amare GBX FIT™

WORLD'S FIRST QUADBIOTIC
FOR WEIGHT LOSS

amare®

TECHNICAL DATA SHEET

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GBX FIT™

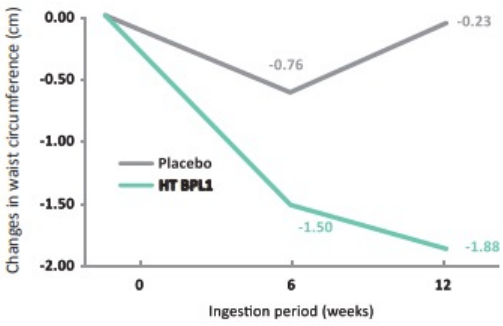
The world's first QUADbiotic formula in a convenient & cool purple pill that targets the gut microbiome for healthy weight loss.

KEY INGREDIENTS

Bifidobacterium Lactis: 1. (Postbiotics HT BPL1) – HT-BPL1 is a vegan heat treated postbiotic, scientifically proven to aid in weight management and support metabolic health. Studies have shown this powerful ingredient reduces visceral fat and cholesterol levels, whilst containing strong anti-inflammatory properties.

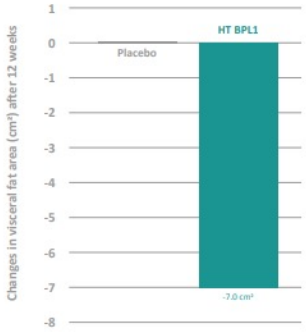
In a human clinical study of abdominally obese men and women, HT BPL1 resulted in a **significant decrease of waist circumference** compared to the placebo after **ONLY** 12 weeks.[5]

39% of study subjects in the HT BPL1 intervention group experienced a decreased waist circumference of 2cm or more at 12 weeks.[6]



After **ONLY** 12 weeks, subjects in the HT BPL1 intervention group showed a significant reduction in abdominal visceral fat area, compared to baseline.

Overall, 55% of participants taking HT BPL1 saw a reduction in visceral fat area.[6]



Studies show (as seen below) that certain probiotics that are dead also carry nutrients that carry health benefits – in this case weight loss/management. Based on the clinical studies, after 3 months of use, subjects who received BPL1 experienced significant reductions in waist circumference and abdominal visceral fat compared to placebo. Waist reductions of 1.75cm and 1.9cm were seen in the heat killed BPL1. There is a synergistic effect when combining functional fibers like Invavea with BPL1 where there was a 35% reduction in visceral fat, as compared to declines of 18.7% and 12.7% which is 3.5lbs per 10lbs of visceral fat. (Which is why we use this fiber in combination with BPL1 as discussed below and Sunfiber, Bimuno, Isofiber in other Amare products.)

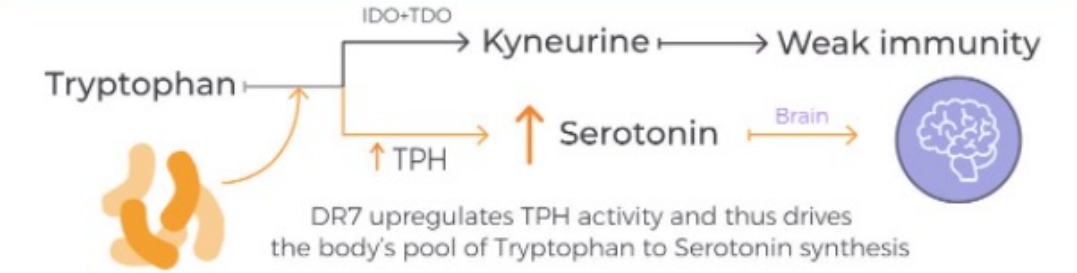
Lactobacillus Plantarum DR7 – A Probiotic that works via the gut-brain axis and is shown to optimize the serotonin pathway and gut modulation where it influences the norepinephrine pathway with increased dopamine levels. The importance of tryptophan-serotonin modulation could be one of several mechanisms involved demonstrating that DR7 lowers symptoms of stress and anxiety, as well as biomarker cortisol.

DR7 & Stress - Benefits on the human body

- **Stress** is a feeling of emotional or physical tension caused by an existing stress-causing factor.
- **Anxiety** is stress that continues after the stressor is gone.

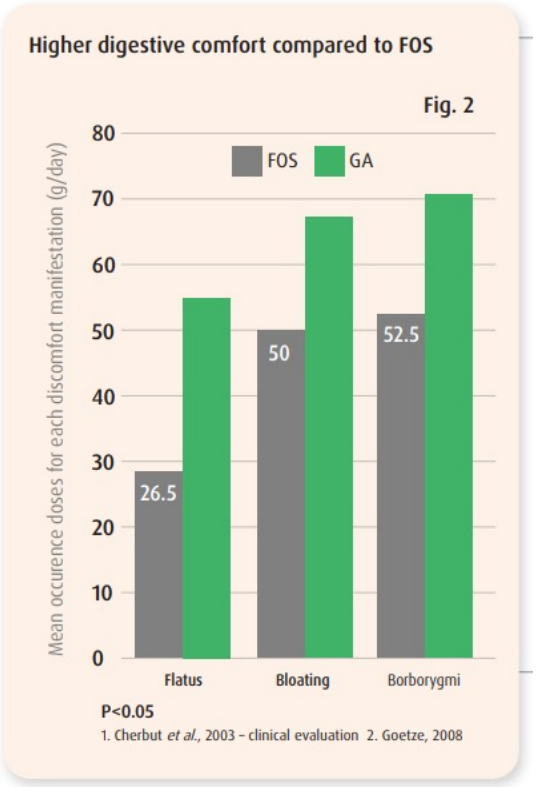
Chronic stress puts you at risk for health problems:

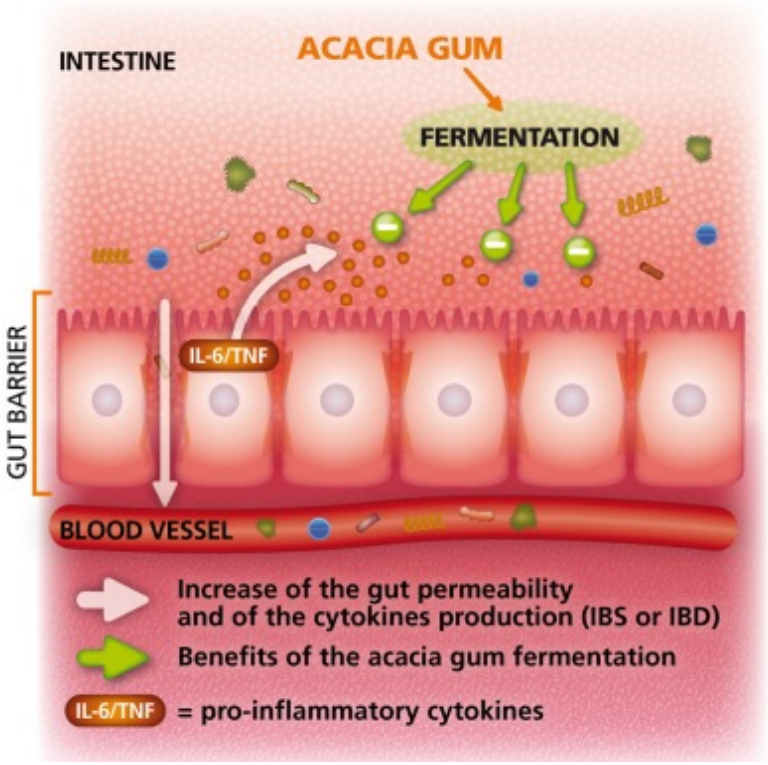
- Hypertension
- Heart disease
- Diabetes
- Obesity
- Depression
- Skin problems
- Menstrual problems



Acacia Gum – is an all-natural, organic and GMO-free prebiotic ingredient sourced from carefully selected acacia trees in Africa. It offers a unique sustainable commitment and delivers fiber enrichment that helps foster the flourishing of probiotics in the microbiome. This an ideal clean label ingredient for fiber fortification and prebiotic claims. Prebiotic effect of acacia fiber has been largely demonstrated for 40 years in more than 40 studies that have shown profound synergistic effects with specific bacterial strains, like the above BPL1. It is FODMAP friendly, and has a carbon neutral footprint. Previous studies have demonstrated that inavea helps to restore the gut barrier and improve gut diversity through the mechanism of providing probiotics fuel. (prebiotics feed probiotics)

Rich in soluble fiber, acacia fiber is sourced from the sap of the Acacia Senegal tree, a plant native to parts of Africa, Pakistan, and India. Also known as gum arabic and acacia fiber, acacia gum is also a prebiotic that can stimulate the growth of beneficial bacteria in the intestines. It is also associated in studies to increase satiety and lowering peak blood glucose response in healthy human subjects.

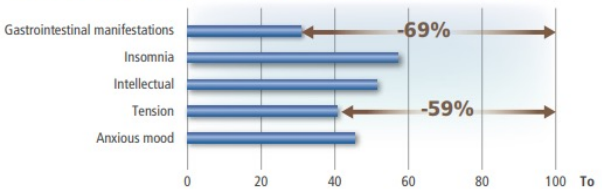


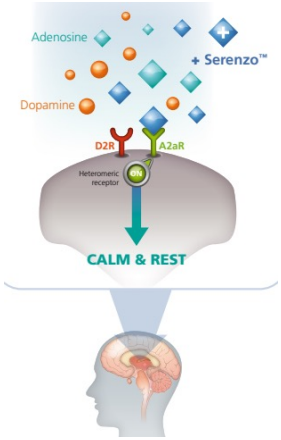


The sourcing of our acacia gum has been increasingly more sustainable for over 50 years in France. We have been recognized in France with NGO, SOS SAHEL, and the preservation of acacia forests for the environment.

Sweet Orange Peel Extract – This organic sweet orange peel (Citrus sinensis (L.) Osbeck) extract sourced from Costa Rica contains beneficial compounds derived from plant sources called Phytobiotics. This specific compound regulates stress through the dopamine and adenosine pathways. This ingredient is shown to reduce by 50% the feelings of stress, 53% of global stress and inhibits the stress response receptors in human beings. With stress being the #1 factor in cortisol and obesity, modulating these pathways is a key contributor to overall mental wellness and weight management.

- **Significant reduction of subjective feeling of stress** as demonstrated by the HAM-A questionnaire:





CLINICAL STUDIES

Lipoteichoic acid from Bifidobacterium animalis subsp. lactis BPL1: a novel postbiotic that reduces fat deposition via IGF-1 pathway

Ferran Balaguer,María Enrique,Silvia Llopis,Marta Barrena,Verónica Navarro,Beatriz Álvarez,Empar Chenoll,Daniel Ramón,Marta Tortajada,Patricia Martorell

First published: 23 February 2021 https://doi.org/10.1111/1751-7915.13769Citations: 2

Summary

Obesity and its related metabolic disorders, such as diabetes and cardiovascular disease, are major risk factors for morbidity and mortality in the world population. In this context, supplementation with the probiotic strain Bifidobacterium animalis subsp. lactis BPL1 (CECT8145) has been shown to ameliorate obesity biomarkers. Analyzing the basis of this observation and using the pre-clinical model Caenorhabditis elegans, we have found that lipoteichoic acid (LTA) of BPL1 is responsible for its fat-reducing properties and that this attribute is preserved under hyperglycaemic conditions. This fat-reducing capacity of both BPL1 and LTA-BPL1 is abolished under glucose restriction, as a result of changes in LTA chemical composition. Moreover, we have demonstrated that LTA exerts this function through the IGF-1 pathway, as does BPL1 strain. These results open the possibility of using LTA as a novel postbiotic, whose beneficial properties can be applied therapeutically and/or preventively in metabolic syndrome and diabetes-related disorders.

An Infant Milk Formula Supplemented with Heat-Treated Probiotic Bifidobacterium animalis subsp. lactis CECT 8145, Reduces Fat Deposition in C. elegans and Augments Acetate and Lactate in a Fermented Infant Slurry

by Ángela Silva 1,†,Nuria Gonzalez 1,†,Ana Terrén 2,Antonio García 2,3,4,Juan Francisco Martinez-Blanch 5,Vanessa Illescas 5,Javier Morales 6,Marcos Maroto 2,Salvador Genovés 1,Daniel Ramón 1,5,Patricia Martorell 1 andEmpar Chenoll 1,5,*ORCID

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Abstract

Pediatric obesity has a growing health and socio-economical impact due to cardiovascular and metabolic complications in adult life. Some recent studies suggest that live or heat-treated probiotics have beneficial effects in preventing fat deposition and obesity in preclinical and clinical sets. Here, we have explored the effects of heat-treated probiotic Bifidobacterium animalis subsp. lactis CECT 8145 (HT-BPL1), added as a supplement on an infant milk formula (HT-BPL1-IN), on Caenorhabditis elegans fat deposition and short-chain fatty acids (SCFAs) and lactate, using fermented baby fecal slurries. We have found that HT-BPL1-IN significantly reduced fat deposition in C. elegans, at the time it drastically augmented the generation of some SCFAs, particulary acetate and organic acid lactate. Data suggest that heat-treated BPL1 maintains its functional activities when added to an infant powder milk formula.

Lactobacillus plantarum DR7 alleviates stress and anxiety in adults: a randomized, double-blind, placebo-controlled study

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Received: 12 October 2018 / Accepted: 28 December 2018

Abstract

Probiotics have been reported to exert beneficial effects along the gut-brain axis. This randomised, double-blind
and placebo-controlled human study aimed to evaluate such properties of Lactobacillus plantarum DR7 and its
accompanying mechanisms in stressed adults. One hundred and eleven (n=111; DR7 n=56, placebo n=55) stressed
adults were recruited based on moderate stress levels using the PSS-10 questionnaire. The consumption of DR7
(1×109 cfu/day) for 12 weeks reduced symptoms of stress (P=0.024), anxiety (P=0.001), and total psychological scores (P=0.022) as early as 8 weeks among stressed adults compared to the placebo group as assessed by the DASS-42 questionnaire. Plasma cortisol level was reduced among DR7 subjects as compared to the placebo, accompanied by reduced plasma pro-inflammatory cytokines, such as interferon-□ and transforming growth factor-□ and increased plasma anti-inflammatory cytokines, such as interleukin 10 (P<0.05). DR7 better improved cognitive and memory functions in normal adults (>30 years old), such as basic attention, emotional cognition, and associate learning (P<0.05), as compared to the placebo and young adults (<30 years old). The administration of DR7 enhanced the serotonin pathway, as observed by lowered expressions of plasma dopamine □-hydroxylase (DBH), tyrosine hydroxylase (TH), indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase accompanied by increased expressions of tryptophan hydroxylase-2 and 5-hydroxytryptamine receptor-6, while stabilising the dopamine pathway as observed via stabilized expressions of TH and DBH over 12 weeks as compared to the placebo (P<0.05). Our results indicated that DR7 fulfil the requirement of a probiotic strain as per recommendation of FAO/WHO and could be applicable as a natural strategy to improve psychological functions, cognitive health and memory in stressed adults.

Lactobacillus plantarum DR7 Modulated Bowel Movement and Gut Microbiota Associated with Dopamine and Serotonin Pathways in Stressed Adults

Guoxia Liu 1, Hui-Xian Chong 2, Fiona Yi-Li Chung 2, Yin Li 1, Min-Tze Liong 2
Affiliations expand
PMID: 32610495 PMCID: PMC7370301 DOI: 10.3390/ijms21134608
Free PMC article

Abstract

We have previously reported that the administration of Lactobacillus plantarum DR7 for 12 weeks reduced stress and anxiety in stressed adults as compared to the placebo group, in association with changes along the brain neurotransmitters pathways of serotonin and dopamine-norepinephrine. We now aim to evaluate the effects of DR7 on gut functions, gut microbiota compositional changes, and determine the correlations between microbiota changes and the pathways of brain neurotransmitters. The administration of DR7 prevented an increase of defecation frequency over 12 weeks as compared to the placebo ($p = 0.044$), modulating the increase of stress-induced bowel movement. Over 12 weeks, alpha diversity of gut microbiota was higher in DR7 than the placebo group across class ($p = 0.005$) and order ($p = 0.018$) levels, while beta diversity differed between groups at class and order levels ($p < 0.001$). Differences in specific bacterial groups were identified, showing consistency at different taxonomic levels that survived multiplicity correction, along the phyla of Bacteroides and Firmicutes and along the classes of Deltaproteobacteria and Actinobacteria. Bacteroidetes, Bacteroidia, and Bacteroidales which were reduced in abundance in the placebo group showed opposing correlation with gene expression of dopamine beta hydrolase (DBH, dopamine pathway; $p < 0.001$), while Bacteroidia and Bacteroidales showed correlation with tryptophan hydroxylase-II (TPH2, serotonin pathway; $p = 0.001$). A correlation was observed between DBH and Firmicutes ($p = 0.002$), Clostridia ($p < 0.001$), Clostridiales ($p = 0.001$), Blautia ($p < 0.001$), and Romboutsia ($p < 0.001$), which were increased in abundance in the placebo group. Blautia was also associated with TDO ($p = 0.001$), whereas Romboutsia had an opposing correlation with TPH2 ($p < 0.001$). Deltaproteobacteria and Desulfovibrionales which were decreased in abundance in the placebo group showed opposing correlation with DBH ($p = 0.001$), whereas Bilophila was associated with TPH2 ($p = 0.001$). Our present data showed that physiological changes induced by L. plantarum DR7 could be associated with changes in specific taxa of the gut microbiota along the serotonin and dopamine pathways.

Lactobacillus plantarum DR7 improved brain health in aging rats via the serotonin, inflammatory and apoptosis pathways

Authors: Zaydi, A.I. 1 ; Lew, L.-C. 1 ; Hor, Y.-Y. 1 ; Jaafar, M.H. 1 ; Chuah, L.-O. 1 ; Yap, K.-P. 2 ; Azlan, A. 3 ; Azzam, G. 3 ; Liong, M.-T. 1 ;
Source: Beneficial Microbes, Volume 11, Number 8, 2 December 2020, pp. 753-766(14)
Publisher: Wageningen Academic Publishers
DOI: https://doi.org/10.3920/BM2019.0200

Aging processes affect the brain in many ways, ranging from cellular to functional levels which lead to cognitive decline and increased oxidative stress. The aim of this study was to investigate the potentials of Lactobacillus plantarum DR7 on brain health including cognitive and memory functions during aging and the impacts of high fat diet during a 12-week period. Male Sprague-Dawley rats were separated into six groups: (1) young animals on normal diet (ND, (2) young

animals on a high fat diet (HFD), (3) aged animals on ND, (4) aged animals on HFD, (5) aged animals on HFD and L. plantarum DR7 (109 cfu/day) and (6) aged animals receiving HFD and lovastatin. To induce ageing, all rats in group 3 to 6 were injected sub-cutaneously at 600 mg/kg/day of D-galactose daily. The administration of DR7 has reduced anxiety accompanied by enhanced memory during behavioural assessments in aged-HFD rats ($P<0.05$). Hippocampal concentration of all three pro-inflammatory cytokines were increased during aging but reduced upon administration of both statin and DR7. Expressions of hippocampal neurotransmitters and apoptosis genes showed reduced expressions of indoleamine dioxygenase and P53 accompanied by increased expression of TPH1 in aged- HFD rats administered with DR7, indicating potential effects of DR7 along the pathways of serotonin and oxidative senescence. This study provided an insight into potentials of L. plantarum DR7 as a prospective dietary strategy to improve cognitive functions during aging. This study provided an insight into potentials of L. plantarum DR7 as a prospective dietary strategy to improve cognitive functions during aging.

Randomized Controlled Trial Nutrients
2021 Feb 14;13(2):618. doi: 10.3390/nu13020618.
Acacia Gum Is Well Tolerated While Increasing Satiety and Lowering Peak Blood Glucose Response in Healthy Human Subjects

Riley Larson 1, Courtney Nelson 1, Renee Korczak 1, Holly Willis 1, Jennifer Erickson 1, Qi Wang 2, Joanne Slavin 1
Affiliations expand
PMID: 33672963 PMCID: PMC7918852 DOI: 10.3390/nu13020618
Free PMC article

Abstract

Acacia gum (AG) is a non-viscous soluble fiber that is easily incorporated into beverages and foods. To determine its physiological effects in healthy human subjects, we fed 0, 20, and 40 g of acacia gum in orange juice along with a bagel and cream cheese after a 12 h fast and compared satiety, glycemic response, gastrointestinal tolerance, and food intake among treatments. Subjects (n = 48) reported less hunger and greater fullness at 15 min (p = 0.019 and 0.003, respectively) and 240 min (p = 0.036 and 0.05, respectively) after breakfast with the 40 g fiber treatment. They also reported being more satisfied at 15 min (p = 0.011) and less hungry with the 40 g fiber treatment at 30 min (p = 0.012). Subjects reported more bloating, flatulence, and GI rumbling on the 40 g fiber treatment compared to control, although values for GI tolerance were all low with AG treatment. No significant differences were found in area under the curve (AUC) or change from baseline for blood glucose response, although actual blood glucose with 20 g fiber at 30 min was significantly less than control. Individuals varied greatly in their postprandial glucose response to all treatments. AG improves satiety response

and may lower peak glucose response at certain timepoints, and it is well tolerated in healthy human subjects. AG can be added to beverages and foods in doses that can help meet fiber recommendations.

Pharmacological benefits of Acacia against metabolic diseases: intestinal-level bioactivities and favorable modulation of gut microbiota

Manas Ranjan Saha & Priyankar Dey (2021) Pharmacological benefits of Acacia against metabolic diseases: intestinal-level bioactivities and favorable modulation of gut microbiota, Archives of Physiology and Biochemistry, DOI: 10.1080/13813455.2021.1966475

Abstract

Context

Obesity-associated chronic metabolic disease is a leading contributor to mortality globally. Plants belonging to the genera Acacia are routinely used for the treatment of diverse metabolic diseases under different ethnomedicinal practices around the globe.

Objective

The current review centers around the pharmacological evidence of intestinal-level mechanisms for metabolic health benefits by Acacia spp.

Results

Acacia spp. increase the proportions of gut commensals (Bifidobacterium and Lactobacillus) and reduces the population of opportunistic pathobionts (Escherichia coli and Clostridium). Acacia gum that is rich in fibre, can also be a source of prebiotics to improve gut health. The intestinal-level anti-inflammatory activities of Acacia are likely to contribute to improvements in gut barrier function that would prevent gut-to-systemic endotoxin translocation and limit “low-grade” inflammation associated with metabolic diseases.

Conclusion

This comprehensive review for the first time has emphasised the intestinal-level benefits of Acacia spp. which could be instrumental in limiting the burden of metabolic disease.

Prospective evaluation of probiotic and prebiotic supplementation on diabetic health associated with gut microbiota

Author links open overlay panelNazeha A.KhalilabNehad R.EltahanbHeba M.ElaktashbSamarAlyacShahrul RazidSarbinide
https://doi.org/10.1016/j.fbio.2021.101149Get rights and content

Abstract

Background

Gut microbiota are critical for proper metabolic functions. Gut health can often be improved with dietary modulation, especially with probiotic and prebiotic. These supplements can stimulate immune system responses and prevent colonization by pathogen. Many diseases, such as diabetes mellitus, heart diseases, obesity, and cancers, benefit from proper function of intestinal microflora. Diabetes is an endocrine disease typically controlled, at least in part, with dietary intervention.

Aims

The current study main aim was to study the potential health benefits of probiotic and prebiotic supplements on the treatment of diabetes.

Methods

Male rats were divided into negative and positive control groups. Additional groups were fed 5% of yogurt, gum Arabic or a combination. Total colonic microbiota, Bifidobacterium spp., Lactobacillus spp., and Clostridium spp., were counted. Blood glucose, lipid profiles, and kidney function, with histology, were analyzed.

Results

Gut microflora was significantly improved, especially in rats fed with pro/prebiotics. Serum lipid profiles significantly improved ($p \leq 0.05$) after feeding yogurt and gum Arabic in combination; HDL levels were significantly decreased ($p \leq 0.05$). Kidney function was also significantly enhanced ($p \leq 0.05$) after feeding with this mixture.

In conclusion

Yogurt and gum Arabic are highly recommended (level of 5%) for controlling diabetes and improvement of lipid, glucose, and kidney profiles; however, human trials are needed.

Gut Health-Promoting Benefits of a Dietary Supplement of Vitamins with Inulin and Acacia Fibers in Rats by Malén Massot-Cladera 1,2ORCID,Ignasi Azagra-Boronat 1,2ORCID,Àngels Franch 1,2ORCID,Margarida Castell 1,2ORCID,Maria J. Rodríguez-Lagunas 1,2ORCID andFrancisco J. Pérez-Cano 1,2,*ORCID

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(This article belongs to the Special Issue Diet and Microbiome in Health and Aging)

Abstract

The study's objective was to ascertain whether a nutritional multivitamin and mineral supplement enriched with two different dietary fibers influences microbiota composition, mineral absorption, and some immune and metabolic biomarkers in adult rats. Nine-week-old Wistar rats were randomly assigned into four groups: the reference group; the group receiving a daily supplement based on a food matrix with proteins, vitamins, and minerals; and two other groups receiving this supplement enriched with inulin (V + I) or acacia (V + A) fiber for four weeks. Microbiota composition was determined in cecal content and mineral content in fecal, blood, and femur samples. Intestinal IgA concentration, hematological, and biochemical variables were evaluated. Both V + I and V + A supplementations increased Firmicutes and Actinobacteria phyla, which were associated with a higher presence of Lactobacillus and Bifidobacterium spp. V + A supplementation increased calcium, magnesium, phosphorus, and zinc concentrations in femur. V + I supplementation increased the fecal IgA content and reduced plasma total cholesterol and uric acid concentration. Both fiber-enriched supplements tested herein seem to be beneficial to gut-health, although differently.

The Effect of Gum Arabic (Acacia senegal) on Cardiovascular Risk Factors and Gastrointestinal Symptoms in Adults at Risk of Metabolic Syndrome: A Randomized Clinical Trial

by Amjad H. Jarrar 1,Lily Stojanovska 1,2,Vasso Apostolopoulos 2ORCID,Jack Feehan 2,3ORCID,Mo'ath F. Bataineh 4,Leila Cheikh Ismail 5,6 andAyesha S. Al Dhaheri 1,*ORCID

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Nutrients 2021, 13(1), 194; https://doi.org/10.3390/nu13010194
Received: 13 December 2020 / Revised: 5 January 2021 / Accepted: 6 January 2021 / Published: 9 January 2021

Abstract

Gum Arabic (GA) is a widely-used additive in food processing, but is also historically used in a number of traditional therapies. It has been shown to have a broad range of health benefits, particularly in improving important cardiovascular risk indicators. Metabolic syndrome and its associated cardiac outcomes are a significant burden on modern healthcare systems, and complementary interventions to aid in its management are required. We aimed to examine the effect of GA on those with, or at risk of, metabolic syndrome to identify an effect on improving important disease parameters related to cardiovascular outcomes. A single-blind, randomized, placebo-controlled trial was conducted to identify the effects of daily GA supplementation on metabolic and cardiovascular risk factors. A total of 80 participants were randomized to receive 20 g of GA daily (n = 40) or placebo (1 g pectin, n = 40) for 12 weeks. Key endpoints included body-anthropometric indices, diet and physical activity assessment, and blood chemistry (HbA1c, fasting glucose, and blood lipids). Of the 80 enrolled, 61 completed the study (intervention: 31, control: 30) with 19 dropping out due to poor treatment compliance. After 12 weeks, the participants receiving the GA showed significant decreases in systolic and diastolic blood pressure, fat-free body mass, energy and carbohydrate consumption, and fasting plasma glucose, as well as increased intake of dietary fiber. They also reported improvements in self-perceived bloating and quality of bowel movements, as well as a decreased appetite score following GA consumption. These results suggest that GA could be a safe and beneficial adjunct to other treatments for those with, or at risk of, metabolic syndrome.

Effect of sweet orange aroma on experimental anxiety in humans

Tiago Costa Goes 1, Fabrício Dias Antunes, Péricles Barreto Alves, Flavia Teixeira-Silva

Abstract

Objectives: The objective of this study was to evaluate the potential anxiolytic effect of sweet orange (Citrus sinensis) aroma in healthy volunteers submitted to an anxiogenic situation.

Design: Forty (40) male volunteers were allocated to five different groups for the inhalation of sweet orange essential oil (test aroma: 2.5, 5, or 10 drops), tea tree essential oil (control aroma: 2.5 drops), or water (nonaromatic control: 2.5 drops). Immediately after inhalation, each volunteer was submitted to a model of anxiety, the video-monitored version of the Stroop Color-Word Test (SCWT).

Outcome measures: Psychologic parameters (state-anxiety, subjective tension, tranquilization, and sedation) and physiologic parameters (heart rate and gastrocnemius electromyogram) were evaluated before the inhalation period and before, during, and after the SCWT.

Results: Unlike the control groups, the individuals exposed to the test aroma (2.5 and 10 drops) presented a lack of significant alterations ($p>0.05$) in state-anxiety, subjective tension and tranquillity levels throughout the anxiogenic situation, revealing an anxiolytic activity of sweet orange essential oil. Physiologic alterations along the test were not prevented in any treatment group, as has previously been observed for diazepam.

Conclusions: Although more studies are needed to find out the clinical relevance of aromatherapy for anxiety disorders, the present results indicate an acute anxiolytic activity of sweet orange aroma, giving some scientific support to its use as a tranquilizer by aromatherapists.

OSH in Figures: Stress at Work – Facts and Figures

January 2009
Publisher: EU-OSHA
Milczarek, Malgorzata & Schneider, Elke & González, Eusebio. (2009). OSH in Figures: Stress at Work – Facts and Figures.

Work-related stress is one of the biggest health and safety challenges that we face in Europe. Stress is the second most frequently reported work-related health problem, affecting 22% of workers from the EU 27 (in 2005), and the number of people suffering from stress-related conditions caused or made worse by work is likely to increase.This report discusses the prevalence of stress and the trends in work-related stress in the Member States of the European Union (based on international and national data), identifying those groups particularly exposed to stress in their working lives, subdivided by age, gender, sector, occupation, and employment status. Areas for future research and action are also indicated.

Adenosine A2A Receptors in Psychopharmacology: Modulators of Behavior, Mood and Cognition

Hai-Ying Shen1,* and Jiang-Fan Chen2

Abstract

The adenosine A2A receptor (A2AR) is in the center of a neuromodulatory network affecting a wide range of neuropsychiatric functions by interacting with and integrating several neurotransmitter systems, especially dopaminergic and glutamatergic neurotransmission. These interactions and integrations occur at multiple levels, including (1) direct receptor- receptor cross-talk at the cell membrane, (2) intracellular second messenger systems, (3) trans-synaptic actions via striatal collaterals or interneurons in the striatum, (4) and interactions at the network level of the basal ganglia. Consequently, A2ARs constitute a novel target to modulate various psychiatric conditions. In the present review we will first summarize the molecular interaction of adenosine receptors with other neurotransmitter systems and then discuss the potential applications of A2AR agonists and antagonists in physiological and pathophysiological conditions, such as psychostimulant action, drug addiction, anxiety, depression, schizophrenia and learning and memory.

Flavor components of monoterpenes in citrus essential oils enhance the release of monoamines from rat brain slices

Syuichi Fukumoto 1, Emi Sawasaki, Satoshi Okuyama, Yoshiaki Miyake, Hidehiko Yokogoshi

Abstract

Citrus essential oils have been utilized widely in traditional medicine, and there are various reports of actions such as effects on behavior and effects on pain stimulation response due to exposure. However, there are no reports concerning effects on neurotransmitters after ingestion, and uptake within the brain. We used brain tissue slices to investigate the effect of compounds in lemon essential oil on monoamine release. We investigated R-limonene, gamma-terpinene and citral, major components of lemon essential oil; S-limonene, an isomer of R-limonene and metabolites of these compounds. The effect of each compound on monoamine release from brain tissue slices was found to be dose-dependent. R-Limonene and its S-isomer demonstrated differences with regard to monoamine release from brain tissue. S-Limonene and its metabolites were found to have a stronger effect than the R-isomer. Limonene metabolites taken up in vivo were also found to have a stronger effect on monoamine release than both the R-form and the S-form. In an investigation of dopamine release using stratum slices, terpinene and pinene demonstrated no clear differences in activity attributable to isomers. However, rho-cymene, a gamma-terpinene metabolite, was found to have a stronger effect than gamma-terpinene. These results suggest that the metabolites of these monoterpene compounds contained in citrus essential oils have a stronger effect on monoamine release from brain tissue than the monoterpene compounds themselves.

Anxiolytic-like effect of sweet orange aroma in Wistar rats

Claudia Brito Faturi 1, José Roberto Leite, Péricles Barreto Alves, Adriane Conte Canton, Flavia Teixeira-Silva

Abstract

Aromatherapy is the use of essential oils as an alternative treatment for medical purposes. Despite the lack of sufficient scientific proof, it is considered a holistic complementary therapy employed to enhance comfort and decrease distress. Citrus fragrances have been particularly used by aromatherapists for the treatment of anxiety symptoms. Based on this claim, the present study investigated the effects of Citrus sinensis (sweet orange) essential oil on Wistar, male rats evaluated in the elevated plus-maze followed by the light/dark paradigm. The animals were exposed to the orange aroma (100, 200 or 400 microl) for 5 min while in a Plexiglas chamber and were then immediately submitted to the behavioural tests. At all doses, C.sinensis oil demonstrated anxiolytic activity in at least one of the tests and, at the highest dose, it presented significant effects in both animal models, as indicated by increased exploration of the open arms of the elevated plus-maze (time: p=0.004; entries: p=0.044) and of the lit chamber of the light/dark paradigm (time: p=0.030). In order to discard the possibility that this outcome was due to non-specific effects of any odour exposure, the behavioural response to Melaleuca alternifolia essential oil was also evaluated, using the same animal models, but no anxiolytic effects were observed. These results suggest an acute anxiolytic activity of sweet orange essence, giving some scientific support to its use as a tranquilizer by aromatherapists.

PHGG or placebo. Treatment efficacy was evaluated by the Francis Severity IBS score, the IBS quality-of-life scores and scored parameters of weekly journal of symptoms. Deltas of changes between the final and baseline scores were compared between two groups.

RESULTS:

Of 121 patients who underwent randomization, 108 patients (49 in the PHGG group and 59 in the placebo group) had all the data needed for intention-to-treat analysis. A 12-week administration of PHGG led to a significant improvement of journal bloating score in the PHGG group versus placebo (-4.1±13.4 versus -1.2±11.9, P=0.03), as well as in bloating+gasses score (-4.3±10.4 versus -1.12±10.5, P = 0.035). The effect lasted for at least 4 weeks after the last PHGG administration. PHGG had no effect on other journal reported IBS symptoms or on Severity and Quality of life scores. There were no significant side effects associated with PHGG ingestion. The rate of dropouts was significantly higher among patients in the placebo group compared with the PHGG group (49.15% versus 22.45%, respectively, P = 0.01).

CONCLUSIONS:

The results of this study support the administration of 6 g/day PHGG for IBS patients with bloating.

Phyto-Biotic Blend – Selected Background Documents

Biol Pharm Bull. 2017;40(6):902-909. doi: 10.1248/bpb.b17-00141.

Anti-stress Effect of Green Tea with Lowered Caffeine on Humans: A Pilot Study.

Unno K, Yamada H, Iguchi K, Ishida H, Iwao Y, Morita A, Nakamura Y.

Abstract

Theanine, an amino acid in tea, has significant anti-stress effects on animals and humans. However, the effect of theanine was blocked by caffeine and gallate-type catechins, which are the main components in tea. We examined the anti-stress effect of green tea with lowered caffeine, low-caffeine green tea, on humans. The study design was a single-blind group comparison and participants (n=20) were randomly assigned to low-caffeine or placebo tea groups. These teas (≥500 mL/d), which were eluted with room temperature water, were taken from 1 week prior to pharmacy practice and continued for 10 d in the practice period. The participants ingested theanine (ca. 15 mg/d) in low-caffeine green tea. To assess the anxiety of participants, the state-trait anxiety inventory test was used before pharmacy practice. The subjective stress of students was significantly lower in the low-caffeine-group than in the placebo-group during pharmacy practice. The level of salivary ?-amylase activity, a stress marker, increased significantly after daily pharmacy practice in the placebo-group but not in the low-caffeine-group. These results suggested that the ingestion of low-caffeine green tea suppressed the excessive stress response of students.

Pharmacol Biochem Behav. 2013 Oct;111:128-35.

Anti-stress effect of theanine on students during pharmacy practice: positive correlation among salivary '-amylase activity, trait anxiety and subjective stress.

Unno K, Tanida N, Ishii N, Yamamoto H, Iguchi K, Hoshino M, Takeda A, Ozawa H, Ohkubo T, Juneja LR, Yamada H.

Abstract

PURPOSE:

Theanine, an amino acid in tea, has significant anti-stress effect on experimental animals under psychosocial stress. Anti-stress effect of theanine on humans was evaluated in 5th-year university students during pharmacy practice.

METHOD:

The study design was a single-blind group comparison and participants (n=20) were randomly assigned to theanine or placebo groups. Theanine or placebo (lactose) tablets (200 mg, twice a day, after breakfast and lunch) were taken from 1 week prior to the pharmacy practice and continued for 10 days in the practice period. To assess the anxiety of the participants, the state-trait anxiety inventory test was carried out before the pharmacy practice. Salivary '-amylase activity (sAA) was measured as a marker of sympathetic nervous system activity.

RESULTS:

In the placebo-group, sAA in the morning (pre-practice sAA) was higher than in theanine-group during the pharmacy practice (p=0.032). Subjective stress was significantly lower in the theanine-group than in the placebo-group (p=0.020). These results suggest that theanine intake had anti-stress effect on students. Furthermore, students with higher pre-practice sAA showed significantly higher trait anxiety in both groups (p=0.015). Similarly, higher pre-practice sAA was correlated to shorter sleeping time in both groups (p=0.41×10(-3)).

CONCLUSION:

Stressful condition increased the level of sAA that was essentially affected by individual trait anxiety. The low levels of pre-practice sAA and subjective stress in the theanine-group suggest that theanine intake suppressed initial stress response of students assigned for a long-term commitment of pharmacy practice.

Nutrients. 2016 Jan 19;8(1). pii: E53. doi: 10.3390/nu8010053.
Anti-Stress, Behavioural and Magnetoencephalography Effects of an L-Theanine-Based Nutrient Drink: A Randomised, Double-Blind, Placebo-Controlled, Crossover Trial.

White DJ, de Klerk S, Woods W, Gondalia S, Noonan C, Scholey AB.

Abstract

L-theanine ('-glutamylethylamide) is an amino acid found primarily in the green tea plant. This study explored the effects of an L-theanine-based nutrient drink on mood responses to a cognitive stressor. Additional measures included an assessment of cognitive performance and resting state alpha oscillatory activity using magnetoencephalography (MEG). Thirty-four healthy adults aged 18-40 participated in this double-blind, placebo-controlled, balanced crossover study. The primary outcome measure, subjective stress response to a multitasking cognitive stressor, was significantly reduced one hour after administration of the L-theanine drink when compared to placebo. The salivary cortisol response to the stressor was reduced three hours post-dose following active treatment. No treatment-related cognitive performance changes were observed. Resting state alpha oscillatory activity was significantly greater in posterior MEG sensors after active treatment compared to placebo two hours post-dose; however, this effect was only apparent for those higher in trait anxiety. This change in resting state alpha oscillatory activity was not correlated with the change in subjective stress response or the cortisol response, suggesting further research is required to assess the functional relevance of these treatment-related changes in resting alpha activity. These findings further support the anti-stress effects of L-theanine.

Crit Rev Food Sci Nutr. 2017 May 24;57(8):1681-1687.
L-theanine, unique amino acid of tea, and its metabolism, health effects, and safety.

Türközü D, Şanlier N.

Abstract

Tea has been a very popular beverage around the world for centuries. The reason that it is delicious, enabling hydration, showing warming and relaxing effect can be mentioned why it is consumed so much in addition to its prominent health effects. Although the catechins and caffeine are the primary bioactive components that are related with the health effects of the tea, the health effects of theanine amino acid, which is a nonproteinic amino acid special to tea, has become prominent in recent years. It has been known that the theanine amino acid in tea has positive effects especially on relaxing, cognitive performance, emotional status, sleep quality, cancer, cardiovascular diseases, obesity, and common cold. The results of acute and chronic toxicity tests conducted on the safety of theanine express that L-theanine is reliable in general even if it is consumed too much with diet. However, it has not revealed a clear evidence-based result yet regarding theanine metabolism, health effects, and its safety. Within this frame, chemical structure of theanine, its biosynthesis, dietary sources, metabolism, health effects, and safety are discussed in present study.

Scientific World Journal. 2014;2014:419032

Effects of L-theanine on posttraumatic stress disorder induced changes in rat brain gene expression.

Ceremuga TE, Martinson S, Washington J, Revels R, Wojcicki J, Crawford D, Edwards R, Kemper JL, Townsend WL, Herron GM, Ceremuga GA, Padron G, Bentley M.

Abstract

Posttraumatic stress disorder (PTSD) is characterized by the occurrence of a traumatic event that is beyond the normal range of human experience. The future of PTSD treatment may specifically target the molecular mechanisms of PTSD. In the US, approximately 20% of adults report taking herbal products to treat medical illnesses. L-theanine is the amino acid in green tea primarily responsible for relaxation effects. No studies have evaluated the potential therapeutic properties of herbal medications on gene expression in PTSD. We evaluated gene expression in PTSD-induced changes in the amygdala and hippocampus of Sprague-Dawley rats. The rats were assigned to PTSD-stressed and nonstressed groups that received either saline, midazolam, L-theanine, or L-theanine + midazolam. Amygdala and hippocampus tissue samples were analyzed for changes in gene expression. One-way ANOVA was used to detect significant difference between groups in the amygdala and hippocampus. Of 88 genes examined, 17 had a large effect size greater than 0.138. Of these, 3 genes in the hippocampus and 5 genes in the amygdala were considered significant ($P < 0.05$) between the groups. RT-PCR analysis revealed significant changes between groups in several genes implicated in a variety of disorders ranging from PTSD, anxiety, mood disorders, and substance dependence.

Nutr Neurosci. 2014 Nov;17(6):279-83.

Advantageous effect of theanine intake on cognition.

Tamano H, Fukura K, Suzuki M, Sakamoto K, Yokogoshi H, Takeda A.

Abstract

Theanine, γ-glutamylethylamide, is one of the major amino acid components in green tea. On the basis of the preventive effect of theanine intake after weaning on stress-induced impairment of recognition memory, the advantageous effect of theanine intake on recognition memory was examined in young rats, which were fed water containing 0.3% theanine for 3 weeks after weaning. The rats were subjected to object recognition test. Object recognition memory was maintained in theanine-administered rats 48 hours after the training, but not in the control rats. When in vivo dentate gyrus long-term potentiation (LTP) was induced, it was more greatly induced in theanine-administered rats than in the control rats. The levels of brain-derived neurotropic factor and nerve growth factor in the hippocampus were significantly higher in theanine-administered rats than in the control rats. The present study indicates the advantageous effect of theanine intake after weaning on recognition memory. It is likely that theanine intake is of advantage to the development of hippocampal function after weaning.

Brain Res Bull. 2013 Jun;95:1-6.
Preventive effect of theanine intake on stress-induced impairments of hippocamapal long-term potentiation and recognition memory.

Tamano H, Fukura K, Suzuki M, Sakamoto K, Yokogoshi H, Takeda A.

Abstract

Theanine, γ-glutamylethylamide, is one of the major amino acid components in green tea. On the basis of the preventive effect of theanine intake after birth on mild stress-induced attenuation of hippocamapal CA1 long-term potentiation (LTP), the present study evaluated the effect of theanine intake after weaning on stress-induced impairments of LTP and recognition memory. Young rats were fed water containing 0.3% theanine for 3 weeks after weaning and subjected to water immersion stress for 30min, which was more severe than tail suspension stress for 30s used previously. Serum corticosterone levels were lower in theanine-administered rats than in the control rats even after exposure to stress. CA1 LTP induced by a 100-Hz tetanus for 1s was inhibited in the presence of 2-amino-5-phosphonovalerate (APV), an N-methyl-d-aspartate (NMDA) receptor antagonist, in hippocampal slices from the control rats and was attenuated by water immersion stress. In contrast, CA1 LTP was not significantly inhibited in the presence of APV in hippocampal slices from theanine-administered rats and was not attenuated by the stress. Furthermore, object recognition memory was impaired in the control rats, but not in theanine-administered rats. The present study indicates the preventive effect of theanine intake after weaning on stress-induced impairments of hippocampal LTP and recognition memory. It is likely that the modification of corticosterone secretion after theanine intake is involved in the

preventive effect.

Brain Res. 2013 Mar 29;1503:24-32.
Protective effect of l-theanine on chronic restraint stress-induced cognitive impairments in mice.

Tian X, Sun L, Gou L, Ling X, Feng Y, Wang L, Yin X, Liu Y.

Abstract
The present work was aimed to study the protective effect of l-theanine on chronic restraint stress (CRS)-induced cognitive impairments in mice. The stress was produced by restraining the animals in well-ventilated polypropylene tubes (3.2 cm in diameter ×10.5 cm in length) for 8h once daily for 21 consecutive days. L-theanine (2 and 4 mg/kg) was administered 30 min before the animals subjected to acute immobilized stress. At week 4, mice were subjected to Morris water maze and step-through tests to measure the cognitive function followed by oxidative parameters and corticosterone as well as catecholamines (norepinephrine and dopamine) subsequently. Our results showed that the cognitive performances in CRS group were markedly deteriorated, accompanied by noticeable alterations in oxidative parameters and catecholamine levels in the hippocampus and the cerebral cortex as well as corticosterone and catecholamine levels in the serum. However, not only did l-theanine treatment exhibit a reversal of the cognitive impairments and oxidative damage induced by CRS, but also reversed the abnormal level of corticosterone in the serum as well as the abnormal levels of catecholamines in the brain and the serum. This study indicated the protective effect of l-theanine against CRS-induced cognitive impairments in mice.

J Physiol Anthropol. 2012 Oct 29;31:28.
Effects of L-theanine or caffeine intake on changes in blood pressure under physical and psychological stresses.
Yoto A, Motoki M, Murao S, Yokogoshi H.

Abstract
BACKGROUND:
L-theanine, an amino acid contained in green tea leaves, is known to block the binding of L-glutamic acid to glutamate receptors in the brain, and has been considered to cause anti-stress effects by inhibiting cortical neuron excitation. Both L-theanine and caffeine, which green tea contains, have been highlighted for their beneficial effects on cognition and mood.
METHODS:
In this study, we investigated the effects of orally administered L-theanine or caffeine on mental task performance and physiological activities under conditions of physical or psychological stress in humans. Fourteen participants each underwent three separate trials, in which they orally took either L-theanine + placebo, caffeine + placebo, or placebo only.

RESULTS:

The results after the mental tasks showed that L-theanine significantly inhibited the blood-pressure increases in a high-response group, which consisted of participants whose blood pressure increased more than average by a performance of a mental task after placebo intake. Caffeine tended to have a similar but smaller inhibition of the blood-pressure increases caused by the mental tasks. The result of the Profile of Mood States after the mental tasks also showed that L-theanine reduced the Tension-Anxiety scores as compared with placebo intake.

CONCLUSIONS:

The findings above denote that L-theanine not only reduces anxiety but also attenuates the blood-pressure increase in high-stress-response adults.

Exp Physiol. 2013 Jan;98(1):290-303.
Ingestion of theanine, an amino acid in tea, suppresses psychosocial stress in mice.

Unno K, Iguchi K, Tanida N, Fujitani K, Takamori N, Yamamoto H, Ishii N, Nagano H, Nagashima T, Hara A, Shimoi K, Hoshino M.

Abstract

The antistress effect of theanine (□-glutamylethylamide), an amino acid in tea, was investigated using mice that were psychosocially stressed from a conflict among male mice in conditions of confrontational housing. Two male mice were housed in the same cage separated by a partition to establish a territorial imperative. When the partition was removed, the mice were co-housed confrontationally. As a marker for the stress response, changes in the adrenal gland were studied in comparison to group-housed control mice (six mice in a cage). Significant adrenal hypertrophy was observed in mice during confrontational housing, which was developed within 24 h and persisted for at least 1 week. The size of cells in the zona fasciculata of the adrenal gland, from which glucocorticoid is mainly secreted, increased (□1.11-fold) in mice during confrontational housing, which was accompanied by a flattened diurnal rhythm of corticosterone and ACTH in blood. The ingestion of theanine (>5 μg ml(-1)) prior to confrontational housing significantly suppressed adrenal hypertrophy. An antidepressant, paroxetin, suppressed adrenal hypertrophy in a similar manner in mice during confrontational housing. In mice that ingested theanine, behavioural depression was also suppressed, and a diurnal rhythm of corticosterone and ACTH was observed, even in mice that were undergoing confrontational housing. Furthermore, the daily dose of theanine (40 μg ml(-1)) blocked the counteracting effects of caffeine (30 μg ml(-1)) and catechin (200 μg ml(-1)). The present study demonstrated that theanine prevents and relieves psychosocial stress through the modulation of hypothalamic-pituitary-adrenal axis activity.

Free Radic Res. 2011 Aug;45(8):966-74.
Theanine intake improves the shortened lifespan, cognitive dysfunction and behavioural depression that are induced by chronic psychosocial stress in mice.

Unno K, Fujitani K, Takamori N, Takabayashi F, Maeda K, Miyazaki H, Tanida N, Iguchi K, Shimoi K, Hoshino M.

Abstract

To evaluate the psychosocial effect on lifespan and cognitive function, this study investigated the effect of confrontational housing on mice because conflict among male mice is a psychosocial stress. In addition, it investigated the anti-stress effect of theanine (?-glutamylethylamide), an amino acid in tea. Mice were housed under confrontation. That is, two male mice were separately housed in the same cage with a partition for establishing the territorial imperative in each mouse. Then, the partition was removed and mice were co-housed confrontationally (confront-housing) using a model mouse of accelerated-senescence (SAMP10) that exhibited cerebral atrophy and cognitive dysfunction with ageing. It was found that mice began to die earlier under confront-housing than group-housed control mice. Additionally, it was found that cerebral atrophy, learning impairment and behavioural depression were higher in mice under the stressed condition of confront-housing than age-matched mice under group-housing. Furthermore, the level of oxidative damage in cerebral DNA was higher in mice housed confrontationally than group-housed control mice. On the other hand, the consumption of purified theanine (20 μg/ml, 5-6 mg/kg) suppressed the shortened lifespan, cerebral atrophy, learning impairment, behavioural depression and oxidative damage in cerebral DNA. These results suggest that psychosocial stress accelerates age-related alterations such as oxidative damage, lifespan, cognitive dysfunction and behavioural depression. The intake of theanine might be a potential candidate for suppression of disadvantage under psychosocial stress.

Phytother Res. 2011 Nov;25(11):1636-9.
Antidepressant-like effects of L-theanine in the forced swim and tail suspension tests in mice.

Yin C, Gou L, Liu Y, Yin X, Zhang L, Jia G, Zhuang X.

Abstract

L-theanine (γ-glutamylethylamide), an amino acid component of green tea, has been shown to reduce mental and physical stress, and to improve memory function. In this study, the antidepressant effect of L-theanine was investigated in mice using the forced swim test, tail suspension test, open-field test and reserpine test. L-theanine produced an antidepressant-like effect, since the administration of L-theanine at doses of 1, 4 and 20 mg/kg for 10 successive days significantly reduced the immobility time in both the forced swim test and tail suspension test, compared with the control group, without accompanying changes in ambulation in the open-field test. Moreover, L-theanine significantly antagonized reserpine-induced ptosis and hypothermia. Taken together, these results indicate that L-theanine possessed an antidepressant-like effect in mice, which may be mediated by the central monoaminergic neurotransmitter system.

Free Radic Biol Med. 2009 Dec 1;47(11):1601-10.
l-Theanine, an amino acid in green tea, attenuates beta-amyloid-induced cognitive dysfunction and neurotoxicity: reduction in oxidative damage and inactivation of ERK/p38 kinase and NF-kappaB pathways.

Kim TI, Lee YK, Park SG, Choi IS, Ban JO, Park HK, Nam SY, Yun YW, Han SB, Oh KW, Hong JT.

Abstract

Amyloid beta (Abeta)-induced neurotoxicity is a major pathological mechanism of Alzheimer disease (AD). In this study, we investigated the inhibitory effect of l-theanine, a component of green tea (Camellia sinensis), on Abeta(1-42)-induced neuronal cell death and memory impairment. Oral treatment of l-theanine (2 and 4 mg/kg) for 5 weeks in the drinking water of mice, followed by injection of Abeta(1-42) (2 microg/mouse, icv), significantly attenuated Abeta(1-42)-induced memory impairment. Furthermore, l-theanine reduced Abeta(1-42) levels and the accompanying Abeta(1-42)-induced neuronal cell death in the cortex and hippocampus of the brain. Moreover, l-theanine inhibited Abeta(1-42)-induced extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase as well as the activity of nuclear factor kappaB (NF-kappaB). l-Theanine also significantly reduced oxidative protein and lipid damage and the elevation of glutathione levels in the brain. These data suggest that the positive effects of l-theanine on memory may be mediated by suppression of ERK/p38 and NF-kappaB as well as the reduction of macromolecular oxidative damage. Thus, l-theanine may be useful in the prevention and treatment of AD.

Neurotoxicology. 2008 Jul;29(4):656-62.
Protective effect of the green tea component, L-theanine on environmental toxins-induced neuronal cell death.

Cho HS, Kim S, Lee SY, Park JA, Kim SJ, Chun HS.

Abstract

Several environmental neurotoxins and oxidative stress inducers are known to damage the nervous system and are considered major factors associated with the selective vulnerability of nigral dopaminergic neurons in Parkinson's disease (PD). Gamma-glutamylethylamide (L-theanine), a natural glutamate analog in green tea, has been shown to exert strong anti-ischemic effect. In this study, we investigated the protective effects of L-theanine on neurotoxicity induced by PD-related neurotoxicants, rotenone and dieldrin in cultured human dopaminergic cell line, SH-SY5Y. Our initial experiments revealed that L-theanine (500 microM) attenuated both rotenone- and dieldrin-induced DNA fragmentation and apoptotic death in SH-SY5Y cells. In addition, L-theanine partially prevented both rotenone- and dieldrin-induced heme oxygenase-1 (HO-1) up-regulation. Both rotenone- and dieldrin-induced down-regulation of extracellular signal-regulated kinase1/2 (ERK1/2) phosphorylation was significantly blocked

by pretreatment with L-theanine. Furthermore, pretreatment with L-theanine significantly attenuated the down-regulation of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) production in SH-SY5Y cells. These results suggest that L-theanine directly provide neuroprotection against PD-related neurotoxicants and may be clinically useful for preventing PD symptoms.

Biol Psychol. 2007 Jan;74(1):39-45.
L-Theanine reduces psychological and physiological stress responses.

Kimura K, Ozeki M, Juneja LR, Ohira H.

Abstract

L-Theanine is an amino acid contained in green tea leaves which is known to block the binding of L-glutamic acid to glutamate receptors in the brain. Because the characteristics of L-Theanine suggest that it may influence psychological and physiological states under stress, the present study examined these possible effects in a laboratory setting using a mental arithmetic task as an acute stressor. Twelve participants underwent four separate trials: one in which they took L-Theanine at the start of an experimental procedure, one in which they took L-Theanine midway, and two control trials in which they either took a placebo or nothing. The experimental sessions were performed by double-blind, and the order of them was counterbalanced. The results showed that L-Theanine intake resulted in a reduction in the heart rate (HR) and salivary immunoglobulin A (s-IgA) responses to an acute stress task relative to the placebo control condition. Moreover, analyses of heart rate variability indicated that the reductions in HR and s-IgA were likely attributable to an attenuation of sympathetic nervous activation. Thus, it was suggested that the oral intake of L-Theanine could cause anti-stress effects via the inhibition of cortical neuron excitation.

Nutrition. 2007 May;23(5):419-23.
Effects of Applephenon and ascorbic acid on physical fatigue.

Ataka S, Tanaka M, Nozaki S, Mizuma H, Mizuno K, Tahara T, Sugino T, Shirai T, Kajimoto Y, Kuratsune H, Kajimoto O, Watanabe Y.

Abstract

OBJECTIVE:

We examined the effects of Applephenon and ascorbic acid administration on physical fatigue.

METHODS:

In a double-blinded, placebo-controlled, three-way crossover design, 18 healthy volunteers were randomized to oral Applephenon (1200 mg/d), ascorbic acid (1000 mg/d), or placebo for 8 d. The fatigue-inducing physical task consisted of workload trials on a bicycle ergometer at fixed workloads for 2 h on two occasions. During the test, subjects performed non-workload trials with maximum velocity for 10 s at 30 min (30-min trial) after the start of the test and 30 min before the end of the test (210-min trial).

RESULTS:

The change in maximum velocity between the 30- and 210-min trials was higher in the group given Applephenon than in the group given placebo; ascorbic acid had no effect.

CONCLUSION:

These results suggest that Applephenon attenuates physical fatigue, whereas ascorbic acid does not.

Nutrients. 2015 May 26;7(6):3959-98.
Apples and cardiovascular health--is the gut microbiota a core consideration?

Koutsos A, Tuohy KM, Lovegrove JA.

Abstract

There is now considerable scientific evidence that a diet rich in fruits and vegetables can improve human health and protect against chronic diseases. However, it is not clear whether different fruits and vegetables have distinct beneficial effects. Apples are among the most frequently consumed fruits and a rich source of polyphenols and fiber. A major proportion of the bioactive components in apples, including the high molecular weight polyphenols, escape absorption in the upper gastrointestinal tract and reach the large intestine relatively intact. There, they can be converted by the colonic microbiota to bioavailable and biologically active compounds with systemic effects, in addition to modulating microbial composition. Epidemiological studies have identified associations between frequent apple consumption and reduced risk of chronic diseases such as cardiovascular disease. Human and animal intervention studies demonstrate beneficial effects on lipid metabolism, vascular function and inflammation but only a few studies have attempted to link these mechanistically with the gut microbiota. This review will focus on the reciprocal interaction between apple components and the gut microbiota, the potential link to cardiovascular health and the possible mechanisms of action.

J Nutr. 2014 Feb;144(2):146-54.
Dietary flavonoids from modified apple reduce inflammation markers and modulate gut microbiota in mice.

Espley RV, Butts CA, Laing WA, Martell S, Smith H, McGhie TK, Zhang J, Paturi G, Hedderley D, Bovy A, Schouten HJ, Putterill J, Allan AC, Hellens RP.

Abstract

Apples are rich in polyphenols, which provide antioxidant properties, mediation of cellular processes such as inflammation, and modulation of gut microbiota. In this study we compared genetically engineered apples with increased flavonoids [myeloblastis transcription factor 10 (MYB10)] with nontransformed apples from the same genotype, "Royal Gala" (RG), and a control diet with no apple. Compared with the RG diet, the MYB10 diet contained elevated concentrations of the flavonoid subclasses anthocyanins, flavanol monomers (epicatechin) and oligomers (procyanidin B2), and flavonols (quercetin glycosides), but other plant secondary metabolites were largely unaltered. We used these apples to investigate the effects of dietary flavonoids on inflammation and gut microbiota in 2 mouse feeding trials. In trial 1, male mice were fed a control diet or diets supplemented with 20% MYB10 apple flesh and peel (MYB-FP) or RG apple flesh and peel (RG-FP) for 7 d. In trial 2, male mice were fed MYB-FP or RG-FP diets or diets supplemented with 20% MYB10 apple flesh or RG apple flesh for 7 or 21 d. In trial 1, the transcription levels of inflammation-linked genes in mice showed decreases of >2-fold for interleukin-2 receptor (Il2rb), chemokine receptor 2 (Ccr2), chemokine ligand 10 (Cxcl10), and chemokine receptor 10 (Ccr10) at 7 d for the MYB-FP diet compared with the RG-FP diet ($P < 0.05$). In trial 2, the inflammation marker prostaglandin E(2) (PGE(2)) in the plasma of mice fed the MYB-FP diet at 21 d was reduced by 10-fold ($P < 0.01$) compared with the RG-FP diet. In colonic microbiota, the number of total bacteria for mice fed the MYB-FP diet was 6% higher than for mice fed the control diet at 21 d ($P = 0.01$). In summary, high-flavonoid apple was associated with decreases in some inflammation markers and changes in gut microbiota when fed to healthy mice.

Gut. 2005 Feb;54(2):193-200.

Apple polyphenol extracts prevent damage to human gastric epithelial cells in vitro and to rat gastric mucosa in vivo.

Graziani G, D'Argenio G, Tuccillo C, Loguercio C, Ritieni A, Morisco F, Del Vecchio Blanco C, Fogliano V, Romano M.

Abstract

BACKGROUND:

Fresh fruit and vegetables exert multiple biological effects on the gastrointestinal mucosa.

AIM:

To assess whether apple extracts counteract oxidative or indomethacin induced damage to gastric epithelial cells in vitro and to rat gastric mucosa in vivo.

METHODS:

Apple extracts were obtained from freeze dried apple flesh of the "Annurca" variety. Cell damage was induced by incubating MKN 28 cells with xanthine-xanthine oxidase or

indomethacin and quantitated by MTT. In vivo gastric damage was induced by indomethacin 35 mg/kg. Intracellular antioxidant activity was determined using the (2,2'-azinobis (3-ethylbenzothiazolin-6-sulfonate) method. Malondialdehyde intracellular concentration, an index of lipid peroxidation, was determined by high pressure liquid chromatography with fluorometric detection.

RESULTS:

(1) Apple extracts decreased xanthine-xanthine oxidase or indomethacin induced injury to gastric epithelial cells by 50%; (2) catechin or chlorogenic acid (the main phenolic components of apple extracts) were equally effective as apple extracts in preventing oxidative injury to gastric cells; and (3) apple extracts (i) caused a fourfold increase in intracellular antioxidant activity, (ii) prevented its decrease induced by xanthine-xanthine oxidase, (iii) counteracted xanthine-xanthine oxidase induced lipid peroxidation, and (iv) decreased indomethacin injury to the rat gastric mucosa by 40%.

CONCLUSIONS:

Apple extracts prevent exogenous damage to human gastric epithelial cells in vitro and to the rat gastric mucosa in vivo. This effect seems to be associated with the antioxidant activity of apple phenolic compounds. A diet rich in apple antioxidants might exert a beneficial effect in the prevention of gastric diseases related to generation of reactive oxygen species.

Mol Nutr Food Res. 2017 May 12.

Grape seed proanthocyanidin extract ameliorates inflammation and adiposity by modulating gut microbiota in high-fat diet mice.

Liu W, Zhao S, Wang J, Shi J, Sun Y, Wang W, Ning G, Hong J, Liu R.

Abstract

SCOPE:

Obesity and associated metabolic complications is a worldwide public health issue. Gut microbiota have been recently linked to obesity and its related inflammation. In this study, we have explored the anti-inflammatory effect of grape seed proanthocyanindin extract (GSPE) in the high-fat diet (HFD)-induced obesity and identified the contribution of the gut microbiota to GSPE effects on metabolism.

METHODS AND RESULTS:

Mice were fed a normal diet and a high-fat diet with or without GSPE (300 mg/kg body weight/day) by oral gavage for 7 weeks. Supplementation with GSPE significantly decreased plasma levels of inflammatory factors such as TNF-?, IL-6 and MCP-1, companied with ameliorated macrophage infiltration in epidydimal fat and liver tissues. Furthermore, GSPE also reduced epidydimal fat mass and improved insulin sensitivity. 16S rDNA analyses revealed that GSPE supplementation modulated the gut microbiota composition and certain bacteria including Clostridium XIVa, Roseburia and Prevotella. More importantly, depleting gut microbiota by antibiotics treatment abolished the beneficial effects of GSPE on inflammation and adiposity.

CONCLUSION:
Our study identifies the novel links between gut microbiota alterations and metabolic benefits by GSPE supplementation, providing possibilities for the prevention and treatment of metabolic disorders by targeting gut microbiota through a potential prebiotic agent GSPE.

Mol Nutr Food Res. 2017 Feb 20.
Chronic supplementation with dietary proanthocyanidins protects from diet-induced intestinal alterations in obese rats.

Gil-Cardoso K, Ginés I, Pinent M, Ardévol A, Arola L, Blay M, Terra X.

Abstract
SCOPE:
Increased attention has been paid to the link between altered intestinal function and elevated incidence of metabolic disorders, such as in obesity. This study investigated in obese rats the role of grape seed proanthocyanidin extract (GSPE) chronic treatment, taken in a low, moderate, or high dose, on obesity-associated intestinal alterations in response to a cafeteria diet (CAF).
METHODS AND RESULTS:
To evaluate the degree of intestinal inflammation, reactive oxygen species (ROS) production and myeloperoxidase (MPO) activity were measured as well as the expression of inflammatory-related genes. The barrier integrity was assessed by quantifying the gene expression of tight-junction components and measuring the plasma LPS. GSPE decreased the ROS levels and MPO activity, without substantial differences among the doses. The supplementation with moderate and high GSPE doses significantly decreased iNOS expression compared to the CAF group, and the same pattern was observed in the low-dose animals with respect to IL-1 expression. Moreover, the results show that GSPE significantly increases zonulin-1 expression with respect to the CAF animals.
CONCLUSION:
This study provides evidence for the ameliorative effect of a proanthocyanidin extract on high-fat/high-carbohydrate diet-induced intestinal alterations, specifically reducing intestinal inflammation and oxidative stress and suggesting a protection against a barrier defect.

Oncotarget. 2016 Dec 6;7(49):80313-80326. doi: 10.18632/oncotarget.13450.
Dietary grape seed proanthocyanidins (GSPs) improve weaned intestinal microbiota and mucosal barrier using a piglet model.

Han M, Song P, Huang C, Rezaei A, Farrar S, Brown MA, Ma X.

Abstract

Proanthocyanidins have been suggested as an effective antibiotic alternative, however their mechanisms are still unknown. The present study investigated the effects of grape seed proanthocyanidins on gut microbiota and mucosal barrier using a weaned piglet model in comparison with colistin. Piglets weaned at 28 day were randomly assigned to four groups treated with a control ration, or supplemented with 250 mg/kg proanthocyanidins, kitasamycin/colistin, or 250 mg/kg proanthocyanidins and half-dose antibiotics, respectively. On day 28, the gut chyme and tissue samples were collected to test intestinal microbiota and barrier function, respectively. Proanthocyanidins treated piglets had better growth performance and reduced diarrhea incidence ($P < 0.05$), accompanied with decreased intestinal permeability and improved mucosal morphology. Gene sequencing analysis of 16S rRNA revealed that dietary proanthocyanidins improved the microbial diversity in ileal and colonic digesta, and the most abundant OTUs belong to Firmicutes and Bacteroidetes spp.. Proanthocyanidins treatment decreased the abundance of Lactobacillaceae, and increased the abundance of Clostridiaceae in both ileal and colonic lumen, which suggests that proanthocyanidins treatment changed the bacterial composition and distribution. Administration of proanthocyanidins increased the concentration of propionic acid and butyric acid in the ileum and colon, which may activate the expression of GPR41. In addition, dietary proanthocyanidins improved the antioxidant indices in serum and intestinal mucosa, accompanied with increasing expression of barrier occludin. Our findings indicated that proanthocyanidins with half-dose colistin was equivalent to the antibiotic treatment and assisted weaned animals in resisting intestinal oxidative stress by increasing diversity and improving balance of gut microbes.

Food Funct. 2016 Apr;7(4):1959-67. doi: 10.1039/c6fo00032k.
In vitro extraction and fermentation of polyphenols from grape seeds (Vitis vinifera) by human intestinal microbiota.

Zhou L, Wang W, Huang J, Ding Y, Pan Z, Zhao Y, Zhang R, Hu B, Zeng X.

Abstract

The effects of several parameters on the extraction yield of total polyphenols from grape seeds by pressurized liquid extraction were investigated. The highest recovery of total polyphenols occurred at 80 °C within 5 min, and a single extraction allowed a recovery of more than 97% of total polyphenols. Following the purification with macroporous resin, the effects of grape polyphenols (>94.8%) on human intestinal microbiota were monitored over 36 h incubation by fluorescence in situ hybridization, and short-chain fatty acids (SCFAs) were measured by HPLC. The result showed that the grape polyphenols promoted the changes in the relevant microbial populations and shifted the profiles of SCFAs. Fermentation of grape polyphenols resulted in a significant increase in the numbers of Bifidobacterium spp. and Lactobacillus-Enterococcus group and inhibition in the growth of the Clostridium histolyticum group and the Bacteroides-Prevotella group, with no significant effect on the population of total bacteria. The findings suggest that grape polyphenols have potential prebiotic effects on modulating

the gut microbiota composition and generating SCFAs that contribute to the improvements of host health.

Curr Obes Rep. 2015 Dec;4(4):389-400.
Gut Microbiota Dysbiosis in Obesity-Linked Metabolic Diseases and Prebiotic Potential of Polyphenol-Rich Extracts.

Anhê FF, Varin TV, Le Barz M, Desjardins Y, Levy E, Roy D, Marette A.

Abstract

Trillions of microorganisms inhabit the human body, strongly colonizing the gastro-intestinal tract and outnumbering our own cells. High-throughput sequencing techniques and new bioinformatic tools have enabled scientists to extend our knowledge on the relationship between the gut microbiota and host's physiology. Disruption of the ecological equilibrium in the gut (i.e., dysbiosis) has been associated with several pathological processes, including obesity and its related comorbidities, with diet being a strong determinant of gut microbial balance. In this review, we discuss the potential prebiotic effect of polyphenol-rich foods and extracts and how they can reshape the gut microbiota, emphasizing the novel role of the mucin-degrading bacterium Akkermansia muciniphila in their metabolic benefits.

Food Funct. 2014 Oct;5(10):2558-63.
Grape seed extract improves epithelial structure and suppresses inflammation in ileum of IL-10-deficient mice.

Yang G, Wang H, Kang Y, Zhu MJ.

Abstract

Defect in intestinal epithelial structure is a critical etiological factor of several intestinal diseases such as inflammatory bowel disease. The objective of this study was to evaluate the effect of grape seed extract (GSE), which contains a mixture of polyphenols, on ileal mucosal structure and inflammation in interleukin (IL)-10-deficient mice, a common model for studying inflammatory bowel disease. Wild-type and IL-10-deficient mice were fed GSE at 0 or 1% (based on dry feed weight) for 16 weeks. GSE supplementation decreased crypt depth and increased ($P < 0.05$) the ratio of villus/crypt length in the terminal ileum. Consistently, the dietary GSE decreased ($P < 0.05$) proliferation and enhanced ($P < 0.05$) differentiation of epithelial cells. These changes in gut epithelium were associated with the suppression of nuclear factor kappa-light-chain-enhancer of activated B-cell (NF-□B) signaling. Furthermore, compared with WT mice, IL-10 deletion promoted beclin-1 and AMPK expression, both of which were decreased to normal

by GSE supplementation. These changes were associated with alterations in epithelial barrier function as indicated by reduced pore forming claudin-2 protein expression and increased barrier forming claudin-1 protein expression in the ileum of GSE supplemented mice. In summary, our data indicates that GSE exerts protective effects to the ileal epithelial structure in IL-10-deficient mice possibly through the suppression of inflammatory response.

Gut Liver. 2013 May;7(3):282-9.
Gastroprotective Effects of Grape Seed Proanthocyanidin Extracts against Nonsteroid Anti-Inflammatory Drug-Induced Gastric Injury in Rats.

Kim TH, Jeon EJ, Cheung DY, Kim CW, Kim SS, Park SH, Han SW, Kim MJ, Lee YS, Cho ML, Chang JH, Min JK, Kim JI.

Abstract

BACKGROUND/AIMS:

To investigate the gastroprotective effects of grape seed proanthocyanidin extracts (GSPEs) against nonsteroid anti-inflammatory drug (NSAID)-induced gastric mucosal injury in rats.

METHODS:

Sprague-Dawley rats were randomly allocated to the normal control, indomethacin, low-dose GSPE, high-dose GSPE and misoprostol groups. All groups except the normal control group received pretreatment drugs for 6 consecutive days. On the 5th and 6th day, indomethacin was administered orally to all groups except for normal control group. The microscopic features of injury were analyzed. The levels of gastric mucosal glutathione, gastric mucosal prostaglandin E2 (PGE2), and proinflammatory cytokines were investigated.

RESULTS:

The total areas of ulceration in the GSPE and misoprostol groups were significantly decreased compared with the indomethacin group ($p<0.05$). However, a difference in ulcer formation among the drug treatment groups was not observed. Meanwhile, the glutathione levels in the high-dose GSPE group were higher than those of both the indomethacin and misoprostol groups ($p<0.05$) and were similar to those of the normal control group. Additionally, there was no difference among the groups in the levels of gastric mucosal PGE2 and proinflammatory cytokines.

CONCLUSIONS:

High-dose GSPE has a strong protective effect against NSAID-induced gastric mucosal injury, which may be associated with the antioxidant effects of GSPE.

Can J Physiol Pharmacol. 2010 Sep;88(9):888-98. doi: 10.1139/y10-071.
Effects of proanthocyanidins from grape seed on treatment of recurrent ulcerative colitis in rats.
Wang YH, Yang XL, Wang L, Cui MX, Cai YQ, Li XL, Wu YJ.

Abstract

The aim of the present study was to investigate the therapeutic effect and mechanism of proanthocyanidins from grape seed (GSPE) in the treatment of recurrent ulcerative colitis (UC) in rats. To induce recurrent colitis, rats were instilled with 2,4,6-trinitrobenzenesulfonic acid (TNBS) (80 mg/kg) into the colon through the cannula in the first induced phase, and then the rats were instilled a second time with TNBS (30 mg/kg) into the colon on the sixteenth day after the first induction UC. Rats were intragastrically administered GSPE (200 mg/kg) per day for 7 days after twice-induced colitis by TNBS. Sulfasalazine at 500 mg/kg was used as a positive control drug. Rats were killed 7 days after GSPE treatment. The colonic injury and inflammation were assessed by macroscopic and macroscopic damage scores, colon weight/length ratio (mg/cm), and myeloperoxidase activity. Then, superoxide dismutase, glutathione peroxidase, inducible nitric oxide synthase (iNOS) activities, and the levels of malonyldialdehyde, glutathione, and nitric oxide in serum and colonic tissues were measured. Compared with the recurrent UC group, GSPE treatment facilitated recovery of pathologic changes in the colon after induction of recurrent colitis, as demonstrated by reduced colonic weight/length ratio and macroscopic and microscopic damage scores. The myeloperoxidase and iNOS activities with malonyldialdehyde and nitric oxide levels in serum and colon tissues of colitis rats were significantly decreased in the GSPE group compared with those in the recurrent UC group. In addition, GSPE treatment was associated with notably increased superoxide dismutase, glutathione peroxidase activities, and glutathione levels of colon tissues and serum of rats. GSPE exerted a protective effect on recurrent colitis in rats by modifying the inflammatory response, inhibiting inflammatory cell infiltration and antioxidation damage, promoting damaged tissue repair to improve colonic oxidative stress, and inhibiting colonic iNOS activity to reduce the production of nitric oxide.

Food Funct. 2016 Apr;7(4):1788-96. doi: 10.1039/c5fo01096a.

Impact of increasing fruit and vegetables and flavonoid intake on the human gut microbiota.

Klinder A, Shen Q, Heppel S, Lovegrove JA, Rowland I, Tuohy KM.

Abstract

Epidemiological studies have shown protective effects of fruits and vegetables (F&V) in lowering the risk of developing cardiovascular diseases (CVD) and cancers. Plant-derived dietary fibre (non-digestible polysaccharides) and/or flavonoids may mediate the observed protective effects particularly through their interaction with the gut microbiota. The aim of this study was to assess the impact of fruit and vegetable (F&V) intake on gut microbiota, with an emphasis on the role of flavonoids, and further to explore relationships between microbiota and factors associated with CVD risk. In the study, a parallel design with 3 study groups, participants in the two intervention groups representing high-flavonoid (HF) and low flavonoid (LF) intakes were asked to increase their daily F&V intake by 2, 4 and 6 portions for a duration of 6 weeks each, while a third (control) group continued with their habitual diet. Faecal samples were collected at baseline and after each dose from 122 subjects. Faecal bacteria enumeration was performed by

fluorescence in situ hybridisation (FISH). Correlations of dietary components, flavonoid intake and markers of CVD with bacterial numbers were also performed. A significant dose X treatment interaction was only found for Clostidium leptum-Ruminococcus bromii/flavefaciens with a significant increase after intake of 6 additional portions in the LF group. Correlation analysis of the data from all 122 subjects independent from dietary intervention indicated an inhibitory role of F&V intake, flavonoid content and sugars against the growth of potentially pathogenic clostridia. Additionally, we observed associations between certain bacterial populations and CVD risk factors including plasma TNF-α, plasma lipids and BMI/waist circumference.

Curr Obes Rep. 2015 Dec;4(4):389-400.
Gut Microbiota Dysbiosis in Obesity-Linked Metabolic Diseases and Prebiotic Potential of Polyphenol-Rich Extracts.

Anhê FF, Varin TV, Le Barz M, Desjardins Y, Levy E, Roy D, Marette A.

Abstract

Trillions of microorganisms inhabit the human body, strongly colonizing the gastro-intestinal tract and outnumbering our own cells. High-throughput sequencing techniques and new bioinformatic tools have enabled scientists to extend our knowledge on the relationship between the gut microbiota and host's physiology. Disruption of the ecological equilibrium in the gut (i.e., dysbiosis) has been associated with several pathological processes, including obesity and its related comorbidities, with diet being a strong determinant of gut microbial balance. In this review, we discuss the potential prebiotic effect of polyphenol-rich foods and extracts and how they can reshape the gut microbiota, emphasizing the novel role of the mucin-degrading bacterium Akkermansia muciniphila in their metabolic benefits.

Gut. 2016 Feb;65(2):330-9.
The gut microbiota and host health: a new clinical frontier.
Marchesi JR, Adams DH, Fava F, Hermes GD, Hirschfield GM, Hold G, Quraishi MN, Kinross J, Smidt H, Tuohy KM, Thomas LV, Zoetendal EG, Hart A.

Abstract

Over the last 10-15 years, our understanding of the composition and functions of the human gut microbiota has increased exponentially. To a large extent, this has been due to new 'omic' technologies that have facilitated large-scale analysis of the genetic and metabolic profile of this microbial community, revealing it to be comparable in influence to a new organ in the body and offering the possibility of a new route for therapeutic intervention. Moreover, it might be more accurate to think of it like an immune system: a collection of cells that work in unison with the host and that can promote health but sometimes initiate disease. This review gives an update on the current knowledge in the area of gut disorders, in particular metabolic syndrome and obesity-related disease, liver disease, IBD and colorectal cancer. The potential

of manipulating the gut microbiota in these disorders is assessed, with an examination of the latest and most relevant evidence relating to antibiotics, probiotics, prebiotics, polyphenols and faecal microbiota transplantation.

Clin Ther. 2015 May 1;37(5):984-95.
Gut-Microbiota-Brain Axis and Its Effect on Neuropsychiatric Disorders With Suspected Immune Dysregulation.

Petra AI, Panagiotidou S, Hatziagelaki E, Stewart JM, Conti P, Theoharides TC.

Abstract

PURPOSE:

Gut microbiota regulate intestinal function and health. However, mounting evidence indicates that they can also influence the immune and nervous systems and vice versa. This article reviews the bidirectional relationship between the gut microbiota and the brain, termed the microbiota-gut-brain (MGB) axis, and discusses how it contributes to the pathogenesis of certain disorders that may involve brain inflammation.

METHODS:

Articles were identified with a search of Medline (starting in 1980) by using the key words anxiety, attention-deficit hypersensitivity disorder (ADHD), autism, cytokines, depression, gut, hypothalamic-pituitary-adrenal (HPA) axis, inflammation, immune system, microbiota, nervous system, neurologic, neurotransmitters, neuroimmune conditions, psychiatric, and stress.

FINDINGS:

Various afferent or efferent pathways are involved in the MGB axis. Antibiotics, environmental and infectious agents, intestinal neurotransmitters/neuromodulators, sensory vagal fibers, cytokines, and essential metabolites all convey information to the central nervous system about the intestinal state. Conversely, the hypothalamic-pituitary-adrenal axis, the central nervous system regulatory areas of satiety, and neuropeptides released from sensory nerve fibers affect the gut microbiota composition directly or through nutrient availability. Such interactions seem to influence the pathogenesis of a number of disorders in which inflammation is implicated, such as mood disorder, autism-spectrum disorders, attention-deficit hypersensitivity disorder, multiple sclerosis, and obesity.

IMPLICATIONS:

Recognition of the relationship between the MGB axis and the neuroimmune systems provides a novel approach for better understanding and management of these disorders. Appropriate preventive measures early in life or corrective measures such as use of psychobiotics, fecal microbiota transplantation, and flavonoids are discussed.

Biomed Res Int. 2015;2015:850902.
A survey of modulation of gut microbiota by dietary polyphenols.

Dueñas M, Muñoz-González I, Cueva C, Jiménez-Girón A, Sánchez-Patán F, Santos-Buelga C, Moreno-Arribas MV, Bartolomé B.

Abstract

Dietary polyphenols present in a broad range of plant foods have been related to beneficial health effects. This review aims to update the current information about the modulation of the gut microbiota by dietary phenolic compounds, from a perspective based on the experimental approaches used. After referring to general aspects of gut microbiota and dietary polyphenols, studies related to this topic are presented according to their experimental design: batch culture fermentations, gastrointestinal simulators, animal model studies, and human intervention studies. In general, studies evidence that dietary polyphenols may contribute to the maintenance of intestinal health by preserving the gut microbial balance through the stimulation of the growth of beneficial bacteria (i.e., lactobacilli and bifidobacteria) and the inhibition of pathogenic bacteria, exerting prebiotic-like effects. Combination of in vitro and in vivo models could help to understand the underlying mechanisms in the polyphenols-microbiota-host triangle and elucidate the implications of polyphenols on human health. From a technological point of view, supplementation with rich-polyphenolic stuffs (phenolic extracts, phenolic-enriched fractions, etc.) could be an effective option to improve health benefits of functional foods such as the case of dairy fermented foods.

Eur J Nutr. 2015 Apr;54(3):325-41.
Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review.

Duda-Chodak A, Tarko T, Satora P, Sroka P.

Abstract

The intestinal microbiome plays an important role in the metabolism of chemical compounds found within food. Bacterial metabolites are different from those that can be generated by human enzymes because bacterial processes occur under anaerobic conditions and are based mainly on reactions of reduction and/or hydrolysis. In most cases, bacterial metabolism reduces the activity of dietary compounds; however, sometimes a specific product of bacterial transformation exhibits enhanced properties. Studies on the metabolism of polyphenols by the intestinal microbiota are crucial for understanding the role of these compounds and their impact on our health. This review article presents possible pathways of polyphenol metabolism by intestinal bacteria and describes the diet-derived bioactive metabolites produced by gut microbiota, with a particular emphasis on polyphenols and their potential impact on human health. Because the etiology of many diseases is largely correlated with the intestinal microbiome, a balance between the host immune system and the commensal gut microbiota is crucial for maintaining health. Diet-related and age-related changes in the human intestinal microbiome and their consequences are summarized in the paper.

Mech Ageing Dev. 2014 Mar-Apr;136-137:59-69.
Cognitive decline, dietary factors and gut-brain interactions.

Caracciolo B, Xu W, Collins S, Fratiglioni L.

Abstract

Cognitive decline in elderly people often derives from the interaction between aging-related changes and age-related diseases and covers a large spectrum of clinical manifestations, from intact cognition through mild cognitive impairment and dementia. Epidemiological evidence supports the hypothesis that modifiable lifestyle-related factors are associated with cognitive decline, opening new avenues for prevention. Diet in particular has become the object of intense research in relation to cognitive aging and neurodegenerative disease. We reviewed the most recent findings in this rapidly expanding field. Some nutrients, such as vitamins and fatty acids, have been studied longer than others, but strong scientific evidence of an association is lacking even for these compounds. Specific dietary patterns, like the Mediterranean diet, may be more beneficial than a high consumption of single nutrients or specific food items. A strong link between vascular risk factors and dementia has been shown, and the association of diet with several vascular and metabolic diseases is well known. Other plausible mechanisms underlying the relationship between diet and cognitive decline, such as inflammation and oxidative stress, have been established. In addition to the traditional etiological pathways, new hypotheses, such as the role of the intestinal microbiome in cognitive function, have been suggested and warrant further investigation.

J Proteome Res. 2012 Oct 5;11(10):4781-90.
Metabolomics view on gut microbiome modulation by polyphenol-rich foods.

Moco S, Martin FP, Rezzi S.

Abstract

Health is influenced by genetic, lifestyle, and diet determinants; therefore, nutrition plays an essential role in health management. Still, the substantiation of nutritional health benefits is challenged by the intrinsic macro- and micronutrient complexity of foods and individual responses. Evidence of healthy effects of food requires new strategies not only to stratify populations according to their metabolic requirements but also to predict and measure individual responses to dietary intakes. The influence of the gut microbiome and its interaction with the host is pivotal to understand nutrition and metabolism. Thus, the modulation of the gut microbiome composition by alteration of food habits has potentialities in health improvement or even disease prevention. Dietary polyphenols are naturally occurring constituents in vegetables and fruits, including coffee and cocoa. They are commonly associated to health benefits, although mechanistic evidence in vivo is not yet fully understood. Polyphenols are extensively

metabolized by gut bacteria into a complex series of end-products that support a significant effect on the functional ecology of symbiotic partners that can affect the host physiology. This review reports recent nutritional metabolomics inspections of gut microbiota-host metabolic interactions with a particular focus on the cometabolism of cocoa and coffee polyphenols.

J Agric Food Chem. 2012 Sep 12;60(36):8776-82.
Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber.

Tuohy KM, Conterno L, Gasperotti M, Viola R.

Abstract

Whole plant foods, including fruit, vegetables, and whole grain cereals, protect against chronic human diseases such as heart disease and cancer, with fiber and polyphenols thought to contribute significantly. These bioactive food components interact with the gut microbiota, with gut bacteria modifying polyphenol bioavailability and activity, and with fiber, constituting the main energy source for colonic fermentation. This paper discusses the consequences of increasing the consumption of whole plant foods on the gut microbiota and subsequent implications for human health. In humans, whole grain cereals can modify fecal bacterial profiles, increasing relative numbers of bifidobacteria and lactobacilli. Polyphenol-rich chocolate and certain fruits have also been shown to increase fecal bifidobacteria. The recent FLAVURS study provides novel information on the impact of high fruit and vegetable diets on the gut microbiota. Increasing whole plant food consumption appears to up-regulate beneficial commensal bacteria and may contribute toward the health effects of these foods.

Fitoterapia. 2011 Jan;82(1):53-66.
The intestinal microbiome: a separate organ inside the body with the metabolic potential to influence the bioactivity of botanicals.
Possemiers S, Bolca S, Verstraete W, Heyerick A.

Abstract

For many years, it was believed that the main function of the large intestine was the resorption of water and salt and the facilitated disposal of waste materials. However, this task definition was far from complete, as it did not consider the activity of the microbial content of the large intestine. Nowadays it is clear that the complex microbial ecosystem in our intestines should be considered as a separate organ within the body, with a metabolic capacity which exceeds the liver with a factor 100. The intestinal microbiome is therefore closely involved in the first-pass metabolism of dietary compounds. This is especially true for botanical supplements, which are

now marketed for various health applications. Being of natural origin, their structural building blocks, such as polyphenols, are often highly recognized by the human and especially the intestinal microbial metabolism machinery. Intensive metabolism results in often low circulating levels of the original products, with the consequence that final health effects of botanicals are often related to specific active metabolites which are produced in the body rather than being related to the product's original composition. Understanding how such metabolic processes contribute to the in situ exposure is therefore crucial for the proper interpretation of biological responses. A multidisciplinary approach, characterizing the food and phytochemical intake as well as the metabolic potency of the gut microbiota, while measuring biomarkers of both exposure and response in target tissues, is therefore of critical importance. With polyphenol metabolism as example, this review describes how the incorporation of microbial metabolism as an important variable in the evaluation of the final bioactivity of botanicals strongly increases the relevance and predictive value of the outcome. Moreover, knowledge about intestinal processes may offer innovative strategies for targeted product development.

Digestive Performance Blend – Selected Background Documents
Eur Rev Med Pharmacol Sci. 2016;20(1):146-9.
The effect of ginger (Zingiber officinalis) and artichoke (Cynara cardunculus) extract supplementation on gastric motility: a pilot randomized study in healthy volunteers.

Lazzini S, Polinelli W, Riva A, Morazzoni P, Bombardelli E.

Abstract

OBJECTIVE:

Prodigest® is the standardized combination of artichoke and ginger extracts. This combination was safe and effective in the treatment of functional dyspepsia. However, further evidence could be useful to shed new lights on the effect of Prodigest® on gastric motility. This pilot randomized study on healthy volunteers investigates the prokinetic activity of Prodigest®.

SUBJECTS AND METHODS:

This was a randomized, cross-over study in healthy volunteers comparing Prodigest® versus placebo. Eleven healthy volunteers were enrolled. Each participant underwent two evaluations, at a 7-day interval. Ten minutes before the main meal, the baseline area of gastric volume was determined by ultrasonography. The subject was then given one Prodigest® or placebo capsule and, then consumed a standardized meal. One hour after the meal, the gastric volume was measured again. Two weeks after the second evaluation, three subjects repeated the above-mentioned procedures taking two capsules of Prodigest®.

RESULTS:

The mean gastric area at baseline was 3.2 ± 0.5 cm(2); after the meal, this figure was 8.4 ± 0.7 cm(2) with Prodigest® and 11.0 ± 1.5 cm2 with placebo ($p<0.001$). The after-meal gastric area was significantly smaller, with a -24% difference, following the combination of extracts, as compared with placebo ($p<0.001$). The effect of two capsules of Prodigest® seems to be

more evident but due to the very small number of the patients sample further clinical data are necessary before confirming the dose-related effects.

CONCLUSIONS:

This pilot study shows that Prodigest®, a standardized extract of ginger and artichoke, significantly promotes gastric emptying in healthy volunteers without being associated with notable adverse effects.

Evid Based Complement Alternat Med. 2015;2015:915087.
The Effect of Ginger (Zingiber officinalis) and Artichoke (Cynara cardunculus) Extract Supplementation on Functional Dyspepsia: A Randomised, Double-Blind, and Placebo-Controlled Clinical Trial.

Giacosa A, Guido D, Grassi M, Riva A, Morazzoni P, Bombardelli E, Perna S, Faliva MA, Rondanelli M.

Abstract

Objective. Functional dyspepsia (FD) is a frequent clinical finding in western world. The aim of this study is to compare the efficacy of a ginger and artichoke supplementation versus placebo in the treatment of FD. Methods. A prospective multicentre, double blind, randomized, placebo controlled, parallel-group comparison of the supplement and placebo over a period of 4 weeks was performed. Two capsules/day were supplied (before lunch and dinner) to 126 FD patients (supplementation/placebo: 65/61). Results. After 14 days of treatment, only supplementation group (SG) showed a significant amelioration (SG: α S = +1.195 MCA score units (u), P = 0.017; placebo: α P = +0.347 u, P = 0.513). The intercept (α) resulted to be significantly higher in SG than in placebo (α S - α P = +0.848 u, P < 0.001). At the end of the study, the advantage of SG versus placebo persists without variation (β S - β P = +0.077 u, P = 0.542). In SG, a significant advantage is observed for nausea (β S - β P = -0.398 u, P < 0.001), epigastric fullness (β S - β P = -0.241, P < 0.001), epigastric pain (β S - β P = -0.173 u, P = 0.002), and bloating (β S - β P = -0.167 u, P = 0.017). Conclusions. The association between ginger and artichoke leaf extracts appears safe and efficacious in the treatment of FD and could represent a promising treatment for this disease.

J Diet Suppl. 2017 Mar 4;14(2):173-185.
Yeast β-Glucan Modulates Inflammation and Waist Circumference in Overweight and Obese Subjects.

Mosikanon K, Arthan D, Kettawan A, Tungtrongchitr R, Prangthip P.

Abstract

Increased inflammation occurs with excessive adiposity and yeast β-glucan modulates immune responses. This study investigated the potential effect of yeast β-glucan on inflammatory cytokines in overweight/obese people. A randomized, double blinded, placebo-controlled, clinical trial design enrolled 44 overweight/obese participants with body mass index ≥23 kg/m2, randomized to two groups receiving

β-glucan 477 mg/capsule (n = 22) or placebo (n = 22) orally for six weeks. At weeks one to two, participants received 1 β-glucan or placebo capsule/day and at four weeks two tablets/day. Anthropometric changes, lipid profiles, liver and renal functions, and inflammatory cytokines were measured. β-glucan reduced waist circumference ($p = 0.037$) and blood pressure ($p = 0.006$) compared with controls after six weeks of intervention. No statistical significance between groups was observed for triglyceride, cholesterol, lipid profile, liver and renal function, or energy and nutrient intake compared with controls at week six. β-glucan increased interlukin-10 (IL-10), an anti-inflammatory cytokine, by 23.97% from baseline at week two ($p < 0.001$) and 31.12% at week six ($p < 0.001$) and was significantly increased compared with controls at week two ($p < 0.001$) until week six ($p < 0.001$). β-glucan reduced pro-inflammatory cytokines IL-6 at week six ($p = 0.005$) and tumor necrosis factor-α at week two ($p = 0.037$) compared with controls. Supplementation of yeast β-glucan for six weeks modulated pro-cytokines that accelerate overweight/ obese comorbidities and reduced blood pressure as well as waist circumference, the strong risk factors for cardiovascular disease, in overweight/obese subjects. Thus, β-glucan might have the potential to decrease comorbid conditions associated with overweight/ obesity.

Nutr J. 2014 Apr 28;13:38.
Immune-modulatory effects of dietary Yeast Beta-1,3/1,6-D-glucan.

Stier H, Ebbeskotte V, Gruenwald J.

Abstract

Beta-glucans are a heterogeneous group of natural polysaccharides mostly investigated for their immunological effects. Due to the low systemic availability of oral preparations, it has been thought that only parenterally applied beta-glucans can modulate the immune system. However, several in vivo and in vitro investigations have revealed that orally applied beta-glucans also exert such effects. Various receptor interactions, explaining possible mode of actions, have been detected. The effects mainly depend on the source and structure of the beta-glucans. In the meantime, several human clinical trials with dietary insoluble yeast beta-glucans have been performed. The results confirm the previous findings of in vivo studies. The results of all studies taken together clearly indicate that oral intake of insoluble yeast beta-glucans is safe and has an immune strengthening effect.

Mol Nutr Food Res. 2014 Jan;58(1):183-93.
Effects of orally administered yeast-derived beta-glucans: a review.

Samuelsen AB, Schrezenmeir J, Knutsen SH.

Abstract

Yeast-derived beta-glucans (Y-BG) are considered immunomodulatory compounds suggested to enhance the defense against infections and exert anticarcinogenic effects. Specific preparations have received Generally Recognized as Safe status and acceptance as novel food ingredients by European Food Safety Authority. In human trials, orally administered Y-BG significantly reduced

the incidence of upper respiratory tract infections in individuals susceptible to upper respiratory tract infections, whereas significant differences were not seen in healthy individuals. Increased salivary IgA in healthy individuals, increased IL-10 levels in obese subjects, beneficial changes in immunological parameters in allergic patients, and activated monocytes in cancer patients have been reported following Y-BG intake. The studies were conducted with different doses (7.5-1500 mg/day), using different preparations that vary in their primary structure, molecular weight, and solubility. In animal models, oral Y-BG have reduced the incidence of bacterial infections and levels of stress-induced cytokines and enhanced antineoplastic effects of cytotoxic agents. Protective effects toward drug intoxication and ischemia/reperfusion injury have also been reported. In conclusion, additional studies following good clinical practice principles are needed in which well-defined Y-BG preparations are used and immune markers and disease endpoints are assessed. Since optimal dosing may depend on preparation characteristics, dose-response curves might be assessed to find the optimal dose for a specific preparation.

J Diet Suppl. 2013 Sep;10(3):171-83.
Baker's yeast beta glucan supplementation increases salivary IgA and decreases cold/flu symptomatic days after intense exercise.

McFarlin BK, Carpenter KC, Davidson T, McFarlin MA.

Abstract

Strenuous exercise, such as running a marathon, is known to suppress mucosal immunity for up to 24 hr, which can increase the risk of developing an upper respiratory tract infection (URTI) and reduced performance capacity (Allgrove JE, Geneen L, Latif S, Gleeson M. Influence of a fed or fasted state on the s-IgA response to prolonged cycling in active men and women. Int J Sport Nutr Exerc Metab. 2009;19(3):209-221; Barrett B, Locken K, Maberry R, Schwamman J, Brown R, Bobula J, Stauffacher EA. The Wisconsin Upper Respiratory Symptom Survey (WURSS): a new research instrument for assessing the common cold. J Fam Pract. 2002;51(3):265; Carpenter KC, Breslin WL, Davidson T, Adams A, McFarlin BK. Baker's yeast beta glucan supplementation increases monocytes and cytokines post-exercise: implications for infection risk? Br J Nutr. 2012;1-9). While many dietary interventions have been used to combat postexercise immune suppression, most have been ineffective. The key purpose of this study was to determine if baker's yeast β-glucan (BG) could positively affect the immune system of individuals undergoing intense exercise stress using two experiments. In the first (E1; N = 182 men and women), BG was compared to placebo supplementation for the incidence of URTI symptoms for 28 days postmarathon. In the second (E2; N = 60 men and women) changes in salivary immunoglobulin A (IgA) were evaluated after 50-min of strenuous cycling when participants had been supplemented for 10 days with either BG (250 mg/day) or placebo (rice flour). For E1, subjects reported URTI symptoms using a daily health log. For E2, saliva was collected prior to, immediately, and 2-hr postexercise using a salivette. Data for E1 and E2 were analyzed using separate analyses of

variance (ANOVAs) with repeated measures ($p < .05$). In E1, BG was associated with a 37% reduction in the number of cold/flu symptom days postmarathon compared to placebo ($p = .026$). In E2, BG was associated with a 32% increase in salivary IgA ($p = .048$) at 2 hr after exercise compared to placebo. In summary, the present study demonstrates that BG may reduce URTI symptomatic days and improve mucosal immunity (salivary IgA) postexercise.

J Am Coll Nutr. 2012 Aug;31(4):295-300.
Baker's yeast beta-glucan supplement reduces upper respiratory symptoms and improves mood state in stressed women.

Talbott SM, Talbott JA.

Abstract

OBJECTIVE:

Several studies have shown a baker's yeast beta-1,3/1,6-d-glucan, extracted from Saccharomyces cerevisiae, is effective in reducing the incidence of cold and flu symptoms. This study evaluated the effect of a specific beta-glucan supplement (Wellmune) on upper respiratory tract symptoms and psychological well-being in women with moderate levels of psychological stress.

METHODS:

Healthy women (38 ± 12 years old) prescreened for moderate levels of psychological stress, self-administered a placebo (n = 38) or 250 mg of Wellmune (n = 39) daily for 12 weeks. We used the Profile of Mood States (POMS) psychological survey to assess changes in mental/physical energy levels (vigor) and overall well-being (global mood state). A quantitative health perception log was used to track upper respiratory symptoms.

RESULTS:

Subjects in the Wellmune group reported fewer upper respiratory symptoms compared to placebo (10% vs 29%), better overall well-being (global mood state: 99 ± 19 vs 108 ± 23, $p < 0.05$), and superior mental/physical energy levels (vigor: 19.9 ± 4.7 vs 15.8 ± 6.3, $p < 0.05$).

CONCLUSIONS:

These data show that daily dietary supplementation with Wellmune reduces upper respiratory symptoms and improves mood state in stressed subjects, and thus it may be a useful approach for maintaining immune protection against daily stressors.

Anticancer Agents Med Chem. 2013 Jun;13(5):709-19.
β-Glucans and their applications in cancer therapy: focus on human studies.

Aleem E.

Abstract

β-glucans belong to a group of polysaccharides located in the cell wall of bacteria, fungi including mushrooms, as well as cereals such as barley and oats. All β-glucans are glucose polymers linked together by a (β 1-3) linear β-glycosidic chain core and they differ by their length and branching structures. They are considered biological response modifiers with immunomodulatory and health beneficial effects including anticancer properties. Few studies using purified β- glucans were performed, but their anticancer potential was demonstrated mainly through studies using extracts from mushrooms, yeast or other sources which contain β-glucan as a key component. Their anticancer effects were demonstrated mainly in in vitro and in vivo experimental systems but fewer studies from human populations are available. β-glucans have been used as adjuvant therapy in clinical trials, mainly in the Far East, with a positive effect on patients' survival and quality of life. The mechanism of action is suggested to be through its stimulation of the immune system. This review focuses on human studies; clinical trials and epidemiological data assessing the efficacy and safety of mushroom-derived β- glucans in cancer treatment and prevention. The potential direct effects of β-glucans on cancer cells are also described.

Anticancer Agents Med Chem. 2013 Jun;13(5):699-708.
The effects of β-glucans on cancer metastasis.

Yoon TJ, Koppula S, Lee KH.

Abstract

Beta-glucans (β-glucans), naturally occurring polysaccharides, are present as constituents of the cell wall of cereal grains, mushrooms, algae, or microbes including bacteria, fungi, and yeast. Since Pillemer et al. first prepared and investigated zymosan in the 1940s and others followed with the investigation of β-glucans in the 1960s and 1970s, researchers have well established the significant role of β-glucans on the immune system relative to cancer treatment, infection immunity, and restoration of damaged bone marrow. However, information on their biological role in anti-metastatic activity remains limited. As an immunomodulating agent, β-glucan acts through the activation of innate immune cells such as macrophages, dendritic cells, granulocytes, and natural killer cells. This activation triggers the responses of adaptive immune cells such as CD4(+) or CD8(+) T cells and B cells, resulting in the inhibition of tumor growth and metastasis. Reports have shown that β-glucans exert multiple effects on cancer cells and cancer prevention. However the mechanisms of their actions appear complex due to differences in source, chemical structure, insufficiently defined preparation, and molecular weight, hence the inconsistent and often contradictory results obtained. This review is focused on the potential of β-glucans as anti-metastatic agents and the known mechanisms underlying their biological effects.

Br J Nutr. 2013 Feb 14;109(3):478-86.
Baker's yeast β-glucan supplementation increases monocytes and cytokines post-exercise: implications for infection risk?

Carpenter KC, Breslin WL, Davidson T, Adams A, McFarlin BK.

Abstract

Strenuous aerobic exercise is known to weaken the immune system, and while many nutritional supplements have been proposed to boost post-exercise immunity, few are known to be effective. The purpose of the present study was to evaluate whether 10 d of supplementation with a defined source of baker's yeast β-glucan (BG, Wellmune WGP®) could minimise post-exercise immunosuppression. Recreationally active men and women (n 60) completed two 10 d trial conditions using a cross-over design with a 7 d washout period: placebo (rice flour) and baker's yeast BG (250 mg/d of β-1,3/1,6-glucans derived from Saccharomyces cerevisiae) before a bout of cycling (49 ± 6 min) in a hot (38 ± 2°C), humid (45 ± 2 % relative humidity) environment. Blood was collected at baseline (before supplement), pre- (PRE), post- (POST) and 2 h (2H) post-exercise. Total and subset monocyte concentration was measured by four-colour flow cytometry. Plasma cytokine levels and lipopolysaccharide (LPS)-stimulated cytokine production were measured using separate multiplex assays. Total ($CD14^+$) and pro-inflammatory monocyte concentrations ($CD14^+/CD16^+$) were significantly greater at POST and 2H ($P<0·05$) with BG supplementation. BG supplementation boosted LPS-stimulated production of IL-2, IL-4, IL-5 and interferon-γ (IFN-γ) at PRE and POST ($P<0·05$). Plasma IL-4, IL-5 and IFN-γ concentrations were greater at 2H following BG supplementation. It appears that 10 d of supplementation with BG increased the potential of blood leucocytes for the production of IL-2, IL-4, IL-5 and IFN-γ. The key findings of the present study demonstrate that BG may have potential to alter immunity following a strenuous exercise session.

Nutrition. 2012 Jun;28(6):665-9.
Influence of yeast-derived 1,3/1,6 glucopolysaccharide on circulating cytokines and chemokines with respect to upper respiratory tract infections.

Fuller R, Butt H, Noakes PS, Kenyon J, Yam TS, Calder PC.

Abstract

OBJECTIVE:

Wellmune WGP is a food supplement containing a refined 1,3/1,6 glucopolysaccharide that improves the antimicrobial activity of the innate immune cells by the priming of lectin sites. This study aimed to investigate whether Wellmune decreases the frequency and severity of upper respiratory tract infection (URTI) symptoms over 90 d during the peak URTI season in healthy university students. The secondary aims included an assessment of plasma cytokine and chemokine levels.

METHODS:

This was a randomized, double-blinded, placebo-controlled trial lasting 90 d. One hundred healthy individuals (18-65 y old, mean age ~21 y) were randomized to 250 mg of Wellmune once daily or to an identical rice flour-based placebo. Health was recorded daily and two or more reported URTI symptoms for 2 consecutive days triggered a medical assessment and blood collection within 24 h. The URTI symptom severity was monitored. Plasma cytokines

and chemokines were measured at day 0, day 90, and during the confirmed URTI.

RESULTS:

Ninety-seven participants completed the trial (Wellmune, n = 48; placebo, n = 49). The Wellmune tended to decrease the total number of days with URTI symptoms (198 d, 4.6%, versus 241 d, 5.5% in the control group, P = 0.06). The ability to "breathe easily" was significantly improved in the Wellmune group; the other severity scores showed no significant difference. Cytokines and chemokines were not different between the groups at study entry or day 90, but monocyte chemotactic protein-1 was lower in the Wellmune group during the URTI.

CONCLUSION:

Wellmune may decrease the duration and severity of URTI. Larger studies are needed to demonstrate this.

Endocr Metab Immune Disord Drug Targets. 2009 Mar;9(1):67-75.
Glucans as biological response modifiers.

Novak M, Vetvicka V.

Abstract

Beta-D-glucans belong to a group of natural, physiologically active compounds, generally called biological response modifiers. Glucans represent highly conserved structural components of cell walls in yeast, fungi, or seaweed. Despite long history of research, the exact mechanisms of glucan action remain unsolved. The present review starts with the history of glucans. Next, the detailed information about the possible glucan sources is followed by a description of the mechanisms of action. Physiological functions of glucan suggest the possible use of glucans not only as non-specific immunomodulator, but also as its possible future use as a drug.

Physiol Behav. 2008 May 23;94(2):276-84.
Dietary modulation of immune function by beta-glucans.

Volman JJ, Ramakers JD, Plat J.

Abstract

The immune response can be modulated by nutrients like beta-glucans, which are glucose polymers that are major structural components of the cell wall of yeast, fungi, and bacteria, but also of cereals like oat and barley. There is a lot of structural variation in the beta-glucans from these different sources, which may influence their physiological functions. In this review the current status concerning possibilities to modulate immune function by beta-glucans is discussed. In vitro as well as in vivo studies in animals and humans show that especially beta-glucans derived from fungi and yeast have immune modulating properties. Most frequently

evaluated are effects on leukocyte activity, which has been suggested to contribute to the increased resistance against infections observed after beta-glucan interventions. Although most studies supply the beta-glucans parenteral (e.g. intravenous or subcutaneous), also enteral administrated (dietary) beta-glucan influence the immune response. Although more human studies are needed, it is tempting to suggest that dietary beta-glucans may be a useful tool to prime the host immune system and increase resistance against invading pathogens.

Mutat Res. 2008 Mar-Apr;658(3):154-61.
beta-Glucans in promoting health: prevention against mutation and cancer.

Mantovani MS, Bellini MF, Angeli JP, Oliveira RJ, Silva AF, Ribeiro LR.

Abstract

The polysaccharides beta-glucans occur as a principal component of the cellular walls. Some microorganisms, such as yeast and mushrooms, and also cereals such as oats and barley, are of economic interest because they contain large amounts of beta-glucans. These substances stimulate the immune system, modulating humoral and cellular immunity, and thereby have beneficial effect in fighting infections (bacterial, viral, fungal and parasitic). beta-Glucans also exhibit hypocholesterolemic and anticoagulant properties. Recently, they have been demonstrated to be anti-cytotoxic, antimutagenic and anti-tumorogenic, making them promising candidate as pharmacological promoters of health.

Mar Drugs. 2014 Jan 28;12(2):851-70.
Fucoidan as a marine anticancer agent in preclinical development.

Kwak JY1.

Abstract

Fucoidan is a fucose-containing sulfated polysaccharide derived from brown seaweeds, crude extracts of which are commercially available as nutritional supplements. Recent studies have demonstrated antiproliferative, antiangiogenic, and anticancer properties of fucoidan in vitro. Accordingly, the anticancer effects of fucoidan have been shown to vary depending on its structure, while it can target multiple receptors or signaling molecules in various cell types, including tumor cells and immune cells. Low toxicity and the in vitro effects of fucoidan mentioned above make it a suitable agent for cancer prevention or treatment. However, preclinical development of natural marine products requires in vivo examination of purified compounds in animal tumor models. This review discusses the effects of systemic and local administration of fucoidan on tumor growth, angiogenesis, and immune reaction and whether in vivo and in vitro results are likely applicable to the development of fucoidan as a marine anticancer drug.

J Nutr. 2013 Nov;143(11):1794-8.
Supplementation of elderly Japanese men and women with fucoidan from seaweed increases immune responses to seasonal influenza vaccination.

Negishi H, Mori M, Mori H, Yamori Y.

Abstract

The elderly are known to have an inadequate immune response to influenza vaccine. Mekabu fucoidan (MF), a sulfated polysaccharide extracted from seaweed, was previously shown to have an immunomodulatory effect. We therefore investigated antibody production after influenza vaccination in elderly Japanese men and women with and without oral MF intake. A randomized, placebo-controlled, double-blind study was conducted with 70 volunteers >60 y of age. They were randomly assigned to 1 of 2 groups, consuming either MF (300 mg/d) or placebo for 4 wk, and then given a trivalent seasonal influenza vaccine. Serum was sampled at 5 and 20 wk after vaccination to measure the hemagglutination inhibition titer and natural killer cell activity. The MF group had higher antibody titers against all 3 strains contained in the seasonal influenza virus vaccine than the placebo group. Titers against the B/Brisbane/60/2008 (B) strain increased substantially more in the MF group than in the placebo group over the product consumption period. The immune response against B antigen met the European Union Licensure criteria regarding the geometric mean titer ratio in the MF group (2.4), but not in the placebo group (1.7). In the MF group, natural killer cell activity tended to increase from baseline 9 wk after MF intake ($P = 0.08$). However, in the placebo group no substantial increase was noted at 9 wk, and the activity decreased substantially from 9 to 24 wk. In the immunocompromised elderly, MF intake increased antibody production after vaccination, possibly preventing influenza epidemics.

Molecules. 2016 Apr 27;21(5).
Polysaccharides from the Marine Environment with Pharmacological, Cosmeceutical and Nutraceutical Potential.

Ruocco N, Costantini S, Guariniello S, Costantini M.

Abstract

Carbohydrates, also called saccharides, are molecules composed of carbon, hydrogen, and oxygen. They are the most abundant biomolecules and essential components of many natural products and have attracted the attention of researchers because of their numerous human health benefits. Among carbohydrates the polysaccharides represent some of the most abundant bioactive substances in marine organisms. In fact, many marine macro- and microorganisms are good resources of carbohydrates with diverse applications due to their biofunctional properties. By acting on cell proliferation and cycle, and by modulating different metabolic pathways, marine polysaccharides (including mainly chitin, chitosan, fucoidan, carrageenan and alginate) also have numerous pharmaceutical activities, such as antioxidative, antibacterial, antiviral,

immuno-stimulatory, anticoagulant and anticancer effects. Moreover, these polysaccharides have many general beneficial effects for human health, and have therefore been developed into potential cosmeceuticals and nutraceuticals. In this review we describe current advances in the development of marine polysaccharides for nutraceutical, cosmeceutical and pharmacological applications. Research in this field is opening new doors for harnessing the potential of marine natural products.

Mar Drugs. 2016 Mar 18;14(3).
Looking Beyond the Terrestrial: The Potential of Seaweed Derived Bioactives to Treat Non-Communicable Diseases.

Collins KG, Fitzgerald GF, Stanton C, Ross RP.

Abstract

Seaweeds are a large and diverse group of marine organisms that are commonly found in the maritime regions of the world. They are an excellent source of biologically active secondary metabolites and have been shown to exhibit a wide range of therapeutic properties, including anti-cancer, anti-oxidant, anti-inflammatory and anti-diabetic activities. Several Asian cultures have a strong tradition of using different varieties of seaweed extensively in cooking as well as in herbal medicines preparations. As such, seaweeds have been used to treat a wide variety of health conditions such as cancer, digestive problems, and renal disorders. Today, increasing numbers of people are adopting a "westernised lifestyle" characterised by low levels of physical exercise and excessive calorific and saturated fat intake. This has led to an increase in numbers of chronic Non-communicable diseases (NCDs) such as cancer, cardiovascular disease, and diabetes mellitus, being reported. Recently, NCDs have replaced communicable infectious diseases as the number one cause of human mortality. Current medical treatments for NCDs rely mainly on drugs that have been obtained from the terrestrial regions of the world, with the oceans and seas remaining largely an untapped reservoir for exploration. This review focuses on the potential of using seaweed derived bioactives including polysaccharides, antioxidants and fatty acids, amongst others, to treat chronic NCDs such as cancer, cardiovascular disease and diabetes mellitus.

Adv Food Nutr Res. 2014;72:195-213.
Anticancer effects of fucoidan.

Senthilkumar K, Kim SK.

Abstract

Recently, there has been an increased interest in the pharmacologically active natural compounds isolated and used for remedies of various kinds of diseases, including cancer. The great deal of interest has been developed to isolate bioactive compounds from marine resources because of

their numerous health beneficial effects. Among marine resources, marine algae are valuable sources of structurally diverse bioactive compounds. Fucoidan is a sulfated polysaccharide derived from brown seaweeds and has been used as an ingredient in some dietary supplement products. Fucoidan has various biological activities including antibacterial, antioxidant, anti-inflammatory, anticoagulant, and antitumor activities. So this chapter deals with anticancer effects of fucoidan.

J Med Food. 2014 Jul;17(7):830-2.
Effect of fucoidan administration on insulin secretion and insulin resistance in overweight or obese adults.

Hernández-Corona DM, Martínez-Abundis E, González-Ortiz M.

Abstract

The aim of this article is to evaluate the effect of fucoidan administration on insulin secretion and insulin sensitivity in overweight or obese adults. A randomized, double-blind, placebo-controlled clinical trial was carried out in 25 obese or overweight volunteers. Thirteen patients received an oral dose of 500 mg of fucoidan once daily before breakfast and 12 patients received placebo for 3 months. Before and after the intervention, fasting glucose and 2-h postload, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and insulin levels were measured. Low-density lipoprotein cholesterol (LDL-C) and homeostasis model analysis formulas (HOMA) for β-cell function and insulin resistance were calculated. The results showed a significant decrease in diastolic blood pressure (71.7 ± 12.2 vs. 67.8 ± 13.8 mmHg; P<.05) and LDL-C (3.1 ± 0.5 vs. 2.7 ± 0.6 mmol/l; P<.01) with increase in insulin levels (60.6 ± 24.0 vs. 78.6 ± 32.4 pmol/l; P<.05), HOMA β-cell (35.0 ± 20.8 vs. 50.6 ± 18.7; P<.05) and HOMA IR (1.9 ± 1.2 vs. 2.6 ± 1.8; P<.05) were observed after fucoidan administration. We conclude that fucoidan administration during a 3-month period in overweight or obese adults decreased diastolic blood pressure and LDL-C concentrations, increasing insulin secretion and insulin resistance.

Am J Chin Med. 2013;41(1):131-44.
Immunomodulatory activities of medicinal mushroom Grifola frondosa extract and its bioactive constituent.

Wu SJ1, Lu TM, Lai MN, Ng LT.

Abstract

Grifola frondosa (GF), a high value medicinal mushroom in China and Japan, is popularly consumed as traditional medicines and health foods, especially for enhancing immune functions. In this study, our aim was to examine the immunomodulatory activities of GF and its bioactive compound ergosterol peroxide (EPO) in lipopolysaccharide (LPS)-induced human monocytic

(THP-1) cells. At low concentrations, EPO but not other extracts showed a full protection against LPS-induced cell toxicity. EPO significantly blocked MyD88 and VCAM-1 expression, and cytokine (IL-1β, IL-6 and TNF-α) production in LPS-stimulated cells. It also effectively inhibited NF-κB activation, which was further confirmed with siRNA treatment. These results conclude that EPO may play an important role in the immunomodulatory activity of GF through inhibiting the production of pro-inflammatory mediators and activation of NF-κB signaling pathway.

J Cancer Res Clin Oncol. 2009 Sep;135(9):1215-21.
A phase I/II trial of a polysaccharide extract from Grifola frondosa (Maitake mushroom) in breast cancer patients: immunological effects.

Deng G, Lin H, Seidman A, Fornier M, D'Andrea G, Wesa K, Yeung S, Cunningham-Rundles S, Vickers AJ, Cassileth B.

Abstract

BACKGROUND:

Cancer patients commonly use dietary supplements to "boost immune function". A polysaccharide extract from Grifola frondosa (Maitake extract) showed immunomodulatory effects in preclinical studies and therefore the potential for clinical use. Whether oral administration in human produces measurable immunologic effects, however, is unknown.

METHODS:

In a phase I/II dose escalation trial, 34 postmenopausal breast cancer patients, free of disease after initial treatment, were enrolled sequentially in five cohorts. Maitake liquid extract was taken orally at 0.1, 0.5, 1.5, 3, or 5 mg/kg twice daily for 3 weeks. Peripheral blood was collected at days -7, 0 (prior to the first dosing), 7, 14, and 21 for ex vivo analyses. The primary endpoints were safety and tolerability.

RESULTS:

No dose-limiting toxicity was encountered. Two patients withdrew prior to completion of the study due to grade I possibly related side effects: nausea and joint swelling in one patient; rash and pruritus in the second. There was a statistically significant association between Maitake and immunologic function ($p < 0.0005$). Increasing doses of Maitake increased some immunologic parameters and depressed others; the dose-response curves for many endpoints were non-monotonic with intermediate doses having either immune enhancing or immune suppressant effects compared with both high and low doses.

CONCLUSIONS:

Oral administration of a polysaccharide extract from Maitake mushroom is associated with both immunologically stimulatory and inhibitory measurable effects in peripheral blood. Cancer patients should be made aware of the fact that botanical agents produce more complex effects than assumed, and may depress as well as enhance immune function.

Ann Transl Med. 2014 Feb;2(2):14.
Immune-enhancing effects of Maitake (Grifola frondosa) and Shiitake (Lentinula edodes) extracts.

Vetvicka V, Vetvickova J.

Abstract

BACKGROUND:

The role of glucan in stimulation of immune reactions has been studied for several decades. In this report, we focused on the effects of orally administered glucan Maitake and Shiitake on immune reactions.

MATERIALS AND METHODS:

We measured phagocytosis, NK cell activity, and secretion of IL-6, IL-12, IFN-γ as well as C-reactive protein (CRP) after 14 days of oral application of tested glucans. For comparison, active hexose correlated compound (AHCC) was used in all reactions.

RESULTS:

We found significant stimulation of defense reaction. In all cases, the most active was the Maitake-Shiitake combination, with Maitake alone being the second strongest, followed by Shiitake on its own and AHCC.

CONCLUSIONS:

Short-term oral application of natural immunomodulating glucans from Maitake and Shiitake mushrooms strongly stimulated both the cellular and humoral branch of immune reactions. These activities were significantly higher than those of AHCC.

J Am Coll Nutr. 2015;34(6):478-87.
Consuming Lentinula edodes (Shiitake) Mushrooms Daily Improves Human Immunity: A Randomized Dietary Intervention in Healthy Young Adults.

Dai X, Stanilka JM, Rowe CA, Esteves EA, Nieves C Jr, Spaiser SJ, Christman MC, Langkamp-Henken B, Percival SS.

Abstract

BACKGROUND:

Mushrooms are widely cited for their medicinal qualities, yet very few human intervention studies have been done using contemporary guidelines.

OBJECTIVE:

The aim of this study was to determine whether consumption of whole, dried Lentinula edodes (shiitake) mushrooms could improve human immune function. Primary objectives were to ascertain whether L. edodes consumption would improve γδ-T cell proliferation and activation responses, quantify a dose response, and elicit cytokine secretion patterns. Secondary objectives included determining changes in natural killer T (NK-T) cell proliferation

and activation, secretory immunoglobulin A (sIgA) in saliva, and C-reactive protein (CRP) in serum.

DESIGN:

Fifty-two healthy males and females, aged 21-41 years, participated in a 4-week parallel group study, consuming either 5 or 10 g of mushrooms daily. Each subject had blood drawn before and after 4 weeks of daily L. edodes consumption. Saliva and serum were also collected. Peripheral blood mononuclear cells were cultured in autologous serum for 24 hours or 6 days, stained, and examined by flow cytometry.

RESULTS:

Eating L. edodes for 4 weeks resulted in increased ex vivo proliferation of γδ-T (60% more, $p < 0.0001$) and NK-T (2-fold more, $p < 0.0001$) cells. Both cell types also demonstrated a greater ability to express activation receptors, suggesting that consuming mushrooms improved cell effector function. The increase in sIgA implied improved gut immunity. The reduction in CRP suggested lower inflammation. The pattern of cytokines secreted before and after mushroom consumption was significantly different; consumption resulted in increased interleukin (IL)-4, IL-10, tumor necrosis factor (TNF)-α, and IL-1α levels, a decreased macrophage inflammatory protein-1α/chemokine C-C ligand 3 (MIP-1α/CCL3) level, and no change to IL-6, IL-1β, MIP-1β, IL-17 and interferon (IFN)-γ levels.

CONCLUSIONS:

Regular L. edodes consumption resulted in improved immunity, as seen by improved cell proliferation and activation and increased sIgA production. The changes observed in cytokine and serum CRP levels suggest that these improvements occurred under conditions that were less inflammatory than those that existed before consumption.

Nutr Rev. 1996 Nov;54(11 Pt 2):S91-3.

Functional properties of edible mushrooms.

Chang R.

Abstract

Edible mushrooms such as shiitake may have important salutary effects on health or even in treating disease. A mushroom characteristically contains many different bioactive compounds with diverse biological activity, and the content and bioactivity of these compounds depend on how the mushroom is prepared and consumed. It is estimated that approximately 50% of the annual 5 million metric tons of cultivated edible mushrooms contain functional "nutraceutical" or medicinal properties. In order of decreasing cultivated tonnage, Lentinus (shiitake), Pleurotus (oyster), Auricularia (mu-er), Flammulina (enokitake), Tremella (yin-er), Hericium, and Grifola (maitake) mushrooms have various degrees of immunomodulatory, lipid-lowering, antitumor, and other beneficial or therapeutic health effects without any significant toxicity. Although the data for this functional food class are not as strong as those for other functional foods such as cruciferous vegetables, because of their potential usefulness in preventing or treating

serious health conditions such as cancer, acquired immune deficiency syndrome (AIDS), and hypercholesterolemia, functional mushrooms deserve further serious investigation. Additionally, there is a need for epidemiological evidence of the role of this functional food class.

Nat Rev Gastroenterol Hepatol. 2016 Dec;13(12):691-706.
Diet, microorganisms and their metabolites, and colon cancer.

O'Keefe SJ.

Abstract

Colorectal cancer is one of the so-called westernized diseases and the second leading cause of cancer death worldwide. On the basis of global epidemiological and scientific studies, evidence suggests that the risk of colorectal cancer is increased by processed and unprocessed meat consumption but suppressed by fibre, and that food composition affects colonic health and cancer risk via its effects on colonic microbial metabolism. The gut microbiota can ferment complex dietary residues that are resistant to digestion by enteric enzymes. This process provides energy for the microbiota but culminates in the release of short-chain fatty acids including butyrate, which are utilized for the metabolic needs of the colon and the body. Butyrate has a remarkable array of colonic health-promoting and antineoplastic properties: it is the preferred energy source for colonocytes, it maintains mucosal integrity and it suppresses inflammation and carcinogenesis through effects on immunity, gene expression and epigenetic modulation. Protein residues and fat-stimulated bile acids are also metabolized by the microbiota to inflammatory and/or carcinogenic metabolites, which increase the risk of neoplastic progression. This Review will discuss the mechanisms behind these microbial metabolite effects, which could be modified by diet to achieve the objective of preventing colorectal cancer in Western societies.

Pharmacol Ther. 2016 Aug;164:144-51
Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis.

Sivaprakasam S, Prasad PD, Singh N.

Abstract

Epidemiological studies have linked increased incidence of inflammatory diseases and intestinal cancers in the developed parts of the world to the consumption of diets poor in dietary fibers and rich in refined carbohydrates. Gut bacteria residing in the intestinal lumen exclusively metabolize dietary fibers. Butyrate, propionate and acetate, which are collectively called short-chain fatty acids (SCFAs), are generated by fermentation of dietary fibers by gut microbiota. Evidences indicate that SCFAs are key players in regulating beneficial effect of dietary fibers and gut microbiota on our health. SCFAs interact with metabolite-sensing G protein-coupled receptors GPR41, GPR43 and GPR109A expressed in gut epithelium and immune cells. These interactions induce mechanisms that play a key role in maintaining homeostasis in gut and other

organs. This review summarizes the protective roles of GPR41, GPR43 and GPR109A in dietary fibers-, gut microbiota- and SCFAs-mediated suppression of inflammation and carcinogenesis in gut and other organs.

Neurosci Lett. 2016 Jun 20;625:56-63.
Butyrate, neuroepigenetics and the gut microbiome: Can a high fiber diet improve brain health?

Bourassa MW, Alim I, Bultman SJ, Ratan RR.

Abstract

As interest in the gut microbiome has grown in recent years, attention has turned to the impact of our diet on our brain. The benefits of a high fiber diet in the colon have been well documented in epidemiological studies, but its potential impact on the brain has largely been understudied. Here, we will review evidence that butyrate, a short-chain fatty acid (SCFA) produced by bacterial fermentation of fiber in the colon, can improve brain health. Butyrate has been extensively studied as a histone deacetylase (HDAC) inhibitor but also functions as a ligand for a subset of G protein-coupled receptors and as an energy metabolite. These diverse modes of action make it well suited for solving the wide array of imbalances frequently encountered in neurological disorders. In this review, we will integrate evidence from the disparate fields of gastroenterology and neuroscience to hypothesize that the metabolism of a high fiber diet in the gut can alter gene expression in the brain to prevent neurodegeneration and promote regeneration.

Digestion. 2016;93(3):176-81.
Physiological Role of Gut Microbiota for Maintaining Human Health.

Andoh A.

Abstract

BACKGROUND:

The human body is colonized by an extremely complex and abundant aggregation of microbes, collectively referred to as the gut microbiota. Recent studies have focused on the link between these microbes and our health.

SUMMARY:

Diet contributes to shaping the gut microbial structure and influences metabolic functions of the host. Alteration of the microbial structure and function (dysbiosis) is associated with the pathogenesis of various disorders. Fermentation is the process by which anaerobic bacteria (Firmicutes and Bacteroidetes) break down indigestible carbohydrates to short-chain fatty acids (SCFAs; acetate, propionate and butyrate), collaborating with species specialized in oligosaccharide fermentation (e.g. Bifidobacteria). Butyrate and propionate can regulate

intestinal physiology and immune function, while acetate acts as a substrate for lipogenesis and gluconeogenesis. The gut microbiota regulates immune homeostasis via the induction of regulatory T cells and Th17 cells. In addition, butyrate has strong anti-inflammatory effects possibly through the inhibition of histone deacetylase activity. Metabolic products generated by the gut microbiota, such as SCFAs, GABA, tryptophan, serotonin and catecholamine, transmit a signal to resident cells in the gut.

Food Funct. 2016 Apr;7(4):1731-40.
Diet, microbiota, and dysbiosis: a 'recipe' for colorectal cancer.

Vipperla K, O'Keefe SJ.

Abstract

The food we consume feeds not only us, but also a vast and diverse community of microbiota within our gastrointestinal tract. In a process of symbiotic co-evolution, the gut microbiota became essential for the maintenance of the health and integrity of our colon. The advent of next-generation DNA sequencing technology and metabolic profiling have, in the recent years, revealed the remarkable complexity of microbial diversity and function, and that the microbiota produce a wide variety of bioactive products that are not only active at the mucosal surface, but also absorbed and circulated throughout the body, influencing distant organ health and function. As a result, several microbiota compositional patterns and their associations with both health and disease states have been identified. Importantly, a disturbed microbiota-host relationship, termed dysbiosis, is now recognized to be the root cause for a growing list of diseases, including colorectal cancer (CRC). There is mounting in vitro and in vivo evidence to suggest that diet selects for the microbiota composition and several health promoting and deleterious effects of diet are, in fact, mediated by the microbiota. Recent findings of the feasibility of dietary fiber to boost the colonic microbial synthesis of anti-proliferative and counter carcinogenic metabolites, particularly butyrate, underscores the prerequisite of dietary modification as a key measure to curb the pandemic of CRC in westernized countries. Better understanding of the diet-microbiota interplay and large-scale studies to evaluate the efficacy of dietary modification and gut microbiota modulation in reversing dysbiosis and restoring health could offer novel preventative and/or therapeutic strategies against westernized diseases, which are now considered the chief threat to public health.

Age (Dordr). 2015 Oct;37(5):98.
Improving healthspan via changes in gut microbiota and fermentation.

Keenan MJ, Marco ML, Ingram DK, Martin RJ.

Abstract

Dietary resistant starch impact on intestinal microbiome and improving healthspan is the topic of this review. In the elderly population, dietary fiber intake is lower than recommended. Dietary resistant starch as a source of fiber produces a profound change in gut microbiota and fermentation in animal models of aging. Dietary resistant starch has the potential for improving healthspan in the elderly through multiple mechanisms as follows: (1) enhancing gut microbiota profile and production of short-chain fatty acids, (2) improving gut barrier function, (3) increasing gut peptides that are important in glucose homeostasis and lipid metabolism, and (4) mimicking many of the effects of caloric restriction including upregulation of genes involved in xenobiotic metabolism.

Nat Rev Endocrinol. 2015 Oct;11(10):577-91.
Short-chain fatty acids in control of body weight and insulin sensitivity.

Canfora EE, Jocken JW, Blaak EE.

Abstract

The connection between the gut microbiota and the aetiology of obesity and cardiometabolic disorders is increasingly being recognized by clinicians. Our gut microbiota might affect the cardiometabolic phenotype by fermenting indigestible dietary components and thereby producing short-chain fatty acids (SCFA). These SCFA are not only of importance in gut health and as signalling molecules, but might also enter the systemic circulation and directly affect metabolism or the function of peripheral tissues. In this Review, we discuss the effects of three SCFA (acetate, propionate and butyrate) on energy homeostasis and metabolism, as well as how these SCFA can beneficially modulate adipose tissue, skeletal muscle and liver tissue function. As a result, these SCFA contribute to improved glucose homeostasis and insulin sensitivity. Furthermore, we also summarize the increasing evidence for a potential role of SCFA as metabolic targets to prevent and counteract obesity and its associated disorders in glucose metabolism and insulin resistance. However, most data are derived from animal and in vitro studies, and consequently the importance of SCFA and differential SCFA availability in human energy and substrate metabolism remains to be fully established. Well-controlled human intervention studies investigating the role of SCFA on cardiometabolic health are, therefore, eagerly awaited.

Nat Rev Microbiol. 2014 Oct;12(10):661-72.
The gut microbiota, bacterial metabolites and colorectal cancer.

Louis P, Hold GL, Flint HJ.

Abstract

Accumulating evidence suggests that the human intestinal microbiota contributes to the aetiology

of colorectal cancer (CRC), not only via the pro-carcinogenic activities of specific pathogens but also via the influence of the wider microbial community, particularly its metabolome. Recent data have shown that the short-chain fatty acids acetate, propionate and butyrate function in the suppression of inflammation and cancer, whereas other microbial metabolites, such as secondary bile acids, promote carcinogenesis. In this Review, we discuss the relationship between diet, microbial metabolism and CRC and argue that the cumulative effects of microbial metabolites should be considered in order to better predict and prevent cancer progression.

J Clin Gastroenterol. 2011 Nov;45 Suppl:S120-7.
Fermentation in the human large intestine: its physiologic consequences and the potential contribution of prebiotics.

Macfarlane GT1, Macfarlane S.

Abstract

The human large intestine harbors a complex microbiota containing many hundreds of different bacterial species. Although structure/function relationships between different components of the microbiota are unclear, this complex multicellular entity plays an important role in maintaining homeostasis in the body. Many of the physiologic properties of the microbiota can be attributed to fermentation and the production of short-chain fatty acids (SCFAs), particularly acetate, propionate, and butyrate. In healthy people, fermentation processes are largely controlled by the amounts and different types of substrate, particularly complex carbohydrates that are accessible to bacteria in the colonic ecosystem. However, other factors impact on bacterial metabolism in the large gut, including large bowel transit time, the availability of inorganic terminal electron acceptors, such as nitrate and sulfate, and gut pH. They all affect the types and levels of SCFA that can be formed by the microbiota. This is important because to a large extent, acetate, propionate, and butyrate have varying physiologic effects in different body tissues. Prebiotics such as galactooligosaccharides together with inulins and their fructooligosaccharide derivatives have been shown to modify the species composition of the colonic microbiota, and in various degrees, to manifest several health-promoting properties related to enhanced mineral absorption, laxation, potential anticancer properties, lipid metabolism, and anti-inflammatory and other immune effects, including atopic disease. Many of these phenomena can be linked to their digestion and SCFA production by bacteria in the large gut.

Nutr Res Rev. 2010 Dec;23(2):366-84.
From the gut to the peripheral tissues: the multiple effects of butyrate.
Guilloteau P, Martin L, Eeckhaut V, Ducatelle R, Zabielski R, Van Immerseel F.

Abstract

Butyrate is a natural substance present in biological liquids and tissues. The present paper

aims to give an update on the biological role of butyrate in mammals, when it is naturally produced by the gastrointestinal microbiota or orally ingested as a feed additive. Recent data concerning butyrate production delivery as well as absorption by the colonocytes are reported. Butyrate cannot be detected in the peripheral blood, which indicates fast metabolism in the gut wall and/or in the liver. In physiological conditions, the increase in performance in animals could be explained by the increased nutrient digestibility, the stimulation of the digestive enzyme secretions, a modification of intestinal luminal microbiota and an improvement of the epithelial integrity and defence systems. In the digestive tract, butyrate can act directly (upper gastrointestinal tract or hindgut) or indirectly (small intestine) on tissue development and repair. Direct trophic effects have been demonstrated mainly by cell proliferation studies, indicating a faster renewal of necrotic areas. Indirect actions of butyrate are believed to involve the hormono-neuro-immuno system. Butyrate has also been implicated in down-regulation of bacteria virulence, both by direct effects on virulence gene expression and by acting on cell proliferation of the host cells. In animal production, butyrate is a helpful feed additive, especially when ingested soon after birth, as it enhances performance and controls gut health disorders caused by bacterial pathogens. Such effects could be considered for new applications in human nutrition.

Am J Clin Nutr. 2016 Aug;104(2):526-36.
Zinc carnosine works with bovine colostrum in truncating heavy exercise-induced increase in gut permeability in healthy volunteers.

Davison G, Marchbank T, March DS, Thatcher R, Playford RJ.

Abstract

BACKGROUND:

Heavy exercise causes gut symptoms and, in extreme cases, heat stroke that is due to the increased intestinal permeability of luminal toxins.

OBJECTIVE:

We examined whether zinc carnosine (ZnC), a health-food product taken alone or in combination with bovine colostrum (a natural source of growth factors), would moderate such effects.

DESIGN:

Eight volunteers completed a 4-arm, double-blind, placebo-controlled crossover protocol (14 d of placebo, ZnC, colostrum, or ZnC plus colostrum) before undertaking standardized exercise 2 and 14 d after the start of treatment. Changes in epithelial resistance, apoptosis signaling molecules, and tight junction (TJ) protein phosphorylation in response to a 2°C rise in body temperature were determined with the use of Caco-2 and HT29 intestinal cells.

RESULTS:

Body temperature increased 2°C, and gut permeability (5-h urinary lactulose:rhamnose ratios) increased 3-fold after exercise (from 0.32 ± 0.016 baseline to 1.0 ± 0.017 at 14 d; $P < 0.01$). ZnC or colostrum truncated the rise by 70% after 14 d of treatment. The combination treatment

gave an additional benefit, and truncated exercise induced increase at 2 d (30% reduction; P < 0.01). A 2°C temperature rise in in vitro studies caused the doubling of apoptosis and reduced epithelial resistance 3-4-fold. ZnC or colostrum truncated these effects (35-50%) with the greatest response seen with the combination treatment (all P < 0.01). Mechanisms of action included increasing heat shock protein 70 and truncating temperature-induced changes in B cell leukemia/lymphoma-2 associated X protein and B cell lymphoma 2. ZnC also increased total occludin and reduced phosphorylated tyrosine claudin, phosphorylated tyrosine occludin, and phosphorylated serine occludin, thereby enhancing the TJ formation and stabilization.

CONCLUSION:

ZnC, taken alone or with colostrum, increased epithelial resistance and the TJ structure and may have value for athletes and in the prevention of heat stroke in military personnel. This trial was registered at www.isrctn.com as ISRCTN51159138.

Scand J Gastroenterol. 2014 Feb;49(2):164-72.
Efficacy of zinc-carnosine chelate compound, Polaprezinc, enemas in patients with ulcerative colitis.

Itagaki M, Saruta M, Saijo H, Mitobe J, Arihiro S, Matsuoka M, Kato T, Ikegami M, Tajiri H.

Abstract

OBJECTIVES:

Ulcerative colitis (UC) is a chronic, relapsing and remitting intestinal inflammatory disorder. Zinc is known to be efficacious for the repair of damaged tissue and has been shown to protect against gastric ulceration. This study focused on Polaprezinc (PZ), N-(3-aminopropionyl)-L-histidinato zinc, which accelerates ulcer healing through actions such as prostaglandin-independent cytoprotection and antioxidative activity.

METHODS:

In this randomized, placebo-controlled, investigator-blinded trial, 28 patients with active UC at The Jikei University Hospital were randomly divided into two groups: one treated with a 150 mg PZ enema (n = 18) and the other not treated with a PZ enema (n = 10). All patients received usual induction therapy. Clinical symptoms, endoscopic findings and histological findings were evaluated at entry and one week later.

RESULTS:

In the PZ group, modified Matts' endoscopic scores were significantly improved after treatment compared to baseline in the rectum (p = 0.004), sigmoid colon (p = 0.03) and descending colon (p = 0.04). In the non-PZ group, scores were not significantly improved in the rectum (p = 0.14) and descending colon (p = 0.34), but were improved in the sigmoid colon (p = 0.04). In the PZ group, the Mayo scores at baseline and at Day 8 were 9.1 ± 1.6 and 5.8 ± 2.7 (p = 0.00004), respectively, and in the placebo group, the scores were 8.9 ± 1.7 and 7.4 ± 2.1 (p = 0.009), respectively. Clinical response or remission was significantly better in the PZ group

(71%) than in the placebo group (10%).
CONCLUSIONS:
A zinc-carnosine chelate compound, PZ, enema may become a useful new add-on treatment to accelerate mucosal healing in UC.

BMC Gastroenterol. 2013 Jul 4;13:108.
Effectiveness of polaprezinc for low-dose aspirin-induced small-bowel mucosal injuries as evaluated by capsule endoscopy: a pilot randomized controlled study.

Watari I, Oka S, Tanaka S, Aoyama T, Imagawa H, Shishido T, Yoshida S, Chayama K.

Abstract
BACKGROUND:
Treatment of low-dose aspirin (LDA)-induced small-bowel injury has not been established. Polaprezinc, a chelate of zinc and L-carnosine, may be efficacious for such injury. We conducted a pilot randomized controlled study to investigate whether polaprezinc is effective against LDA-induced small-bowel injuries.
METHODS:
Consecutive patients under long-term (>3 months) LDA treatment and who agreed to participate in our study underwent initial capsule endoscopy (CE). Patients with LDA-induced small-bowel injury apparent upon initial CE (n = 20) were randomized into a polaprezinc (150 mg/day for 4 weeks) group and a control (no polaprezinc treatment) group. All underwent follow-up CE after 4 weeks. Changes in the number and characteristics of small-bowel mucosal injuries were compared within and between the two groups.
RESULTS:
The median number of reddened lesions and erosions/ulcers upon follow-up CE in the polaprezinc group significantly decreased ($P < 0.05$). However, there was no significant difference in the median number of reddened lesions and erosions/ulcers upon follow-up CE in the control group.
CONCLUSIONS:
Co-administration of polaprezinc may be effective against small-bowel mucosal injury associated with long-term LDA therapy.

Gut. 2007 Feb;56(2):168-75.
Zinc carnosine, a health food supplement that stabilises small bowel integrity and stimulates gut repair processes.

Mahmood A, FitzGerald AJ, Marchbank T, Ntatsaki E, Murray D, Ghosh S, Playford RJ.

Abstract

BACKGROUND:

Zinc carnosine (ZnC) is a health food product claimed to possess health-promoting and gastrointestinal supportive activity. Scientific evidence underlying these claims is, however, limited.

AIM:

To examine the effect of ZnC on various models of gut injury and repair, and in a clinical trial.

METHODS:

In vitro studies used pro-migratory (wounded monolayer) and proliferation ([(3)H]-thymidine incorporation) assays of human colonic (HT29), rat intestinal epithelial (RIE) and canine kidney (MDCK) epithelial cells. In vivo studies used a rat model of gastric damage (indomethacin/restraint) and a mouse model of small-intestinal (indomethacin) damage. Healthy volunteers (n = 10) undertook a randomised crossover trial comparing changes in gut permeability (lactulose:rhamnose ratios) before and after 5 days of indomethacin treatment (50 mg three times a day) with ZnC (37.5 mg twice daily) or placebo coadministration.

RESULTS:

ZnC stimulated migration and proliferation of cells in a dose-dependent manner (maximum effects in both assays at 100 micromol/l using HT29 cells), causing an approximate threefold increase in migration and proliferation (both $p<0.01$). Oral ZnC decreased gastric (75% reduction at 5 mg/ml) and small-intestinal injury (50% reduction in villus shortening at 40 mg/ml; both $p<0.01$). In volunteers, indomethacin caused a threefold increase in gut permeability in the control arm; lactulose:rhamnose ratios were (mean (standard error of mean)) 0.35 (0.035) before indomethacin treatment and 0.88 (0.11) after 5 days of indomethacin treatment ($p<0.01$), whereas no significant increase in permeability was seen when ZnC was coadministered.

CONCLUSION:

ZnC, at concentrations likely to be found in the gut lumen, stabilises gut mucosa. Further studies are warranted.