapy became the main treatment.⁴

Other Arsenic preparations in use, before the 20th century, were De Valagin's and Donovan's solutions both contained Arsenic compounds as one of their constituents and were used as a therapeutic agent for a similar type of disorders.^{9,11}

Until the year 1940, compounds of Arsenic were the main therapeutic agents for Syphilis before the invention of the antibiotic era with penicillin in the lead.²¹

Syphilis, otherwise called the "Great Pox" was a scourge next only to plague in the middle ages and remained so, till about 1910, when Paul Ehrlich, a German physician discovered a drug "Salvarsan" known as "Magic bullet" for Syphilis treatment, in which Arsenic was one of the main constituents. Salvarsan, chemically called dioxy-diamino-arsenobenzol-dihydrochlorite which is now known as Arsphenamine was the first drug in the series of drugs developed for the treatment of Syphilis. In 1911, Paul Ehrlich developed neoarsphenamine or neo-Salvarsan and by 1920, various Arsenic compounds like neoarsphenamine, arsphenamine, mapharsan, and acetarsol in combination with mercury or bismuth were the main treatment modality for Syphilis that penicillin became the main treatment from year 1943 onwards.^{6,23,26,27}

Research on Arsenic poison and Arsenic therapeutics is going on for several decades. All the researchers are interested to examine these things

from their parent branch of health science. SCOPUS database indexed these documents accordingly.

Research documents are published in different forms. Some research papers are published as original research papers, some are published as conference papers, book chapters, and review papers. **Table 3** indicates different types of documents published on Arsenic poisoning and therapeutic uses from 2008 to 2021.

The researchers are from different corners of the globe. It indicates that research on Arsenic is commonly cherished throughout the world. Table 4 indicates the researcher's affiliation with the top 10 countries of the world.

It is found from the SCOPUS database that all the documents indexed during the study period are not published in a common language. Table 5 is showing the different languages in which the documents are published. To compare both aspects of Arsenic research here is an attempt to study different journals in which documents are published in the above-mentioned study period.

4. Conclusion

Arsenic has been a source of constant fascination and has influenced the human psyche since time immemorial, owing to Arsenic's ability to act both as a therapeutic and toxic agent. The continuous focus on Arsenic research, as evidenced by publication in leading journals of the world, bears testimony to Arsenic's enigmatic appeal. A critical study of the publications on Arsenic can open new vistas in Arsenic research, especially among the new enthusiastic young toxicologists; of the world.

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