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Emulsifiers as food additives: An overview on the impact to obesity and gut diseases

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Abstract
Emulsifiers, which are added to most processed foods to aid texture and extend shelf life, can alter the gut microbiota composition and localization to induce intestinal inflammation that promotes the development of inflammatory bowel disease (IBD) and metabolic syndrome. Inflammatory bowel disease (IBD), which comprises Crohn's disease and ulcerative colitis, affects many people and is often severe and devastating. Metabolic syndrome is a group of very common obesity-related disorders that can lead to type-2 diabetes, cardiovascular and/or liver diseases. Addition of emulsifiers to food promotes bacterial translocation across epithelial cells which also augments main features of obesity namely adiposity and metabolic inflammation. Studies have proven that emulsifiers might affect the gut microbiota to promote these inflammatory diseases. Clinically designed experiments using mice have been conducted to test this possibility. Results of current studies with regards to the effect of emulsifiers to gut health highlight that existing means of testing and approving food additives may not be sufficient to preclude the use of chemicals that promote diseases driven by low-grade inflammation and/or which will cause disease primarily in susceptible hosts.

Keywords: Emulsifiers, Gut health, bacterial translocation, metabolic syndrome, Inflammatory Bowel Disease

Introduction
Food additives are natural or artificial constituents that could be incorporated to food in minute quantities to perform technological functions such as extending shelf life, adding colour and flavour. Following the EU regulation, preservatives are food additives that protect against the action of microorganisms (fungi and/or bacteria) and thereby extend the shelf life of foodstuff [1]. In processed food products, lipids need to be stabilized using emulsifiers [2]. Emulsifiers are a type of food additives that can be used to improve the texture of food and prevent mixtures from separating. Emulsifiers are used in margarine, mayonnaise, creamy sauces, candy, ice cream, packaged processed foods and baked goods. In present, two common emulsifiers namely carboxy methyl cellulose (CMC) and polysorbate-80 (P80), are in question due to the increased risk of obesity and irritable bowel syndrome in mice tested using these emulsifiers. Based on the results of the clinical trials using mice, drastic disruptions in the gut bacteria of mice were recorded even in extremely low concentrations of emulsifiers. The intestinal tract is inhabited by a large and diverse community of microbes collectively referred to as the gut microbiota. While the gut microbiota provides important benefits to its host, especially in metabolism and immune development, disturbance of the microbiota-host relationship is associated with numerous chronic inflammatory diseases, including inflammatory bowel disease and the group of obesity-associated diseases collectively referred to as metabolic syndrome [3]. Therefore, new research studies suggest that emulsifiers could alter the delicate composition of microbes in the gut, trigger intestinal inflammation and increase the risk of inflammatory bowel disease and a cluster of obesity-related conditions known as metabolic syndrome in human as well [4]. It is recorded that obesity is allied with altered gut microbiota and low-grade inflammation. Both dietary habits and food composition contribute to the onset of such diseases [5]. Emulsifiers, in a variety of foods, have shown to induce body weight gain, low grade inflammation and metabolic disorders. These dietary compounds promote gut microbiota alteration and gut barrier dysfunction leading to negative metabolic alterations. As mentioned in previous research studies, there is an impact of dietary emulsifiers on the accessibility of specific nutrients to the gut bacteria [6]. Emulsifiers are detergent-like molecules; CMC and P80 affect lipid absorption in the intestine, increasing lipid and bile acid flux into the gut lumen. This phenomenon contribute not only to the modulation of the gut microbiota composition, but also gut inflammation. Hence, emulsifiers contribute to the modulation of energy sources in the gut.

Structure and function of emulsifiers

An emulsifier is a molecule that holds surface activity due to the amphiphilic properties, where hydrophilic and lipophilic regions exist within the same molecular structure. This structure helps the emulsifier to interact with both phases especially in an oil in water emulsion, developing a protective layer at interface in which dispersed phase droplets are prevented from amalgamation [7]. Function of emulsifiers in food systems can be characterized as to promote emulsion stability, control agglomeration of fat globules, and stabilize aerated systems; to improve texture and shelf life of starch containing products by complex formation with starch components; to modify rheological properties of wheat doughs by interactions with gluten proteins; to improve consistency and texture of fat-based products by controlling polymorphism and crystal structure of fats [8].

Mechanisms of action of emulsifiers on the gut lining

Gut is lined with mucus that keeps the microbes at a safe distance. Things that interrupt the interactions between gut bacteria and the protective mucus may have the probability to promote the onset of diseases associated with chronic gut inflammation [5]. Dietary emulsifiers such as carboxy methyl cellulose (CMC) and polysorbate-80 (P80) are used in numerous foods at concentrations up to 2%. A recent study suggested that the growth in dietary emulsifier consumption over the past half century may contribute to a higher incidence of inflammatory bowel disease (IBD) and metabolic syndrome [3]. P80 has been studied for toxicity and carcinogenic potential [9] and is permitted by the US Food and Drug Administration for consumption in selected foods at up to 1.0%. CMC has not been extensively studied but is considered 'generally regarded as safe (GRAS)' and used in various foods at up to 2.0% [10]. To study the underlying truth between the relationship of obesity, gut diseases and dietary emulsifiers, clinical trials have been conducted using mice. Mice were administered with the emulsifiers, carboxy methyl cellulose (CMC) or polysorbate-80 (P80) via drinking water (1.0% w/v or v/v) respectively for 12 weeks. At regular intervals, the composition of the microbes in the guts of the mice were tested using advanced genetic methods. Carboxy methyl cellulose consumption was shown to have long-lasting negative effects, such as increased adiposity and myeloperoxidase activity in the intestine, whereas the deleterious effects of polysorbate-80 were reversible [11]. An alteration in the microbial types and numbers in the gut over time was observed [3]. The study has showed that both emulsifiers are involved in the development of inflammation that resembles inflammatory bowel disease (IBD) since they promote chronic gut inflammation leading to vigorous colitis in mice, lacking Toll-like receptor 5 (TLR5 $^{-/-}$), or Interleukin 10 (Il10 $^{-/-}$), that lead to developing intestinal inflammation [12]. TLR5 $^{-/-}$ receptor is shown to be involved in the onset of many diseases, which includes inflammatory bowel disease [13]. Interleukin 10 is a cytokine with multiple, pleiotropic, effects in immune regulation and inflammation [14]. Alterations in microbiota composition included reduced levels of bacteroidales, associated with health [15-17], and increased levels of several mucolytic operational taxanomic units (OTUs) including Ruminococcus Gnavus [18]. Gut bacteria have been suggested to be involved in the development of low-grade inflammation in obese individuals [19] since they produce pro-inflammatory molecules such as lipopolysaccharides (LPS), flagellins and peptidoglycans. It is reported that emulsifier consumption has reduced the overall microbial diversity and raised the microbiota pro-inflammatory properties, remarkably via an increase in flagellin and lipolysaccharide (LPS) release [20]. Flagellin is a globular protein and it is the principle component of bacterial flagellum which causes inflammation in body and endotoxin LPS is a cell wall constituent of Gram-negative bacteria, which becomes liberated into the gut lumen upon bacterial cell lysis [21]. The inflammation caused by flagellin and LPS have links to inflammatory bowel disorders such as Crohn's disease and ulcerative colitis as well as metabolic syndrome and diabetes [21]. It is also reported that high-energy diets, in particular high-fat diets, are associated with high plasma LPS concentrations in humans and mice [22-25].

Bacterial translocation due to emulsifiers

A new study using mice has highlighted how emulsifiers added to various foods, promotes an effect called "bacterial translocation", where bacteria move across epithelial cells [3]. This, triggers the ill-health effects. Furthermore, as the microbes changes the mucus layers of the intestine and alter it, some bacteria makes a transition into this region. This is an area normally devoid of bacteria. Remarkably, based on the previous studies using mice, these changes have corresponded with chronic colitis which developed in the mice. Consumption of emulsifiers in processed foods may promote Crohn's disease (CD) by increasing bacterial translocation [26]. Crohn's disease is a type of inflammatory bowel disease (IBD) that may affect any part of the gastrointestinal tract from mouth to anus [27]. Emulsifiers increase gut permeability which results in increased bacterial translocation which causes inadequate clearance of intra macrophage bacteria such as *E. coli* and formulate granulomata, abscess and fistula [26].

Dietary emulsifier-induced low-grade inflammation and colon carcinogenesis

Recent findings suggest that low-grade inflammation in the intestine is promoted by consumption of dietary emulsifiers, an omnipresent component of processed foods which alter the composition of gut microbiota [28]. Gut microbiota is the mutual term for the large assorted community of microorganisms that resides in the intestine, play an important role in health by promoting immune system development and metabolism [29]. Alterations in microbiota composition, plays a crucial role in the pathogenesis of many intestinal disorders comprising inflammatory bowel disease (IBD) which is also associated with Colorectal cancer [30]. It is suggested that emulsifiers could be involved in colorectal cancer development through the elevation of low-grade intestinal inflammation and alterations of the intestinal microbiota. This has been tested by a well-established murine model of colitis-associated cancer (CAC) using the carcinogen azoxymethane (AOM), followed by two cycles of dextran sulfate sodium (DSS) in mice subjected to chronic exposures of two frequently used emulsifiers, CMC and P80. It was resulted that dietary emulsifying agents are responsible to create and maintain a pro-inflammatory environment in the colon, associated with alterations of the proliferation/apoptosis balance that resulted in aggravated carcinogenesis [28].

Conclusion

Dietary emulsifiers alter microbiota localization, composition and pro-inflammatory potential. It is also suggested through several studies that emulsifiers promote colitis and metabolic syndrome. However, it cannot be simply decided that emulsifiers are responsible for obesity. Current studies have

only been conducted in rodents that where chronically exposed to P80 and CMC. Large scale human studies need to be conducted to afford proof for a related connection amid emulsifiers, gut microbiota and metabolic syndrome. But current studies are capable and sufficient to explain that it is important to revise the food additives, especially emulsifiers that are prone to arouse complex diseases such as metabolic syndrome driven by alterations in microbiota composition and low-grade inflammation.

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