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REVIEW ARTICLE

Gut Microbiota as a Panacea to Ameliorate Melamine and other Environmental Pollutants Related Toxicological Effects: Underlying Myths and Realities

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ABSTRACT
Melamine comprising of six atoms of nitrogen per molecule is a nitrogenous organic compound with considerable higher content of nitrogen which in standard protein measuring assays is read as high protein. Foods and milk are adulterated illegally with melamine boosting the protein content artificially as the standard assays fail to differentiate the nitrogen from protein or non-protein sources. Many toxicities and health associated effects have been seen as a result of such adulteration. Similar outcomes are anticipated as a result of pollutants or contaminants in the environment including heavy metals. This review highlights the essence of gut microbiome in negotiating with the melamine or other environmental pollutants. The gut microbiota and associated activities certainly have a role in ameliorating the ill-effects of melamine induced toxicity but the impact of long-term exposure to melamine and the interaction between gut microbiota and melamine on human health, yet to be established. Undoubtedly, Gut microbiota is an important player and cannot be ignored whenever it comes to evaluating the melamine toxicity. Future awaits on harnessing the hidden potential of microbiota as a possible therapeutic target using high-throughput next-generation sequencing and metagenomics so as to ameliorate the toxic effects associated with melamine and other environmental pollutants.
Keywords: *Melamine, Gut microbiome, Toxicity, Human health, Therapeutic target, Environmental pollutants.*

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INTRODUCTION

Melamine has been a known food adulterant for a while now containing high amounts of nitrogen possessing six atoms of nitrogen per molecule; thereby named as a nitrogenous compound which boosts the protein content significantly [1]. Most of the protein estimation assays rely upon the nitrogen content for the protein concentration in foods. These protein assays fail to differentiate the nitrogen obtained from the protein and non-protein sources. This led to the illegal use of melamine by the food manufacturers as an adulterant in children milk. Many toxicological effects including kidney stones, nephrotoxicity and renal failure were seen in children who consumed such contaminated milk with melamine addition. Children, who got exposed to melamine, may have deleterious consequences especially on the development of gut microflora and other related host physiological functions associated with the gut microbiota. The need of the hour is to develop effective methods to assess such kind of

adulterants in milk. The bigger question is how does the gut microbiota deal with such kind of toxicity? Does it mitigate the toxicological effects associated with melamine contamination?

One of the studies in China revealed that melamine could be used to poison animals and children as severe nephrotoxicity and blockages of renal tubules were reported upon addition of melamine to pet foods and milk [2,3]. A study revealed that suppressed intestinal microbial flora as a result of antibiotic treatment in rats could lead to significant attenuation of the melamine toxicity because of melamine excretion [4]. It was suggested that untreated rats' faeces containing *Klebsiella terrigena* could bio transform the melamine into cyanuric acid resulting in more pronounced toxicological effects including nephrotoxicity. The above facts certainly points towards the role of gut microbiota mediating the melamine induced toxicological effects. In contrast, the increased fluid intake significantly reduced the melamine induced nephrotoxicological effects [5]. It was realized that not only melamine but other environmental pollutants as well do have a bidirectional interaction with the host gut microbiota reducing the toxicity to the host which is feasible through the action of a variety of enzymes [6]. Thus, it is imperative to look into the ability of such chemicals like melamine and other environmental pollutants to affect the composition and functioning of the microbiota so that underlying consequences on the adverse or ill effects on the host could be monitored[7]. Moreover, replenishment of lost microbial flora with the help of probiotics could be very helpful in restoring the gut microbiota homeostasis [8] and relieving the symptoms associated with environmental pollutants or melamine induced toxicity and microbiota dysbiosis (Fig. 1). As shown in figure 1, Melamine as a result of gut microbiota dysbiosis may induce activation of mitogen-activated protein kinase (MAPK), Nuclear factor kappa B (NF-κB), and reactive oxygen species (ROS), thereby resulting in chronic inflammation, apoptosis and increased fibrosis along with formation of cyanuric acid, which ultimately may lead to enhanced nephrotoxicity, kidney related disorders and carcinogenesis as well. However, probiotics may restore the gut microbiota homeostasis and reverse the ill-effects associated with melamine induced dysbiosis.

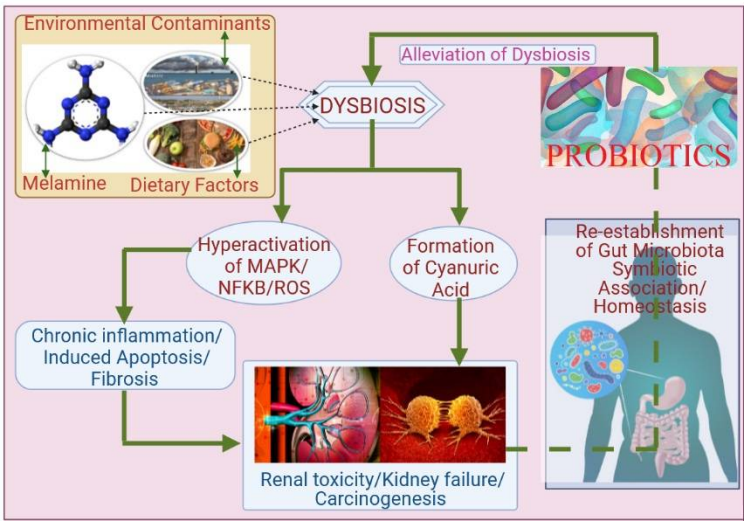

Figure 1: Illustration of potential mode of action of probiotics involving gut microbiota modulation alleviating the melamine-associated dysbiosis and nephrotoxicological effects.

THE ESSENCE OF GUT MICROBIOTA

Gut microbiota certainly holds the central stage in mitigating the ill effects on the host induced by the chemicals including melamine and other environmental contaminants. However, the bidirectional interaction network between the Gut microbiota and chemicals or environmental pollutants still needs to be delineated emphasizing the need to understand microbiome in greater detail [9,10]. What sorts of endogenous detoxifying enzymes are involved in the process impacting the gut microbial interaction with harmful chemicals like melamine and other xenobiotic metabolites [11].

MELAMINE-GUT MICROBIOTA ASSOCIATED EFFECTS

Melamine is synthesized from urea, which further produces cyanic acid, cyanuric acid, ammeline, and ammelide etc. Melamine when combined with formaldehyde produces melamine foam, resin, glue, dry erase boards, fabrics, housewares, and flame retardants etc. The melamine degraded substances may be added to dairy products or animal feed in order to meet the appearance of acceptable protein content;

milk, eggs, fish, and meat of livestock given adulterated feed are the major means of spread of melamine. In continuation to this, it is also a derivative of arsenical drugs. One of most commonly used drug is Melarsoprol which is used for the treatment of African trypanosomiasis disease. In animals, melamine is not metabolized, however, the ingested melamine is excreted, and gets eliminated in the urine. In toxicity studies it has been shown that melamine has a low acute toxicity as evident from the LD50 values. Direct exposure to the compound results in skin & eye irritation, also if the same gets inhaled it causes irritation in the respiratory tract as well. The digestive tract irritation, nausea, vomiting, and diarrhoea are also the end result of oral ingestion of the compound [12].

In a study it has been observed that *Klebsiella* has a deep role in melamine metabolism as this bacterium helps in increasing cyanuric acid production, which as a result contributes in the formation of kidney and bladder stones. Also in melamine-exposed children due to formed cyanuric acid, renal damage is observed [13]. The *Klebsiella* genus is present ubiquitously in the environment as well as in the intestinal tract, pharynx, and on the largest organ i.e. skin of humans. Although the occurrence of this genus is widespread and noticeable in the environment, still the limited data is available for humans so far. Human microbes are divergent in nature these can vary significantly from person to person due to various factors such as diet and geographic location etc.[14,15].

In a study, 100 gm of melamine was administered orally to sheep, which resulted in the kidney damage. It was discovered that the sheep perished on the 11th day. In a different protocol, sheep were given a daily dose of 25gm–50gm of melamine for 7–9 days, and again, all of the sheep were perished. Zheng et al. worked on various groups of Wistar rats in which one group of rats were exposed to 600 mg/kg/day dosage of melamine alone for 15 days, while the other group were either following a 4-days course of an antibiotic, killed many species of gut microbes, or antibiotic alone [4]. Rats that were exposed to the antibiotic treatment alone or without melamine had shown no kidney damage or lesser kidney damage as compared to those which fed just melamine [16]. This suggests the reduction of specific gut bacterial species helped in reducing the renal damage. In continuation to the same, it was also seen that the reduction at bacterial levels was linked with an increase of the urinary excretion of melamine [17,18].

In another study, the faeces of young male rats were cultured. The faecal bacteria were shown to convert melamine into cyanuric acid. This was realized that due to deamination if melamine is used as the sole nitrogen source, it seems to be highly effective. Also, with other sources of nitrogen including "a soy broth" the production of melamine was substantially reduced.

OTHER FACTORS ASSOCIATED WITH GUT MICROBIOME ALTERATION

Toxicity in gut microbiome, results in functional alterations such as alterations in microbial metabolites, loss of diversity, and alterations in energy metabolism in humans. These are the main microbial disorders which adversely impact the host health, probably increases the disease occurrence risk as well [19]. Therefore, the toxicity in the gut (gut microbiome) is a novel connection between diseases in humans and environment (Table 1). Also the changes at microbiome level due to environmental exposures are confrontational, providing mechanistic insights in reference to the environmental driven gut microbiome-associated diseases [20, 21].

Table 1: Effect of Gut Microbiota on some common Diseased States

Disease	Altered metabolic pathway	Effect on Microbiome Levels	Effect of Diet on the disease	Gut-derived Metabolites	References
Inflammatory bowel disease (IBD)	Hippurate, 4-cresol sulphate, Formate	Decrease in *Clostridium, Lactobacillus, Firmicutes*	Vegetable, Butyrate, omega-3 fatty acids, and antioxidants intake decreases the impact of disease (IBD).	Acetate, Short chain fatty acids, Butyrate, Lactate, Isovalerate,	[22-24]
		Increased *Bacteroidete, Proteobacteria, Clostridium*	Carbohydrate, Fat intake has an impact on the disease (IBD).		

Obesity	Glycoside Hydrolases, Glycosyl Transferases, Polysaccharide lyases Carbohydrate-binding modules Carbohydrate Esterases	*Bacteroidetes* decreased Increased *Firmicutes*	Vegetable and Protein intake in diet decreases the obesity levels.	GABA, Lipopolysaccharide (LPS), TMAO, Bile Acids, GLP-1, Oxalate, Polysaccharide A	[24]
Hypertension	Elevated membrane transport, lipopolysaccharide biosynthesis and steroid level degradation, while in controls the metabolism of amino acid, cofactors and vitamins was found to be higher.	Dominance of *Firmicutes* and *Bacteroidetes*. Influence on blood pressure by regulating expenditure of energy, Intestinal metabolism of catecholamines, Gastrointestinal & renal ion transport	High sodium diet is harmful.		[25]

Alterations in Microbial Metabolites

Microbial metabolites produced have an impact on human health (Table 1). Alterations in the microbial metabolites affect metabolism and physiology profiles in the host cells (Fig. 2).

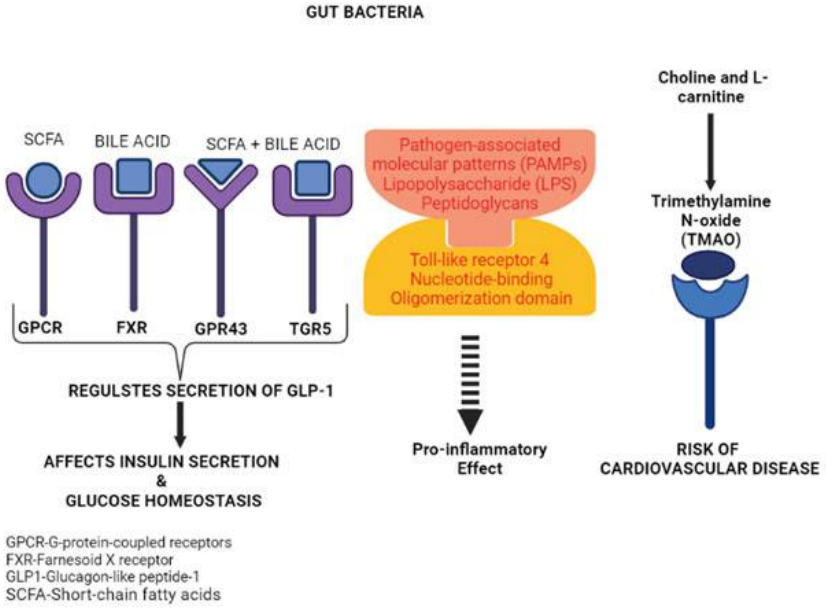

Figure 2: Bacterial metabolites as signalling molecules; binding to receptors and activating diverse signalling cascades.

Loss of Diversity

Humans have a complex ecosystem of microbes, as there are approximately trillions of bacteria which reside in the human gut. These bacteria play a significant role in deciding one's health. Diversity loss (microbial ecosystem) is associated with gut related disorders such as: *Clostridium difficile* associated disease (CDAD) and irritable bowel syndrome (IBS) [26,27] . The gut microbial ecosystem diversity can be compromised by various environmental factors, which makes the microbial ecosystem lesser resistant and more vulnerable to pathogen attack in the body. For example, antibiotics have an impact on gut microbial ecosystem, which induce the alterations in microbiome metabolic features that further increase its susceptibility to *Clostridium difficile* infection (disturbance of healthy bacteria in the colon). Gut microbiome exposure to toxic environmental chemicals probably reduces species diversity [28-30].

Interference in Energy Metabolism

Gut microbiome plays a vital role in energy metabolism, as human system is not capable of degrading most plant polysaccharides. The production of SCFAs helps in the degradation of the same. The gut microbiome's energy production is well correlated with its microbial composition. Moreover in some of the studies it has been observed that the energy balance and host body weight is having an association with the gut microbiome types (*Firmicutes* and *Bacteroidetes*). Turnbaugh et al. reported from a study, in which mice that were germ-free and had the faecal microbiota of obese mice transplanted, gained more weight than mice that were lean [31,32]. In another study Smith et al. observed from an experiment in which mice were treated with the microbiota from people suffering with Kwashiorkor, and affected with severe weight loss [33]. Consequently, it is probable that gut microbiota toxicity obstructs with energy abstraction, resulting in disorders like obesity or malnutrition [34, 19].

Environmental Exposures

Gut microbiome toxicity can be triggered by xenobiotics (antibiotics, artificial sweeteners, heavy metals, pesticides). These also have an impact on human gut microbiome in either direct or indirect manner. The chemicals generated or exposed from environmental pollution are capable of interrupting specific metabolic pathway or gene expression in the body [35]. As a result, an imbalanced gut eco-system may be a consequence from the selection of resistant bacteria after specific exposure. Many of environmental chemicals have an indirect impact on the gut microbiome through the influence on host physiology. Heavy metals, antibiotics, pesticides, and artificial sweeteners etc. are the xenobiotics which cause gut microbiome toxicity with significant functional alterations [36-38].

Artificial Sweeteners

In the modern world, the food industry has grown vastly with a variety of food additives including preservatives, artificial sweeteners, emulsifiers etc. Even with these food additives the safety of gut microbiome was not taken into consideration. Also, these are poorly metabolized by the human body. There are many compounds which have been identified being toxic in nature and have an adverse effect on gut microbiome. For example, cyclamate, which is metabolized by gut into cyclohexylamine is carcinogenic in nature. Other type is stevioside and xylitol which can also be metabolized by the gut bacteria that induces toxicity levels of gut microbiome [39-41].

Pesticides

The use of pesticides in agriculture is a major concern in reference to health effects of humans. It has also been established that most of pesticides are confirmed to be harmless to people only because of their targeted mechanisms do not exist in the human body. These fail to consider the microbes in the gut; likewise shikimate pathway, a target of herbicide glyphosate, is present in gut bacteria in humans. In bacteria, this pathway works in linking the metabolised carbohydrates to the biosynthesised folates and aromatic amino acids[42-44]. Also, in another example; 2,4-dichlorophenoxyacetic acid, which is an herbicide, that has an impact on plant hormones, may have an effect on gut bacteria because bacteria can also produce plant hormones. The association of gut microbiome toxicity and pesticide exposure have been demonstrated with many examples; such as in mice and zebrafish, it has been observed that the fungicide imazalil altered the gut microbiome composition. In another study, mouse gut microbiome was exposed to Arsenic with 4 ppm dosage for 13 weeks which showed perturbations in the gut microbiome of mouse. The diazinon in combination with malathion has an impact on the quorum sensing of gut bacteria, which is another major gut microbial perturbation [45,46].

Metallic Elements with High Density

It is another factor linked with the environmental contaminants getting wider attention in the present scenario. Gut bacteria have a critical role in the biotransformation of metallic compounds with high density (arsenic, cobalt, chromium, cadmium and nickel) which elevates the toxicity levels [47]. The human gut has the capability to transform inorganic arsenic into organic arsenic species, which is less toxic in nature. Moreover, methyl-mercury is de-methylated by gut bacteria and generates toxic inorganic mercury. In a study, rats were exposed to heavy metals which have shown perturbations in functional profiles in the gut microbiome due to the presence of heavy metal pollutants such as arsenic, cobalt, chromium, cadmium and nickel; and other heavy metal compounds [48]. Arsenic exposed to drinking water for 4 weeks, initiated different metabolite profiles in mouse gut. Also, diverse bacterial metabolic pathways were perturbed upon exposure of arsenic dosage for 13 weeks. Almost every heavy metal compound disturbs the gut microbial functions of mice with perturbed pathways and metabolites[49-51].

FUTURE PROSPECTS

From regulatory perspective, there needs a strict regulation and monitoring by food agency regulators of respective countries along with imposition of higher degree safety reforms in order to contain the spread

of melamine-tainted food products, melamine adulteration malpractices and the underlying renal damaging nephropathic effects. Can we have some useful and sensitive diagnostic markers which can reveal early changes at the renal front and the answer is yes to some extent as evidenced in some earlier studies [13]. Moreover, one needs to have an in-depth look at the mode of action of melamine in establishing nephropathic effects along with assessment in a variety of human kidney cell lines. Melamine associated end products should be estimated with ultrasensitive methods including fluorescent-based or isotope-based and nano-particle labelling methods. Pathological and biological parameters upon melamine exposure need to be understood for the development of therapeutic strategies. Some efficient protein detection methods have been developed in the past capable of detecting melamine and its analogues [10, 11]. Also, urinary melamine was considered as a point of care detection for melamine adulteration [12].

CONCLUSIONS

As we know that Diversity of microbiota is known to fluctuate throughout the development process of an individual which are also influenced by the environmental as well as host conditions. Gut microbiota dysbiosis due to melamine or exposure to other environmental pollutants can have a significant impact on the physiological parameters and health of the individual as a result of host microbiota-pollutants interaction resulting in gut dysbiosis [7]. For example, the microbiota-gut brain axis homeostasis is extremely important in the prevention of neuropsychiatric disorders. Due to increased anthropogenic and industrial activities globally, there has been a constant threat of environmental toxins, therefore inclusive public health programmes and studies are required to conduct epidemiological surveys in order to know the population exposure to toxins and environmental contaminants or chemicals like melamine which may predispose the population risk towards disease(s). The gut microbiota and associated activities certainly have a role in ameliorating the ill-effects of melamine induced toxicity but the impact of long-term exposure to melamine and the interaction between gut microbiota and melamine on human health, yet to be established. Undoubtedly, Gut microbiota is an important player and cannot be ignored whenever it comes to evaluating the melamine toxicity. Future awaits on harnessing the hidden potential of microbiota as a possible therapeutic target using high-throughput next-generation sequencing and metagenomics so as to ameliorate the toxic effects associated with melamine and other environmental pollutants.

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CONFLICT OF INTEREST: Nil

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