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The Influence of GMOs on the Composition of the Gut Microbiome

Shawnia Rakhshani
College of Saint Benedict/Saint John's University, srakhshan001@csbsju.edu

Hailey Wight
College of Saint Benedict/Saint John's University, hwight001@csbsju.edu

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By

SHAWNIA RAKHSHANI, HAILEY WIGHT

College of Saint Benedict

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Introduction

Genetically modified organisms have been used for decades in agriculture across the world. The use of GMOs has been advertised as a solution to many agricultural issues. However, people have raised concerns about GMOs reshaping human health, and more importantly, the composition of the gut microbiome. The gut microbiome has a vital role in human health through digestion, immune abilities, and protection against disease-causing bacteria. If any disturbances occur in the microbiome, it can have negative effects on an individual's overall health and wellbeing.

Genetically modified organisms (GMOs) are organisms that have had their genetic material adjusted in a way that does not occur naturally. These alterations are utilized with biotechnology techniques, such as transgenic technology or gene editing, to remove or add a specific gene or characteristic to the desired organism (National Geographic Society, 2018). The relationship between GMOs and the gut microbiome composition can depend upon the type of GMO being consumed, the host themselves, and the individual's overall habits and diet. Understanding the various types of genetic modification methods can provide insight into the potential repercussions of GMOs on the human gut microbiome. Genetic modifications have been made possible with CRISPR, selection, cross breeding, mutagenesis, and conjugation for years in agriculture (NRC, 2004). One of the most common methods of genetic modification today is CRISPR-Cas9, which can be performed using different approaches including direct transfer of the desired gene or direct manipulation of the target plant genome (Karami et al., 2018). Numerous methods of biotechnologies allow for the modification of organisms and development of GMO products for a diverse array of purposes.

Biological context

The human gut microbiome is composed of multiple species of bacteria. The gut microbiome generally consists of *Prevotella, Ruminococcus, Bacteroidetes*, and *Firmicutes*, which are among the most commonly identified bacterial phyla and genera. In the typical adult, *Firmicutes* are the most abundant, followed by *Bacteroidetes* (Rinninella et al., 2019). Bacteria within the gut microbiome are involved in balancing the beneficial and opportunistic bacterial composition, and manufacturing serotonin, enzymes, and vitamins. With respect to the immune system, the human gut microbiome not only protects the host from external pathogens by producing antimicrobial substances but also serves as a significant component in the development of intestinal mucosa and immune system (Hou et al., 2022). For instance, vitamin K, which is a product of bacteria, is involved in both immune and metabolic functions. When an imbalance is displayed in bacterial species, it can result in gastrointestinal diseases including obesity, IBS, and type 2 diabetes (Bull & Plummer, 2014). In order to maintain a healthy ratio of bacteria, one should understand what can interfere with the composition of the gut microbiome to prevent diseases from arising.

Diving deeper into the biological context, few studies have been completed describing what interferes with gut microbiome flora. The area of focus in this paper is the GMO consumption, but it is imperative to see what the food we eat alone can do to our gut microbiome. A study was conducted by De Filippo et al. (2010) to determine gut microbial composition based on dietary habits within the human population. Fecal microbiota of 15 European and 14 African children were compared, providing a diverse approach to the research. The African children consumed a traditional rural African diet while the European children consumed a western diet.

Through high throughput 16S rDNA sequencing (a method used to identify bacteria present within a given sample down to the species level) and biochemical analysis, gut microbiome differences were measured. The results displayed a considerable difference in bacterial colonization between the two populations, with the African children having higher microbial richness and biodiversity than the European children (De Filippo et al., 2010). The microbes cannot adapt easily in the gut for the European children since their diet is less rich than the African children. A diet that is considered to be rich is high in nutrients- such as whole grains, fruits, vegetables, and dairy. *Actinobacteria* and *Bacteroidetes* were seen more in the African children than the European children. Similarly, *Firmicutes* and *Proteobacteria* were more prolific in the gut microbiome of the European children versus the African children (De Filippo et al., 2010). The data implies that the European children's high-calorie intake could be the cause of the given bacterial species' higher quantities. This study suggests that diets play a strong role in the diversity and composition of the gut microbiome.

Understanding how the foods we consume create variation in gut bacterial ratios is also crucial to interpret our body's metabolic system. A study was conducted at the FAS Center for Systems Biology in Massachusetts, examining how one's diet can rapidly affect the human gut microbiome. Two different diets were tested, both a plant-based diet and an animal-based diet, consumed over the course of five days by six males and four females. The research discovered that foodborne microbes have the ability to survive as they travel through the digestive system and can become metabolically active within the gut. Specifically with the animal-based diet, they found an overall increase in forms of bacteria present in the fecal cultures (David et al., 2014). With regard to those ingesting the plant diet, RNA transcripts from many plant viruses were detected, indicating that plant pathogens were able to travel into the gut through consumption. Their findings indicated that through the animal-based diet, levels of deoxycholic concentrations were notably increased, which contribute to the introduction of microbial species into the gut as well as microbial metabolism and liver cancer development (David et al., 2014). Their findings showed that conducting more extensive research could establish stronger connections between nutrition and microbial dynamics, leading to a better comprehension of how our diets affect us.

The human gut microbiome plays an essential role in many physiological mechanisms, including nutrition and immune function, host metabolism, and physiology. Disruption of the gut microbiome can lead to significant health issues such as obesity, malnutrition, systematic diseases like diabetes, and chronic inflammatory diseases (Guinane & Cotter, 2013). Researchers have investigated many strategies to understand how modifications occur in the gut microbiome composition. Ghosh et al. (2020) conducted a trial to determine if a Mediterranean diet would change the gut microbiome composition. 612 subjects participated in an intervention where they were profiled before and after their twelve-month trial. The diet focused on ingesting more whole grains, fruits, and legumes in comparison to animal proteins. Their results indicated that dietary adjustments contributed to microbial diversity, decreased debility, and an improvement in cognitive functioning (Ghosh et al., 2020). This study suggests that improving one's diet to regulate the gut microbiome composition can lead to the potential of promoting healthier aging.

Furthermore, it is worth noting that while improving our diet can positively shape our health, some of the crops we commonly eat, such as corn, soybeans, rice, squash, and potatoes, are genetically modified organisms. Bt corn, or Bacillus thuringiensis corn, is one of the most widely cultivated GM crops. This GM product is genetically modified to produce the insecticide Bt toxin. By making this toxin, corn can resist pests, reducing the need for pesticides (Gassman & Reisig, 2023). How much GM food do we consume yearly? To answer this, EWG researchers started with the U.S. Department of Agriculture's 2011 data on per capita consumption of four foods commonly derived from genetically engineered crops: sugar, corn-based sweeteners, salad oil and "corn products." Federal data calculated that an average American consumes genetically engineered foods in large quantities. Data determined that 68 pounds of beet sugar, 58 pounds of corn syrup, 38 pounds of soybean oil and 29 pounds of corn-based products, are consumed yearly, for a total of 193 pounds (Sharp, 2023). Although this number does not include genetically engineered animal feed that people may consume directly from eating proteins or the thousands of other types of genetically modified foods, this number is quite alarming to say the least. This evaluation represents only a small fraction of the overall research on GMO products, as the science of GM products is continuously advancing, requiring further research into the consumption of GMOs.

Importance

It is essential to recognize how the foods we consume can interfere with our health. While using GMOs for crops in developing countries can lead to a population increase, resulting in an increase in food supply and economic benefits for households, their ability to interfere with overall human health must be acknowledged. The Department of Agricultural Economics and Rural Development in Germany conducted a study focusing on GMOs in relation to food security. Since GM crops contribute to increased food production which leads to more accessible food, this can negatively impact food quality and nutrient composition. Four rounds of comprehensive panel data were collected over several years between 2002 and 2008 from farm households in India, where insect-resistant GM cotton has been widely adopted. A multistage sampling procedure was used, with four states selected, namely Maharashtra, Karnataka, Andhra Pradesh, and Tamil Nadu (Qaim & Kouser, 2013). These four states cover a wide variety of different cotton-growing situations, and with that, produce 60% of all cotton in central and southern India. Calorie consumption data was obtained along with regression models to display the relationship between dietary quality and the use of GMOs. Results showed that Bt (GM multiple organism cotton) adoption has significantly increased the consumption of calories from more nutritious foods, thus also contributing to improved dietary quality. The results also state that the income gains through Bt cotton adoption among smallholder farm households in India have positive implications for food security and dietary quality. GM crops are not a universal remedy for the problems of hunger and malnutrition (Qaim & Kouser, 2013). This article demonstrates how GM crops can be beneficial to one's health by producing large quantities of food and making it more accessible.

Moreover, the use of GMOs in developing countries can benefit citizens financially, but the impression on one's health requires more attention. A meta-analysis of 40 studies was conducted at the Department of Agricultural Economics in Belgium to observe the use of GM technology in developing countries. Strategically, Argentina, Brazil, China, and India were used for sampling since they are the largest producers of transgenic products in terms of developing countries. The results displayed that using GM technology improved environmental, social, and economic performance for each country (Azadi et al., 2022). In terms of the human health being modified by GMOs, the National Academies of Science conducted a report in 2016 discussing the effects. Claims regarding human health and safety of GMO foods include increased risks of cancers, kidney disease, obesity, celiac disease, diabetes, and allergies (National Academies of Science, Engineering, and Medicine [NAP], 2016). With this evidence, it is crucial to understand the potential implications of GMOs on the gut microbiome composition to establish a safe and sustainable food supply for the growing population.

Presentation of Research

Historical Development

Genetic engineering has been around for over 50 years, making crops resistant to disease or pests while also making them more productive. This became more of a focus beginning in the 1930s, with the addition of hybrid crops. In the 1940s, plant breeders began using chemicals and radiation to change a given organism's DNA structure. By the 1970s, biochemists had figured out how to insert a portion of bacterial DNA into another bacterium. The first actual GM product was approved in 1982, as a human insulin product to treat diabetes. Four years later, the Coordinated Framework for the Regulation of Biotechnology was created to form regulations for the safety of GMOs. In 1987, the first identified CRISPR- Cas9 came from *Escherichia coli* (bacteria) and *Haloferax mediterranei* (archaea). Since there was a lack of knowledge in DNA sequencing at the time, this method wasn't utilized to edit genes for another eleven years (Ishino et.al, 2018). Eventually, in 1994 the Flavr Savr tomato was created as the first actual GM produce and was deemed safe by the FDA for consumption (Wunderlich & Gatto, 2015). The genetic modification of the tomato allowed it to ripen more gradually, giving it a longer shelf life. Two years after the introduction of Flavr Savr, in 1996, herbicide-resistant soybeans were introduced into the food system to allow farmers to use the widely applicable herbicide glyphosate (Roundup) in fields to kill a wide range of weeds without harming their glyphosate-resistant (Roundup Ready) crops (Wunderlich & Gatto, 2015). Since then, the advantages of bio engineering crops have extended past shelf life and transitioned into also aiding in pest resistance.

The early 2000s allowed for the release of more GM produce. From 1996 to 2014, Bt corn usage grew from just 1% to 80% of US corn acreage, and Bt cotton grew from 15% to 84%. It wasn't until 2005 when the role of CRISPR loci in protecting prokaryotes from foreign genetic material was presented, and the Cas9 enzyme was discovered. As a result, cutting a DNA sequence at a specific genetic location and inserting or deleting DNA sequences became a common approach used in the process of gene modification (Ishino et.al, 2018). Stacked traits, also known as the process of merging two or more genes of interest, account for most of both GE cotton and corn grown in the United States. GE cotton accounts for 96% acreage, 79% of which is stacked trait, and 93% of corn acreage is GE, with 76% of the crops containing stacked traits. In addition to corn, soybeans, and cotton, the United States currently grows GM canola, sugar beets, alfalfa, papaya, and squash. With that, more guidelines and standards have been implemented to regulate overall safety (Wunderlich & Gatto, 2015). It was not until 2015 that the FDA (The Food and Drug Administration) approved genetically modified salmon. This was the first actual genetic modification of an animal for human consumption (FDA, 2022). Since then, crops are still being produced and approved for sale and new techniques are being developed to make these genetic changes in a more efficient way.

Over the years, the increase in the use of GMOs has created a debate among those who justify the integration of GMOs into the food supply and those who fear the increased production of GM products poses health risks. Many argue that GM crops have the potential to help feed the population as their usage increases. Controversies and public concern surrounding GM foods and crops commonly focus on human and environmental safety, labelling and consumer choice, intellectual property rights, ethics, food security, poverty reduction and environmental conservation.

A problematic aspect when discussing genetic modification is the lack of knowledge regarding the risks associated with recombinant technology and how it interacts with pests and herbal resistance. Resistance can evolve whenever selective pressure is strong enough. If these cultivars are planted on a commercial scale, strong selective pressure will occur in that habitat, which could cause the evolution of resistant insects in a few years, nullify the effects of the transgenic crop (Bawa & Anilakumar, 2013). One of the main focuses of GMO crops is to promote protection against herbicide or the pest resistance, with an emphasis on single genes. However, these technologies can present risks to overall food safety, due to occasional unpredictability. It has been explained that genetic modification of food can result in unintended changes in composition (National Academics of Sciences, Engineering, and Medicine [NAP], 2016). While GM crops may provide benefits through herbicide and pest resistance, consideration is necessary when determining risks associated with recombinant technology due to the resistance evolution and dietary protection.

Another issue that has sparked debate pertains to the health risks associated with ingesting genetically modified foods. How organisms are being inserted with genes which will change their gene expression, and how these gene products are affected. In one study done by Butler and Reichhardt (1999), bean plants that were genetically modified to increase cysteine and methionine content were discarded after the discovery that the expressed protein of the transgene was highly allergenic (Butler & Reichhardt, 1999). Since these alterations are products of transgenic methods, any potential risk involving allergenicity and toxicity should be considered. Conner and Jacobs (1999) researched the genetic engineering of crops as a genetic hazard in the human diet. It was concluded the idea of newly expressed enzymes could cause metabolites to diverge from one secondary metabolic pathway to another (Conner & Jacobs, 1999). Incorporating new genes that were not previously in the organism may lead to unexpectable increases or decreases in non-targeted biochemicals. These simple changes in metabolism can lead to an increase in toxic concentrations, therefore secondary and pleiotropic effects should be evaluated.

It is crucial to understand how GMOs can interfere with the human body beyond allergenicity and metabolism. A 2019 review for Food and Chemical Toxicology discussed the effects of the DNA derived from a GMO once it enters our body, which can comprise its integrity. The gastrointestinal tract (GIT) is often the most likely entry route for foreign DNA into the body as it regularly absorbs nutrients. The epithelial cells of the GIT lumen are continuously exposed to foreign dietary DNA, allowing for absorption of harmful genetic materials. As new DNA fragments from external sources of dietary materials are processed within host tissues, the bloodstream, and the GI tract, it can lead to horizontal gene transfer. This mechanism is used by bacteria to cultivate higher concentrations in our bodies (Muhammad et al., 2018). More information is necessary to understand the biological risks associated with the absorption of foreign DNA material and the consequences for the overall integrity of the GIT.

Current Status

The research on how GMOs can create variation within the composition of the gut microbiome in humans is currently in its preliminary stages, and there are not many conclusive findings regarding their overall impression. Currently, a divide exists amongst scientists who believe there are negative effects on gut health and those who have found no significant differences due to GMO consumption. More research is needed to fully understand the overall relationship between consuming GMO products and the composition of the gut microbiome. Although there is a lack in research to demonstrate a direct influential relationship between GMO consumption and the human gut microbiome composition, more recent studies have been identifying the connection between ingesting GMOs and animal health, and how altering one's diet can benefit our microbial diversity. With respect to the gut microbiome composition, new technology has been in the works to promote bacterial health and allow us to edit our genes by being able to target certain bacterial communities. Many studies on how the microbiome affects our health are lacking knowledge on how the microbes interact with each other. This is due to the fact that bacterial species are not easy to culture in the lab, leading to more difficulty in developing gene editing tools for them. Scientists are working on deleting specific genes from specific strains within the gut microbiome which can help assign function to them, resulting in a better conclusion on how these given functions can interfere with our health (Khanna, 2021). These gene editing tools will help us better differentiate what is caused merely by association within microbes while allowing us to alter our gut bacteria into a desired condition.

GMOs

The debate regarding if GMOs can interfere with human health, specifically the gut microbiome, is ongoing. Many studies have suggested that consuming GMO products can lead to variations in the gut microbiome composition. Other studies have indicated that the changes in the composition gut microbiome are insignificant, implying that consumption of GMO products have little to no effect. Information has been on both ends of the spectrum, with some studies emphasizing the extent of the harmful effects and others producing inconclusive or conflicting results, lacking substantial answers. Despite the controversial findings and diverse approaches, research has consistently demonstrated the importance of understanding our consumption and how it can shape the gut microbiome composition.

The aim of developing GMOs has been to improve agricultural productivity, enhance the nutritional benefits of crops, and minimize the use of harmful chemicals. Data has shown that GMO crops have been effective in growing crop yields, which can be beneficial in responding to challenges with food scarcity in some regions along with providing a larger food supply for a growing world population. Along with that, there are some GMO crops that have been created to have resistance to certain pests and harmful diseases, minimizing the use of toxic pesticides and chemicals. A meta-analysis conducted by Pellegrino et al. (2018) discussed the benefits of modifying crops regarding an increase in yield. Genetically modified maize was used as researchers aimed to measure soil biomass decomposition along with overall yield. It was determined that there was an increase in grain yield from 5.6% to 24.5% depending on the hybrid form, with a decrease in toxin concentrations (mycotoxins reducing 28.8%, fumonisin decreasing by 30.6%, and thricotecens decreasing 36.5%). The genetically modified maize had an increase of yield by 10.1%, indicating an improvement through the hybrid genetic modification (Pellegrino et al., 2018). With food demand increasing in a growing population, the use of GMO crops to cultivate higher yields of produce can be beneficial in maintaining the necessary supply. As food demand is on the rise, the use of GM crops to maintain higher yields of products can be beneficial, but it is also crucial to understand the significance of the food you are consuming and how that interferes with the gut microbiome composition.

Research indicates that your diet and lifestyle habits can alter the composition of the gut microbiome. Manor et al. (2020) conducted a study to determine the connections between the composition of the gut microbiome and host factors amongst 3,409 healthy participants. The researchers used 16S amplicon sequencing- a technique used to sequence and analyze the 16S rRNA gene present in bacterial and archaeal genomes. The 16S rRNA gene is highly conserved, but also contains hypervariable regions that can be used to distinguish between different species/strains. For all participants to determine the gut microbiome composition through stool samples. Interestingly, the study found strong evidence of connections between physical activity and microbiome diversity, with more physical activity positively correlating with diversity within the microbiome composition. With that, poor bowel health paired with an increased consumption of sugary drinks both negatively impacted microbiome diversity (Manor et al., 2020). This study suggests that there is a correlation between the host's lifestyle and diet and the overall gut microbiome composition. It also provides insight into the implications of directing approaches in modifying diet habits to improve gut health. Opting for a healthier diet and lifestyle can generate a favorable outcome for the composition of the gut microbiome, ultimately improving overall health and wellbeing.

Many studies that try to determine the relationship between GMOs and the composition of the gut microbiome have been focused on animals, most commonly rats and mice; with less studies conducted on humans. Animal studies can be more mechanistic in nature, allowing us to perform procedures that would be impossible or unethical to perform on humans, and enabling us to control factors like genetics, which are often uncontrollable in human studies, unless identical twins are used. A study done by Carman et al. (2013) focused on a toxicology report on pigs that are being fed a GM soy and corn diet versus the same diet with non-GM ingredients. The research highlighted that pigs in the United States are usually fed a mixed corn and soy diet, containing a high proportion of GM varieties. The results determined that pigs that were fed the GMO diet displayed much more severe stomach inflammation than the pigs on the non-GM diet, with a rate of 32% to 12%, respectively (Carman et al., 2013). These results highlighted the potential effects of GMO in feed for animals and in turn, for humans as well. It also points out the need for further research as humans and pigs do have similar gastrointestinal tracts. Many GMO crops are consumed by humans, posing concern about the outcome being similar (Carman et al., 2013). In order to solidify these claims, equivalent research on human ingestion and outcomes must be completed as pigs and humans are not identical in overall health functioning. This study assists in identifying the potential effects of GMOs on the gut microbiome composition, which in turn can transform overall human health.

However, animal studies do allow researchers to gain a better understanding of potential effects or outcomes in given studies. The College of Food Science and Nutritional Engineering in

China also conducted a study on GI health in rats after consuming genetically modified rice (Bacillus thuringiensis insecticidal toxin (Bt) rice) after 90 days. A safety assessment model was composed measuring sub chronic toxicity along with microflora composition, intestinal permeability, epithelial structure, fecal enzymes, bacterial activity, and intestinal immunity. The methods section of the study provided details on the rice material used, which was genetically modified insect-resistant rice T2A-1, and the animal diets. Rats were either fed a nutritionally complete AIN93G diet (containing all essential nutrients required for rodent growth and maintenance, including amino acids, vitamins, minerals, and energy sources) or a diet containing a maximum of 70% Cry2A rice (a genetically modified rice variety containing a gene from Bacillus thuringiensis) mixed with 70% parent line rice based on the AIN93G diet. Tissue samples were taken (from stomach, duodenum, jejunum, ileum, colon, liver, and kidney), DNA extraction was completed, horizontal gene transfer (using real time PCR along with SYBR green technique), and RNA isolation (Yuan et al., 2013). Significant differences were found between rice-fed groups and AIN93G-fed control groups in several parameters, whereas no differences were observed between genetically modified and non-genetically modified groups. Due to the safety assessment model not displaying differences in rats GI health after consuming GM rice, the same may not be said if testing a human due to physiological differences.

Relying on animal studies to make conclusions about the effects of human GM consumption has been found to lack conclusive findings. Another study done by Mesnage et al. (2019) investigated the physiological effects in rats after consuming MON810 and NK603 (two versions of genetically modified corn) crops over six months. Researchers reviewed the fecal microbiota of the rats ingesting the GM crops in comparison to rats consuming non-GM maize diets

(Mesnage et al., 2019). They also measured the consumption of the Bt toxin and Roundup resistance in addition to these varying diets. Their results determined that there were no differences in the microbiome composition between the two groups of rats, but rather a difference between the male and female rats, which is evidence that there is no effect on ingesting GM diets. It was also found that there was no effect on the microbiome when comparing the consumption of the Bt toxin and Roundup resistance NK603 (glyphosate tolerant corn), suggesting no effect on the microbiome regardless of the contaminants (Mesnage et al., 2019). Results imply that while there was no difference in the microbiome composition amongst rats with a non-GM versus GM based diet, the outcome could be different for humans, due to differing health functions and overall metabolism. While animal studies can provide insight into potential effects, human studies are necessary to accurately identify substantive outcomes of human GMO consumption. Human studies would also provide reliable information that can be used to inform and regulate public health policies related to consuming GMO products. Given the open-ended assumptions and lack of concrete knowledge surrounding GMOs and human health, it is essential to address these discrepancies amongst studies to improve consumer knowledge and uncertainty.

Many people remain skeptical about the safety of GMOs and the lack of consumer knowledge may contribute to this perception. Today, the United States dominates in the production of genetically modified crops, providing 73.1 million hectares of land and producing 40% of the global GMO crops (Wunderlich & Gatto, 2015). Despite such high levels of production and sale, consumer knowledge of GMO products is quite low. A study by the Food Policy Institute discovered that 16% of consumers know nothing about GMOs, 48% said they know little, 30% knew a reasonable amount, and only 5% knew significant information about GMOs (Wunderlich & Gatto, 2015). This could be due to misinformation, unfamiliarity, or the lack of labeling for GM products in the US. Surprisingly, in another study, many participants feared that consuming GM products could alter their own genes or enter their reproductive cells and be passed onto their children (Wunderlich & Gatto, 2015). There is no doubt that these assumptions would lead consumers to avoid purchasing or consuming any GM products as it instills fear and uneasiness and creates a negative perspective towards biotechnology. However, it was found that after reading about the benefits of GMOs, individuals who are more knowledgeable of GMOs are more secure in the benefits of the products and can rationalize the use (Wunderlich & Gatto, 2015). This suggests that more knowledge on GMOs positively correlates with a favorable outlook on GMO products. More recently, a survey of around 1,700 US adults determined that 40% of American consumers avoid consuming GMOs, 71% were worried about GMOs creating health issues, and 48% of consumers want to be completely knowledgeable of what products are in their food (Wunderlich & Gatto, 2015). A major concern in the US in relation to GMO products is the lack of transparency, especially without the requirement of labeling certain products when genetically modified. While GMO products have been around for many years, there still is so much that consumers do not know or understand about them. To potentially increase consumer's confidence in GM products and allow for more sales, there needs to be more public education and transparency. Until labeling is mandated, and the population is educated properly, limited knowledge and misinformation will continue to interfere with perceptions on GM products.

Due to the potential risks to overall human health and the environment, many people avoid consuming GM produce. The validified benefits and safety of consuming GMO products are still a topic of debate amongst professionals and society due to these uncertainties. According to a survey done by Vasquez (2017), of 3,256 participants, many people found that their health conditions had improved after removing GMO products from their diet. It was also discussed that through given methods, GMOs can cause consequences for digestion and overall human health (Vasquez, 2017). These survey results suggest that by removing GMO products from your diet, you can potentially improve your overall health and improve digestion. It is important to acknowledge that while these conclusions were made, it is still possible that varying dietary factors could have also contributed to the improvements in health conditions; eating more organic products and reducing the intake of processed and unhealthy foods were also listed amongst potential reasons for improved health along with removal of GMOs.

It is possible that some GMOs can be more beneficial for our overall health and gut microbiome composition than others. Some GMOs can be designed to improve certain functioning within our body. Others are developed to increase nutritional value content of crops or minimize the need for harmful chemicals or pesticides. Martínez et al. (2013) conducted a cross-over trial to determine if whole grains affect metabolism and if these affects can be beneficial for the gut microbiome. The study consisted of four-week treatments with 28 healthy individuals consuming 60g of whole grain barley, brown rice, or an equal mixture of both daily (Martínez et al., 2013). Researchers collected fecal and blood samples at the beginning and end of each treatment, along with pyrosequencing 16S rRNA gene tags, and inflammatory and metabolic markers. Their results determined that each of these treatments increased microbial diversity, the consumption of whole grains allowed for variations in the gut microbiome composition, and processes for metabolic dysfunction were also improved (Martínez et al., 2013). This information implies that ingesting whole grains can also provide metabolic and immunological benefits for the individual. Interestingly, this trial can also lead to a stronger understanding on whether microbiomes can be altered in obese versus average weight individuals. This study implies that consuming whole grains can have a significant effect on the fecal microbiome composition, while also improving metabolic processes in healthy individuals. Assumptions can be made that the addition of whole grains into your diet can be beneficial for overall health, insinuating the importance or need for specific foods to provide benefits for gut health.

Some believe that the foods we ingest have no influence on our gut health, but studies have been conducted examining the "damage" to our gut microbes- short and long term. Scientists at the University of Pennsylvania analyzed how long-term dietary patterns can be associated with gut microbial enterotypes (clusters of bacterial communities in the gut). Across 98 healthy volunteers, factors including age, genetics, and diet were recorded to observe each individuals differences within the gut microbiome composition. Of these, diet is the only factor with the ability to change and presents the simplest route for therapeutic intervention. The basis for enterotype clustering is unknown but appears independent of nationality, sex, age, or body mass index (BMI). For methods, diet information was collected using two questionnaires that queried recent diet ("Recall") and habitual long-term diet (food frequency questionnaire; "FFQ"). Second, ten individuals were sequestered in a hospital environment in a controlled-feeding study to compare high-fat/low-fiber and low-fat/high-fiber diets (Wu et al., 2011). 16S ribosomal DNA (rDNA) sequencing was used to calculate pairwise UniFrac distances among the microbial communities along with microbiome association. A microbial taxon was created-results showed changes in microbiome composition within 24 hours of the controlled feeding. This means alternative enterotype states are associated with long-term diets (Wu et al., 2011). Although some may believe there is not strong enough evidence of our foods altering gut health, this study highlights the ability of the GI microbiome to be significantly shaped by what we consume.

Furthermore, individuals do not believe that the ratio of gut microbes modify our body mass. The Institute of Health Sciences in Poland aimed to observe the effects of consuming prebiotics and probiotics in relation to the gut microbiome whilst reducing body fat. Obesity is a cause of numerous diseases, because of an unhealthy diet or physical inactivity. The gut microbiome of adult individuals consists mainly of bacteria belonging to two types: Bacteroidetes and Firmicutes. Numerous studies show that the ratio of these bacteria is different in obese compared to normal-weight individuals; however, some studies do not confirm the relationship between the Bacteroidetes/Firmicutes ratio, diet, and body mass index. The study was carried out simultaneously in two centers at the Institute of Public Health of the Jagiellonian University Medical College in Krakow (group A) and the Karol Macknowski Medical University in Poznan (group B) according to identical protocols. After evaluating body weight and health risks of intervention, a qualified dietitian established a weight reduction diet with a fixed caloric intake of 1100–1300 kcal. Results after three months showed a significant decrease in body weight and fat (Jagielski et al., 2023). After having set restrictions on calorie ingestion, it is clear that the ratio of gut microbes is different in a healthier diet individual.

Along with the benefits of ingesting GMOs, another advantage may be that there is no overarching harm in feeding them to animals. The Pig Development Department in Ireland conducted a study to determine the effects of ingesting GM maize for female pigs. Bt maize (a genetically modified form of corn) was fed to the pigs during gestation and lactation on maternal and offspring immunity to observe if there was any result of inflammation or transgenic change. Female pigs were assigned to one of two treatments (n = 12/treatment); 1) non-Bt control maize diet or 2) Bt-MON810 maize diet, which were fed for ∼143 days throughout gestation and lactation. Immune function was assessed by leukocyte phenotyping, hematology, and Cry1Ab-specific antibody presence in blood on days 0, 28 and 110 of gestation and at the end of lactation (Buzoianu et al., 2012). Results showed the blood monocyte count and percentage were higher ($P<0.05$), while granulocyte percentage was lower ($P<0.05$) in Bt maize-fed pigs on day 110 of gestation. Leukocyte count and granulocyte count and percentage were lower ($P<0.05$), while lymphocyte percentage was higher ($P<0.05$) in offspring of Bt maize-fed pigs. Bt maize-fed pigs had a lower percentage of monocytes on day 28 of lactation and of CD4+CD8+ lymphocytes on day 110 of gestation, day 28 of lactation and overall ($P<0.05$), (Buzoianu et al., 2012). This result showed no sign of inflammation, so they concluded that ingesting GMO corn did not cause any "harm". Even though this study was not done on humans and presented no significant findings, these conclusions can still be particularly beneficial when considering the consumption of GMO products.

Other than the foods we eat, genetics can play a large role in the composition of the human gut microbiome. The Department of Molecular Biology & Genetics in New York conducted a study to determine how our genetics help shape the gut microbiome. 1,000 fecal samples were collected from 977 individuals, which included 416 twin pairs. This data subset allowed for the assessment of the genotype's impact overall and on the gut microbiome along with if taxa within the gut are heritable. It was determined that MZ twins had more similar compositions within their microbiome than those of DZ twins (Goodrich et al., 2014). The results indicated that the significant number of specific species in the gut microbiome are partly shaped by the host's genetic makeup. It was also suggested that environmental factors can shape certain microbe communities in the gut, rather than them being heritable. Their findings determined that host genetics can modify the human gut microbiome composition while also affecting the host metabolism. It was also determined that microbial phenotypes are heavily structured by the individual's genetic state, allowing for more understanding of the nature of bacteria and how to use them to promote health (Goodrich et al., 2014). This study provides a stronger understanding of the gut microbiome composition, demonstrating the significance of multiple elements in addition to metabolism.

Improving the Current Status of GMOs with relation to Gut Microbiome

Enhancing the understanding of the possible modifications that GMOs can have on the gut microbiome composition requires further research and the establishment of distinct regulations and guidelines. Currently, the labeling of GM foods is not mandatory in the United States. In 1922, the FDA announced a Statement of Policy that stated GE foods did not require labeling since they were not materially different from nonmodified versions, only material information needed to be included on the label. Under the Federal Food, Drug, and Cosmetic Act, material information includes environmental risks, nutritional content, and usage. In a recent survey completed by 1700 US adults, only 52% of consumers knew what GMOs were. Overall, 40% of consumers report avoiding GMOs in their diets, 71% were concerned about health repercussions, and 48% would like to know exactly what goes into the foods they eat (Wunderlich & Gatto, 2015). By pushing for labeling of GM foods and initiating more regulation, consumers will be more comfortable consuming the foods they eat and will be aware of potential health risks warranted.

It would be important to conduct more studies with humans that can demonstrate the effects of ingesting GM products on the gut microbiome composition. This would allow for stronger correlations between the consumption of GMOs and the human gut microbiome composition rather than relying on animal studies for insight into implications. Human studies can provide valuable insights, but they pose challenges. To accurately establish causality, it is necessary to utilize longitudinal designs and control for numerous host factors such as genetics, co-morbidities, age, sex, and overall lifestyle. Mandatory labeling laws should be implemented as they could include information or any risks towards the human gut microbiome and overall health. The government should also introduce more thorough safety assessments for the GM products, examining long-term risks and possibilities. The government could also consider reviewing patent laws to promote the use of diverse crop varieties, minimizing the health risks. Public awareness campaigns could be used to increase public awareness using social media and education for consumers about GMOs and their impression on human health.

Conclusions & Recommendations

Preliminary studies have determined there may be positive and negative influences on the gut microbiome composition after ingesting GMOs. Identifying which GMOs are safe and promote microbial diversity in contrast to those that are detrimental to the composition of gut microbiome, would allow individuals to make dietary choices that could improve their health. When talking about GMOs, we know that some are more safe or healthier than others. We can conclude that by educating ourselves on which GMO products could be beneficial versus harmful for our gut health, we can help shape our diets to benefit our gut microbiome composition.

More research should be done focusing on humans and GMO consumption in a longitudinal way; to observe ratios of *Bacteroidetes* and *Firmicutes* in relation to systematic and chronic diseases which can be caused over time rather than focusing on shorter periods of time. Studies are needed to understand the long-term effects of consuming GMOs on the human gut microbiome. With this, the research should involve wider and more diverse human populations along with an examination of the effects of specific types of GMOs. It would also be beneficial to determine the certain mechanisms that GMOs use to modify the gut microbiome composition through more comprehensive safety assessments of GM products. It would also be advantageous to improve on GMO transparency. Consumers need to have access to information regarding the GMOs that they may be consuming. Those that are producing GMO crops and products should be direct about the forms of modifications that are being made to their products while also providing information about any possible effects they may have on the gut microbiome and overall human health. Governments and policy makers should also implement labeling requirements for GMO products to allow consumers to be knowledgeable about what products they are purchasing, including information regarding the modification types and potential outcomes. Ultimately, diverse diets should be encouraged, including a variety of fruits, vegetables, whole grains, and legumes to promote a healthy gut microbiome.

An additional policy change would be increasing awareness of what the gut microbiome truly is. It would be essential to increase public knowledge on how the gut microbiome can interfere with our health and immunity based on the studies that have been done on diets and its relationship with the microbiome composition. By promoting consumers to eat a diverse diet, it can help minimize possible impacts of GMOs on the gut microbiome and overall health.

With GMO technologies constantly being improved and advanced, there could be new developments to make GMO products safer and healthier, adjusting negative aspects along the way. At the rate that these technologies have changed, this process could be improved in the direction that it needs to, to benefit the greater population. With that, targeted gene editing techniques could be developed, to modify single genes without the addition of foreign DNA, reducing potential risks. The development of organic GMOs could also be promoted using sustainable farming practices and reducing the use of pesticides and herbicides. Organic GMOs can also be specifically designed to have limited effects on the human gut microbiome. There are many foods that are a result of genetic modification that we all consume today. It would be highly advantageous to have more research and data highlighting what certain GMO products can do to our gut microbiome composition and overall health; both positively and negatively.

If we continue the use of GMOs, we can consider the need for some GMOs to be healthier and safer, and with that, we can produce foods that contain more nutritional value in a safe way. With this, it can also be more cost effective and quicker to feed the greater population, and in turn, help feed billions of people.

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