EXCLI Journal 2021;20:1091-1095 – ISSN 1611-2156
Received: May 20, 2021, accepted: June 02, 2021, published: June 09, 2021

Letter to the editor:

PLANT POLYPHENOLS EFFECT ON GUT MICROBIOTA: RECENT ADVANCEMENTS IN CLINICAL TRIALS

Ayshwarya Lakshmi Chelakkot[#], Cijo George Vazhappilly[1]*

[1] Department of Biotechnology, American University of Ras Al Khaimah, Ras Al Khaimah, United Arab Emirates
[#] independent scholar

* **Corresponding author:** Cijo George Vazhappilly, Department of Biotechnology, American University of Ras Al Khaimah, Ras Al Khaimah, 10021, UAE, Tel.: +971-7-246-8842, E-mail: cijo.vazhappilly@aurak.ac.ae

http://dx.doi.org/10.17179/excli2021-3900

Dear Editor,

The diverse microbial community present in the human intestine plays a vital role in translating the food to nutrients and metabolites essential for maintaining host physiology, including digestion, lipid and glucose metabolism, immune homeostasis, and proper development of the brain and cognitive functions (Klinder et al., 2016; Park et al., 2020). Altering the gut microbiota through dietary interventions for the prevention or treatment of disorders might lead to developing a novel concept called 'personalized nutrition' and help better understand the effects of dietary bioactive compounds on the host microbiome.

Recent research and clinical trials have identified the beneficial effects of a plant-based diet to increase bacterial diversity and ameliorate various disorders, including intestinal disorders, obesity-related endotoxemia, and cardiovascular disorders (Vazhappilly et al., 2019, 2021; Guglielmetti et al., 2020). Fruits and berries are rich in polyphenols and modulate gut microbiota by increasing the global fecal bacteria (Klinder et al., 2016; Moreno-Indias et al., 2016; Teixeira et al., 2017; Ntemiri et al., 2020; Rahman et al., 2021). For instance, in obese and overweight people, a change in the gut microbiota, with a consequent decrease in endotoxemia, through probable modulation of the *Faecalibacterium*, *Odoribacter*, and *Parvimonas*, was noted on consuming pomegranate extract (González-Sarrías et al., 2018). Consumption of two SunGold kiwi fruits per day increased plasma vitamin C and fasting glucose significantly, decreased HbA1c levels, and improved cardiovascular and metabolic markers (Wilson et al., 2018). Modulation of gut microbiota using red wine also showed protective effects on obesity-related metabolic disorders (Moreno-Indias et al., 2016). The polyphenols in cocoa powder and green tea, especially flavanols epicatechin and catechin, are metabolized by the microbiota with increased bioavailability and similar protective outcomes (Janssens et al., 2016; Gómez-Juaristi et al., 2019; Ángel García-Merino et al., 2020; Vilela et al., 2020). A deeper understanding of the correlation between dietary metabolites and gut microbiota is, therefore, essential to attain beneficial effects of modulating host-microbiome under disease conditions. The below table summarizes the recent clinical findings on the relation between various dietary polyphenols and gut microbiota.

Table1: Correlation between plant polyphenols and gut microbiota

Key Findings	Reference
Though endowed with properties of tumor cell suppression due to its antioxidant and anti-inflammatory actions, curcumin is poorly absorbed when administered orally and consequently less effective. APG-157, a botanical drug containing curcumin among other polyphenols, on the other hand, is absorbed well and is reported to be potentially beneficial when combined with immunotherapy by reducing inflammation and increasing T cell concentration in the tumor.	Basak et al., 2020
A diet naturally rich in polyphenols and/or long-chain n-3 polyunsaturated fatty acids (LCn3) increased the diversity of the predominant fecal bacteria; the polyphenols increased *Clostridium leptum* (clostridial cluster IV), which was directly associated with good glucose tolerance, by early secretion of insulin. The study also alluded to an improvement of the cardiometabolic risk profile.	Vetrani et al., 2020
In an *in vitro* colon system study, polyphenol-rich fractions of blueberry (BB) containing anthocyanins/flavonol glycosides (ANTH/FLAV), proanthocyanidins (PACs), sugar/acid fraction (S/A), and total polyphenols (TPP) were found to have a distinct effect on fecal microbiota composition. Effective promotion of microbiome alpha diversity was observed with ANTH/FLAV and PAC fractions as opposed to the S/A and TPP fractions, which has been attributed to the differentially responsive taxa. Older compared to the younger group showed an abundance of gut microbiota diversity with BB consumption, which correlated with increased antioxidant activity of blood.	Ntemiri et al., 2020
Flavonoid-rich (FR) orange juice treatment, in contrast to Flavonoid Low (FL) treatment, resulted in an abundance of *Lachnospiraceae* family, namely, Lachnospiraceae_uc, Eubacterium_g4, Roseburia_uc, Coprococcus_g_uc, Agathobacter_uc, and showed a positive correlation with brain-derived neurotrophic factor (BDNF). Treatment with flavonoids also improved depression in young adults, probably due to an alteration in the stool microbiome.	Park et al., 2020
A randomized, double-blinded, crossover clinical trial, comparing urinary excretion of isoflavones and their metabolites, after soybean meal (SBM) and fermented soybean meal (FSBM) consumption, suggested a benefit for FSBM, in terms of higher excretion of all metabolites, a higher (67 %) urinary recovery of isoflavones, and prevalence of O-demethylangolensin-producer metabotype (72 %), while that of equol-producer was similar (11 %), and non-producer was low (17 %). The results suggested an improvement in the bioavailability of isoflavones and a reduction in the impact of gut microbiota on its metabolism following fermentation.	de Oliveira Silva et al., 2020
A crossover interventional trial studying the impact of increased intestinal permeability on the bioavailability of polyphenols showed a significant difference in the urinary levels of phase II and microbiota-derived metabolites in subjects with healthier barrier integrity and those with disrupted integrity. The disturbance in the gut microbial metabolism and phase II methylation process and the microbiota-derived metabolites were found to be responsible for the biological activity of dietary polyphenols against age-related intestinal permeability disruption.	Hidalgo-Liberona et al., 2020
A study comparing the efficacy of green tea and its extract epigallocatechin-3-gallate (EGCG) as an antimicrobial in mouthwash in children showed a significant reduction in the mutants *streptococci* and *lactobacilli* in the oral cavity after rinsing with EGCG solution. Even though ECGC showed a better antimicrobial activity, both EGCG and green tea were found to be alternatives for chlorhexidine-based mouthwashes.	Vilela et al., 2020

Key Findings	Reference
An improved insulin sensitivity consequent to an increase in the phosphorylation of adenosine monophosphate protein kinase in skeletal muscle of obese subjects was observed with consumption of genistein for two months. The improvement in insulin sensitivity is also attributed to an increase in *Akkermansia muciniphila*, following a decrease in gut microbiota dysbiosis and metabolic endotoxemia, following genistein treatment.	Guevara-Cruz et al., 2020
A placebo-controlled interventional study in athletes elucidated a beneficiary effect for daily intake of 5 g of cocoa (425 mg of flavanols), with significant reduction of body fat percentage, especially in trunk, viscera, and lower limbs, associated with an elevation of plasma follistatin and decrease in leptin, while the myostatin levels remained static. Despite the reduction in body fat, the performance status of these athletes remained status quo.	Ángel García-Merino et al., 2020
Daily consumption of orange juice showed improvement in the blood biochemical parameters like low-density lipoprotein-cholesterol, insulin sensitivity, and glucose in young women. It also showed a positive and beneficial change in the composition and metabolic activity of the microbiota and an increase in the population of fecal *Bifidobacterium spp*. and *Lactobacillus spp*. A PCR-DGGE of the microbiota found the composition of total bacteria to be similar. A reduction in ammonia and an increase in the production of SCFAs were also elucidated. The study implies a positive effect on the daily consumption of orange juice in young women.	Lima et al., 2019
Effect of olive pomace-enriched biscuit formulation (OEP), which delivers 17.1 ± 4.01 mg/100 g of hydroxytyrosol and its derivative on analysis, showed an up-regulation of the microbial polyphenol biotransformation in the intestine, as evidenced by a significant increase in the excretion of small phenolic acids in urine. OEP also significantly elevated homovanillic acid and 3,4-dihydroxy-phenylacetic acid (DOPAC) in fasted plasma samples, indicating clearance of these compounds from blood and an extended-release and uptake from the intestine. However, the study failed to show any change in ox-LDL or urinary isoprostane.	Conterno et al., 2019
A study on the targets of curcumin natural polyphenols on non-alcoholic fatty liver disease (NAFLD) was found to be amino acids, TCA cycle, bile acids, and gut microbiota. Phospholipid curcumin supplement led to a significant reduction in 3-methyl-2-oxovaleric acid, 3-hydroxyisobutyrate, kynurenine, succinate, citrate, α-ketoglutarate, methylamine, trimethylamine, hippurate, indoxyl sulfate, chenodeoxycholic acid, taurocholic acid, and lithocholic acid.	Chashmniam et al., 2019
Dietary intervention with functional foods in patients with type 2 diabetes (T2D) who exhibit intestinal dysbiosis, characterized by an increase in *Prevotella copri*, showed a reduction *P. cori* and increased species with anti-inflammatory effects, namely, *Faecalibacterium prausnitzii* and *Akkermansia muciniphilia*. A significant reduction in AUC for glucose, total and LDL cholesterol, FFAs, HbA1c, triglyceride, and CRP, as well as an increase in antioxidant activity, was also observed. The study concludes on a beneficial effect on fecal microbiota, pointing to novel avenues for improving glycemic control, dyslipidemia, and inflammation with long-term adherence to high-fiber, polyphenol-enriched, vegetable-protein-based diet.	Medina-Vera et al., 2019
A significant increase in the flow-mediated dilation (FMD) was observed with consumption of Aronia (*Aronia melanocarpa*) whole fruit and extract powder for 12 weeks, with an increase in the circulating polyphenols. Though there was no change in the gut microbiota diversity, an increase in Anaerostipes was observed with consumption of Aronia extract, while the whole fruit consumption led to a significant increase in Bacteroids. In healthy men, Aronia consumption resulted in improved endothelial function and modulated gut microbiota composition, indicating a potential benefit for maintaining cardiovascular health.	Istas et al., 2019

Acknowledgment

The authors thank the American University of Ras Al Khaimah for the support and facilities provided.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

Ángel García-Merino J, Moreno-Pérez D, De Lucas B, Montalvo-Lominchar MG, Muñoz E, Sánchez L, et al., Chronic flavanol-rich cocoa powder supplementation reduces body fat mass in endurance athletes by modifying the follistatin/myostatin ratio and leptin levels. Food Funct. 2020;11:3441–50.

Basak SK, Bera A, Yoon AJ, Morselli M, Jeong C, Tosevska A, et al. A randomized, phase 1, placebo-controlled trial of APG-157 in oral cancer demonstrates systemic absorption and an inhibitory effect on cytokines and tumor-associated microbes. Cancer. 2020;126:1668–82.

Chashmniam S, Mirhafez SR, Dehabeh M, Hariri M, Azimi Nezhad M, Nobakht M. Gh BF. A pilot study of the effect of phospholipid curcumin on serum metabolomic profile in patients with non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled trial. Eur J Clin Nutr. 2019;73: 1224–35.

Conterno L, Martinelli F, Tamburini M, Fava F, Mancini A, Sordo M, et al. Measuring the impact of olive pomace enriched biscuits on the gut microbiota and its metabolic activity in mildly hypercholesterolaemic subjects. Eur J Nutr. 2019;58: 63–81.

de Oliveira Silva F, Lemos TCC, Sandôra D, Monteiro M, Perrone D. Fermentation of soybean meal improves isoflavone metabolism after soy biscuit consumption by adults. J Sci Food Agric. 2020;100:2991–8.

Gómez-Juaristi M, Sarria B, Martínez-López S, Clemente LB, Mateos R. Flavanol bioavailability in two cocoa products with different phenolic content. A comparative study in humans. Nutrients. 2019;11:1–19.

González-Sarrías A, Romo-Vaquero M, García-Villalba R, Cortés-Martín A, Selma MV, Espín JC. The endotoxemia marker lipopolysaccharide-binding protein is reduced in overweight-obese subjects consuming pomegranate extract by modulating the gut microbiota: A randomized clinical trial. Mol Nutr Food Res. 2018;62:1–32.

Guevara-Cruz M, Godinez-Salas ET, Sanchez-Tapia M, Torres-Villalobos G, Pichardo-Ontiveros E, Guizar-Heredia R, et al. Genistein stimulates insulin sensitivity through gut microbiota reshaping and skeletal muscle AMPK activation in obese subjects. BMJ Open Diabetes Res Care. 2020;8:1–9.

Guglielmetti S, Bernardi S, Del Bo' C, Cherubini A, Porrini M, Gargari G, et al., Effect of a polyphenol-rich dietary pattern on intestinal permeability and gut and blood microbiomics in older subjects: Study protocol of the MaPLE randomised controlled trial. BMC Geriatr. 2020;20:1–10.

Hidalgo-Liberona N, González-Domínguez R, Vegas E, Riso P, Del Bo C, Bernardi S, et al. Increased intestinal permeability in older subjects impacts the beneficial effects of dietary polyphenols by modulating their bioavailability. J Agric Food Chem. 2020;68: 12476–84.

Istas G, Wood E, Le Sayec M, Rawlings C, Yoon J, Dandavate V, et al. Effects of aronia berry (poly)-phenols on vascular function and gut microbiota: A double-blind randomized controlled trial in adult men. Am J Clin Nutr. 2019;110:316–29.

Janssens PLHR, Penders J, Hursel R, Budding AE, Savelkoul PHM, Westerterp-Plantenga MS. Long-term green tea supplementation does not change the human gut microbiota. PLoS One. 2016;11:1–15.

Klinder A, Shen Q, Heppel S, Lovegrove JA, Rowland I, Tuohy KM. Impact of increasing fruit and vegetables and flavonoid intake on the human gut microbiota. Food Funct. 2016;7:1788–96.

Lima ACD, Cecatti C, Fidélix MP, Adorno MAT, Sakamoto IK, Cesar TB, et al. Effect of daily consumption of orange juice on the levels of blood glucose, lipids, and gut microbiota metabolites: controlled clinical trials. J Med Food. 2019;22:202–10.

Medina-Vera I, Sanchez-Tapia M, Noriega-López L, Granados-Portillo O, Guevara-Cruz M, Flores-López A, et al. A dietary intervention with functional foods reduces metabolic endotoxaemia and attenuates biochemical abnormalities by modifying faecal microbiota in people with type 2 diabetes. Diabetes Metab. 2019;45:122–31.

Moreno-Indias I, Sánchez-Alcoholado L, Pérez-Martínez P, Andrés-Lacueva C, Cardona F, Tinahones F, et al., Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients. Food Funct. 2016;7:1775–87.

Ntemiri A, Ghosh TS, Gheller ME, Tran TTT, Blum JE, Pellanda P, et al., Whole blueberry and isolated polyphenol-rich fractions modulate specific gut microbes in an in vitro colon model and in a pilot study in human consumers. Nutrients. 2020;12:1–21.

Park M, Choi J, Lee HJ. Flavonoid-rich orange juice intake and altered gut microbiome in young adults with depressive symptom: A randomized controlled study. Nutrients. 2020;12:1–16.

Rahman S, Mathew S, Nair P, Ramadan WS, Vazhappilly CG. Health benefits of cyanidin-3-glucoside as a potent modulator of Nrf2-mediated oxidative stress. Inflammopharmacology. 2021; eoub ahead of print. https://doi.org/10.1007/s10787-021-00799-7.

Teixeira LL, Costa GR, Dörr FA, Ong TP, Pinto E, Lajolo FM, et al., Potential antiproliferative activity of polyphenol metabolites against human breast cancer cells and their urine excretion pattern in healthy subjects following acute intake of a polyphenol-rich juice of grumixama (Eugenia brasiliensis Lam.). Food Funct. 2017;8:2266–74.

Vazhappilly CG, Ansari SA, Al-Jaleeli R, Al-Azawi AM, Ramadan WS, Menon V, et al., Role of flavonoids in thrombotic, cardiovascular, and inflammatory diseases. Inflammopharmacology. 2019;27:863–9.

Vazhappilly CG, Amararathna M, Cyril AC, Linger R, Matar R, Merheb M, et al., Current methodologies to refine bioavailability, delivery, and therapeutic efficacy of plant flavonoids in cancer treatment. J Nutr Biochem. 2021;94:108623.

Vetrani C, Maukonen J, Bozzetto L, Della Pepa G, Vitale M, Costabile G, et al. Diets naturally rich in polyphenols and/or long-chain n-3 polyunsaturated fatty acids differently affect microbiota composition in high-cardiometabolic-risk individuals. Acta Diabetol. 2020;57:853–60.

Vilela MM, Salvador SL, Teixeira IGL, Del Arco MCG, De Rossi A. Efficacy of green tea and its extract, epigallocatechin-3-gallate, in the reduction of cariogenic microbiota in children: A randomized clinical trial. Arch Oral Biol. 2020;114:104727.

Wilson R, Willis J, Gearry RB, Hughes A, Lawley B, Skidmore P, et al., Sungold kiwifruit supplementation of individuals with prediabetes alters gut microbiota and improves vitamin C status, anthropometric and clinical markers. Nutrients. 2018;10(7):895.