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Review Article

Effects of bisphenol A, phthalates and triclosan on gut microbiome and its impact on host pathophysiology across different species

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ABSTRACT

Environmental pollutants like endocrine disrupting chemicals (EDCs), unhealthy lifestyle and genetic predisposition have a major impact on the gut microbiota leading to dysbiosis, thus causing chronic diseases. This narrative review highlights the impact of three most common EDCs, bisphenol A (BPA), phthalates and triclosan in terms of increase in opportunistic pathogens, alterations in host metabolic profiles and immune response and associated pathophysiological changes across different species. BPA exposure led to a significant increase in *Bacteroides*, *Firmicutes*, *Proteobacteria* and *Akkermansia spp*. in all species (mice, zebra fish, rabbits, humans and rats). Phthalates exposure showed diverse changes in gut microbiota. Infants showed increased abundance of *Firmicutes* and events of antibiotic resistance after triclosan exposure. Changes in amino acid metabolism and biosynthesis of purines, pyrimidines and serotonin were found irrespective of the EDC type. Associated pathophysiological changes included increase in inflammatory cytokines, disruption of intestinal barrier, colonic inflammation, etc. The evidence from this review reveals that EDCs cause dysbiosis in all species. Any of these species could be used as models to test potential preventive and therapeutic interventions. Overall, gut microbiome profile should be considered as part of screening for chronic diseases among susceptible individuals and aim towards restoring healthy microbiome.

Keywords: Gut dysbiosis, Endocrine disrupting chemicals, Bisphenol A, Phthalates, Triclosan, Species

INTRODUCTION

The human 'gut microbiota' harbors a consortium of microorganisms, majority of which are bacteria, yeasts, fungi and viruses. Metagenomic shotgun sequencing and 16s rRNA sequencing of stool samples has revealed four predominant bacterial phyla- *Firmicutes*, *Proteobacteria*, *Actinobacteria* and *Bacteriodetes* in the gut.[1]

The gut microbiota maintains a fine balance between healthy and disease conditions. It can also act as an endocrine organ and perform diverse functions such as metabolizing complex undigested food and release of compounds like short chain fatty acids, bile, choline, gaseous metabolites, etc. which then act as hormones and regulate or influence host metabolism.[2]

Some of the other functions of gut bacteria include protection against pathogens, host immunity regulation, synthesis of essential metabolites, etc. Thus, it is evident that the gut microbiota and host metabolism are inter-related. These bacteria are susceptible to alterations in host environment and body conditions.

If a proper equilibrium is maintained, they are harmless to the host. However, alterations in gut microbiome can lead to dysbiosis (reduction in bacterial diversity and loss of beneficial bacteria) and increase the risk of many chronic diseases or disorders. There is increasing evidence in literature regarding association of gut microbiota and diseases like cancer, diabetes, digestive diseases, obesity, liver diseases, altered immunity and neurodegenerative disorders.[3-5] Pesticides, drugs, heavy metals, endocrine

disrupting chemicals (EDCs) like micro plastics, etc can enter the host through various routes and can cause gut microbiome dysbiosis (Figure 1). A chemical or a mixture of chemicals which is non- natural that can alter with production, secretion and metabolism of normal hormones in the body is termed as an 'EDC'.[6]

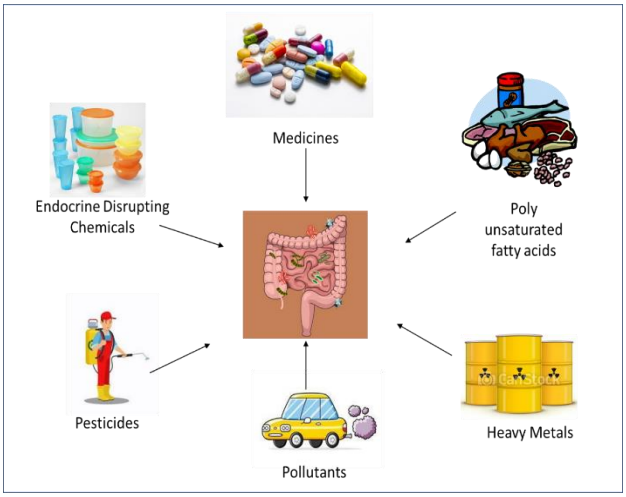

Figure 1: Factors affecting gut microbiome.

It is evident that early life exposure to environmental pollutants poses a great risk for developmental programming of diseases that have an onset in adult life, through disruption of normal epigenetic regulations. Also, exposure to such pollutants in prenatal or early postnatal life increases the risk of chronic diseases like diabetes, cancer, obesity, psychiatric impairments, etc. According to several studies, these environmental pollutants can cross the placental barrier and get accumulated in foetal tissues. Such exposure thus increases the risk of developing diseases such as cancer, immune dysregulation, obesity and many more during the adult life.[7] The aim of the review was to highlight the role of three environmental pollutants that act as EDCs namely Bisphenol A, Phthalates and Triclosan in gut microbiome dysbiosis and its correlation with pathophysiological responses of the host.

MOLECULAR MECHANISM OF EDCs

EDCs mainly interfere with the hormone receptors and the nuclear receptors. The nuclear receptors are a family of transcription factors that are regulated by ligands and activated by steroid hormones, such as progesterone and estrogen, and various other molecules which include retinoic acid, oxysterols, and thyroid hormones.[8] The EDCs can act as agonists thus inducing gene expression or as antagonists by inhibiting the activity of the receptor.[9] Alternatively, the EDCs can also exert toxic effects by mimicking estrogen and androgen hormone actions by binding to specific endogenous receptors. This leads to impairment in activation, synthesis, and secretion of endocrine hormones, thus causing gut dysbiosis as well as influencing several host physiological processes.[10,11]

Action of bisphenol A (BPA)

BPA is a widely used chemical in industries and hence is manufactured on a large scale. It is an EDC or xenoestrogen and it mimics body's hormones which can interfere with production, secretion and functioning of normal hormones. It is also shown to have neurotoxic effects like abnormal development of dendrites and axons of neurons, changes in synaptogenesis, etc.[12] Polycarbonate plastics, epoxy resins, packaging material of food and drinks cans, baby bottles, dental filling, etc. are predominantly made of BPA. Humans mainly get exposed to BPA through diet. It leaches into the food from epoxy resin coatings of canned food and the degree to which it leaches depends on the temperature of the food/ drink in the container. Exposure to BPA has been linked with various health effects resulting in reproductive endocrine and metabolic disorders, obesity, hormone dependent tumours, and many others including gut dysbiosis (Figure 2).[13]

Action of phthalates

Plasticizers like phthalates are found in children's toys, medical equipment, vinyl flooring, clothing, detergents, personal care products, and plastic packaging film. Plasticizers added to plastics increase their flexibility and even though integrated to polymer chains, they are not bound to the matrix and hence are quite unstable. They leach into the surrounding environment, increasing our risk of exposure. Being an EDC, phthalates also exert same effect as that of BPA. Humans can unknowingly ingest them from the environment, eatables, routine household products and can lead to dysfunction. Di [2-ethylhexyl) phthalate (DEHP)] a commonly used phthalate might have toxic effects on reproductive organs, heart, kidney, lungs, liver, etc even at low exposure, and can also lead to gut dysbiosis (Figure 2).[14]

Action of triclosan

Triclosan, a broad-spectrum antibiotic, is commonly used in personal care products like toothpastes, detergents, liquid soaps, etc.[15] Triclosan gets absorbed in the body through epidermis of skin and internal membranes of the intestines. It can also enter food chain and water, thus resulting in ingestion by human.[16] It has been found that humans on an average get exposed to TCS through a number of consumer products were estimated to be 0.047-0.073 mg/kg/day.[17]

Triclosan is known to interfere with body's thyroid hormone metabolism and it also is a potential EDC just like BPA and phthalates. It also plays a key role in gut dysbiosis and associated diseases (Figure 2). The effect of three compounds under this review namely BPA, phthalates and triclosan are described in two major categories namely gut microbiome dysbiosis and associated pathophysiological and metabolic changes in the host (Table 1).

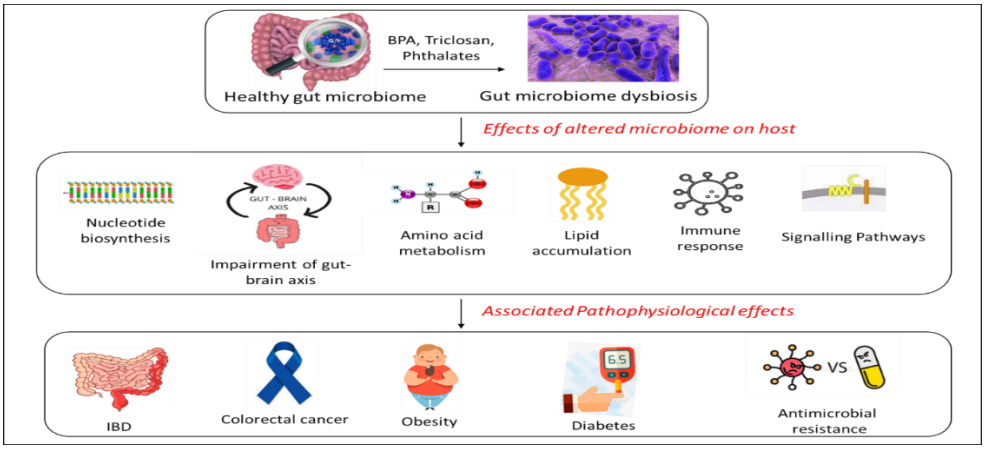

Figure 2: Effects of BPA, phthalates and triclosan on the host.

Table 1: A summary of effects of environmental pollutants on gut microbiota and host pathophysiology.

Environmental pollutant	Animal model	Dosage	Outcome	References
BPA	California mice (*Peromyscus californicus*)	50 g/kg feed weight	1. ↑ Bacteroides, mollicutes, prevotellaceae, erysipelotrichaceae, akkermansia, methanobrevibacter, Sutterella 2. Increased risk of IBD, colorectal cancer and development of metabolic disorders	Javurek et al, 2016
BPA	Zebra fish (Danio rerio)	0, 2 and 20 µg/l	1. Dominance of Proteobacteria, Actinobacteria and Hyphomicrobium 2. Decrease in body weight and serotonin levels	Chen et al, 2018
BPA	C57BL/6 mice	50 µg/kg-body weight/day	1. Reduced levels of tryptophan and other metabolites that decreased colonic inflammation	Deluca et al, 2018
BPA	CD1 mice	50 µg/kg-body weight/day	1. ↑ Proteobacteria and ↓Akkermansia 2. Increase in intestinal permeability, endotoxins and inflammatory cytokines	Feng et al, 2020
BPA	Rabbit offsprings	200 g of BPA/kg body weight/day	1. ↓ Oscillospira and Ruminococcaceae 2. Reduced levels of SCFA and increased levels of systemic LPS	Reddivari et al, 2017
BPA	C3H/HeN mice	50 g/kg	1. ↓ Bifidobacteria, Firmicutes and Clostridium spp. 2. Decrease in faecal antimicrobial and lysozyme activity	Malaise et al, 2017
BPA	C57BL/6J Mice	5 µg/kg/day	1. Significant increase in Oscillospira, Prevotella, Lachnospiraceae, Lactobacillus, Streptococcus, Dehalobacterium. 2. Effect on oxidative phosphorylation, PPAR signalling, fatty acid metabolism	Diamante et al, 2021
BPA	California mice (Peromyscus californicus)	5 mg/kg and 50 mg/kg feed weight	1. ↑ Clostridiales, Dehalobacterium, Oscillospira, Ruminococcus, Clostridiales and decrease in levels of Odoribacter Alphaproteobacteria, Coprococcus, etc. 2. Effect on gut-brain axis	Kaur et al, 2020

Continued.

Environmental pollutant	Animal model	Dosage	Outcome	References
Phthalates	C57BL/6J mice	1 or 10 mg/kg body weight/day	1. ↑ Mollicutes RF9, *Lachnoclostridium*, *Parabacteroides*, *Enterococcus* ↓ Akkermansia, Odoribacter, Clostridium, Lactobacillus and Fluviicola 2. ↑ Amino acids like phenylalanine, tryptophan, nucleosides/ nucleotides like uredines, uracil and vitamins like riboflavin	Lei et al, 2019
Phthalates	Zebra Fish (Danio rerio)	20 mg DEHP/day	1. Presence of Rothia, Adhaeribacter and Novosphingobium 2. Increased obesity due to increased biosynthesis of unsaturated fatty acids	Buerger et al, 2020
Phthalates	Zebra Fish (Danio rerio)	3 mg/kg DEHP	1. ↑ Fusobacteria, Bacteroidetes, Verrucomicrobia, Gammaproteobacteria and decrease in Saccharibacteria 2. Decrease in oxidative phosphorylation and benzoate degradation, glycerophospholipid metabolism and tryptophan metabolism	Ondrej et al
Phthalates	Sprague Dawley rats, Wistar rats, BALB/c mice, C57BL/6J mice	300, 1000, 3000 mg/kg body weight/day	1. SD rats: ↑ Proteobacteria, Firmicutes Oscillospira, Peptostreptococcaceae, Mycoplasma, Roseburia, Clostridiaceae, Sutterella, Clostridiales, RF32, Christensenellaceae, Blautia C57BL/6J mice: ↓ Proteobacteria and Actinobacteria BALB/c mice: ↑ Runimococcaceae and Rikenellaceae and decrease in Bacteriodetes Wistar rats: ↓ Coprococcus, Dehalobacteriaceae; increase in Adlercreutzia, Eubacateriaceae 2. Effect on metabolism	Wang et al, 2020
Phthalates	Mus musculus, CD-1 mice	100 mg/kg/ day	1. ↑ Firmicutes, Bacteroidetes, Actinobacteria, Adlercreutzia, Butyricimonas, Parabacteroides, Prevotella and Ruminococcus 2. Abnormal energy metabolism and immune responses	Feng et al
Phthalates	Humans	-	1. ↓ Bifidobacterium longum and Streptococcus. Transient increase in opportunity pathogens like Haemophilus parainfluenzae and Staphylococcus.	Yang et al, 2020
Phthalates	Mice	500 and 1500 mg/kg body weight	1. ↑ Firmicutes, Bacteroidetes, Verrucomicrobia, Turicibacter, Actinobacteria, and Epsilonbacteraeota 2. Pathways of tyrosine, ubiquinone, amino acids, carbohydrates, steroids, nucleotides, tryptophan, etc. were significantly affected. Female reproductive toxicity was observed.	Feng Fu et al, 2021

Continued.

Environmental pollutant	Animal model	Dosage	Outcome	References
Phthalates	C57BL/6J Mice	0.1-1 mg/kg	1. ↑ *Prevotella Firmicutes and α-proteobacteria Desulfovibrio, Sutterella* and ↓ Verrucomicrobia, of Oscillospira, Bacteroidetes, Parabacteroides Odoribacter, Akkermansia, and Helicobacter 2. Increased levels of serum LPS, Toll like receptor 4 and inflammatory cytokines like IL-1β, IL-6, TNF-α led to impaired lipid metabolism and inflammation via impaired gut liver axis.	Xiong et al, 2020
Triclosan	C57BL/6 Mice	2 ppm Triclosan water solution	1. ↑ Clostridiales; Bacilli; Turicibacterales, Christensenellaceae, Bacilli and ↓ Clostridium, Turicibacterales was observed. 2. Enrichment of bacterial genes encoding multidrug resistance efflux pumps like acriflavin resistance protein, multidrug-efflux transporter, Na (+)/drug antiporter and inner membrane transporter CmeB. Increased expression of glycosyltransferase and hence increase in biosynthesis of core oligosaccharides.	Gao et al, 2017
Triclosan	BALB/c Mice	40 mg/kg	1. Significant ↑ E. faecalis, Firmicutes and Bacteroidetes, Lactobacillus and Shigella.	Wang et al, 2018
Triclosan	Zebra fish	100 µg/kg fish a day	1. ↑ Cetobacterium, Shewanella, Aeromonas, Aeromonadaceae, and the class CK-1C4-19 and ↓ levels of Plesiomonas and Aeromonadacea 2. Increased antimicrobial resistance.	Glauke et al, 2016
Triclosan	Humans	Use of wash products (Soaps, toothpaste, dishwashing liquid) containing Triclosan	1. Significant levels of Bacteroides fragilis, Proteobacteria (pathogenic and non- pathogenic species), Escherichia coli	Ribado et al, 2017
Triclosan	Humans	In vitro experiment using Triple Shime (Triple Simulator of the Human Intestinal Microbial Ecosystem)	1. ↓ Lachnospiraceae Clostridium, Fusobacterium Synergistaceae Cloacibacillus and Alcaligenaceae Sutrella, Bacteroidaceae Bacteroides, and Rikenellacaea. Levels of Klebsiella pneumoniae were constant. 2. Effect on microbial metabolites (Decrease in SCFA concentrations)	Mahalak et al, 2020
Triclosan	C57BL/6 Mice	10-80 ppm	1. ↑ Proteobacteria 2. Colonic inflammation and colon tumour was observed.	Sanidad et al

Continued.

Environmental pollutant	Animal model	Dosage	Outcome	References
Triclosan	Rats	50 mg TCS/kg body weight per day	1. ↑ Bacteroidetes and decreased abundance of Verrucomicrobia, Akkermansia 2. Metabolic abnormalities including lipid accumulation obesity and diabetes.	Yeu Ma et al, 2020
Triclosan	Humans (newborn children)	Exposure of women to different household products containing Triclosan	1. Enrichment in *Lachnospiraceae, Coriobacteriaceae*. Reduced abundance of Pasteurellaceae and Clostridium and Enterobacteriaceae 2. Increased BMI among 1-3-year-old children and obesity among 3-year-olds.	Mon et al
Triclosan	C57BL/6 Mice	10 to 80 ppm	1. 75% reduction in the abundance of Bifidobacterium 2. Low grade colonic effects which could lead to colon cancer.	Yang et al, 2018
Triclosan	BALB/CJ mice and knockout TLR-2 mice	5, 50 and 500 mg/kg	1. ↑ Deltaproteobacteria, Clostridia and Erysipelotrichi and ↓ levels of Bacteroides	Hirota et al, 2019

Note: This table highlights various effects of BPA, phthalates and triclosan exposure on gut microbiota and associated pathophysiological changes in the host, at different doses along with the test model under study. (↑- increase in abundance; ↓- decrease in abundance).

EFFECTS OF BPA

Gut microbiome dysbiosis

In all the test models studied, diverse patterns of relative abundances of bacteria were observed. In mice and rabbits, *bacteroidetes (Bacteroides spp* and *Odoribacter spp)*, firmicutes like *Ruminococcus spp* and proteobacteria were present in high abundance.[18,19] In a separate study involving mice, there was a decrease in levels of verrucomicrobia and akkermansia, whereas increased abundance of proteobacteria was observed.[20] Methanobrevibacter spp (phylum eukaryota), acinetobacter and jeotgalicoccus were predominant in BPA fed rabbits.[19] Abundance of proteobacteria like hyphomicrobium and actinobacteria was observed in zebra fish.[21] Gut dysbiosis patterns in parents and offsprings (P0 and F1 generation, respectively) in mice models showed varied results. In the female parental control group (P0), *firmicutes* (lactococcus) were abundant whereas in F1 control females, the abundance of *proteobacteria (Oxalobacter spp), bacteriodetes (prevotella*), *firmicutes* (*Blautia spp, clostridium, Mogibacteriaceae, Enterobacteriaceae, Lachnospiraceae, Dorea spp, Oscillospira spp, Ruminococcus spp, Lactobacillus spp,* and *Allobaculum spp*) and *Verrucomicrobia* (*Dehalobacterium spp, Akkermansia muciniphila*) showed an increase.[22-24] In female parental test mice (P0), abundance of firmicutes (*Mogibacteriaceae,* and *Clostridiales*) and *Proteobacteria* (*Sutterella spp*), was observed, whereas in female test progeny (F1), levels of *Actinobacteria* (*Bifidobacterium spp*) and firmicutes like *Mogibacteriacea* were high and that of bacteroidetes (*Prevotella*) were low.[22,23] Proteobacteria like *Desulfovibrio spp* were high in male parental control groups (P0) as well as in F1 control males and other *Proteobacteria* (*Bacteroides spp., Porphyromonadaceae, Desulfovibrio spp.*), *Firmicutes* (*Clostridiaceae, Ruminococcaceae, Lactobacillus, Blautia producta, Coriobacteriaceae, Peptostreptococcaceae, Allobaculum spp, Ruminococcus spp, Dorea spp, Blautia spp, Burkholderiales, Coprococcus and Streptococcus*), *Bacteriodetes* (Parabacteroides distasonis) and dehalobacterium, were consistently significant at all-time points in F1 control males only.[22-24] In male parental test groups (P0), firmicutes (mollicutes) and bacteriodetes (prevotellaceae) were significant whereas in F1 test males there was a decrease in actinobacteria (bifidobacteria) and firmicutes like *Clostridium spp*.[25] But some *Firmicutes* (lactobacillus, coprococcus, ruminococcus, streptococcus) and dehalobacterium were consistently significant at all-time points.[23] Conversely, abundance of *Bacteriodetes* like *Odoribacter spp, bacteroidales*, other firmicutes (Clostridiaceae, *Anaeroplasma spp*, Carnobacteriaceae, *Lactobacillus spp*, Ruminococcaceae, *Lachnospiraceae oscillospira spp*, Coprococcus), *Akkermansia spp*, and cyanobacteria was greatly reduced.[24]

Pathophysiological and metabolic changes in the host

In a study showing changes in metabolism due to BPA exposure, higher levels of *Sutterella spp* and clostridiales had a negative effect on various metabolic activities like metabolism of amino acids (histidine, lysine, tryptophan), linoleic acid, arachidonic acid, biosynthesis of tropane-piperidine- pyridine alkaloid, stilbenoid-diarylheptanoid-gingerol, NOD-like receptor signalling pathway, antigen processing and presentation.[26] However, in control groups,

these bacterial changes were positively associated with glycolysis/gluconeogenesis, metabolism of starch and sucrose, butanoate and phosphanate, pentose-glucoronate interconversions, carbohydrate digestion and absorption. Steroid hormone biosynthesis, caffeine and insulin signalling pathway and sulphur metabolism and was affected in F1 males. Another study observed sex specific effect on the liver metabolic pathways.[23] Pathways of oxidative phosphorylation, RNA metabolism, citrate cycle, insulin signalling, PPAR signalling, glycan biosynthesis and amino acid metabolism were enriched in females whereas along with these, fatty acid metabolism, drug metabolism and mTOR signalling were enriched in males. Increase in levels of carbohydrates like rhamnose, D-galactose, D-glucose, etc; deoxycholic acid, allocholic acid, pantothenic acid, and other metabolites like L-lysine, L-glutamic acid, ornithine, uridine, etc was reported.[24] Another study indicated that, the faeces of BPA exposed offsprings showed significantly reduced levels of gut bacterial metabolites such as acetic acid and propionic acid. On the other hand, butyric acid and histidine levels dropped in the control offsprings.[27] Colonic and liver inflammation was observed due to perinatal exposure to BPA which was associated with perturbation in gut microbiota composition and metabolic profiles. Intestinal inflammatory changes associated with exposure to BPA revealed reduced concentrations of precursors for serotonin synthesis i.e.; 5-Hydroxyindoleacetic acid (HIAA) and tryptophan (Trp) which are the metabolic products of serotonin.[28] This resulted in a shift in microbiota derived aromatic amino acids (MDAs) in the intestinal lumen causing intestinal inflammation. Also, intestinal inflammation due decrease in gut microbial diversity, and increased proteobacteria was observed. Thus, exposure to BPA affects the metabolism of the essential amino acid tryptophan and in turn increases the risk of autoimmune diseases like IBD. Additionally, colonic inflammation and the symptoms of IBD are exacerbated due to reduction in serotonin reuptake.

Effects of BPA on gut liver axis and correlation of several microbial flora with immune parameters leading to hepatic inflammation were studied.[20] Decrease in abundance of akkermansia had a direct association with increased levels of inflammatory cytokines, like TNF-a, IL-1b and IL-18 serum lipopolysaccharide (LPS). A negative correlation between the increased abundance of akkermansia and levels of serum LPS, IL-1b, IL-18, TNF-a, Alanine Aminotransferase (ALT) and liver tri glyceride (TG) was observed. However, their levels increased and serum HDL-C level decreased with the abundance of rikenella. Owing to increase in the serum LPS level due to disruption of gut microbiota and damage of the intestinal barrier, hepatic inflammation via TLR4/NF-KB pathway, resulting into hepatic steatosis was observed. Increased thickness of the intestinal mucus and improved gut barrier function which increases immune response is the characteristic feature of akkermansia. Thus, there could be a direct association between increased levels of endotoxin, content of hepatic lipid and inflammatory response and decreased abundance of akkermansia and poor function of the intestinal barrier due to BPA exposure. IgA is responsible for maintaining integrity of the gut barrier and the homeostasis between host, gut microbiome and antimicrobial activity. BPA exposure resulted in reduced faecal lysozyme and antimicrobial activity against peptidoglycan since it showed more *E. coli* colony formation as compared to the control.[29]

EFFECT OF PHTHALATES

Gut microbiome dysbiosis

In studies involving DEHP fed mice, there was a significant increase in the abundance of *firmicutes* (*lachnoclostridium, Mollicutes RF9, enterococcus)* and bacteriodetes (*parabacteroides*) whereas a decrease in the levels of other firmicutes (*Clostridium spp,* lactobacillus), bacteriodetes (Odoribacter and Fluviicola) and Akkermansia.[30] Another study on mice found that DEHP adulterated microplastics showed higher effect on gut microbiota as compared to virgin micro plastics (MPs). Both, control (virgin MPs) and treatment (MPs with DEHP) groups were dominated by *firmicutes* (*lactobacillus),* *bacteroidetes* (*Butyricimonas, parabacteroides*) and actinobacteria (*Adlercreutzia*). However, other bacteriodetes like prevotella and firmicutes like Ruminococcus showed a remarkable increase only in treatment group (MPs. with DEHP).[22] In other studies, relative abundance of prevotella, firmicutes and α-proteobacteria (desulfovibrio, sutterella) was significantly increased whereas verrucomicrobia, bacteroidetes, actinobacteria, and epsilonbacteraeota, decreased.[31,32]

A study involving murine rodents demonstrated changes in microbiota with increased dose of DEHP.[26] There was a significant elevation in the abundance of proteobacteria, firmicutes (oscillospira, peptostreptococcaceae, mycoplasma, roseburia, sutterella, clostridiales, RF32, christensenellaceae, blautia), actinobacteria (arthrobacter) and bacteriodetes (porphyromonas) only in Sprague Dawley (SD) rats whereas that of bacteriodetes like prevotella and bacteroides was reduced. In Wistar rats and C57LB/6J mice, firmicutes (roseburia, tenericutes, ruminococcus) actinobacteria (adlercreutzia), and eubacateriaceae showed an increasing trend whereas firmicutes (coprococcus, ruminococcus, lachnospiraceae, allobaculum, lactobacillus, clostridiaceae), proteobacteria (desulfovibrio,), actinobacteria (bifidobacterium, adlercreutzia), bacteriodetes (prevotella) and dehalobacteriaceae showed a decreasing trend.[33] A significant decrease in abundance of bacteroides S24-7 was observed in BALB/c mice, whereas runimococcaceae and rikenellaceae were significantly increased. Effect of phthalates on microbiota of new-born human babies showed that control groups had higher abundances of actinobacteria (*Bifidobacterium longum, rothia* and *Bifidobacterium breve*) firmicutes (streptococcus, *Enterococcus faecium*, veillonella*)* and *Klebsiella*.[28] On

the other hand, DEHP exposed groups showed abundance of pathogens such as *Haemophilus parainfluenzae* and Staphylococcus and decrease in abundance of *Bifidobacterium longum* and streptococcus.[34] Studies involving zebra fish revealed increase in abundance of actinobacteria (rothia, Adhaeribacter), firmicutes (enterococcus) bacteriodetes (fusobacteria, bacteroidetes, bacteroidia) and proteobacteria (gammaproteobacteria, novosphingobium) and decrease in Saccharibacteria.[18,25]

Pathophysiological and metabolic changes in the host

A study assessing the faecal metabolite profile after DEHP exposure demonstrated that there was a heterogeneous distribution of metabolites across the different organisms.[35] In less than 50% of the genera, certain fermentation products (benzaldehyde and indole-3-acetate) associated with rare reactions and in more than 90% of the bacterial genera, some common metabolites (amino acids- phenylalanine and tryptophan, nucleosides/ nucleotides- uredines, uracil and vitamins- riboflavin) associated with certain common reactions were observed. Alterations in microbial metabolites were found to be sex dependent.[27] Shift in microbiota was primarily found to be associated with decreased oxidative phosphorylation and benzoate degradation. In males, however, an increased capacity for glycerophospholipid metabolism was thought to be associated with lower levels of choline and tryptophan metabolism. Decreased metabolites such as L-glutamine (in males) and D-fructose 6-phosphate (in females) could have a great impact on immune cells and enterocytes thus affecting immune functions. Another study reported effect of changes in gut microflora on host metabolism.

Bacteria such as *Lactobacillus, Adlercreutzia, Butyricimonas, Parabacteroides, Prevotella*, and *Ruminococcus* which play pivotal roles in regulating immune function and host energy metabolism, showed a significant alteration upon DHEP exposure.[22] Implications of altered microbiota on obesity indicated an increase in formation of lipid droplets in the intestine and liver which correlated with increase in abundance of bacteroidetes in DEHP exposed group.[18] It is previously known that changes in this phylum are associated with obesity and other metabolic and gastrointestinal disorders. Short chain fatty acids (SCFA) are known to have regulatory roles in the lipid metabolism and hence availability of SCFA through the gut microbiome is an important factor for host metabolic function. Increased biosynthesis of unsaturated fatty acids and decreased carbohydrate metabolism was primarily observed. Alteration in metabolic profile in a dose dependent manner was demonstrated in a study that observed pathways of amino acid metabolism, ubiquinone metabolism and synthesis and degradation of ketone bodies were affected in low dose DEHP exposed groups.[32] As against that, steroid biosynthesis, purine, pyrimidine and riboflavin metabolism was affected in high dose DEHP exposed groups. Effect of DEHP on lipid metabolism and gut-liver axis showed that concentrations of mevalonate, acetyl-CoA, malonyl-CoA, saturated and unsaturated fatty acids (metabolites of Triglyceride synthesis pathway), HMG-CoA (metabolite of the cholesterol synthesis pathway), significantly increased in a dose dependent manner.[31] Also, a significant increase in TNF-α, TLR4-NF-KB, IL-6 and IL-1β levels and decrease in the expression of occludin and claudin 1 (tight junction proteins) leading to disruption of intestinal barrier function and thus inflammation of colon tissue was noted.

EFFECT OF TRICLOSAN

Gut microbiome dysbiosis

A study on effect of triclosan on human pregnant mothers and subsequently their children showed that the gut microbiota of infants living in homes with higher use of disinfectant products was enriched in *Firmicutes* (*Lachnospiraceae, Ruminococcus*), and *Coriobacteriaceae* whereas a reduction in abundance of proteobacteria (pasteurellaceae, haemophilus) and firmicutes such as clostridium and haemophilus was noted. Conversely, reduced faecal abundance of proteobacteria (enterobacteriaceae) was observed in infants residing in homes with frequent use of eco-friendly products.[29] Studies involving pregnant women exposed to many products with triclosan like wash products, toothpastes, etc.; indicated abundance of actinobacteria (*Bacteroides fragilis*), proteobacteria and bacteriodetes (*Bacteroides caccae*) in the infants.[36,37] In contrast, mothers, showed abundance of proteobacteria (both pathogenic and non-pathogenic species). Study among healthy individuals (free from antibiotics exposure), showed a significant decrease in firmicutes (lachnospiraceae, clostridium), fusobacterium, synergistaceae, cloacibacillus, alcaligenaceae, bacteriodetes (bacteroides, parabacteroides, rikenellacaea) and proteobacteria (enterobacteriacaea, trabulsiella, sutterella). Studies involving mice demonstrated effect on the abundance and variety of intestinal microbiota.[19,30,34,37,38] A significant increase of proteobacteria, firmicutes (clostridia, erysipelotrichi, *E. faecalis*) and a decrease of actinobacteria (bifidobacterium), *bacteroides*, *firmicutes* (*lactobacillus*) and *proteobacteria* (*E. coli*) was observed. Some proteobacteria (cetobacterium, shewanella, aeromonas, pseudomonas, rhodobacteraceae) were predominant while others such as enterobacteriaceae, plesiomonas and aeromonadacea showed a decreasing trend in Zebrafish.[39]

Pathophysiological and metabolic changes in the host

Two studies reported increased abundance of many bacterial genes including those encoding Na (+)/drug antiporter, acriflavin resistance protein, multidrug-efflux transporter and inner membrane transporter CmeB, leading to activation of multidrug resistance efflux pumps and development of resistance to many antibiotics including triclosan.[30,35] A significant enrichment in bacterial genes encoding glycosyltransferase, (for

biosynthesis of the core oligosaccharides) and others related to LPS assembly pathway was observed. Change in membrane structure led to the development of resistance to triclosan in gut bacteria. Antibiotic resistance mechanisms (production of beta-lactamase, resistance to erythromycin, vancomycin, fluoroquinolones, teicoplanin, methicillin resistant Staphylococci (MRSA), BlaR1 family regulatory sensor-transducer disambiguation, etc.) in the gut microbiome significantly increased in triclosan exposure group thus posing a threat to mankind. A significant reduction in microbial metabolite SCFA resulting in reduced bacterial density was observed.[16] Associated long terms effects on metabolism like increased abundance of bacteriodetes causing lipid accumulation were reported.[13]

Reduced abundance of *Akkermansia muciniphila*, which has a role in improving metabolism in obese and diabetic mice was observed that could later contribute to metabolic disorder. Higher faecal levels of several bacteria were found to be associated with raised BMI and in turn obesity at different stages of development such as lachnospiraceae at age 3-4 months resulted in increased BMI at the age of one.[40] *Coriobacteriaceae, Erysipelotrichaceae* and *Ruminococcaceae* at age 1 and age 3; enterococcaceae and clostridiaceae at age 3 but not age 1. At three years, higher faecal levels of lachnospiraceae were found to be associated with either overweight or obesity. Low-grade colonic inflammation reducing gut microbial diversity and decreasing abundance of beneficial gut bacteria such as bifidobacterium was observed indicating a pro inflammatory effect of triclosan exposure on colon.[34] In germ-free mice, importance of gut microbiota for biological effect of triclosan was proven by inhibition of basal inflammation. Triclosan, the commonly used antimicrobial agent could thus have adverse effects on colonic inflammation and associated tumorigenesis via alteration of the gut microbiota.

RELATION BETWEEN GUT MICROBIOME DYSBIOSIS AND HOST PATHOPHYSIOLOGY

In this review, the articles which made use of various test systems such as mice, rabbits, rats, zebra fish, humans were used to compare the effect of environmental pollutants, BPA, Phthalates and Triclosan on the gut microbiota and associated pathophysiological changes. Bacterial diversity was observed with many variations in species abundances due to a specific environmental pollutant as well as among all the pollutants as a whole. These variations were mainly dose dependent, sex dependent and generation dependent. It is evident that BPA exposure led to significant increase in bacteroides, firmicutes (clostridia, mogibacteria), proteobacteria and *Akkermansia spp* in all the test systems involved. Plastics containing phthalates are a major problem to the marine life since large amount of plastic waste is thrown in the water bodies.[41] Nevertheless, phthalates are commonly used in household materials and humans are continuously exposed to them in some way. Exposure to phthalates however showed quite varied results *i.e.*, species diversity and abundance was not very consistent among all test systems. Bacteria like bacteriodetes (bacteroides, prevotella, parabacteria), firmicutes (ruminococcus, enterococcus) and actinobacteria, were common among all test systems (excluding humans) which showed an increasing trend on DEHP exposure. Major declining trend was observed among akkermansia, bacteriodetes (odoribacteria, prevotella, bacteroides), firmicutes (clostridium, coprococcus), dehalobacteriaceae, and desulfovibrio in all models excluding humans. Some of these are commensals and hence their dysbiosis might lead to some gastrointestinal diseases. However, some uncommon bacteria also were observed on exposure to phthalates such as adlercreutzia, butyricimonas, parabacteroides, oscillospira, peptostreptococcaceae, mycoplasma, roseburia, christensenellaceae and blautia. Bacterial dysbiosis observed in humans is not like that observed in animal models.

In one study involving newborn human babies, there was a significant decrease in good bacteria like bifidobacterium, streptococcus, etc. and an enrichment of opportunistic pathogens like haemophilus, staphylococcus, Klebsiella, etc was observed. This clearly explains that exposure to phthalates leads to gut dysbiosis and can in turn cause gastrointestinal (GI) disorders. Triclosan exposure also led to varied changes in microbial profiles in humans as test systems and other model organisms. Proteobacteria, Firmicutes, Bacteroides and fusobacteria were commonly found in increased abundance and enterobacteriaceae, plesiomonas, aeromonadacea, clostridiales; bacilli; turicibacterales, christensenellaceae, *E. coli and* lactobacillus are the ones which showed a significant decrease in all the models excluding humans. In studies involving human newborn infants, the gut microbiome was predominated by lachnospiraceae and coriobacteriaceae along with some opportunistic pathogens. All the above environmental pollutants showed dose dependent effects on the gut microbial dysbiosis as well as the changes in metabolic profiles and associated pathophysiological effects. It has been observed that the bacteria which show abundance after exposure to such environmental pollutants, mainly plastics, can transfer antibiotic resistance via horizontal gene transfer (HGT).[42,43]

Alteration in gut microbiota can further lead to changes in host's metabolic profiles, and pathophysiological effects. Classic changes in metabolic profiles irrespective of the chemical to which exposure occurred were found in metabolism of amino acids including histidine, tryptophan; nitrogen, biosynthesis of purines- pyrimidines, serotonin, alteration in lipid accumulation, faecal lysosomal synthesis, signalling pathways, antigen processing and presentation, decreased short chain fatty acid synthesis, interleukin levels etc. These metabolic changes were associated with pathophysiological manifestations. Most commonly observed were intestinal inflammation, increased intestinal permeability,

impairment of gut-liver axis, decrease in thickness of intestinal mucus, colonic and liver inflammation, etc. Metabolic alterations driven by the gut microbiota resulted in diseases like IBD, Inflammatory Bowel Syndrome (IBS), colorectal cancer, immune system disorders, diabetes and obesity.[44]

The colonization and development of gut microbiota begins right at the time of birth, when the child is exposed to the external environment. Since then, there are many factors defining the composition of the microbiota as, 'gut microbiome' is not constant throughout the life of an individual. It keeps changing according to the type and quantum of exposure. Factors like the age, sex, genetic makeup of the host, vaginal /caesarean birth, diet, irrational use of medication, antibiotics and nutritional supplements, environment, hygiene, etc. also determine the gut microbiota.[45,34] Cigarette smoking, alcohol and tobacco consumption can exacerbate the alteration in gut microbiota. Studies have shown that chronic consumption of alcohol has caused decrease in beneficial and commensal bacteria like bacteroides and increased some pathogenic species like streptococcus, etc. These bacteria convert alcohol to acetaldehyde, a carcinogenic agent (can cause colorectal cancer).[46]

One of the observations of the review was that majority of studies made use of mice models and very few actually studied the effects on humans. There are many challenges in performing prospective studies in humans as it is unethical to expose human subjects to such environmental pollutants. The test animals are treated with a properly formulated and controlled dose of the test chemical (here environmental pollutants). But in reality, humans are unknowingly exposed to wide range of doses of the chemicals through various sources. They can also be exposed to more than one or a combination of chemicals simultaneously. It is not a defined formulated exposure. Hence, the gut microbiota and the level of dysbiosis will be different in humans depending upon the situation where exposure occurs. Also, there are many confounders which can also cause a variation in the study and analysis of the host microbe relationship, and they remain limitations of such studies.[47] Considering all these aspects, level of similarity of gut microbiota, metabolic profiles and associated pathophysiological changes between the test animals and humans is debatable. However, animal studies help to understand and evaluate the general consequences of exposure to environmental pollutants on the gut microbiota, the host-microbe relationship and help deduce strategies or treatments or solutions to prevent the disease.

Evidence to restore 'good microbiota' to alter disease conditions is increasingly changing patient management through use of probiotics to increase healthy microbial flora or by implanting faeces from healthy individuals. This concept has emerged as a therapeutic modality widely known as 'faecal microbiota transplantation' which has been successful to overcome the complications of gut microbiota dysbiosis.[48] It has been commonly used to treat gastrointestinal diseases such as IBD (ulcerative colitis), IBS, and others.[49] Exposure to environments pollutants is something beyond our control, however, the strategies to restore the gut microbiota can have preventive and therapeutic potential.

CONCLUSION

It is evident that environmental pollutants are leading cause of gut microbiome dysbiosis and associated physiological and metabolic alterations in the host. It was interesting to observe how these pollutants influence the gut microbiome across different species that were studied. We thus recommend that any of these species can be good models to study any preventive or therapeutic interventions to alter the course of chronic disease susceptibility and prognosis. Gut microbiome screening, obtaining the microbial and metabolic profile of the individual could be included as part of as part of screening for chronic diseases among susceptible individuals. Assessment of gut microbiota profile of the individual will enable treating physicians to evaluate the potential risks and accordingly provide necessary advice on what type of food to consume, which products to be avoided, and other preventive measures to be adopted. As a public health measure, there is a need to create awareness among public importantly through schools and reduce the exposure to such chemicals for their long and healthy lives. Further research needs to identify threshold value of the concentration of these pollutants that might result in development of disease. Long term, cohort studies of individuals living in different habitats, with varying dietary patterns being exposed to different endocrine disruptors will help to map the pattern of microbial dysbiosis and associated physiological changes resulting in chronic diseases. Further, there is a need to consider gut microbiome profile as part of screening for chronic diseases among susceptible individuals and aim towards restoring healthy microbiome.

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