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Review Article

Arsenic Influence in Gut microbiome

Gut Microbiome and Health Assessment Due To Arsenic Toxicity: A Review

Abhishek jain[1], Swati jain[2], Roshni jain[3], Swati singh thakur[4], and Subodh kumar jain[5]*

[1,3,4]Department of Biotechnology, Dr. Harisingh Gour Vishwavidyalaya, Sagar-470003, Madhya Pradesh, India

[2,5]Department of Zoology, Dr. Harisingh Gour Vishwavidyalaya, Sagar-470003, Madhya Pradesh, India

Abstract: Arsenic is considered as a class I carcinogen and first among toxicants ranked by the Environmental Protection Agency. Arsenic toxicity includes deleterious effect on gut microbiota, gastrointestinal disorder, immunological disturbances, disrupting metabolism and compromising the host health. Over 10^3–10^4 microorganisms with possibly 500 to 1,000 different species inhabit within the gut with 150 times more genes than the human genome. They help to digest food and play an essential role in our well-being. Gut microbiota affects our whole metabolism as well as the immune system of the host. Arsenic induced toxicity is a major health challenge leading to many neurological and immunological problems and inhibits the growth of many bacterial species common in the gastrointestinal tract. The Gut microbiome carries multiple functions that are beneficial to the hosts. Arsenic exposure will be a critical concern for human health. Human gut microbiomes may be biochemically responsible for arsenic metabolism, change in the arsenic compounds and several arsenical transformations that may lead to arsenic toxicity. Arsenic metabolism occurs in the liver by arsenic methyltransferase (AS_3MT) which methylates it into the inorganic arsenic, and ultimately eliminated through urine. Recent studies showed that biotransformation of gut microbiome causes alteration of microbiome morphology and physiology that may alter the ArsBC gene activity due to arsenic toxicity. We aimed at summarising that arsenic induced perturbed gut microbiome communities that trigger systemic responses in diverse organs. Due to gut microbiota perturbation, changes in gut permeability and metabolism have been identified, and there is a shift in the population of gut bacterial species having arsenic resistant genes that result in disturbance of host metabolic homeostasis. Here we review known aspects of arsenic gut microbes' interaction, this will help to understand about arsenic toxicity with the gut microbiome and their deleterious effects.

Keywords: Arsenic toxicity, arsenic metabolism, gut microbiome, arsenic-microbe's interaction, host health assessment.

***Corresponding Author**

Subodh kumar jain5* , Department of Zoology, Dr. Harisingh Gour Vishwavidyalaya, Sagar-470003, Madhya Pradesh, India

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1. INTRODUCTION

Arsenic ranks first among toxicants, as indicated by the Environmental Protection Agency (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR).[1] Arsenic is ubiquitous in the environment, and humans are thus exposed to inorganic and organic arsenic through medicinal, criminal, environmental and occupational sources.[2] More than 80% of arsenic compounds are used to manufacture products with agriculture applications such as insecticides, herbicides, fungicides, algaecides, wood preservatives, dyestuffs, and medicines to eradicate tapeworms in sheep and cattles. However, the primary exposure to inorganic arsenic is the ingestion of high metal contaminated drinking water for the general population. Arsenic has been found in groundwater in West Bengal and Bangladesh, and individuals using such water suffer from arsenicosis.[3] The level of arsenic in drinking water is found more than the standard limit (10 µg/L) recommended by the World Health Organization (WHO) and EPA, being toxic to over 200 million people worlwide.[4] Arsenic is found in nature as inorganic arsenic compounds by forming compounds with oxygen, chlorine and sulphur.[5] Accumulation of inorganic arsenic and methylated arsenicals are found in various brain parts, with maximum amount in the pituitary.[6] The impact of microbiomes on host health and diseases is well reported. The gut microbiome is maintained by host environments that affect the host's metabolic, immune, and neuroendocrine functions, making it an important pathway contributing to health inequities.[7] Report showed that the human gut microbiome may biochemically change the arsenic compounds, and several arsenical transformations by bacteria may lead to arsenic toxicity to the host.[8] Arsenic exposure is common through arsenic contaminated water and food, leading to disturbance in gut microbial activities. Microbiome composition and diversity in the gastrointestinal tract (GIT) vary, with individuals playing an essential role in determining the initial fate, mobility and relative toxicity of arsenic, whether inhaled or ingested. Gut microbiome also plays a major role in arsenic redox speciation, which enters GIT by intake of arsenic polluted food and water.[9] Toxicity of arsenic is associated with its metabolism from inorganic to organic forms, namely the trivalent species monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). Inorganic arsenic is more toxic than organic arsenic (MMA, DMA), and arsenite (As (III)) toxicity is greater than arsenate toxicity (As (V)).[10] The disease showing symptom variability is may be due to the link between arsenic metabolism via intestinal microbiota, host exposure, and disease possibility.[9] The disturbance in the gut microbiome could result in gut dysbacteriosis, gastrointestinal infection, immunomodulation, and neurobehavioral changes.[11-13] Therefore, the microbiota of GIT plays a crucial role in the host's health and metabolism, including humans.[14] This review summarises the role of gut microbiomes that may influence the arsenic metabolism and variation in toxicity of arsenic susceptibility to the host health [Figure 1].

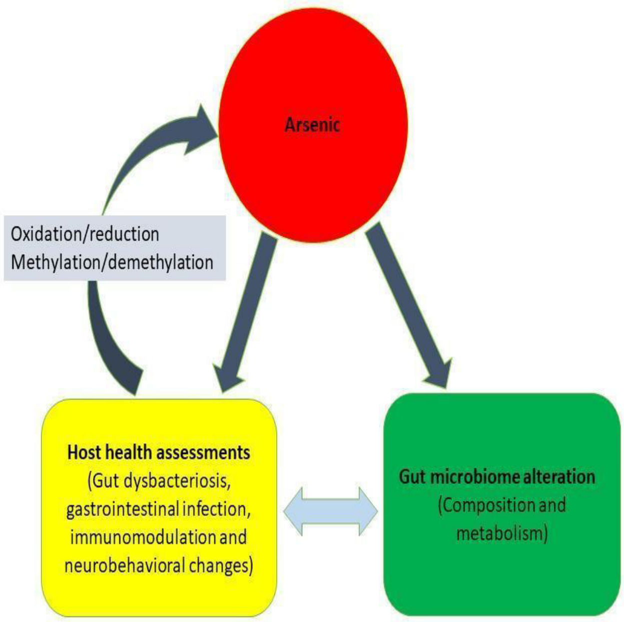

Fig 1: Environmental exposure of arsenic possesses alteration in gut microbiome linked to disease occurrence in hosts. Adapted from: Assefa et al., 2020 [15].

1.1 *Occurrence, distribution and compounds*

Arsenic is a metalloid present ubiquitously in nature. Trace amounts are found in soil, water and air, present as sulfides in combination with ores of lead, copper, nickel, antimony, cobalt and iron. The sources of arsenic are volcanic eruption, smelting of metals, fuel combustion and the practice of pesticides. The water acts as a carrier of arsenic in the environment, and it is used in agrochemical products, pharma companies and glass industries.[16,17] Arsenic is geologically present in groundwater, making it an integral part of drinking water in most parts of the world. On comparing globally, Bangladesh, India, China and Taiwan report the highest level of arsenic.[18] Compounds of arsenic can be categorised into three classes: inorganic, organic, and arsine gas [Table 1].

Table 1. Naturally occurring arsenic and its compounds				
CAS no.	Chemical name	Synonyms	Formula	Reference
		Inorganic arsenic (As)		
1327-53-3	As (III) oxide	As trioxide, arsenous oxide, white As	As_2O_3	16
13768-07-5	Arsenious acid	Arsenious acid	$AsHO_2$	17
7784-34-1	As (III) chloride	As trichloride, arsenous trichloride	$AsCl_3$	17
1303-33-9	As (III) sulfide	As trisulfide orpiment	As_2S_3	17
1303-28-2	As (V) oxide	As pentoxide	As_2O_5	17
7778-39-4	Arsenic acid	*Ortho*-arsenic acid	H_3AsO_4	17
10102-53-1	Arsenic acid	*Meta*-arsenic acid	$HAsO_3$	17
		Organic arsenic		
593-52-2	Methyl arsine	Arsine, methyl	CH_3AsH_2	17
593-57-7	Dimethyl arsine	Arsine, dimethyl	C_2H_7As	17
593-88-4	Trimethylarsine		$(CH_3)_3As$	17
		Arsine gas		
7784-42-1	Arsine	Arsenic hydride	AsH_3	19

Inorganic arsenic has two most common oxidation states: trivalent and pentavalent. Inorganic arsenic compounds with trivalent oxidation state including arsenic trioxide, sodium arsenite and arsenic trichloride, while pentavalent oxidation state includes arsenic pentoxide, arsenic acid, and arsenates,eg. lead arsenate ($PbHAsO_4$) and calcium arsenate [$Ca_3(AsO_4)_2$]. Arsanilic acid ($C_6H_8AsNO_3$), methylarsonic acid (CH_5AsO_3), dimethylarsinic acid ($C_2H_7AsO_2$) and arsenobetaine ($C_5H_{11}AsO_2$) are usual organic arsenic compounds.[20] Arsine gas (AsH_3) is colourless and flammable and generated when arsenic containing compounds release nascent hydrogen. Arsenic toxicity is distinct from the toxicity of inorganic or organic arsenic compounds.[21]

1.2 *Arsenic toxicity*

At present, arsenic exposure is still a major health problem. About 140 million people in 50 countries consume arsenic contaminated water above the WHO standard (0.05mg).[22] Arsenic interferes with general cellular processes like cellular enzymes, cell respiration and mitosis by affecting the sulfhydryl group of cells, thus referred to as protoplasmic poison.[22] Effects of arsenic exposure on lungs, kidney, bladder, liver, testis, uterus and prostate gland lead to cardiac diseases, developmental defects, haematological, neurological and reproductive problems, black foot disease and cancer.[24] Arsenic causes hepatotoxicity indicated by an increase in alkaline phosphatase, acid phosphatase, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) due to hepatic damage. Arsenic is also deposited in the liver and blood and affects enzymatic pathways.[25] Toxicity of arsenic plays a significant role in generating reactive oxygen species (ROS), DNA repair inhibition, abnormal gene expression via epigenetic modifications, altered glucocorticoid and hypothalamus-pituitary-adrenal (HPA) axis pathway signalling and adult neurogenesis.[9] Recent studies suggested that impaired neurological functions are mainly caused in children on exposure to low arsenic concentration.[26] HPA axis is a multi-centre combination involved in modulating a variety of biological and physiological phenomenon. Arsenic exposure leads to a disruption in the system that leads to a chain of widespread effects. Arsenic exposure has been shown to elevate hypothalamic corticotropin releasing factor (CRF), modified corticosterone (CORT) secretion, reduction in hippocampal hydroxysteroid dehydrogenase type 1 (11β-HSD1), and decreased expression of brain derived neurotrophic factor (BDNF). This impairment in the HPA axis leads to molecular and cognitive pathology.[5,27]

1.3 *Absorption, accumulation and methylation*

Arsenic ingestion in human body occurs via food and water, which is absorbed mainly through GIT even at a low dose. The uptake of almost 90% of soluble arsenic is in inorganic trivalent or pentavalent forms.[28] After absorption in the stomach and intestine, it is released into the bloodstream and accumulates in many parts of the brain, muscles, bones, kidneys and lungs in the form of inorganic and methylated arsenicals.[6,29] Flow of arsenic from the blood seems to follow a three-compartment model, which speculates biomethylation of inorganic arsenic.[16] In humans, data based on autopsy indicates the highest concentration of arsenic in skin, nails and hair.[30] Arsenic distribution in the organs shows 2-25 times greater in the kidneys, liver, bile, brain, skeleton, skin, and blood for trivalent than pentavalent forms.[31] Arsenic is detoxified through a process called methylation. It is cycling in any environment, and human exposure is recently considered a bioactivation and detoxification pathway and is directly related to its chemical speciation.[32] Methylation materialises through alternating reductive and oxidative methylation reactions; the addition of methyl group (CH_3) is the main factor for reducing pentavalent to trivalent arsenic.[33] Methylated MMA and DMA are relatively less toxic, having less binding capacity to tissues and greater elimination from the body than unmethylated forms. Arsenic metabolism occurs in the liver. Arsenic methyltransferase (AS_3MT) methylates the inorganic arsenic in liver in the presence of a methyl donor S-adenosylmethionine (SAM) and a cofactor glutathione (GSH) to significant monomethylated (MMA^{III}), monomethylarsonic acid (MMA^{V}) and dimethylated arsenic metabolites (DMA^{III}), and dimethylarsinic acid (DMA^{V}), which is ultimately eliminated through urine [Figure 2].[10,34]

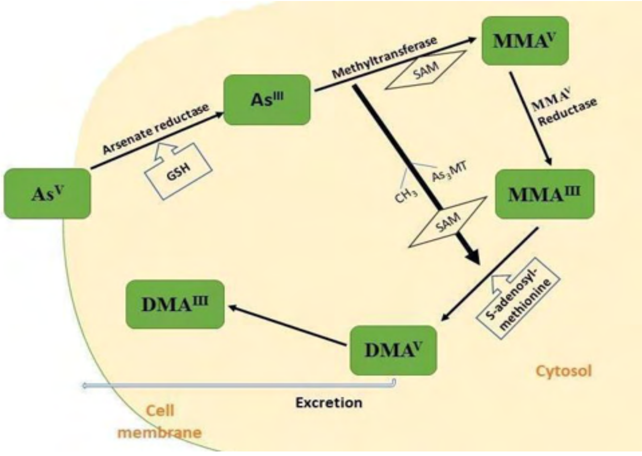

Fig 2. Proposed pathway of arsenic metabolism in the human body. Arsenic methyltransferase (AS3MT) methylates arsenate (As V) reduced to arsenite (As III) in the presence of a methyl donor S-adenosylmethionine (SAM) and a cofactor glutathione (GSH) to significant monomethylated (MMA^{III}), monomethylarsonic acid (MMA^V) and dimethylated arsenic metabolites (DMA^{III}) and dimethylarsinic acid (DMA^V). Adapted from: Marafante E et al., 1985, Khairul Is et al., 2017, Wei S et al., 2019 [10,34,35].

Reports showed that the gut microbiome of humans is directly involved in the arsenic reduction/oxidation methylation pathway. In this process, inorganic arsenic (As V), on reduction, converts into more toxic inorganic arsenic (As III), which on methylation and oxidation transforms into MMA^V simultaneously. On reduction of MMA^V, MMA^{III} is formed, which on oxidative methylation converted into DMA^V, and further reduced to DMA^{III}.[36-37]

2. *Arsenic-Microbe's interaction*

Arsenic-microbes interaction derives from environmental microbiology, where microbial metabolism is the major factor of arsenic speciation, mobility, and toxicity.[8] In all environments, microbes are the leading carriers, where arsenic and microbes coexist together and thus structural part of arsenic cycling for arsenic transformation. Arsenic is transformed by oxidation, reduction, or demethylation based on microbial catalysts.[31] All the reactions carried out by microbes are of self-interest as may be carried out for detoxification of poison or cellular energy generation.[9] Recent studies showed that due to arsenic toxicity, gut microbiome biotransformation cause alteration of microbiome morphology and physiology that may directly alter the ArsBC gene activity.[8] Although ingested arsenic come first in contact with the GIT and effect resident bacteria. Orally ingested arsenic is detoxified and removed from the body by gut microbiomes by affecting their metabolism and making the novel arsenic metabolites accessible to the host.[38] Toxicant killing of microbiome members may alter the maintenance of the gut epithelial barrier, regulate host inflammatory responses, and synthesise or recycle essential metabolites and cofactors involved in the host toxic responses pathway.[8] Exposure of environmentally relevant concentrations of arsenic in drinking water impact the microbial community of the colon to alter both microbiome and host metabolism.[12]

2.1 *Effect on gut microbiome*

Several studies showed that due to arsenic, the constitution of the microbiome community is changed. In the context of phylogenetic examining studies, fish, rodents, and ruminants are compatible in representing arsenic induced disrupting microbiome community constitution.[39,40] Arsenic exposure leads to alteration of microbiome composition in the gut because of various factors, including variable arsenic tolerance and detoxification capacity, e.g. Methyl Arsenite efflux permease (ArsP), non-heme iron-dependent type-I extradiol dioxygenase with lyase activity of C-As bond (ArsI) or methyl arsenite oxidase (ArsH), among genera and species, arsenic–based antibiotics production, e.g. nourseothricin;[41-43] and those changes could have developed arsenic resistance acquired from spontaneous mutations. This may modify host metabolism that, in turn, alter gut microbial community.[44] Reports suggested that mice exposed to arsenic results in elevation of *Bacteroidetes* population.[12] Elevated *Bacteroidetes* number may be due to gram-negative bacteria as they have lipopolysaccharide (LPS) on their outer membrane. The LPS cause widespread inflammation, disrupting normal biological functions, and it is an important virulence factor.[45] Increased concentrations of pathogenic arginine metabolites have been detected in the arsenic exposed mouse circulation. Intracellular pathogens such as *Salmonella typhimurium* increase the level of arginine metabolites by utilising the arginine pool of the host on infection. The elevation in arginine metabolites is a causative factor to perturb the gut microbiomes and infection.[46] The New Hampshire Birth Cohort Study (NHBCS) showed the link between arsenic exposure and gut microbiome constitution in over 1500 pregnant women (18–45 ages) and subsequently in their offsprings. In 204 arsenic exposed six week old infants, urinary samples showed arsenic concentration below the quantification limit of 4.8µg/L and suppressed microbiome composition of several genera (*Firmicutes, Bacteroides,* and *Bifidobacterium)*. They reported sex-dependent differences in the infant gut microbiome composition, leading to perturbation in the gut microbiota community.[47] Six week old female C57B1/6 mice showed variation in the various intestinal flora, leading to clear βdiversity clustering between treated and control individuals, exposing arsenic resulting decrease in order *Streptophyta*, *Clostridiales*, and *Erysipelotrichales,* whereas *Bacillales* were increased in arsenic exposed individuals.[48] Stool microbiome samples of Bangladesh children were analysed who were exposed to arsenic contaminated drinking water and found modified microbiome constitutional shifts, with elevated copy number of *Proteobacteria* and arsB and arsC on increasing arsenic exposure.[49]

3. *Arsenic toxicity to Gut microbiome and host health*

The gut microbiome impacts various biological functions, including metabolic processes, energy cycle, and immune system development.[50] In the human body, cells and gut microbiome due to stored arsenic within them, harmful effects are ensured.[51] Disruption of gut microbiome composition due to arsenic exposure results in host diseases. Bacterial communities are susceptible to altering the host surrounding and thus disturbance in gut microbiomes and secretion of virulence factors such as LPS due to microbiome shift favouring more infective bacterial species, cause an increase in pathogenic arginine metabolites and may be responsible for originating host diseases.[13] Advancement of liver fibrosis and hepatocarcinoma are induced by the change in gut microbiome permeability and rise in pathogen-associated molecular patterns (PAMPs) such as LPS. Moreover, arsenic exposed at a higher dose increases the chances of mitochondria damage to impair energy metabolism and cause cell death.[52] Altered gut microbiome constitution and its functions are associated with oxidative stress and many pathological diseases like diabetes, inflammatory bowel disease (IBD), cancer, Parkinson's disease, cardiovascular diseases, allergies, and inflammatory diseases occurring in hosts due to dysbiosis.[52-54] [Table 2].

Table 2: Arsenic toxicity induced gut microbiome and related health effects

Animal Model	Dose of arsenic exposure	Major findings	References
Mice	Arsenic trioxide (10, and 250 ppb) for 2, 5, and 10 weeks	Arsenic concentration changed the diversity of bacteria at both genetic and morphological levels, especially within two bacterial phylum *Bacteroidetes* and *Firmicutes.* The level of arsenate metabolites was found elevated in the blood. Histopathological study of the liver revealed increased nitrate and nitrite levels at a higher dose and decreased bacterial colonies.	12
Larvae zebrafish 20 days post fertilisation (dpf)	Arsenic compound (10, 50, and 100 ppb) exposure for 20 days	Arsenic alters the microbial composition, diversity and causes dysbiosis, and at higher doses increase the level of class 1 integron gene in developing larval zebrafish microbiota. The higher concentration causes increased expression of the *int* gene (1 integron gene), which is responsible for horizontal transfer of resistance gene and even at the lowest concentration, there was destabilisation in bacterial colonies.	40
Mice C57BL/6	Fed with 10ppm arsenic compound in drinking water for four weeks	The 16S rRNA sequencing after a particular exposure of arsenic revealed imbalanced homeostasis of the host and changed significantly gut microbiota.	46
Mice C57BL/6	One group of mice fed with 50 ppm cadmium chloride and another group with 50 ppm sodium arsenite for two weeks as drinking water	16S rRNA gene amplicon sequencing and untargeted LC-MS/MS metabolomics indicate that bacterial diversity in cadmium was much lower compared to arsenic both quantitatively and qualitatively.	55
Mice C57BL/6	Exposed with 0, 50, and 500 ppb of arsenic with zinc adequate and with 0, 50, and 500 ppb of arsenic with marginally zinc-deficient for six weeks in fresh drinking water	This study was carried out to observe the individual and combined effect of two metals, zinc, and arsenic on the gut microbiota of mice. The zinc was restricted in the diet of mice while arsenic was provided; this resulted in reduced diversity of bacteria while their combined effect modified the diversity. There was also a decrease in zinc levels in plasma, and DNA damage was also reported.	56
Pathogen-free grade C57BL/6 female mice	Treated with 100ppb of sodium arsenite for 13 weeks in drinking water	16S rRNA sequencing data showed that the overall diversity of bacteria was reduced. The expression of genes related to carbohydrate metabolism decreased while lipopolysaccharide synthesis gene, DNA repair gene, and stress responsive gene expression increased after treatment. The expression level of genes related to the synthesis of vitamins B6, B12, and K2 and folic acid elevated.	57
Wild-type and IL-10 gene knockout mice	Arsenic compound exposure (10ppm) for four weeks in drinking water	16S rRNA gene sequencing and HPLC-ICP-MS data showed that due to the absence of IL-10 gene, the rate of infection was higher in the host's gut, which in turn affects the composition of bacteria and as well as arsenic metabolism.	58

3.1 *Gastrointestinal tract disorders*

In the GIT, very high exposure to arsenic causes gastric mucosal hyperaemia and haemorrhagic injury, whereas low and moderate arsenic level alters cell signalling that regulates cell differentiation and functions.[59] Reports suggest that moderate level of arsenic exposure (250 ppb) degrade intestinal microbial biofilms that increase bacterial spores, reduce intracellular inclusion and alter gut microbiome leading to modified physiological functions resulting in the potential opening of niche for pathogenic microbes like, *Bacteroidetes* which may cause GIT related disorders and inflammation.[12] Intestinal microbes are responsible for converting organic arsenic to harmful inorganic arsenic, altering certain microbial population viability. When 50 ppm arsenic is exposed to mice results in variation in microbiome metabolic profile by altering some gut microbial family's abundance suggested by the metagenomic study.[46]

3.2 *Immunological disturbances*

The infectious agents of pathogenic bacteria trigger immune system alterations leading to several immunological disturbances.[60] Dysfunction of mucosal barrier is caused by bacterial penetration product resulting in direct contact of immune cell.[61] Mechanisms implied by chronic microbiome change for disease growth are similar to vascular and metabolic disease, including dysfunctional metabolism, altered lipid - deposition, and chronic inflammation.[62,63] Inflammatory dendritic cells (DCs) promote the secretion of proinflammatory, inflammatory chemokines and prostaglandins, IL-17 produce TNF-α and IL-6 leads to the Th17 cells, which caused inflammation and tissue destruction, which are responsible for various many immune-inflammatory diseases.[64,65] population-based study reveals that arsenic exposure in human placenta and placental blood is related to oxidative stress, inflammation, and immune disruption.[66] Repeated exposure of arsenite to adult mice cause an abundance of bacteria belonging to genera *Alistipes, Bilophila* (causative agent for inflammatory bowel syndrome (IBD)) and *Lactobacillus johnonii*.[67] The production of IL-12 was enhanced in arsenic exposed mice mediated by *Lactococcus lactis*.[68] Arsenic toxicity can contribute to the intestinal microbiota composition and gut-associated immune response. Repeated arsenic exposure caused a transient decrease in the recovery of intestinal bacteria, a shift in the bacterial population with an abundance of arsenic resistance genes, and evidence for host metabolism of arsenite into less-reactive trivalent methylated species. In adult CD-1 mice, arsenic induced a high level of CC chemokines and proinflammatory and anti-inflammatory cytokine secretion in the intestine. Arsenic exposure at PND21 resulted in the development of distinct bacterial populations.[69] Study demonstrated that arsenic induced gut microbiome disturbs the intestinal homeostasis to regulate colon cancer genes. The data indicated downregulation of the Nucleotide domain containing protein 2 (NOD2) and anti-inflammatory cytokines and upregulation of dendritic cells, macrophages and inflammatory cytokines. β- catenin (colon cancer marker) and arrest in Activated inflammatory cytokines (APC) were observed. The results suggested that arsenic altered gut microbiome indirectly shifts inflammatory cytokines mediated immune system destruction and β- catenin.[70] Therefore, the available data indicate that arsenic interactions with the gut microbiome and immune system result in the compromised health status of the host.

3.3 *Disrupting metabolic functions*

The microbial community mainly present on the lining of outer mucosa performed a crucial function in metabolic and host defence by supplying nutrients to regulate fat globules in the epithelial lining of the gut.[71] Mice infected with *Helicobacter trigonum* exposed to arsenic alters gut microbiota showed significant changes in the number and regulatory pattern of the metabolites. Another major pathway perturbed due to arsenic exposure after gut microbiome alteration in phospholipid metabolism in the host, followed by sphingolipid, fatty acid metabolism, cholesterol biosynthesis and metabolism, and tryptophan metabolism. This indicates that changes in the gut microbiome exacerbate arsenic toxicity.[41, 72]

4. CONCLUSION

The present review focus on the influence of arsenic toxicity on the gut microbiome. Disturbance in the gut microbiome leads to a variety of challenges to human health. Under the arsenic microenvironment, the cell membrane of intestinal bacteria may absorb the arsenic via ion channels thus, making it less available to the host, and it may lead to perturbations of gut microbiomes. Further, exposure to arsenic also leads to epigenetic changes in the host, deleterious effects on gut microbiota, endocrine disruption, inhibition of DNA repair, and also affect embryonic development and modification of cellular signalling via altered activation of transcription factors. It acts as an indicator of microbial perturbation and infection. The available data on arsenic microbe interaction suggests that gastrointestinal tract disorder, disruption of metabolic function, and immunological disturbances collectively provide mechanistic insight suggesting that the disturbance in the composition of the microbial profile of gut microbiota directly impacts the host health. However, the precise molecular mechanism of arsenic-induced toxicity on human health is still under investigation. Therefore, more focus will be required to understand the interactions among arsenic toxicity, gut microbiome and host health.

5. AUTHORS CONTRIBUTION STATEMENT

Abhishek Jain and Dr. Subodh Kumar Jain conceptualised and prepared the final manuscript. Swati Jain, Roshni Jain and Swati Singh Thakur helped in the collection of research papers during literature survey. All authors discussed the literature surveyed and helped in writing the manuscript.

6. ACKNOWLEDGEMENT

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7. CONFLICT OF INTEREST

Conflict of interest declared none.

8. REFERENCES

1. ATSDR (Agency for Toxic Substances and Disease Registry). The ATSDR substance priority list. Chinese Academy of Sciences [Internet]. Atlanta: Centres for Disease Control and Prevention. p. 7440-38-2; 2019 [up dated 2020 January 15. RN; [cited May 9 2021]. Availablefrom:http://www.atsdr.cdc.gov/spl/index.html.
2. Orloff K, Mistry K, Metcalf S. Biomonitoring for environmental exposures to arsenic. J Toxicol Environ

Health B Crit Rev. 2009;12(7):509-24. doi: 10.1080/10937400903358934, PMID 20183531.
3. Rahman MM, Chowdhury UK, Mukherjee SC, Mondal BK, Paul K, Lodh D, Biswas BK, Chanda CR, Basu GK, Saha KC, Roy S, Das R, Palit SK, Quamruzzaman Q, Chakraborti D. Chronic arsenic toxicity in Bangladesh and West Bengal, India—a review and commentary. J Toxicol Clin Toxicol. 2001;39(7):683-700. doi: 10.1081/clt-100108509, PMID 11778666.
4. World Health Organization (WHO). Geneva. WHO Press [Internet]. Vol. 1; 2008. Guidelines for drinking-water quality: incorporating first and second addenda to. Recommendations. 3rd ed [cited May 11 2021]. Available from: https://www.who.int/water_sanitation_health/dwq/fulltext.pdf.
5. Sun BF, Wang QQ, Yu ZJ, Yu Y, Xiao CL, Kang CS, Ge G, Linghu Y, Zhu JD, Li YM, Li QM, Luo SP, Yang D, Li L, Zhang WY, Tian G. Exercise prevents memory impairment induced by arsenic exposure in mice: implication of hippocampal BDNF and CREB. PLOS ONE. 2015;10(9):e0137810. doi: 10.1371/journal.pone.0137810, PMID 26368803.
6. Tyler CR, Allan AM. The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: a review. Curr Environ Health Rep. 2014;1(1 (2)):132-47. doi: 10.1007/s40572-014-0012-1, PMID 24860722.
7. Amato KR, Arrieta MC, Azad MB, Bailey MT, Broussard JL, Bruggeling CE, Claud EC, Costello EK, Davenport ER, Dutilh BE, Swain Ewald HA, Ewald P, Hanlon EC, Julion W, Keshavarzian A, Maurice CF, Miller GE, Preidis GA, Segurel L, Singer B, Subramanian S, Zhao L, Kuzawa CW. The human gut microbiome and health inequities. Proc Natl Acad Sci U S A. 2021;118(25):e2017947118. doi: 10.1073/pnas.2017947118, PMID 34161260.
8. Coryell M, Roggenbeck BA, Walk ST. The human gut microbiome's influence on arsenic toxicity. Curr Pharmacol Rep. 2019;5(6):491-504. doi: 10.1007/s40495-019-00206-4, PMID 31929964.
9. McDermott TR, Stolz JF, Oremland RS. Arsenic and the gastrointestinal tract microbiome. Environ Microbiol Rep. 2020;12(2):136-59. doi: 10.1111/1758-2229.12814, PMID 31773890.
10. Marafante E, Vahter M, Envall J. The role of the methylation in the detoxication of arsenate in the rabbit. Chem Biol Interact. 1985;56(2-3):225-38. doi: 10.1016/0009-2797(85)90008-0, PMID 4075449.
11. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, Nielsen T, Pons N, Levenez F, Yamada T, Mende DR, Li J, Xu J, Li S, Li D, Cao J, Wang B, Liang H, Zheng H, Xie Y, Tap J, Lepage P, Bertalan M, Batto JM, Hansen T, Le Paslier D, Linneberg A, Nielsen HB, Pelletier E, Renault P, Sicheritz-Ponten T, Turner K, Zhu H, Yu C, Li S, Jian M, Zhou Y, Li Y, Zhang X, Li S, Qin N, Yang H, Wang J, Brunak S, Doré J, Guarner F, Kristiansen K, Pedersen O, Parkhill J, Weissenbach J, MetaHIT Consortium, Bork P, Ehrlich SD, Wang J. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010;464(7285):59-65. doi: 10.1038/nature08821, PMID 20203603.
12. Dheer R, Patterson J, Dudash M, Stachler EN, Bibby KJ, Stolz DB, Shiva S, Wang Z, Hazen SL, Barchowsky A, Stolz JF. Arsenic induces structural and compositional colonic microbiome change and promotes host nitrogen and amino acid metabolism. Toxicol Appl Pharmacol. 2015;289(3):397-408. doi: 10.1016/j.taap.2015.10.020, PMID 26529668.
13. Rosenfeld CS. Gut dysbiosis in animals due to environmental chemical exposures. Front Cell Infect Microbiol. 2017;7:396. doi: 10.3389/fcimb.2017.00396, PMID 28936425.
14. Leser TD, Mølbak L. Better living through microbial action: the benefits of the mammalian gastrointestinal microbiota on the host. Environ Microbiol. 2009;11(9):2194-206. doi: 10.1111/j.1462-2920.2009.01941.x, PMID 19737302.
15. Assefa S, Köhler G. Intestinal microbiome and metal toxicity. Curr Opin Toxicol. 2020;19:21-7. doi: 10.1016/j.cotox.2019.09.009, PMID 32864518.
16. Agency for toxic substances and diseases registry: toxicological profile for arsenic [Internet]. Atlanta: United States Department of Health and Human Services; 1991 [updated 2020 May 5; [cited May 16 2021]. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=22&tid=3.
17. Gomez-Caminero A, Howe PD, Hughes M, Kenyon E, Lewis D. R. et al. Geneva: environmental health criteria. World Health Organization. P. 224. Arsenic and arsenic compounds. 2nd ed [Internet] [cited May 16 2021]. Available from: http://apps.who.int/iris/bitstream/handle/10665/42366/WHO_EHC_224.pdf;jsessionid=E81CC657306C822C6D00F37170F3EF65?sequence=1.
18. Mahanta R, Chowdhury J, Nath HK. Health costs of arsenic contamination of drinking water in Assam, India. Econ Anal Policy. 2016;49:30-42. doi: 10.1016/j.eap.2015.11.013.
19. Arsenic. Denmark: World health organisation (world health organisation); 2000. Air quality guidelines. 2nd ed [Internet] [cited May 19 2021]. Available from: https://www.euro.who.int/__data/assets/pdf_file/0014/123071/AQG2ndEd_6_1_Arsenic.PD.
20. Fowler BA, Chou C-H CJ, Jones RL, Chen C-J, Nordberg GF, Fowler BA, Nordberg M, Friberg LT. Handbook on the Toxicology of Metals: 4th edition [Internet]. Burlington, USA: Academic Press; 2014 [cited 2021 May 21]. 368-75. Available from: https://booksite.elsevier.com/samplechapters/9780123694133/Sample_Chapters/01~Front_Matter.pdf.
21. Arsenic, metals, fibres and dusts: IARC working group on the evaluation of carcinogenic risks to humans [Internet]. France; Lyon, FR: International Agency for Research on Cancer. p. 41-85; 2014 [cited Apr 15 2021]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK304375.
22. Arsenic. World Health Organization (world health organisation) [Internet]. [Place unknown. Forbury. 2018. 15]. Available from: https://www.who.int/news-room/fact-sheets/detail/arsenic.
23. Gordon JJ, Quastel JH. Effects of organic arsenicals on enzyme systems. Biochem J. 1948;42(3):337-50. doi: 10.1042/bj0420337.
24. Kapaj S, Peterson H, Liber K, Bhattacharya P. Human health effects from chronic arsenic poisoning—a review. J Environ Sci Health A Tox Hazard Subst

Environ Eng. 2006;41(10):2399-428. doi: 10.1080/10934520600873571, PMID 17018421.
25. Dubey NP, Jain SK, Maheshwari HS. Chronic study of arsenic trioxide-induced hepatotoxicity in relation to arsenic liver accumulation in rats. Toxicol Environ Chem. 2014;96(3):491-9. doi: 10.1080/02772248.2014.949129.
26. Rosado JL, Ronquillo D, Kordas K, Rojas O, Alatorre J, Lopez P, Garcia-Vargas G, Del Carmen Caamaño M, Cebrián ME, Stoltzfus RJ. Arsenic exposure and cognitive performance in Mexican school children. Environ Health Perspect. 2007;115(9):1371-5. doi: 10.1289/ehp.9961, PMID 17805430.
27. Goggin SL, Labrecque MT, Allan AM. Perinatal exposure to 50 ppb sodium arsenate induces Hypothalamic-Pituitary-Adrenal Axis dysregulation in maleC57BL/6 mice. Neurotoxicology. 2012;33(5):1338-45. doi: 10.1016/j.neuro.2012.08.010, PMID 22960421.
28. Ishinishi N, Friberg L, Nordberg GF, Vouk BV. Handbook of the toxicology of metals. Amsterdam, NY-Oxford: Elsevier. Vol. II [Internet]; 1986 [cited Apr 25 2021].
29. Saha JC, Dikshit AK, Bandyopadhyay M, Saha KC. A review of arsenic poisoning and its effects on human health. Crit Rev Environ Sci Technol. 1999;29(3):281-313. doi: 10.1080/10643389991259227.
30. Díaz-Barriga F, Santos MA, Mejía JJ, Batres L, Yáñez L, Carrizales L, Vera E, del Razo LM, Cebrián ME. Arsenic and cadmium exposure in children living near a smelter complex in San Luis Potosi, Mexico. Environ Res. 1993;62(2):242-50. doi: 10.1006/enrs.1993.1109, PMID 8344231.
31. Health assessment document for inorganic arsenic [final report] [internet]. Environmental criteria and assessment. NC: Research Triangle Park. Environmental Protection Agency; 1984 March. [cited May 16 2021]. p. 351. Report no. : EPA-600. 8-83-021F.
32. Oremland RS, Dowdle PR, Hoeft S, Sharp JO, Schaefer JK, Miller LG, Switzer Blum J, Smith RL, Bloom NS, Wallschlaeger D. Bacterial dissimilatory reduction of arsenate and sulfate in meromictic Mono Lake, California. Geochim Cosmochim Acta. 2000;64(18):3073-84. doi: 10.1016/S0016-7037(00)00422-1.
33. Vahter M, Concha G. Role of metabolism in arsenic toxicity. Pharmacol Toxicol. 2001;89(1):1-5. doi: 10.1034/j.1600-0773.2001.d01-128.x, PMID 11484904.
34. Khairul I, Wang QQ, Jiang YH, Wang C, Naranmandura H. Metabolism, toxicity and anticancer activities of arsenic compounds. Oncotarget. 2017;8(14):23905-26. doi: 10.18632/oncotarget.14733, PMID 28108741.
35. Wei S, Zhang H, Tao S. A review of arsenic exposure and lung cancer. Toxicol Res (Camb). 2019;8(3):319-27. doi: 10.1039/c8tx00298c, PMID 31160966.
36. Challenger F. Biological methylation. Chem Rev. 1945;36(3):315-61. doi: 10.1021/cr60115a003.
37. Rehman K, Naranmandura H. Arsenic metabolism and thioarsenicals. Metallomics. 2012;4(9):881-92. doi: 10.1039/c2mt00181k, PMID 22358131.
38. Diaz-Bone RA, Van de Wiele TV. Biotransformation of metal(loid)s by intestinal microorganisms. Pure Appl Chem. 2010;82(2):409-27. doi: 10.1351/PAC-CON-09-06-08.
39. Kubachka KM, Kohan MC, Herbin-Davis K, Creed JT, Thomas DJ. Exploring the in vitro formation of trimethylarsinesulfide from dimethylthioarsinic acid in anaerobic microflora of mouse cecum using HPLC-ICP-MS and HPLC-ESI-MS. Toxicol Appl Pharmacol. 2009;239(2):137-43. doi: 10.1016/j.taap.2008.12.008, PMID 19133283.
40. Dahan D, Jude BA, Lamendella R, Keesing F, Perron GG. Exposure to arsenic alters the microbiome of larval zebrafish. Front Microbiol. 2018;9:1323. doi: 10.3389/fmicb.2018.01323, PMID 29977230.
41. Xue J, Lai Y, Chi L, Tu P, Leng J, Liu CW, Ru H, Lu K. Serum metabolomics reveals that gut microbiome perturbation mediates metabolic disruption induced by arsenic exposure in mice. J Proteome Res. 2019;18(3):1006-18. doi: 10.1021/acs.jproteome.8b00697, PMID 30628788.
42. Chen J, Yoshinaga M, Rosen BP. The antibiotic action of methylarsenite is an emergent property of microbial communities. Mol Microbiol. 2019;111(2):487-94. doi: 10.1111/mmi.14169, PMID 30520200.
43. Kuramata M, Sakakibara F, Kataoka R, Yamazaki K, Baba K, Ishizaka M, Hiradate S, Kamo T, Ishikawa S. Arsinothricin, a novel organo arsenic species produced by a rice rhizosphere bacterium. Environ Chem. 2016;13(4):723-31. doi: 10.1071/EN14247.
44. Macur RE, Jackson CR, Botero LM, Mcdermott TR, Inskeep WP. Bacterial populations associated with the oxidation and reduction of arsenic in an unsaturated soil. Environ Sci Technol. 2004;38(1):104-11. doi: 10.1021/es034455a, PMID 14740724.
45. Allcock GH, Allegra M, Flower RJ, Perretti M. Neutrophil accumulation induced by bacterial lipopolysaccharide: effects of dexamethasone and annexin 1. Clin Exp Immunol. 2001;123(1):62-7. doi: 10.1046/j.1365-2249.2001.01370.x, PMID 11167999.
46. Gogoi M, Datey A, Wilson KT, Chakravortty D. Dual role of arginine metabolism in establishing pathogenesis. Curr Opin Microbiol. 2016;29:43-8. doi: 10.1016/j.mib.2015.10.005, PMID 26610300.
47. Hoen AG, Madan JC, Li Z, Coker M, Lundgren SN, Morrison HG, Palys T, Jackson BP, Sogin ML, Cottingham KL, Karagas MR. Sex-specific associations of infants gut microbiome with arsenic exposure in a US population [sci rep:2018:8(1):12627]. doi: 10.1038/s41598-018-30581-9, PMID 30135504.
48. Lu K, Abo RP, Schlieper KA, Graffam ME, Levine S, Wishnok JS, Swenberg JA, Tannenbaum SR, Fox JG. Arsenic exposure perturbs the gut microbiome and its metabolic profile in mice: an integrated metagenomics and metabolomics analysis. Environ Health Perspect. 2014;122(3):284-91. doi: 10.1289/ehp.1307429, PMID 24413286.
49. Dong X, Shulzhenko N, Lemaitre J, Greer RL, Peremyslova K, Quamruzzaman Q, Rahman M, Hasan OS, Joya SA, Golam M, Christiani DC, Morgun A, Kile ML. Arsenic exposure and intestinal microbiota in children from Sirajdikhan, Bangladesh. PLOS ONE. 2017;12(12):e0188487. doi: 10.1371/journal.pone.0188487, PMID 29211769.
50. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial

ecology. Proc Natl Acad Sci U S A. 2005;102(31):11070-5. doi: 10.1073/pnas.0504978102, PMID 16033867.

51. Choiniere J, Wang L. Exposure to inorganic arsenic can lead to gut microbe perturbations and hepatocellular carcinoma. Acta Pharm Sin B. 2016;6(5):426-9. doi: 10.1016/j.apsb.2016.07.011, PMID 27709011.
52. Gilbert JA, Quinn RA, Debelius J, Xu ZZ, Morton J, Garg N, Jansson JK, Dorrestein PC, Knight R. Microbiome-wide association studies link dynamic microbial consortia to disease. Nature. 2016;535(7610):94-103. doi: 10.1038/nature18850, PMID 27383984.
53. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027-31. doi: 10.1038/nature05414, PMID 17183312.
54. Lu K, Knutson CG, Wishnok JS, Fox JG, Tannenbaum SR. Serum metabolomics in a Helicobacter hepaticus mouse model of inflammatory bowel disease reveal important changes in the microbiome, serum peptides, and intermediary metabolism. J Proteome Res. 2012;11(10):4916-26. doi: 10.1021/pr300429x, PMID 22957933.
55. Li X, Brejnrod AD, Ernst M, Rykær M, Herschend J, Olsen NMC, Dorrestein PC, Rensing C, Sørensen SJ. Heavy metal exposure causes changes in the metabolic health-associated gut microbiome and metabolites. Environ Int. 2019;126:454-67. doi: 10.1016/j.envint.2019.02.048, PMID 30844581.
56. Gaulke CA, Rolshoven J, Wong CP, Hudson LG, Ho E, Sharpton TJ. Marginal zinc deficiency and environmentally relevant concentrations of arsenic elicit combined effects on the Gut microbiome. mSphere. 2018;3(6):e00521-18. doi: 10.1128/mSphere.00521-18, PMID 30518676.
57. Chi L, Bian X, Gao B, Tu P, Ru H, Lu K. The Effects of an environmentally relevant level of arsenic on the gut microbiome and its functional metagenome. Toxicol Sci. 2017;160(2):193-204. doi: 10.1093/toxsci/kfx174, PMID 28973555.
58. Lu K, Mahbub R, Cable PH, Ru H, Parry NMA, Bodnar WM, Wishnok JS, Styblo M, Swenberg JA, Fox JG, Tannenbaum SR. Gut microbiome phenotypes driven by host genetics affect arsenic metabolism. Chem Res Toxicol. 2014;27(2):172-4. doi: 10.1021/tx400454z, PMID 24490651.
59. States JC, Barchowsky A, Cartwright IL, Reichard JF, Futscher BW, Lantz RC. Arsenic toxicology: translating between experimental models and human pathology. Environ Health Perspect. 2011;119(10):1356-63. doi: 10.1289/ehp.1103441, PMID 21684831.
60. Kivity S, Agmon-Levin N, Blank M, Shoenfeld Y. Infections and autoimmunity: friends or foes. Trends Immunol. 2009;30(8):409-14. doi: 10.1016/j.it.2009.05.005, PMID 19643667.
61. Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature. 2007;448(7152):427-34. doi: 10.1038/nature06005, PMID 17653185.
62. Caesar R, Fåk F, Bäckhed F. Effects of gut microbiota on obesity and atherosclerosis via modulation of inflammation and lipid metabolism. J Intern Med. 2010;268(4):320-28. doi: 10.1111/j.1365-2796.2010.02270.x, PMID 21050286.
63. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, DuGar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature. 2011;472(7341):57-63. Availab from. doi: 10.1038/nature09922, PMID 21475195.
64. Steinman RM, Banchereau J. Taking dendritic cells into medicine. Nature. 2007;449(7161):419-26. Available from. doi: 10.1038/nature06175, PMID 17898760.
65. Shortman K, Naik SH. Steady-state and inflammatory dendritic-cell development. Nat Rev Immunol. 2007;7(1):19-30. doi: 10.1038/nri1996, PMID 17170756.
66. Ahmed S, Mahabbat-e Khoda S, Rekha RS, Gardner RM, Ameer SS, Moore S, Ekström EC, Vahter M, Raqib R. Arsenic-associated oxidative stress, inflammation, and immune disruption in human placenta and cord blood. Environ Health Perspect. 2011;119(2):258-64. doi: 10.1289/ehp.1002086, PMID 20940111.
67. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505(7484):559-63. doi: 10.1038/nature12820, PMID 24336217.
68. Fernandez A, Horn N, Wegmann U, Nicoletti C, Gasson MJ, Narbad A. Enhanced secretion of biologically active murine interleukin-12 by *Lactococcus lactis*. Appl Environ Microbiol. 2009;75(3):869-71. doi: 10.1128/AEM.01728-08, PMID 19060166.
69. Gokulan K, Arnold MG, Jensen J, Vanlandingham M, Twaddle NC, Doerge DR, Cerniglia CE, Khare S. Exposure to arsenite in CD-1 mice during juvenile and adult stages: effects on intestinal microbiota and gut-associated immune status. mBio. 2018;9(4):1-17. doi: 10.1128/mBio.01418-18, PMID 30108172.
70. Tikka C, Manthari RK, Ommati MM, Niu R, Sun Z, Zhang J, Wang J. Immune disruption occurs through altered gut microbiome and NOD2 in arsenic induced mice: correlation with colon cancer markers. Chemosphere. 2020;246:125791. doi: 10.1016/j.chemosphere.2019.125791.
71. Johansson MEV, Larsson JMH, Hansson GC. The two mucus layers of colon are organised by the MUC2 mucin, whereas the outer layer is a legislator of host-microbial interactions. Proc Natl Acad Sci U S A. 2011;108(1);Suppl 1:4659-65. doi: 10.1073/pnas.1006451107, PMID 20615996.
72. Claus SP, Guillou H, Ellero-Simatos S. The gut microbiota: a major player in the toxicity of environmental pollutants? npj Biofilms Microbiomes. 2017;3:17001. doi: 10.1038/npjbiofilms.2017.