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Dietary Additives and Supplements Revisited: The Fewer, the Safer for Liver and Gut Health

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Abstract

Purpose of Review—The supplementation of dietary additives into processed foods has exponentially increased in the past few decades. Similarly, the incidence rates of various diseases, including metabolic syndrome, gut dysbiosis and hepatocarcinogenesis, have been elevating. Current research reveals that there is a positive association between food additives and these pathophysiological diseases. This review highlights the research published within the past 5 years that elucidate and update the effects of dietary supplements on liver and intestinal health.

Recent Findings—Some of the key findings include: enterocyte dysfunction of fructose clearance causes non-alcoholic fatty liver disease (NAFLD); non-caloric sweeteners are hepatotoxic; dietary emulsifiers instigate gut dysbiosis and hepatocarcinogenesis; and certain prebiotics can induce cholestatic hepatocellular carcinoma (HCC) in gut dysbiotic mice. Overall, multiple reports suggest that the administration of purified, dietary supplements could cause functional damage to both the liver and gut.

Summary—The extraction of bioactive components from natural resources was considered a brilliant method to modulate human health. However, current research highlights that such purified components may negatively affect individuals with microbial dysbiosis, resulting in a deeper break of the symbiotic relationship between the host and gut microbiota, which can lead to

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repercussions on gut and liver health. Therefore, ingestion of these dietary additives should not go without some caution!

Keywords

Gut Microbiome; Hepatocellular Carcinoma; High Fructose Corn Syrup; Artificial Sweeteners; Emulsifiers; Probiotics and Prebiotics

I. Introduction

Since ancient times, natural antimicrobial food additives have been used to extend the shelf life of foods and to reduce the risk of infection and microbial spoilage (1). Nowadays, synthetic additives are utilized to preserve the conditions of modern food processing (1). Since the passing of the Food Additives Amendment (1958), the Food and Drug Administration (FDA) has assessed the safety of various food additives, which has resulted in the Generally Regarded as Safe (GRAS) labelling of high fructose corn syrup (HFCS) (2), artificial sweeteners (3), emulsifiers (4–6), and some probiotics (*i.e. L. acidophilus*) (7). Interestingly, the FDA permits food manufacturers to self-affirm GRAS status for prebiotics (8). While dietary additives have had their merits for food industries, current research suggests that many of them can be harmful for the gut microbiome and the liver (as summarized in Figure 1).

The gut microbiota consists of a variety of microorganisms, including bacteria, archaea and eukarya (9). Over thousands of years, the host and gut microbiota have developed a mutualistic relationship; yet, various environmental factors are still able to either enhance or destroy this symbiotic friendship. When there is a microbial imbalance within the gut (*alias* dysbiosis), this causes alterations in metabolic and immune responses, which can, in turn, begin a domino effect that increases our risk for disease. These include gut-microbiota associated steatosis and non-alcoholic fatty liver disease (NAFLD), which can progress to non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC; most common liver malignancy). The domino effect starts with a compromise in intestinal integrity, which allows gut bacterial- derived microbial-associated molecular patterns (MAMPs) to escape into the portal vein and travel to the liver. These endotoxins then activate toll-like receptors found on hepatic stellate and Kupffer cells, which instigates pro-inflammatory signaling pathways (10–12). This hepatic inflammation, in turn, greatly increases the risk of developing HCC.

Our diet has a strong influence on the gut microbiota and overall host physiology. Much research has gone into understanding how our diet impacts the gut microbiota and its associated diseases. For example, it has been extensively demonstrated that an obesogenic diet can cause spontaneous development of steatosis, fibrosis and HCC (13, 14). Comparatively, the influence of dietary additives on the gut microbiota-HCC axis is relatively underexplored. This review highlights the current research (within the past five years) on what is known about the food additive – gut microbiota – HCC axis. However, considering the lack of current evidence on the relationship between dietary additives and

HCC, most studies presented herein will focus on the high risk precursors for hepatocarcinogenesis.

II. High Fructose Corn Syrup: A Manufactured Sugar

Background

Since the 1970s, the American diet has exhibited a monumental increase in sugar consumption (15). This elevation is mostly attributed to the introduction of high fructose corn syrup (HFCS) in many processed foods and beverages. HFCS is produced by an enzymatic process that leads to the partial isomerization of glucose, resulting in fructose formation (16). Specifically, HFCS is principally found in two forms, HFCS-42 and HFCS-55, with the fructose to glucose ratio being 42/58 and 55/45, respectively (16, 17). While the association between HFCS consumption and health risks was relatively under-explored, current research has linked fructose to being a major risk factor for a variety of diseases, including obesity [as reviewed in (18)], non-alcoholic fatty liver disease (NAFLD) [as reviewed in (17)], hypertension (19, 20), gut dysbiosis (21, 22), and hepatocellular carcinoma (HCC) (23, 24). In line, several studies have reported that an isocaloric-HFCS restricted diet implemented on both lean and obese children reduced hepatic *de novo* lipogenesis (25), steatosis (26), and other indices of metabolic syndrome (27) that could progress to NAFLD. Considering that NAFLD patients have a greater risk in developing hepatocarcinogenesis (28), this may indicate HFCS as a potential liver carcinogen, analogous to the recent report that HFCS enhances intestinal tumor growth (29).

The HFCS-NAFLD Axis

This interrelationship between HFCS and various health consequences has been attributed to the unique hepatic metabolism of fructose [as reviewed in (30)]. While the liver was assumed to be the primary site for fructose clearance, Jang et al. recently demonstrate that, through oral administration of ¹³C-fructose, the small intestine is actually the major location for fructose clearance; yet, this function is impaired under high fructose consumption as it saturates the intestinal fructose clearance capacity, leading to the spillover of fructose into the portal vein, which then accumulates into the liver (31). This overabundance of hepatic fructose can lead to an increase in energy metabolism since fructose is capable of bypassing the phosphofructokinase regulatory step in glycolysis (32). When the energy storages become full, this results in the accumulation of the Krebs cycle byproduct, citrate, which allosterically activates cytoplasmic acetyl-CoA carboxylase (ACC) and thus, initiates hepatic *de novo* lipogenesis (33). Additionally, HFCS consumption results in the downregulation of hepatic peroxisome proliferator-activated receptor α (PPAR α), which is associated with reduced mitochondrial β -oxidation (34). Moreover, hepatic ketohexokinase (KHK; rate limiting enzyme for fructose metabolism) metabolizes fructose without a negative feedback system, resulting in a dramatic decrease in ATP and phosphate levels, which results in hepatic production of uric acid (35). Considering the strong linkage between HFCS and hepatic *de novo* lipogenesis, high fructose-induced enterocyte dysfunction might explain, in part, the role of fructose in promoting NAFLD. Moreover, this might explain the hyperuricemia that is exhibited in adolescent patients with NAFLD (36) and NASH (37). Along with accumulating hepatic fructose, the retention of uric acid may be due to fructose

suppressing intestinal uric acid excretion through the activation of NADPH oxidase (38). The detrimental outcomes of fructose and uric acid has led researchers to target KHK and xanthine oxidase, respectively, for therapeutic approaches. Limiting activity of either enzyme is shown to be protective against steatosis, NAFLD, and NASH (39, 40). Whether these therapeutics can further inhibit against fructose-induced HCC should be explored.

The HFCS-Microbiome Axis

In addition to entering enterohepatic circulation, fructose can travel down to the colon and interact with the gut microbiota. This results in alterations of the fecal bacterial composition, including an 88% increase in the *Firmicutes* (F) to *Bacteroidetes* (B) ratio (22), where an increase in this F/B ratio indicates gut dysbiosis. Similarly, maternal consumption of fructose leads to a significant reduction of the 'beneficial' bacteria (*i.e. Lactobacillus*) within the fecal microbiome (21). Considering the positive correlation between butyrate-producing *Firmicutes* and adiposity (41), this could explain, at least in part, as to why maternal consumption of HFCS increases lipogenesis and adiposity in the offspring for both rats (42) and humans (43). Additionally, elevated KHK expression negatively affects tight junctions (44), which increases gut permeability and endotoxin release into the portal vein (45). These endotoxins (*i.e. LPS*) can travel and activate hepatic toll-like receptor 4 (TLR4), leading to fibrosis and hepatocarcinogenesis (46). Interestingly, citrulline may be a therapeutic option to revert the negative effects of fructose, as it has been reported that citrulline supplementation increases *Bacteroidetes* and *Prevotella* (47) and attenuates liver fat accumulation (48). Moreover, the probiotic strain, *L. brevis* DM9218, can enhance intestinal barrier function, which is associated with reduced hepatic lipopolysaccharide (LPS) levels, retardation of hyperuricemia and amelioration of fructose-induced liver damage (49). It would be interesting to observe whether citrulline or *L. brevis* DM9218 could be utilized as therapeutic options for patients with Hereditary Fructose Intolerance who are prone to develop obesity-independent hepatic steatosis (50).

III. Artificial Sweeteners: A Bitter Sweet Alternative to Sucrose

Background

Sweet taste receptors are ubiquitously found throughout the body, including the gastrointestinal tract. The binding of sucrose and artificial sweeteners to the heterodimeric G-coupled proteins, T1R2 and T1R3, activates both peripheral gustatory and, in turn, brain gustatory nerves, which regulate metabolic responses to maintain energy balance [as reviewed in (51)]. Compared to sucrose, the advantage of non-caloric sweeteners is their limited disruption on energy homeostasis due to the fact that artificial sweeteners are a hundred fold sweeter (52). Currently, there are six non-caloric artificial sweeteners (NAS) on the market: aspartame, saccharin, sucralose, acesulfame potassium, cyclamate and neotame. This section of the review will delve into further detail of each artificial sweetener and their impacts on gut and liver health.

Saccharin

Saccharin (1,2-benzisothiazol-3-one-1,1-dioxide) is the first synthetic artificial sweetener with a 300-fold increase in sweetness, making this NAS one of the most popular substitutes

for sucrose. Yet, there have been alarming reports that saccharin presents hepatotoxic properties (53), where short-term exposure causes transaminitis (*i.e.* ALT, AST and ALP) (54). Moreover, six month exposure of saccharin promotes hepatic inflammation, as indicated by elevations in iNOS and TNF α (55). While no studies have directly linked saccharin to the progression of HCC, the conformational changes that saccharin causes to the promoter of the potent tumor suppressor, p53 (56), could implicate a CD44-independent mechanism of diminished tumor surveillance and promotion of HCC progenitors (57). Similarly, Wistar rats fed saccharin have diminished expression of p27 (a tumor suppressor), while having overexpression of the key oncogene, H-*ras* (58). Along with influencing liver health, saccharin perturbs and alters the gut microbiota, which includes promoting *Bacteroidetes*, *Turicibacter* and *Clostridiales*, while reducing *Firmicutes* (55, 59). Despite the beneficial effects of lowering the F/B ratio, the elevation of pro-inflammatory bacteria (*i.e.* *Turicibacter*) still indicates a potential negative effect of saccharin ingestion. While there is limited information on how saccharin effects intestinal health, the unequivocal hepatotoxicity of saccharin should instigate a reevaluation on its current US acceptable daily intake (ADI) of 5mg/kg body weight.

Aspartame

The N-L- α -aspartyl-L-phenylalanine 1-methyl ester, aspartame, is a synthetic sweetener fortified in foods and beverages. Aspartame is around 200 times sweeter than sucrose (60), which has made this NAS another alternative for sucrose. The ADI of aspartame established by the European Food Safety Authority and FDA are 40 and 50 mg/kg/day, respectively (61). However, recent studies demonstrate the negative impacts of aspartame on gut and liver health, which may cause for an ADI update. For example, multiple studies confirm that long-term intake of aspartame induces liver degeneration, mononuclear cell infiltration, necrosis and fibrosis, which may be mediated through the dysregulation of adipocytokines and an imbalance in redox homeostasis (58, 62–64). Additionally, aspartame in combination with potassium sorbate induces a mitochondrial-mediated apoptosis pathway, which is associated with the loss of the mitochondria membrane potential (65). While aspartame presents hepatotoxic effects, since this NAS is readily metabolized to phenylalanine, aspartic acid and methanol (60, 63), it is difficult to determine whether these byproducts are the true culprits in prompting hepatic damage. In order to address this concern, a recent study demonstrates that folate deficiency aggravates aspartame-induced liver injury. Normally, folate protects against the aspartame byproducts, methanol and formate; therefore, by eliminating folate through the immunosuppressive drug, methotrexate (MTX), it was established that the metabolites may play a part in aspartame-mediated hepatic damage (66). In regards to HCC, there is limited understanding on potential tumorigenic properties for aspartame, except for the analogous effects of saccharin on H-*ras* and p27 (58). Along with hepatic damage and potential carcinogenesis, low-dose aspartame influences the gut microbiota composition through increasing the total fecal bacteria load and the relative abundance of *Enterobacteriaceae* (67). Intriguingly, Martinson et al. recently demonstrate that resident *Enterobacteriaceae* clonal populations, including pathogenic *E. coli*, have little stability within the ‘healthy’ human gut (68). In fact, *E. coli* populations within the gut can have a turnover of over months to a year (68). This low ‘stability’ may explain the strong relationship between the expansion of *Enterobacteriaceae* and inflammatory diseases of the

gastrointestinal tract (69). Alongside, the overgrowth of *Enterobacteriaceae* is associated with the severity of cirrhosis (70–72). This current evidence suggests that aspartame could be linked to gut dysbiotic-associated maladies, including liver disease; therefore, future studies are warranted to elucidate this important gap in the field.

Sucralose

The substituted disaccharide, sucralose (1,6-dichloro-1,6-dideoxy- β -D-fructofuranosyl-4-chloro-4-deoxy- α -D-galactopyranoside), also exhibits potent effects on both intestinal and hepatic health. Sucralose can cause gut dysbiosis as indicated through altered *Proteobacteria* (73, 74) and *Clostridium cluster XIVa* (75) compositions within the fecal microbiome. Moreover, sucralose increases the abundance of other pro-inflammatory bacteria (*i.e.* *Turicibacter*), which is associated with hepatic inflammation (76). Additionally, the administration of sucralose induces various hepatic features, including degeneration of hepatocytes, lymphocyte infiltration and fibrosis (77). When considering liver proteomics, the effect of sucralose may be due to ribosomal inactivation, which enhances gut microbiota-mediated hepatic inflammation (78). Whether this could progress to hepatocarcinogenesis is unclear; yet, a few reviews state that the administration of sucralose presents no carcinogenic properties (79, 80). In contrast to these reports, a recent study demonstrated that a sucralose diet fed to Swiss mice from prenatal to natural life-span death resulted in hematopoietic neoplasias (81), which indicates a potential tumorigenesis property of sucralose. While this is a striking result, it has been reviewed that sucralose may have greater health effects on humans than on rodents (82); therefore, more research is needed to determine the differential effects between this NAS on separate species.

Acesulfame Potassium, Neotame, and Cyclamate

The current information regarding acesulfame potassium (*alias* Ace-K) on hepatic and gut health is limited. In terms of the gut microbiota, the consumption of Ace-K can affect the bacterial composition in a sex-dependent manner (75). Moreover, Ace-K dramatically decreases the relative abundance of multiple genera, including *Lactobacillus* and *Clostridium*, whereas *Bacteroides* is highly expressed (83). Likewise, a recent finding indicates that four-week administration of neotame reduces the α -diversity and alters the β -diversity of the fecal microbiome (84). Analogous to these results, the streptozotocin-high fat diet (STZ-HFD) induced NASH-HCC mouse model is found to be associated with an elevation in *Bacteroides* and a reduction in α -diversity (85). This could implicate Ace-K as a potential promoter of liver disease, including HCC, through alterations in the gut microbiome; however, long-term studies are necessary to elucidate this possibility. Similar to Ace-K, not much information is known about the impact of neotame or cyclamate on liver and gut health; however, considering that cyclamate is converted to cyclohexylamine by the gut microbiota (86), it would be an interesting avenue to see how this gut metabolite could affect human health. Overall, ongoing research is needed to further explore the utilization of these NAS in both rodent and human studies.

IV. Emulsifiers and Flavor Enhancers in Processed Foods

Background

To optimize food appearance, texture and mouthfeel, emulsifiers and flavor enhancers are the key agents. Emulsifiers are comprised of proteins, phospholipids and carbohydrates, where their water-oil suspension are utilized to extend shelf-life and encapsulate unpleasant aroma and/or bioactive compounds [as reviewed in (87)], whereas flavor enhancers intensify and amplify the savor within foods. While these ingredients do possess important merits in terms of food storage and taste, their impact on the gut-liver axis can lead to undesired consequences, including mucosal inflammation and hepatic dysfunction.

Carboxymethylcellulose and Polysorbate 80

The two most popular dietary emulsifiers, carboxymethylcellulose (CMC) and polysorbate 80 (P80), are ubiquitous components of processed foods that enhance texture and extend shelf life (88). Alongside these properties, emulsifiers can alter the murine (89, 90) and human (88) microbiome in a sex-dependent manner, which further promotes metabolic syndrome (91) and colitis (90). Moreover, CMC and P80 promote microbiota encroachment, which is associated with reduced mucus thickness (90, 92). Interestingly, these negative effects of emulsifiers are ablated in germ-free mice and in the highly restricted microbiota, gnotobiotic mouse model termed Altered Schaedler Flora (88). It would be compelling to determine whether certain antibiotics could also protect against the detrimental effects of emulsifiers on the gut microbiota. Additionally, this would elucidate which bacterial species are leading to the low-grade inflammation induced by emulsifiers. This could further provide, at least in part, a therapeutic approach to reduce P80-mediated fatty liver, steatosis, and hepatocyte ballooning, along with diminishing oxidative stress (91). While these emulsifiers are not reported to cause HCC, the fact that P80 can induce pre-HCC risk factors should warrant for future studies to determine whether long-term administration of this emulsifier could reveal potential carcinogenic properties.

Lecithin

Another popular emulsifier, lecithin, is a food additive and the main component of phosphatidylcholine. Interestingly, while lecithin does not directly impact host physiology, its metabolites may cause concern for hepatic and intestinal health. When lecithin or its byproduct choline interacts with the gut microbiota they are metabolized into trimethylamine (TMA), which is further oxidized by hepatic flavin monooxygenases to form trimethylamine N-oxide (TMAO) (93). Besides its endogenous generation, TMA and TMAO can originate from natural food products, like fish. Interestingly, TMAO can get converted back to TMA, predominantly by *Enterobacteriaceae*, which leads to a continuous cycle known as retroconversion (94). While lecithin itself may not be regarded as harmful, TMAO has been indicated to be an independent risk marker and factor for NAFLD (95). Additionally, elevated serum TMAO and diminished serum choline (96), along with diminished urinary TMAO (97), levels are associated with primary liver cancer, including HCC. This overproduction of TMAO may indicate a gut flourish of *Enterobacteriaceae* and a compromised intestinal barrier. Interestingly, it has been reported that the consumption of soy lecithin, as a phospholipid source for infant formula, skews the gut bacterial community

towards elevated *Enterococcaceae* and *Enterobacteriaceae* (98), which are two bacterial strains that are significantly associated with cirrhosis disease progression (99). It is plausible that, analogous to HCC, the relationship between these bacteria and cirrhosis could be related to TMAO production. Besides TMAO generation, there is another metabolic pathway that lecithin can pursue. After its breakdown to choline, this byproduct could be irreversibly oxidized to betaine, leading to the pathway of betaine → homocysteine → methionine → S-adenosylmethionine (SAM) (100). Interestingly, high intakes of choline and betaine is associated with reduced primary liver cancer incidence (100, 101) whereas methionine and SAM is highly associated to HCC risk (101). This one-carbon metabolism from choline to methionine and SAM is linked to DNA methylation (102), which is usually altered during cancer development. Therefore, while lecithin and choline may not directly impact liver cancer development, its metabolism could provide the key components to promote SAM-mediated DNA methylation and thus, promote tumorigenesis.

Monosodium glutamate

Monosodium glutamate (MSG) is a widely, frequently used flavor enhancer and stabilizer in ready-made or packaged foods. It has been recently demonstrated that MSG causes inflammatory infiltration and disorganized hepatic architecture (103). Moreover, MSG-treated rats have elevated serum enzymes for liver dysfunction, which may be due to the over accumulation of glutamine generated from the glutamate counterpart of MSG (103). Additionally, MSG initiates oxidative stress on the liver, as it can dissociate into free radicals (103). Along with inducing liver injury, MSG-treatment promotes the transition from NAFLD to NASH (104) to pre-neoplastic lesions, including HCC (105). The specific mechanisms of MSG-induced HCC needs further clarification. Regarding the gut microbiota, there is limited information as to how MSG alters bacterial diversity. Therefore, future studies are required to elucidate the influence of MSG on gut dysbiosis and HCC.

VI. Probiotics

Background

According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), a probiotic contains “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (106). Some of the probiotics incorporated as food supplements include various strains of *Lactobacillus* and *Bifidobacteria*, along with the *E. coli* strain Nissle 1917 (107). These probiotics have been highly advertised as potent dietary agents against NAFLD [as reviewed in (108)]. This section will go into further details on how probiotics affect the gut microbiome-liver axis.

Probiotics – Microbiota – Liver Axis

One of the popular uses of probiotics is supplementing them into yogurt to alleviate constipation through improved gut motility, which is further associated with a balanced gut microbiota (109). Recently, the utilization of probiotics has expanded towards other health targets. For example, maternal consumption of HFCS during gestation and lactation induces hypertension in rat offspring; yet, this is counteracted when the fructose-fed mothers are also administered *L. casei* (20). This protection may be due to this probiotic boosting propionate-

producing *Prevotella* (20), where propionate is associated with attenuation in hypertension and overall better cardiovascular health (110). Along with directly affecting intestinal bacterial communities, probiotics can influence the enteric nervous system (ENS); for example, *L. rhamnosus* (1×10^{10} CFU/ml) administration induces ROS in a formyl-peptide receptor 1 (FPR1)-dependent manner (111). Moreover, *L. plantarum* RYPR1 contains bile salt hydrolase (BSH) activity, which increases the longevity of this probiotic through the deconjugation of primary bile acids (112). At the same time, however, elevated BSH activity promotes the generation of the even more toxic, secondary bile acids; therefore, this indicates that RYPR1 must contain an unknown protection mechanism against these gut metabolites.

Along with modulating intestinal health, various probiotics have hepatoprotective properties. *L. plantarum*, for example, alleviates aflatoxin-induced hepatic injury (113), while *L. rhamnosus* ameliorates high fructose-induced NAFLD (114). Comparatively, *L. plantarum* promotes antioxidants and the excretion of aflatoxins (113), whereas *L. rhamnosus* boosts the *Bacteroidetes* to *Firmicutes* ratio and heightens tight junction expressions (114). Additionally, *L. rhamnosus* limits the spillover of endotoxins into the portal vein and normalizes hepatic lipid metabolism, which further reduces hepatic inflammation and fat accumulation, respectively (114). Moreover, the butyrate-producing probiotic, *C. butyricum* MIYAIRI 588, prevents the progression from steatosis to hepatocarcinogenesis through Nrf2-mediated upregulation of anti-oxidative enzymes (115). Additionally, *L. johnsonii* BS15 can effectively prevent NAFLD through upregulating antioxidants, suppressing insulin resistance, improving the gut barrier and modulating the microbiota (116). Along with the mentioned *Bifidobacteria* and *Lactobacillus-derived* probiotics, one very popular probiotic in the alleviation of chronic inflammatory diseases is *E. coli* Nissle 1917 [as reviewed in (117)]. Interestingly, the potent effects of Nissle 1917 may be, in part, to their responses in natural selection and competitive fitness, including self-generated mutations to better modulate carbohydrate utilization, stress response and adherence (118).

The previously mentioned examples are single strain probiotics; however, there are many probiotics that contain multiple bacterial strains. The most popular combination for probiotics are members of *Lactobacilli* and *Bifidobacterium* groups, which are fortified in many foods and dietary supplements (119). For example, probiotic yogurt containing *L. acidophilus* La5 and *B. lactis* Bb12 can improve NAFLD markers (120). Likewise, a probiotic capsule containing two strains of *Lactobacilli* and two strains of *Bifidobacterium* is able to alleviate pediatric NAFLD (121). Another combination for a probiotic includes a 1:1:1 ratio of *L. acidophilus*, *B. infantis* and *Bacillus cereus*. Administration of this probiotic flourishes and diminishes anaerobic and aerobic gut bacteria, respectively, during the progression of NAFLD; moreover, the probiotic mixture upregulates tight junctions, which is associated with lessened endotoxin-activation of TLR4 signaling and amelioration of liver pathology (119). VSL#3 (commercialized as Visbiome®) is another popular probiotic that is comprised of eight Gram-positive strains: one *Streptococcus*, four *Lactobacilli*, and three *Bifidobacterium* (122). When treating VSL#3 to aged Wistar rats, this probiotic causes a positive, robust change to the intestinal microbiota through the decrease in the F/B ratio (122). Alongside, VSL#3 administration increased the abundance of anti-inflammatory bacteria (*i.e.* *Prevotella*) along with their metabolites (*i.e.* propionate), promoted IL-10

signaling and inhibited pro-inflammatory helper T cell secretion from the gut to the liver (122). These beneficial effects of VSL#3 foreshadow that this probiotic could alleviate the bountiful levels of liver injury markers (i.e. ALT) during hepatic diseases, but future study is required to confirm this prediction.

Considering that HCC is highly associated with the gut microbiota profile and inflammation in NAFLD (72), these striking findings on probiotic alleviation of NAFLD through modulation of the gut microbiome insinuates that these live microorganisms may be able to prevent hepatocarcinogenesis. Many combinations of probiotic strains (i.e. *L. rhamnosus* LC705 and *Propionibacterium freudenreichii subsp. Shermani*) have been utilized as a dietary approach to reduce the risk of HCC development [as reviewed in (123)]. Likewise, VSL#3 has been proposed as a probiotic to reduce HCC risk (123). Along with being utilized as an independent probiotic, heat-inactivated VSL#3 in combination with *L. rhamnosus* GG (LGG) and viable *E. coli* Nissle 1917 (EcN) generates a novel prebiotic mixture known as Prehop (122). This multi-component probiotic can alleviate gut microbiota-associated HCC development through inhibiting angiogenesis, shifting the bacteria community to *Bacteroidetes*, *Prevotella* and *Oscillibacter*, along with promoting the differentiation of intestinal Treg cells and reducing Th17-mediated inflammation (122). While all of these mentioned probiotics have been reported to provide beneficial effects, there are conflicting reports as to the full effectiveness of these microorganisms. Zmora et al. demonstrates that probiotics have a marked resistance to mucosal colonization; yet, these varied between murine and humans, where in the human gut microbiome, probiotics had region and strain-specified mucosal localization patterns (124). Likewise, Suez et al. observed that probiotics actually delay the reconstitution of the gut microbiome after antibiotic treatment compared to spontaneous/regular recovery (125). Hence, the true 'beneficial' effects of probiotics on the intestinal microbiome needs further investigation.

VII. Prebiotics: Nutrient Extraction a Good Health Compromise?

The current definition of a prebiotic is 'a substrate that is selectively utilized by host microorganisms conferring a health benefit' (126). Generally, these are non-viable substrates that provide essential nutrients for probiotic bacteria, including *Bifidobacterium* and *Lactobacilli* (126). Yet, there is also a chance of cross-feeding, where the fermented product(s) generated from the 'good' bacteria could promote the 'bad' bacteria (127). Examples of prebiotics include fructans, fructo-oligosaccharides, and galacto-oligosaccharides. While prebiotics have been highly advertised to alleviate and prevent various metabolic diseases through the modulation of the gut microbiota [as reviewed in (128)], current controversial research indicates that there are too many variabilities in the results and more studies are required to understand the impact of prebiotics on metabolic, hepatic and intestinal health. This final section of the review will explore the multiple prebiotics that are on the market and the recent updates on how they impact overall health.

Inulin

Originating from chicory roots and Jerusalem artichokes, inulin (β 2→1 linkages) is the most widely studied and utilized plant fructan. It is estimated that U.S daily consumption of

this oligosaccharide ranges from 1.3–3.5g, which is less than half of the recommended amounts (129). To increase the availability of this polysaccharide, inulin is extracted from its natural source then purified as a commercial product for processed foods (129). Along with providing a great source of fiber, inulin fortification has been utilized as a texture modifier and a fat and sugar replacer [reviewed in (129)]. With the recent FDA GRAS status of inulin-containing foods (130), there is no doubt that the consumption of inulin-supplemented foods will positively progress. Likewise, the multiple reports on the health benefits of inulin, including protection against hypertension (20) and high fat diet (HFD)-induced metabolic syndrome (131), will further boost the incorporation of this fructan into people's diets. Interestingly, these positive effects are attributed to inulin modulating the gut microbiome, including preserving the gut barrier integrity (132) and limiting gut-microbiota mediated proteolysis (133). Additionally, this non-digestible carbohydrate promotes the 'good', probiotic gut bacteria, including *Bifidobacteria* (134, 135) and *Lactobacilli* (136). While these are the two prime phyla that are modulated by inulin, heterogeneous reports have made it difficult to elucidate how this fructan can affect other bacteria in the microbiome (131, 135–139). Interestingly, Chassaing and Gewirtz reveal that inulin generates profound differences between the mucosal and fecal microbiome at both the phyla and species levels (137). This suggests that the fecal and intestinal microbiome may have distinct, complex microbial ecosystems.

Inulin has antioxidant properties (140), which has made it a candidate agent to protect against hepatotoxicity. For example, inulin protects against drug- (141) and chemical-induced (142, 143) liver injury through the scavenging of ROS and promoting levels of glutathione in its reduced state. Moreover, in alcoholic-induced liver damage (ALD), inulin promotes better intestinal health and barrier integrity, which lessens the release of endotoxins (*i.e.* LPS) and thus, reduces the activation of the pro-inflammatory TLR4-macrophage axis (136). Alleviation of hepatic injury is further promoted when inulin is paired with the flavenol, catechin (143). Interestingly, catechin alone has greater hepatoprotective effects than inulin alone or in combination with catechin (143). While it seems that inulin has positive effects on liver health, what must be acknowledged is that these rodent studies administered inulin for short time periods, ranging from less than 2 weeks (141), 3 weeks (143), and 6 weeks (136). Likewise, in a recent human study, the association of inulin with NAFLD was only a 3-month study (144), which limits observing the long-term effects of inulin on hepatic health. Alarmingly, our group discovered that prolonged inulin feeding for 24 weeks can result with cholestatic liver cancer in gut dysbiotic mice (145). Specifically, we observed that a subset (40%) of toll-like receptor 5 deficient (*Tlr5*KO) mice developed hyperbilirubinemia and cholemia within 10 days of inulin feeding and then icteric HCC by 6 months. This cholestatic phenotype is associated with a reduction in intestinal intraluminal bile acids, resulting in limited FXR signaling, which would result in the overabundance of these hepatotoxic detergents inside the liver. Moreover, we observed elevations of *Clostridia* in the fecal microbiome, which indicates elevated generation of toxic secondary bile acids (*i.e.* deoxycholate). When considering that deoxycholate provokes the senescence-associated secretory phenotype (SASP) in hepatic stellate cells, this could explain, in part, the promotion of hepatic pro-inflammatory and tumorigenic factors that could progress to HCC (146). In general, more research is

certainly required to further understand the mechanism(s) for inulin-induced cholestatic HCC.

β-glucan

Oats and barley are great resources for obtaining β-glucan, a prebiotic that is distinct from inulin due to differences in molecular weight, solubility and glycosidic linkages [as reviewed in (147)]. The popularity of β-glucan is due to its cholesterol lowering properties through increased bile acid synthesis (148), which is further associated with an increase in bile excretion (149). Due to this property, β-glucan is highly fortified in many foods, including cereal, which is usually in combination with phytate to increase the stabilization of this polysaccharide (150). Interestingly, the structure of β-glucan can vary based on its source (*i.e.* oats vs. barley), which might explain why the polysaccharide originating from oats is more effective in promoting probiotic gut bacteria than barley [as reviewed in (151)]. Similarly, the molecular weight of β-glucan can determine its effectiveness in being a prebiotic, where the difference between 100 and 530 kDa can stimulate and demote probiotic bacteria, respectively (152). Moreover, it has been reported that an intermediate molecular weight of 28 kDa is the most promising candidate to be developed as novel prebiotic (147). Yet, similar to inulin, there are various reports (153–157) as to how β-glucan impacts the gut bacterial composition. What is more consistent is the interaction between β-glucan and the pattern recognition receptor (PRR), dectin-1 (*alias* *Clecl7a*). β-glucan activation of dectin-1 can initiate various immune responses in the gut mucosa, including upregulating IL-10 and retinol dehydrogenases (153). Along with promoting intestinal health, β-glucan has demonstrated beneficial effects towards the liver, including protecting against carbon tetrachloride-induced liver injury (158), alleviating hepatic steatosis (154), ameliorating NASH through anti-fibrotic and anti-oxidative properties (159, 160), and suppressing HCC (161, 162). The anti-tumor properties of β-glucan could be derived from its ability to upregulate CD4 T cell modulation and neutrophil infiltration into tumor cells (163).

FOS, GOS and Pectin

Fructo-oligosaccharides (FOS) and galactose-oligosaccharides (GOS) are two important groups of non-digestible carbohydrates. These prebiotics in natural foods usually exist in low quantities (127), which is why FOS and GOS are heavily fortified in foods. Likewise, pectin (a methylated ester of polygalactouronic acid) is commercially extracted from citrus peels, apple pomace, sugar beet pulp and potato pulp (164). Comparatively, pectin is fortified in foods like yogurt, whereas FOS and GOS are popular supplements in infant formula as a means to mimic the microbiome of breast-fed infants (165). Interestingly, FOS supplementation to suckling rats can sway the adult microbiota, including promoting *Bifidobacteria* and attenuating *Firmicutes* (166), while GOS-containing infant formula can promote *Bifidobacterium* during the first year of life (167). Yet, FOS and GOS can not 100% mimic human milk oligosaccharides, where breast-fed infants have higher *Bifidobacterium* numbers and a lower diversity in comparison to formula-fed infants (165). These differences could arise from a couple of factors, including dosage (168) and whether the polysaccharide originates from a semi-purified or non-purified source (169). Similarly, the physiological effects of pectin can vary based from its natural source; for example,

artichoke-derived pectin can stimulate the growth of *Bifidobacterium*, *Lactobacillus*, *Bacteroidetes* and *Prevotella* more efficiently than sunflower-derived pectin (170). Likewise, apple-derived pectin supplemented to a HFD rebalances the F/B ratio and increases claudin expression, which results in less endotoxemia and TLR4 signaling (171). Moreover, apple pectin (4% wt/wt in drinking water) significantly attenuates the thickness of submucosa and collagen in a radiation-induced intestinal fibrosis rodent model (172). Along with alleviating intestinal fibrosis, citrus pectin can stop the progression of carbon tetrachloride-induced hepatic fibrosis through the inhibition of galectin-3 and induction of apoptosis in stellate cells (173). Similarly, pectin, FOS and GOS can ameliorate liver injury, steatosis, NAFLD, and NASH (174–179). Yet, similar to inulin, these previous studies involved short-term administration, which has limited understanding how these other prebiotics can affect hepatic health long-term. Shockingly, our group demonstrates that FOS and pectin can induce cholestatic HCC and gut dysbiosis (145), but not to the same degree as inulin. This indicates that long-term administration of these prebiotics can cause detrimental effects on both liver and intestinal health.

Future thoughts

Mammals and their gut microbiome have developed a mutualistic ‘give and take’ relationship. Specifically, we provide a nutrient-rich environment for bacteria to thrive, where their microbial colonization and hydrolytic gut metabolites heavily impact our innate immune responses and thus, impact host pathophysiology. We have already mentioned about how we attempt to maintain this gut symbiosis through the utilization of pro- and prebiotics. To take it a few steps further, much research has explored the therapeutic potential of symbiotics, which consists of differential combinations between pro- and prebiotics. Various reports have demonstrated that these symbiotics can alleviate metabolic syndrome (180), promote intestinal health (181–183), and ameliorate steatosis, fibrosis, NAFLD and NASH (184, 185). Hence, these symbiotics might provide a better avenue to therapies on gut and liver health; yet, more research is required the effects of various symbiotic combinations.

VIII. Conclusions

The ever growing population throughout the globe demands exploitation of natural resources, including extraction of various dietary ingredients from multiple foods. Through the advancement in technology, food scientists and industries can isolate and exploit such precious bioactive components from natural resources for human health. At first, this was considered appreciable and commendable as positive results have been reported; however, such bioactive components may not work in isolation or within a certain group of individuals, including microbial dysbiotic patients. In fact, the introduction of these purified ingredients could further break the holobiont relationship between the host and microbiota, which can lead to repercussions on hepatic health (as summarized in Figure 1). While more research is warranted to further determine how these dietary additives effect human health, this review provides a profound leap and in-depth understanding of the food supplements that we ingest on a daily basis.

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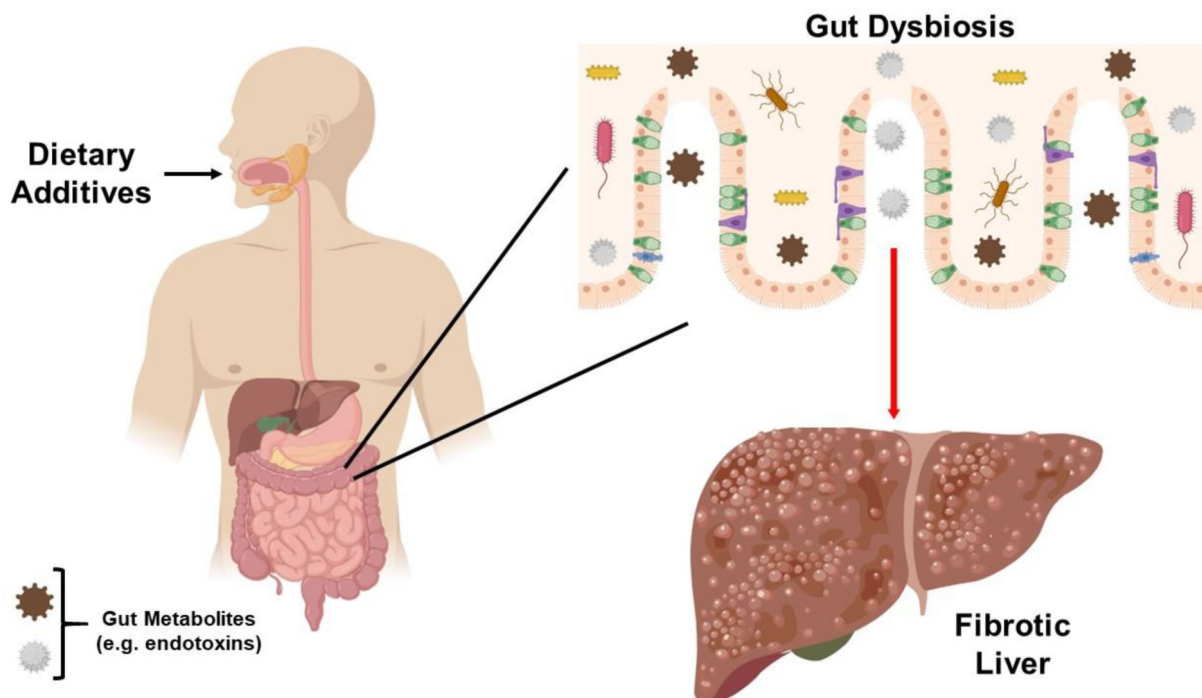


Figure 1: Ingestion of food additives can cause gut dysbiosis and liver dysfunction.

Our diet is one of the greatest influencers on the gut microbiota. An imbalance in intestinal microbiota composition (*alias* gut dysbiosis) can cause systemic effects, including impacting liver health. In this case, the consumption of dietary additives (*i.e.* HFCS, emulsifiers, flavor enhancers, prebiotics) can cause gut dysbiosis, resulting in the generation of gut endotoxins (*i.e.* LPS), which travel through the portal vein towards the liver. These endotoxins can initiate hepatic inflammation, which can progress to fibrosis and hepatocarcinogenesis.