AMARE EDGE™

The all-natural nootropic that supports motivation.*

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AMARE EDGE™

The all-natural nootropic that supports motivation. Mango Leaf, Lychee Fruit, Palm Fruit: 3 synergistically powerful ingredients combined for the first time*

KEY INGREDIENTS

Mango Leaf Extract (Zynamite®) - has a long history of use in tropical areas where mangoes are grown as a "body and brain tonic" to elevate mental and physical energy levels. Recently, mango leaf extracts have been shown to be high in anti-inflammatory compounds called xanthones. These high-xanthone extracts have been studied in seven clinical trials – showing enhanced mental energy (cognitive performance, brain electrophysiology, and reaction time) and improved sports performance (higher power output, reduced fatigue, and accelerated post exercise recovery).

Lychee Fruit Extract (Oligonol®) - is extremely rich in highly-absorbed polyphenols, including catechin monomers and proanthocyanidin oligomers, and has been shown in more than two-dozen clinical trials to reduce body weight, waist circumference (by more than an inch; 3cm), and visceral (belly) fat by 12% (compared to baseline and placebo over 10 weeks). In addition, lychee fruit extract has also been shown to reduce stress hormones (cortisol) and inflammatory cytokines (IL-6 and IL-1beta) in a 4-week randomized controlled trial – and after12-weeks has been shown to improve skin tone, texture, smoothness, and resiliency (reduction in appearance of freckles/blemishes and wrinkle length/depth).

Palm Fruit Extract (Palm Fruit Bioactives complex – PFBc®) - contains a highly unique collection of water-soluble polyphenols (shikimic acid and several derivatives) that support optimal total cardiac output, a decreased workload or pressure on the heart, and a reduction of oxidative and inflammatory stress to help preserve mental wellness. Preclinical research in animals has demonstrated the potent antioxidant properties of palm fruit bioactives (PFBs), which include the upregulation of specific phase II detoxifying enzymes, a decrease in levels of reactive oxygen species, and an increase in the level of intracellular glutathione and heme oxygenase, both of which can profoundly protect delicate heart and brain cells from cellular stress. The beta-amyloid peptide appears to play a key role in the decrease of brain function over time, eventually leading to dementia and Alzheimer's disease. In several preclinical research studies in animals, PFB has been shown to inhibit beta-amyloid aggregation, potentially protecting the brain from age-induced damage. PFB has also been shown to increase levels of nitric oxide synthase and higher levels of nitric oxide, leading to vasodilation of blood vessels; improved oxygen delivery to the heart, muscles, and brain; and overall improvements in physical performance and mental fitness. Recent clinical trials on PFB supplementation in moderately stressed subjects have shown a dramatic increase in oxidation-reduction potential, suggesting not only that PFB can directly protect cells from stress, but it can also enhance the internal cellular machinery that allows the cells to actively protect themselves.

In addition, PFB supplementation resulted in a 22 percent improvement in levels of BDNF, a major contributor to neuronal plasticity, and with improved mood and memory as well as substantial improvements in psychological mood state (50 percent lower depression indices and 25 percent lower fatigue indices), suggesting a dual heart-brain benefit from the collection of flavonoids in PFB.

IsoFiber® (Iso-Malto-Oligosaccharides) - contains a combination of naturally occurring prebiotic plant fibers that are clinically shown to improve the growth of specific probiotic strains that are known to be beneficial to our mental wellness. Also found in MentaBiotics and Kids FundaMentals!

CLINICAL STUDIES

Zynamite® (Mangifera indica Leaf Extract) and Caffeine Act in a Synergistic Manner on Electrophysiological Parameters of Rat Central Nervous System. Food and Nutrition Sciences, 9, 502–518. Dimpfel, W., Wiebe, J., Gericke,N. and Schombert,L. (2018)

Abstract:

Zynamite®, a special extract from Mangifera indica, exerted stimulatory properties on the central nervous system during a pilot study. The question arose if Zynamite® would have a similar action on the central nervous system as caffeine. Two well established animal models were used: a) quantitation of spectral power of field potentials in the freely moving rat and b) induction of long term potentiation (LTP) in the hippocampus slice preparation ex vivo after one week of daily administration. In the presence of 25 mg/kg of Zynamite®, predominantly alpha2 and beta1 spectral frequencies were attenuated in all brain areas during the first hour after administration. Exactly this pattern of frequency changes had been observed in earlier studies with i.p. administration of caffeine. Discriminant analysis confirmed this similarity by projection of Zynamite® and 0.5 mg/kg caffeine into close neighborhood and showing identical colours, which points to a similar mechanism of action in this analysis. In addition, when Zynamite® was combined with very low doses of caffeine synergistic effects were observed. Since alpha2 waves are under the control of dopamine, activation of this neurotransmitter system might be responsible for the stimulating property of Zynamite®. These results are corroborated by the results from the ex vivo study using the hippocampus slice in vitro to follow changes in excitability in the presence of 0.5 mg/kg of caffeine, 25 mg/kg of Zynamite® or their combination in comparison to Placebo after daily administration for one week. Both caffeine and Zynamite® increased LTP. LTP relates to space and time dependent memory. From these studies it is evident that both caffeine and Zynamite® act in similar ways on brain electrical activity, and have potential to improve cognitive function. Bioactive compounds of Zynamite® clearly pass the blood brain barrier to act on the central nervous system. Due to the demonstrated similarity of action, Zynamite® has potential as a CNS-activating nutraceutical that could be used to replace caffeine.

"Mangifera indica (mango). Pharmacogn Rev. 2010;4(7):42–48. doi:10.4103/0973–7847.65325 " ShahKA, Patel MB, PatelRJ, ParmarPK.

Abstract:

Mangifera indica, commonly used herb in ayurvedic medicine. Although review articles on this plant are already published, but this review article is presented to compile all the updated information on its phytochemical and pharmacological activities, which were performed widely by different methods. Studies indicate mango possesses antidiabetic, anti-oxidant, anti-viral, cardiotonic, hypotensive, anti-inflammatory properties. Various effects like antibacterial, anti fungal, anthelmintic, anti parasitic, anti tumor, anti HIV, antibone resorption, antispasmodic, antipyretic, antidiarrhoeal, antiallergic, immunomodulation, hypolipidemic, anti microbial, hepatoprotective, gastroprotective have also been studied. These studies are very encouraging and indicate this herb should be studied more extensively to confirm these results and reveal other potential therapeutic effects. Clinical trials using mango for a variety of conditions should also be conducted.

"A Toxicological Evaluation of Mango Leaf Extract (Mangifera indica) Containing 60% Mangiferin. Journal of Toxicology, 2019, 4763015." Reddeman, R.A., Glávits,R., Endres, J.R., Clewell, A.

Abstract:

A battery of OECD- and GLP-compliant toxicological studies was performed on mango leaf extract (Mangifera indica) containing 60% mangiferin (MLE). No evidence of genotoxicity was found in a bacterial reverse mutation test (Ames). While evidence of clastogenic activity was noted in an in vitro chromosomal aberration test, an in vivo mammalian micronucleus test showed no findings up to the limit dose (2000 mg/kg bw). A 90-day repeated dose oral toxicity study was conducted in rats using doses of 0 (vehicle control), 500, 1000, and 2000 mg/kg bw/day. Based on the lack of mortality or toxic effects in the 90-day study, the NOAEL for MLE in Han:Wist male and female rats was determined to be 2000 mg/kg bw/day, the highest dose tested.E., Hirka, G., Vértesi, A., Szakonyiné, I. P. (2019).

"Comparative pharmacokinetic study of mangiferin after oral administration of pure mangiferin and US patented polyherbal formulation to rats." Kamalla,A.K.,Ramasamy,M.K.,Inampudi,R.J.,Dubey,G.P., Agrawal, A. and Kalliapan, I. (2015)

Abstract

The US patented polyherbal formulation for the prevention and management of type II diabetes and its vascular complications was used for the present study. The xanthone glycoside mangiferin is one of the major effector constituents in the Salacia species with potential anti-diabetic activity. The pharmacokinetic differences of

mangiferin following oral administration of pure mangiferin and polyherbal formulation containing Salacia species were studied with approximately the same dose 30 mg/kg mangiferin and its distribution among the major tissue in Wistar rats. Plasma samples were collected at different time points (15, 30, 60, 120, 180, 240, 360, 480, 600, 1,440, 2,160, and 2880 min) and subsequently analyzed using a validated simple and rapid LC-MS method. Plasma concentration versus time profiles were explored by non-compartmental analysis. Mangiferin plasma exposure was significantly increased when administered from formulation compared to the standard mangiferin. Mangiferin resided significantly longer in the body (last mean residence time (MRTlast)) when given in the form of the formulation (3.65 h). Cmax values of formulation (44.16 µg/mL) administration were elevated when compared to equivalent dose of the pure mangiferin (15.23 µg/mL). Tissue distribution study of mangiferin from polyherbal formulation was also studied. In conclusion, the exposure of mangiferin is enhanced after formulation and administration and could result in superior efficacy of polyherbal formulation when compared to an equivalent dose of mangiferin. The results indicate that the reason which delays the elimination of mangiferin and enhances its bioavailability might the interactions of the some other constituents present in the polyherbal formulation. Distribution study results indicate that mangiferin was extensively bound to the various tissues like the small intestine, heart, kidney, spleen, and liver except brain tissue.

“Xanthone derivatives: new insights in biological activities” M M M Pinto 1, M E Sousa, M S J Nascimento

Abstract

Xanthones or xanthen-9H-ones (dibenzo-gamma-pirone) comprise an important class of oxygenated heterocycles whose role is well-known in Medicinal Chemistry. The biological activities of this class of compounds are associated with their tricyclic scaffold but vary depending on the nature and/or position of the different substituents. In this review, an array of biological/pharmacological effects is presented for both natural and synthetic xanthone derivatives, with an emphasis on some significant studies on structure-activity relationships. The antitumor activity of some xanthones as well as the related targets, particularly PKC modulation studies, is also discussed in detail. Examples of the "hit" compounds involved in cancer therapy, namely DMXAA, psorospermin, mangiferin, norathyriol, mangostins, and AH6809, a prostanoid receptor antagonist, are also mentioned. Finally, a historical perspective of these xanthonic derivatives, their relevance as therapeutic agents and/or their uses as pharmacological tools and as extract components in folk medicine are also highlighted.

“Hypouricaemic action of mangiferin results from metabolite norathyriol via inhibiting xanthine oxidase activity” Yanfen Niu 1, Jia Liu 1, Hai-Yang Liu 2, Li-Hui Gao 1, Guo-Hua Feng 1, Xu Liu 1, Ling Li 1

Abstract

Context Mangiferin has been reported to possess a potential hypouricaemic effect. However, the pharmacokinetic studies in rats showed that its oral bioavailability was only 1.2%, suggesting that mangiferin metabolites might exert the action. Objective The hypouricaemic effect and the xanthine oxidase inhibition of mangiferin and norathyriol, a mangiferin metabolite, were investigated. Inhibition of norathyriol analogues (compounds 3-9) toward xanthine oxidase was also evaluated. Materials and methods For a dose-dependent study, mangiferin (1.5-6.0 mg/kg) and norathyriol (0.92-3.7 mg/kg) were administered intragastrically to mice twice daily for five times. For a time-course study, mice received mangiferin and norathyriol both at a single dose of 7.1 μmol/kg. In vitro, inhibition of test compounds (2.4-2.4 mM) against xanthine oxidase activity was evaluated by the spectrophotometrical method. The inhibition type was identified from Lineweaver-Burk plots. Results Norathyriol (0.92, 1.85 and 3.7 mg/kg) dose dependently decreased the serum urate levels by 27.0, 33.6 and 37.4%, respectively. The action was more potent than that of mangiferin at the low dose, but was equivalent at the higher doses. Additionally, the hypouricaemic action of them exhibited a time dependence. In vitro, norathyriol markedly inhibited the xanthine oxidase activities, with the IC50 value of 44.6 μM, but mangiferin did not. The kinetic studies showed that norathyriol was an uncompetitive inhibitor by Lineweaver-Burk plots. The structure-activity relationships exhibited that three hydroxyl groups in norathyriol at the C-1, C-3 and C-6 positions were essential for maintaining xanthine oxidase inhibition. Discussion and conclusion Norathyriol was responsible for the hypouricaemic effect of mangiferin via inhibiting xanthine oxidase activity.

Mangifera indica L. Leaf Extract in Combination With Luteolin or Quercetin Enhances VO 2 peak and Peak Power Output, and Preserves Skeletal Muscle Function During Ischemia-Reperfusion in Humans. Miriam Gelabert-Rebato 1 2, Julia C Wiebe 2, Marcos Martin-Rincon 1, Nigel Gericke 2, Mario Perez-Valera 1, David Curtelin 1, Victor Galvan-Alvarez 1, Laura Lopez-Rios 1, David Morales-Alamo 1, Jose A L Calbet 1

Abstract

It remains unknown whether polyphenols such as luteolin (Lut), mangiferin and quercetin (Q) have ergogenic effects during repeated all-out prolonged sprints. Here we tested the effect of Mangifera indica L. leaf extract (MLE) rich in mangiferin (Zynamite®) administered with either quercetin (Q) and tiger nut extract (TNE), or with luteolin (Lut) on sprint performance and recovery from ischemia-reperfusion. Thirty young volunteers were randomly assigned to three treatments 48 h before exercise. Treatment A: placebo (500 mg of maltodextrin/day); B: 140 mg of MLE (60% mangiferin) and 50 mg of Lut/day; and C: 140 mg of MLE, 600 mg of Q and 350 mg of TNE/day. After warm-up, subjects performed two 30 s Wingate tests and a 60 s all-out sprint interspaced by 4 min recovery periods. At the end of the 60 s sprint the circulation of both legs was instantaneously occluded for 20 s. Then, the circulation was re-opened and a 15 s sprint performed, followed by 10 s recovery with open circulation, and another 15 s final sprint. MLE supplements enhanced peak (Wpeak) and mean (Wmean) power output by 5.0-7.0% ($P < 0.01$). After ischemia, MLE+Q+TNE increased Wpeak by 19.4 and 10.2% compared with the placebo ($P < 0.001$) and MLE+Lut ($P < 0.05$), respectively. MLE+Q+TNE increased Wmean post-ischemia by 11.2 and 6.7% compared with the placebo ($P < 0.001$) and MLE+Lut ($P = 0.012$). Mean VO2 during the sprints

was unchanged, suggesting increased efficiency or recruitment of the anaerobic capacity after MLE ingestion. In women, peak VO2 during the repeated sprints was 5.8% greater after the administration of MLE, coinciding with better brain oxygenation. MLE attenuated the metaboreflex hyperpneic response post-ischemia, may have improved O2 extraction by the Vastus Lateralis (MLE+Q+TNE vs. placebo, P = 0.056), and reduced pain during ischemia (P = 0.068). Blood lactate, acid-base balance, and plasma electrolytes responses were not altered by the supplements. In conclusion, a MLE extract rich in mangiferin combined with either quercetin and tiger nut extract or luteolin exerts a remarkable ergogenic effect, increasing muscle power in fatigued subjects and enhancing peak VO2 and brain oxygenation in women during prolonged sprinting. Importantly, the combination of MLE+Q+TNE improves skeletal muscle contractile function during ischemia/reperfusion.

"Enhancement of Exercise Performance by 48 Hours, and 15-Day Supplementation with Mangiferin and Luteolin in Men" Miriam Gelabert-Rebato 1 2, Julia C Wiebe 3, Marcos Martin-Rincon 4, Victor Galvan-Alvarez 5, David Curtelin 6, Mario Perez-Valera 7, Julian Juan Habib 8, Alberto Pérez-López 9 10, Tanausú Vega 11, David Morales-Alamo 12, Jose A L Calbet 13

Abstract

The natural polyphenols mangiferin and luteolin have free radical-scavenging properties, induce the antioxidant gene program and down-regulate the expression of superoxide-producing enzymes. However, the effects of these two polyphenols on exercise capacity remains mostly unknown. To determine whether a combination of luteolin (peanut husk extract containing 95% luteolin, PHE) and mangiferin (mango leave extract (MLE), Zynamite®) at low (PHE: 50 mg/day; and 140 mg/day of MLE containing 100 mg of mangiferin; L) and high doses (PHE: 100 mg/day; MLE: 420 mg/day; H) may enhance exercise performance, twelve physically active men performed incremental exercise to exhaustion, followed by sprint and endurance exercise after 48 h (acute effects) and 15 days of supplementation (prolonged effects) with polyphenols or placebo, following a double-blind crossover design. During sprint exercise, mangiferin + luteolin supplementation enhanced exercise performance, facilitated muscle oxygen extraction, and improved brain oxygenation, without increasing the VO_2. Compared to placebo, mangiferin + luteolin increased muscle O_2 extraction during post-exercise ischemia, and improved sprint performance after ischemia-reperfusion likely by increasing glycolytic energy production, as reflected by higher blood lactate concentrations after the sprints. Similar responses were elicited by the two doses tested. In conclusion, acute and prolonged supplementation with mangiferin combined with luteolin enhances performance, muscle O_2 extraction, and brain oxygenation during sprint exercise, at high and low doses.

"A Single Dose of The Mango Leaf Extract Zynamite ® in Combination with Quercetin Enhances Peak Power Output During Repeated Sprint Exercise in Men and Women" Miriam Gelabert-Rebato 1 2, Marcos Martin-Rincon 3, Victor Galvan-Alvarez 4, Angel Gallego-Selles 5, Miriam Martinez-Canton 6, Tanausú Vega-Morales 7, Julia C Wiebe 8, Constanza Fernandez-Del Castillo

9, Elizabeth Castilla-Hernandez 10, Oriana Diaz-Tiberio 11, Jose A L Calbet 12

Abstract

The mango leaf extract rich in mangiferin Zynamite® improves exercise performance when combined with luteolin or quercetin ingested at least 48 h prior to exercise. To determine whether a single dose of Zynamite® administered 1 h before exercise increases repeated-sprint performance, 20 men and 20 women who were physically active were randomly assigned to three treatments following a double-blind cross-over counterbalanced design. Treatment A, 140 mg of Zynamite®, 140 mg of quercetin, 147.7 mg of maltodextrin, and 420 mg of sunflower lecithin; Treatment B, 140 mg of Zynamite®, 140 mg of quercetin, and 2126 mg of maltodextrin and Treatment C, 2548 mg of maltodextrin (placebo). Subjects performed three Wingate tests interspaced by 4 min and a final 15 s sprint after ischemia. Treatments A and B improved peak power output during the first three Wingates by 2.8% and 3.8%, respectively (treatment x sprint interaction, p = 0.01). Vastus Lateralis oxygenation (NIRS) was reduced, indicating higher O2 extraction (treatment × sprint interaction, p = 0.01). Improved O2 extraction was observed in the sprints after ischemia (p = 0.008; placebo vs. mean of treatments A and B). Blood lactate concentration was 5.9% lower after the ingestion of Zynamite® with quercetin in men (treatment by sex interaction, p = 0.049). There was a higher Vastus Lateralis O2 extraction during 60 s ischemia with polyphenols (treatment effect, p = 0.03), due to the greater muscle VO2 in men (p = 0.001). In conclusion, a single dose of Zynamite® combined with quercetin one hour before exercise improves repeated-sprint performance and muscle O2 extraction and mitochondrial O2. consumption during ischemia. No advantage was obtained from the addition of phospholipids.

“Mangiferin and Morin Attenuate Oxidative Stress, Mitochondrial Dysfunction, and Neurocytotoxicity, Induced by Amyloid Beta Oligomers” Elena Alberdi 1 2 3, María Victoria Sánchez-Gómez 1 2 3, Asier Ruiz 1 2 3, Fabio Cavaliere 1 2 3, Carolina Ortiz-Sanz 1 2 3, Tania Quintela-López 1 2 3, Estibaliz Capetillo-Zarate 1 2 3 4, Santiago Solé-Domènech 5, Carlos Matute 1 2 3

Abstract

Amyloid beta- (Aβ-) mediated ROS overproduction disrupts intraneuronal redox balance and exacerbates mitochondrial dysfunction which leads to neuronal injury. Polyphenols have been investigated as therapeutic agents that promote neuroprotective effects in experimental models of brain injury and neurodegenerative diseases. The aim of this study was to identify the neuroprotective effects of morin and mangiferin against Aβ oligomers in cultured cortical neurons and organotypic slices as well as their mechanisms of action. Cell death caused by Aβ oligomers in neuronal cultures was decreased in the presence of micromolar concentrations of mangiferin or morin, which in turn attenuated oxidative stress. The neuroprotective effects of antioxidants against Aβ were associated with the reduction of Aβ-induced calcium load to mitochondria; mitochondrial membrane depolarization; and release of cytochrome c from mitochondria, a key trigger of apoptosis. Additionally, we observed that both polyphenols activated the endogenous enzymatic antioxidant system and

restored oxidized protein levels. Finally, Aβ induced an impairment of energy homeostasis due to a decreased respiratory capacity that was mitigated by morin and mangiferin. Overall, the beneficial effects of polyphenols in preventing mitochondrial dysfunction and neuronal injury in AD cell models suggest that morin and mangiferin hold promise for the treatment of this neurological disorder.

"Antioxidant properties of palm fruit extracts"

Nagendran Balasundram 1, Tan Yew Ai, Ravigadevi Sambanthamurthi, Kalyana Sundram, Samir Samman

Abstract

Phenolic compounds have been shown to exhibit bioactive properties, and in particular antioxidant effects. A phenolic-rich fraction has been isolated from the aqueous by-product obtained during the milling of oil palm fruits. The objectives of the study were to determine the phenolic content of the crude and ethanolic extracts of oil palm fruits and to evaluate the antioxidant properties of these extracts. The total phenolics content of the crude and ethanol extracts as determined by the Folin-Ciocalteu method were found to be 40.3 +/- 0.5 and 49.6 +/- 0.6 mg GAE/g extract (dry basis), respectively. The radical scavenging activity of the extracts determined using 2,2 diphenyl-1-picrylhydrazyl radical (DPPH.) indicated that both crude and ethanol extracts exhibit hydrogen-donating capacity, and have antiradical power (ARP) comparable to ascorbic acid. The DPPH radical scavenging activity of the extracts were less than that of gallic acid, but the time-course variations of the scavenging curves suggest that the extracts acted by a mechanism similar to that of gallic acid. The electron-donating potentials of the extracts were inferred from the hydrogen peroxide scavenging and reducing power assays. The reducing power of crude and ethanol extracts at 1 mM GAE were found to be comparable to that of 0.3 mM gallic acid. The extracts indicated complete scavenging of hydrogen peroxide at concentrations above 0.4 mM GAE. These findings suggest that the crude and ethanol extracts are able to scavenge free radicals, by either hydrogen or electron donating mechanisms, and can therefore act as primary antioxidants.

"Anti-diabetic effects of palm fruit juice in the Nile rat (Arvicanthis niloticus)"

Julia Bolsinger 1, Andrzej Pronczuk 1, Ravigadevi Sambanthamurthi 2, K C Hayes 1

Abstract

With the increasing incidence of metabolic diseases, numerous bioactive phytochemicals have been proffered in the dietary prevention of these conditions. Palm fruit juice (PFJ) possesses bioactive phenolic compounds (referred to as oil palm phenolics; OPP) that may deter diabetes. The objective of the present experiments was to document the degree to which PFJ reduces diabetes symptoms in a variety of circumstances in the Nile rat (Arvicanthis niloticus), a novel model for carbohydrate-induced type 2 diabetes (type 2 diabetes mellitus; T2DM) and the metabolic syndrome. Wild-type male Nile rats (n 100) were fed laboratory chow or semi-

purified diabetogenic diets in five experiments lasting 4-36 weeks. PFJ was provided as a drink or mixed into the diet to provide OPP intakes from 170 to 720 mg gallic acid equivalents/kg body weight per d. Body weight and random and fasting blood glucose were assessed at different time points, and were analysed along with terminal fasting organ weights, insulin, plasma and liver lipids as measures of diabetes progression. PFJ proved to be anti-hyperglycaemic and anti-lipaemic in all experiments relative to untreated controls, delaying T2DM onset and even reversing advancing diabetes. Protection by PFJ was directly related to its OPP content, and no negative effects on energy intake or growth were observed. PFJ was effective both as a drink and mixed into the diet. Results suggest that PFJ may slow the rate of glucose absorption, reduce insulin resistance and/or enhance insulin secretion.

"Consumption of an Oil Palm Fruit Extract Promotes Large Bowel Health in Rats"
Michael A Conlon 1, Ravigadevi Sambanthamurthi 2, Yew Ai Tan 2, Kalyana Sundram 3, Syed Fairus 2, Mahinda Y Abeywardena 1

Abstract

Oil palm fruit is widely used for edible oils, but the health benefits of other components are relatively unknown. We examined if consuming a polyphenol-rich extract of the fruit, from a vegetation by-product of oil processing, which also contains fibre, has gastro-intestinal benefits in rats on a Western-type diet (WD). The oil palm preparation (OPP) was added to food (OPP-F) or drinking water (OPP-D) to provide 50 mg of gallic acid equivalents (GAE)/d and compared to effects of high amylose maize starch (HAMS; 30%) in the diet or green tea extract (GT; 50 mg GAE/d) in drinking water over 4 wk. OPP treatments induced some significant effects ($P < 0.05$) compared to WD. OPP-D increased caecal digesta mass, caecal digesta concentrations of total SCFA, acetate and propionate (OPP-F increased caecal butyrate concentration), the numbers of mucus-producing goblet cells per colonic crypt, and caecal digesta abundance of some bacteria which may provide benefit to the host (Faecalibacterium prausnitzii, Akkermansia muciniphila and Ruminococcus gnavus). HAMS induced similar effects but with greater potency and had a broader impact on microbe populations, whereas GT had minimal impacts. These results suggest dietary OPP may benefit the large bowel.

"A phase I single-blind clinical trial to evaluate the safety of oil palm phenolics (OPP) supplementation in healthy volunteers." Syed Fairus, Soon-Sen Leow, Isa Naina Mohamed, Yew-Ai Tan, Kalyana Sundram & Ravigadevi Sambanthamurthi
Scientific Reports volume 8, Article number: 8217 (2018)

Abstract

Plant phenolics are being increasingly consumed globally with limited scientific and clinical evidence pertaining to safety and efficacy. The oil palm fruit contains a cocktail of phenolics, and palm oil production results in high volumes of aqueous by-products enriched in phenolics and bioactives. Several lines of evidence from in vitro and in vivo animal studies confirmed that the aqueous extract enriched in phenolics and other bioactives collectively known as oil palm phenolics (OPP) is safe and has potent bioactivity. A phase one clinical trial

was conducted to evaluate the safety and effects of OPP in healthy volunteers. In this single-blind trial, 25 healthy human volunteers were supplemented with 450 mg gallic acid equivalent (GAE)/day of OPP or control treatments for a 60-day period. Fasting blood and urine samples were collected at days 1, 30 and 60. Medical examination was performed during these trial interventions. All clinical biochemistry profiles observed throughout the control and OPP treatment period were in the normal range with no major adverse effect (AE) or serious adverse effect (SAE) observed. Additionally, OPP supplementation resulted in improvement of total cholesterol and LDL-C levels, compared to the control treatment. The outcomes support our previous observations that OPP is safe and may have a protective role in reducing cholesterol levels.

"The Effects and Potential Mechanism of Oil Palm Phenolics in Cardiovascular Health: A Review on Current Evidence"
Nurul 'Izzah Ibrahim,1 Syed Fairus,2 and Isa Naina Mohamed1,*

Abstract

Cardiovascular disease (CVD) is globally known as the number one cause of death with hyperlipidemia as a strong risk factor for CVD. The initiation of drug treatment will be recommended if lifestyle modification fails. However, medicines currently used for improving cholesterol and low-density lipoprotein cholesterols (LDL-C) levels have been associated with various side effects. Thus, alternative treatment with fewer or no side effects needs to be explored. A potential agent, oil palm phenolics (OPP) recovered from the aqueous waste of oil palm milling process contains numerous water-soluble phenolic compounds. It has been postulated that OPP has shown cardioprotective effects via several mechanisms such as cholesterol biosynthesis pathway, antioxidant and anti-inflammatory properties. This review aims to summarize the current evidence explicating the actions of OPP in cardiovascular health and the mechanisms that maybe involved for the cardioprotective effects.

"Oil palm phenolics and vitamin E reduce atherosclerosis in rabbits," J Functional Foods 7 (2014) 541-550. C.A.C. Idris, T. Karupaiah, K. Sundram, Y. Tan, N. Balasundram, S.S. Leow, N.S. Nasruddin, R. Sambanthamurthi,

Abstract

The protective effects of oil palm vitamin E and phenolics against atherosclerosis, either singly or in combination, were studied in an atherogenic rabbit model. Rabbits were either fed atherogenic diet only (CTR), or atherogenic diet with vitamin E (VIT E), or atherogenic diet with oil palm phenolics (OPP), or atherogenic diet with both vitamin E and oil palm phenolics (VIT E + OPP). Results from lipid profile and antioxidant analyses were not significantly different between groups ($p > 0.05$). However, fibrous plaques were associated with the CTR group (8.90 ± 5.41%) and these were significantly less ($p < 0.05$) in the VIT E (2.88 ± 2.01%) and OPP (1.48 ± 4.45%) groups. Fibrous plaques were not detected at all in the VIT E + OPP group. Our findings suggest that oil palm

vitamin E and oil palm phenolics individually inhibited atherosclerotic lesion development. However, oil palm vitamin E in combination with oil palm phenolics provided the highest protective effect against development of atherosclerotic lesions.

"Oil palm phenolics (OPP) inhibit pancreatic cancer cell proliferation via suppression of NF-κB pathway" Xiangming Ji 1, Anee Usman 1, Nurul H Razalli 1, Ravigadevi Sambanthamurthi 2, Smiti V Gupta 3

Abstract

BACKGROUND: Oil palm phenolics (OPP) or Palm Juice (PJ), a water soluble extract from the palm fruit (Elaies guineensis) has been documented to have anti-carcinogenic activities in various cancer types.

Materials and methods: To investigate OPP effects in pancreatic cancer (PaCa) cells, two PaCa cell lines (PANC-1 and BxPC-3) were treated with different OPP doses. The anti-proliferative, apoptotic and anti-invasive properties of OPP were evaluated using MTS, cytoplasmic histone-DNA fragmentation and matrigel invasive assays, respectively.

RESULTS: OPP suppressed PaCa proliferation in a dose-dependent manner. Its anti-invasive effects were validated by decreased expressions of MMP-9 and VEGF. Cell-cycle analysis demonstrated that cells were arrested in the S phase. OPP-induced apoptosis was associated with decrease in survivin and Bcl-XL expressions and increased expression of cleaved caspase-3, caspase-9 and PARP.

CONCLUSION: Overall, our results demonstrate the anti-tumor effects of OPP on PaCa cells, providing initial evidence towards its potential therapeutic use.

" Positive outcomes of oil palm phenolics on degenerative diseases in animal models. British Journal of Nutrition. 106(11): 1664-1675 DOI: 10.1017/S0007114511002133" Sambanthamurthi, R., Tan, Y. A., Sundram, K., Hayes, K. C., Abeywardena, M., Leow, S. S., Sekaran, S. D., Sambandan, T. G., Rha, C., Sinskey, A. J., Subramaniam, K., Fairus, S., & Wahid, M. B. (2011).

Abstract

It is well established that plant phenolics elicit various biological activities, with positive effects on health. Palm oil production results in large volumes of aqueous by-products containing phenolics. In the present study, we describe the effects of oil palm phenolics (OPP) on several degenerative conditions using various animal models. OPP reduced blood pressure in a NO-deficient rat model, protected against ischaemia-induced cardiac

arrhythmia in rats and reduced plaque formation in rabbits fed an atherogenic diet. In Nile rats, a spontaneous model of the metabolic syndrome and type 2 diabetes, OPP protected against multiple aspects of the syndrome and diabetes progression. In tumour-inoculated mice, OPP protected against cancer progression. Microarray studies on the tumours showed differential transcriptome profiles that suggest anti-tumour molecular mechanisms involved in OPP action. Thus, initial studies suggest that OPP may have potential against several chronic disease outcomes in mammals.

"Oil palm vegetation liquor: A new source of phenolic bioactives." British Journal of Nutrition. 106(11): 1655-1663. DOI: 10.1017/S0007114511002121 Sambanthamurthi, R., Tan, Y. A., Sundram, K., Abeywardena, M., Sambandan, T. G., Rha, C., Sinskey, A. J., Subramaniam, K., Leow, S. S., Hayes, K. C., & Wahid, M. B. (2011).

Abstract

Waste from agricultural products represents a disposal liability, which needs to be addressed. Palm oil is the most widely traded edible oil globally, and its production generates 85 million tons of aqueous by-products annually. This aqueous stream is rich in phenolic antioxidants, which were investigated for their composition and potential in vitro biological activity. We have identified three isomers of caffeoylshikimic acid as major components of oil palm phenolics (OPP). The 2,2-diphenyl-1-picrylhydrazyl assay confirmed potent free radical scavenging activity. To test for possible cardioprotective effects of OPP, we carried out in vitro LDL oxidation studies as well as ex vivo aortic ring and mesenteric vascular bed relaxation measurements. We found that OPP inhibited the Cu-mediated oxidation of human LDL. OPP also promoted vascular relaxation in both isolated aortic rings and perfused mesenteric vascular beds pre-contracted with noradrenaline. To rule out developmental toxicity, we performed teratological studies on rats up to the third generation and did not find any congenital anomalies. Thus, these initial studies suggest that OPP is safe and may have a protective role against free radical damage, LDL oxidation and its attendant negative effects, as well as vascular constriction in mitigating atherosclerosis. Oil palm vegetation liquor thus represents a new source of phenolic bioactives.

"Differential transcriptomic profiles effected by oil palm phenolics indicate novel outcomes." BMC Genomics. 12(432). DOI: 10.1186/1471-2164-12-432 Leow, S. S., Sekaran, S. D., Sundram, K., Tan, Y. A., & Sambanthamurthi, R. (2011).

Abstract

Plant phenolics are important nutritional antioxidants which could aid in overcoming chronic diseases such as cardiovascular disease and cancer, two leading causes of death in the world. The oil palm (Elaeis guineensis) is a rich source of water-soluble phenolics which have high antioxidant activities. This study aimed to identify the in vivo effects and molecular mechanisms involved in the biological activities of oil palm phenolics (OPP) during healthy states via microarray gene expression profiling, using mice supplemented with a normal diet as biological models.

RESULTS: Having confirmed via histology, haematology and clinical biochemistry analyses that OPP is not toxic

to mice, we further explored the gene expression changes caused by OPP through statistical and functional analyses using Illumina microarrays. OPP showed numerous biological activities in three major organs of mice, the liver, spleen and heart. In livers of mice given OPP, four lipid catabolism genes were up-regulated while five cholesterol biosynthesis genes were down-regulated, suggesting that OPP may play a role in reducing cardiovascular disease. OPP also up-regulated eighteen blood coagulation genes in spleens of mice. OPP elicited gene expression changes similar to the effects of caloric restriction in the hearts of mice supplemented with OPP. Microarray gene expression fold changes for six target genes in the three major organs tested were validated with real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR), and the correlation of fold changes obtained with these two techniques was high (R2 = 0.9653).

CONCLUSIONS: OPP showed non-toxicity and various pleiotropic effects in mice. This study implies the potential application of OPP as a valuable source of wellness nutraceuticals, and further suggests the molecular mechanisms as to how dietary phenolics work in vivo.

"Oil palm phenolics attenuate changes caused by an atherogenic diet in mice." European Journal of Nutrition. 52(2): 443-456. DOI: 10.1007/s00394-012-0346 0 Leow, S. S., Sekaran, S. D., Sundram, K., Tan, Y. A., & Sambanthamurthi, R. (2013).

Abstract

Water-soluble phenolics from the oil palm possess significant biological properties.

PURPOSE: In this study, we aimed to discover the role of oil palm phenolics (OPP) in influencing the gene expression changes caused by an atherogenic diet in mice.

METHODS: We fed mice with either a low-fat normal diet (14.6 % kcal/kcal fat) with distilled water, or a high-fat atherogenic diet (40.5 % kcal/kcal fat) containing cholesterol. The latter group was given either distilled water or OPP. We harvested major organs such as livers, spleens and hearts for microarray gene expression profiling analysis. We determined how OPP changed the gene expression profiles caused by the atherogenic diet. In addition to gene expression studies, we carried out physiological observations, blood hematology as well as clinical biochemistry, cytokine profiling and antioxidant assays on their blood sera.

RESULTS: Using Illumina microarrays, we found that the atherogenic diet caused oxidative stress, inflammation and increased turnover of metabolites and cells in the liver, spleen and heart. In contrast, OPP showed signs of attenuating these effects. The extract increased unfolded protein response in the liver, attenuated antigen presentation and processing in the spleen and up-regulated antioxidant genes in the heart. Real-time quantitative reverse transcription-polymerase chain reaction validated the microarray gene expression fold changes observed. Serum cytokine profiling showed that OPP attenuated inflammation by modulating the Th1/Th2 axis toward the latter. OPP also increased serum antioxidant activity to normal levels.

CONCLUSION: This study suggests that OPP may possibly attenuate atherosclerosis and other forms of cardiovascular disease.

"Gene expression changes in spleens and livers of tumour-bearing mice suggest delayed inflammation and attenuated cachexia in response to oil palm phenolics," J Nutrigenet Nutrigenomics 6(6) (2013) 305-26. S.S. Leow, S.D. Sekaran, K. Sundram, Y. Tan, R. Sambanthamurthi,

Abstract

BACKGROUND/AIM: Plant phenolics can inhibit, retard or reverse carcinogenesis, and may thus help prevent or treat cancer. Oil palm phenolics (OPP) previously showed anti-tumour activities in vivo via a cytostatic mechanism at 1,500 ppm gallic acid equivalent. Here, we report other possible molecular mechanisms by which this extract attenuates cancer, especially those concerning the immune response.

METHODS: We subcutaneously injected J558 myeloma cells in BALB/c mice and supplemented OPP orally at 1,500 ppm gallic acid equivalent. We observed the physiology parameters of these animals and harvested their spleens and livers after 18 h, 1 week and 4 weeks for microarray gene expression analysis using Illumina MouseRef-8 BeadChips.

RESULTS: Time course microarray analysis on spleens after injecting J558 myeloma cells in mice revealed that the immune response of tumour-bearing mice supplemented with OPP was lower compared to controls, thus suggesting delayed inflammation in response to OPP. In livers, cholesterol biosynthesis genes were upregulated while inflammatory genes were downregulated through time, further suggesting attenuation of systemic inflammation and cachexia. These effects correlated with the delayed in vivo development of syngeneic tumours in mice given OPP.

CONCLUSIONS: This study suggests the possible utilisation of OPP as an anti-tumour and anti-cachexia agent.

"Oil palm phenolics confer neuroprotective effects involving cognitive and motor functions in mice," Nutr Neurosci 16(5) (2013) 207-17. S.S. Leow, S.D. Sekaran, Y. Tan, K. Sundram, R. Sambanthamurthi,

Abstract

OBJECTIVES: Phenolics are important phytochemicals which have positive effects on chronic diseases, including neurodegenerative ailments. The oil palm (Elaeis guineensis) is a rich source of water-soluble phenolics. This study was carried out to discover the effects of administering oil palm phenolics (OPP) to mice, with the aim of identifying whether these compounds possess significant neuroprotective properties.

METHODS: OPP was given to BALB/c mice on a normal diet as fluids for 6 weeks while the controls were given distilled water. These animals were tested in a water maze and on a rotarod weekly to assess the effects of OPP on cognitive and motor functions, respectively. Using Illumina microarrays, we further explored the brain gene expression changes caused by OPP in order to determine the molecular mechanisms involved. Real-time

quantitative reverse transcription-polymerase chain reaction experiments were then carried out to validate the microarray data.

RESULTS: We found that mice given OPP showed better cognitive function and spatial learning when tested in a water maze, and their performance also improved when tested on a rotarod, possibly due to better motor function and balance. Microarray gene expression analysis showed that these compounds up-regulated genes involved in brain development and activity, such as those under the regulation of the brain-derived neurotrophic factor. OPP also down-regulated genes involved in inflammation.

"Safety evaluation of water-soluble palm fruit bioactives," Regul Toxicol Pharmacol 88 (2017) 96-105. B.S. Lynch, S. West, A. Roberts,

Abstract

Water-soluble palm fruit bioactives, derived from the aqueous stream of palm oil processing, have shown anti-diabetogenic effects in rodent models. To assess the safety of potential incorporation of this polyphenol-containing material in food, in vitro bacterial reverse mutation and in vitro chromosome aberration assays were conducted along with a 90-day subchronic toxicity study in Sprague-Dawley rats. Water-soluble palm fruit bioactives were inactive in the Ames and in vitro chromosome aberration assays up to the limit doses of 5000 µg/plate and 5000 µg/mL, respectively. In the 90-day feeding study, water-soluble palm fruit bioactives were administered via gavage at doses 0, 500, 1000 or 2000 mg/kg body weight/day. No significant effects were noted on body weight, food consumption, hematology, clinical chemistry, organ weights, and histopathological examination. The No Observable Adverse Effect Level was considered to be 2000 mg/kg body weight/day, the highest dose tested. These data provide evidence to support the safe use of water-soluble palm fruit bioactives in food or food ingredients.

"Palm Fruit Juice Mitigates AZT Mitochondrial Genotoxicity and Does-Dependent Cytotoxicity," J AIDS & Clin Res 5(12) (2014). A.E. Osborne, J.A. Sanchez, M. Solomon, A. Stopa, L.J. Wangh, R. Sambanthamurthi, K.C. Hayes

Abstract:

Chronic use of 3'-Azido-3'-deoxythymidine (AZT) to treat HIV/AIDS causes mitochondrial dysfunction and theaccumulation of mitochondrial mutations. These toxicities have been attributed to increased oxidative damage,among other mechanisms. Palm fruit juice (PFJ), also known as oil palm phenolics (OPP), is a water soluble by-product of oil extraction from the fruit of the oil palm (Elaeis guineensis) that is rich in antioxidants and otherphytochemicals. The capacity of PFJ to mitigate AZT mitochondrial genotoxicity (mutagenesis) as well as dose-dependent cytotoxicity were measured in cultured HepG2 cells. In the presence of PFJ, AZT-induced mutationswere 35% the number of mutations observed in samples treated

with AZT alone in the three regions of themitochondrial genome examined (HV2, CO2, and ND1). Co-treatment with PFJ increased cell survival in thepresence of increasing doses of AZT by up to 350%. These effects were not due to degradation or inactivation ofAZT by PFJ. The discovery of the mitigating effects of PFJ provides a potential means of ameliorating AZT-inducedmutations and possibly other long-term negative side effects of long-term AZT use.

"Effect of oil palm phenolics on gastrointestinal transit, contractility and motility in the rat," J Functional Foods 17 (2015) 928-937. G.S. Patten, M.Y. Abeywardena, K. Sundram, Y. Tan, R. Sambanthamurthi,

Abstract

The effects of a novel water soluble polyphenolics preparation (oil palm phenolics; OPP) on whole gastrointestinal transit, ex vivo proximal and distal colonic contractility and intact expulsion time in the distal colon were examined. Nine weeks of dietary supplementation with OPP at 50 mg gallic acid equivalents (GAE)/rat per day had no effect on gastric emptying compared to the control (AIN-93M), but 30% substituted high amylose maize starch (HAMS) used as a positive resistant starch control, had significantly higher gastric emptying compared to both control and OPP. OPP increased distal colonic contractile response to KCl, PGE2 and angiotensin I compared with the control, whilst HAMS also had similar increased contractile responses. This correlated with faster distal colonic expulsion rates for OPP and HAMS compared with the control. The present study revealed that OPP, like resistant starch, has positive effects on distal colonic contractility and motility with potential putative roles in bowel function and health.

"Achieving sustainable cultivation of oil palm," Burleigh Dodds Science Publishing 2017. R. Sambanthamurthi, M.H. Ng, Y.M. Choo, Chapter 7 – Bioactive compounds in palm oil, in: A. Rival (Ed.),

Abstract:

The effects of oil palm phenolics (OPP) on cell lines were demonstrated in this study. OPP dose-dependent studies in selected cell cultures showed that OPP inhibited the proliferation of mouse IgA-secreting myeloma (J558), estrogen-receptor-positive human breast adenocarcinoma (MCF7) and human lung carcinoma (A549) cells at all doses. However, OPP enhanced the proliferation of Madin Darby Canine Kidney (MDCK) and Aedes albopictus larvae (C6/36) cells at all concentrations, whereas, growth of Syrian Baby Hamster Kidney (BHK) cells was only enhanced with low doses of OPP. 5% OPP in combination with 5% fetal calf serum (FCS) was shown to be as effective as 10% FCS on the growth of BHK and A549 cells. In vivo studies using J558 myeloma cells showed that OPP caused tumor regression. These findings imply that OPP has anti-proliferative effects on tumor cells in vitro and in vivo, but conversely enhances the growth of normal cells.

S.D. Sekaran, S.S. Leow, N. Abobaker, K.K. Tee, K. Sundram, R. Sambanthamurthi, M.B. Wahid, Effects of oil palm phenlics on tumor cells in vitro and in vivo, African J Food Science 4(8) (2010) 495-502.

Abstract:

The effects of oil palm phenolics (OPP) on cell lines were demonstrated in this study. OPP dose-dependent studies in selected cell cultures showed that OPP inhibited the proliferation of mouse IgA-secreting myeloma (J558), estrogen-receptor-positive human breast adenocarcinoma (MCF7) and human lung carcinoma (A549) cells at all doses. However, OPP enhanced the proliferation of Madin Darby Canine Kidney (MDCK) and Aedes albopictus larvae (C6/36) cells at all concentrations, whereas, growth of Syrian Baby Hamster Kidney (BHK) cells was only enhanced with low doses of OPP. 5% OPP in combination with 5% fetal calf serum (FCS) was shown to be as effective as 10% FCS on the growth of BHK and A549 cells. In vivo studies using J558 myeloma cells showed that OPP caused tumor regression. These findings imply that OPP has anti-proliferative effects on tumor cells in vitro and in vivo, but conversely enhances the growth of normal cells.

“Palm fruit chemistry and nutrition,” Asia Pac J Clin Nutr 12(3) (2003) 355-62. K. Sundram, R. Sambanthamurthi, Y.A. Tan

Abstract:

The palm fruit (Elaies guineensis) yields palm oil, a palmitic-oleic rich semi solid fat and the fat-soluble minor components, vitamin E (tocopherols, tocotrienols), carotenoids and phytosterols. A recent innovation has led to the recovery and concentration of water-soluble antioxidants from palm oil milling waste, characterized by its high content of phenolic acids and flavonoids. These natural ingredients pose both challenges and opportunities for the food and nutraceutical industries. Palm oil's rich content of saturated and monounsaturated fatty acids has actually been turned into an asset in view of current dietary recommendations aimed at zero trans content in solid fats such as margarine, shortenings and frying fats. Using palm oil in combination with other oils and fats facilitates the development of a new generation of fat products that can be tailored to meet most current dietary recommendations. The wide range of natural palm oil fractions, differing in their physico-chemical characteristics, the most notable of which is the carotenoid-rich red palm oil further assists this. Palm vitamin E (30% tocopherols, 70% tocotrienols) has been extensively researched for its nutritional and health properties, including antioxidant activities, cholesterol lowering, anti-cancer effects and protection against atherosclerosis. These are attributed largely to its tocotrienol content. A relatively new output from the oil palm fruit is the water-soluble phenolic-flavonoid-rich antioxidant complex. This has potent antioxidant properties coupled with beneficial effects against skin, breast and other cancers. Enabled by its water solubility, this is currently being tested for use as nutraceuticals and in cosmetics with potential benefits against skin aging. A further challenge would be to package all these palm ingredients into a single functional food for better nutrition and health.

"The Pharmacological Potential of Oil Palm Phenolics (OPP) Individual Components," Int J Med Sci 16(5) (2019) 711-719. S.B. Syarifah-Noratiqah, M.S. Zulfarina, S.U. Ahmad, S. Fairus, I. Naina-Mohamed

Abstract

The oil palm tree (Elaeis guineensis) from the family Arecaceae is a high oil-producing agricultural crop. A significant amount of vegetation liquor is discarded during the palm oil milling process amounting to 90 million tons per year around the world. This water-soluble extract is rich in phenolic compounds known as Oil Palm Phenolics (OPP). Several phenolic acids including the three isomers of caffeoylshikimic acid (CFA), p-hydroxybenzoic acid (PHBA), protocatechuic acid (PCA) and hydroxytyrosol are among the primary active ingredients in the OPP. Previous investigations have reported several positive pharmacological potentials by OPP such as neuroprotective and atheroprotective effects, anti-tumor and reduction in Aβ deposition in Alzheimer's disease model. In the current review, the pharmacological potential for CFA, PHBA, PCA and hydroxytyrosol is carefully reviewed and evaluated.

"Palm Fruit Bioactives modulate human astrocyte activity in vitro altering the cytokine secretome reducing levels of TNFalpha," R.P. Weinberg, V.V. Koledova, K. Schneider, T.G. Sambandan, A. Grayson, G. Zeidman, A. Artamonova, R. Sambanthamurthi, S. Fairus, A.J. Sinskey, C. Rha,RANTES and IP-10, Sci Rep 8(1) (2018) 16423.

Abstract

Neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, are becoming more prevalent and an increasing burden on society. Neurodegenerative diseases often arise in the milieu of neuro-inflammation of the brain. Reactive astrocytes are key regulators in the development of neuro-inflammation. This study describes the effects of Palm Fruit Bioactives (PFB) on the behavior of human astrocytes which have been activated by IL-1β. When activated, the astrocytes proliferate, release numerous cytokines/chemokines including TNFα, RANTES (CCL5), IP-10 (CXCL10), generate reactive oxygen species (ROS), and express specific cell surface biomarkers such as the Intercellular Adhesion Molecule (ICAM), Vascular Cellular Adhesion Molecule (VCAM) and the Neuronal Cellular Adhesion Molecule (NCAM). Interleukin 1-beta (IL-1β) causes activation of human astrocytes with marked upregulation of pro-inflammatory genes. We show significant inhibition of these pro-inflammatory processes when IL-1β-activated astrocytes are exposed to PFB. PFB causes a dose-dependent and time-dependent reduction in specific cytokines: TNFα, RANTES, and IP-10. We also show that PFB significantly reduces ROS production by IL-1β-activated astrocytes. Furthermore, PFB also reduces the expression of ICAM and VCAM, both in activated and naïve human astrocytes in vitro. Since reactive astrocytes play an essential role in the neuroinflammatory state preceding neurodegenerative diseases, this study suggests that PFB may have a potential role in their prevention and/or treatment.

"Drosophila larvae fed palm fruit juice (PFJ) delay pupation via expression regulation of hormetic stress response genes linked to ageing and longevity" Soon-Sen Leow 1, Alice Luu 2, Swechhya Shrestha 2, K C Hayes 2, Ravigadevi Sambanthamurthi 3

Abstract

Palm fruit juice (PFJ) containing oil palm phenolics is obtained as a by-product from oil palm (Elaeis guineensis) fruit milling. It contains shikimic acid, soluble fibre and various phenolic acids including p-hydroxybenzoic acid and three caffeoylshikimic acid isomers. PFJ has also demonstrated beneficial health properties in various biological models. Increasing concentrations of PFJ and different PFJ fractions were used to assess growth dynamics and possible anti-ageing properties in fruit flies (Drosophila melanogaster) genotype w1118. Microarray gene expression analysis was performed on whole fruit fly larvae and their fat bodies, after the larvae were fed a control Standard Brandeis Diet (SBD) with or without PFJ. Transcripts from Affymetrix GeneChips were utilised to identify the possible mechanisms involved, with genes having fold changes > |1.30| and $p < 0.05$ considered differentially expressed. PFJ dose-dependently delayed larval growth and pupation, but not percent eclosion from pupae. Eclosed male fruit flies fed PFJ or its fractions during the larval stage tended to have 20-40% improved survival ratings over controls when allowed to age on the control diet (SBD). Microarray analysis of whole fruit fly larvae revealed that 127 genes were up-regulated, while 67 were down-regulated by PFJ. Functional analysis revealed transport and metabolic processes were up-regulated, while development and morphogenesis processes, including the nutrient-sensing Tor gene, were down-regulated by PFJ, whereas microarray analysis of larval fat bodies found 161 genes were up-regulated, while 84 genes were down-regulated. Genes involved in defence response and determination of adult lifespan, including those encoding various heat shock proteins and the antioxidant enzyme Sod2, were up-regulated, while cell cycle and growth genes were down-regulated. Thus, PFJ supplementation lengthened the growth stages in fruit fly larvae that was reflected in extended ageing of adult flies, suggesting that larval expression of hormetic stress response genes was linked to subsequent ageing and longevity.

"Hepatic transcriptome implications for palm fruit juice deterrence of type 2 diabetes mellitus in young male Nile rats." Leow, S.S., Bolsinger, J., Pronczuk, A., Hayes, K.C., Sambanthamurthi, R., 2016.Genes Nutr. 11, 29. DOI: 10.1186/s12263-016-0545-z

Background

The Nile rat (NR, Arvicanthis niloticus) is a model of carbohydrate-induced type 2 diabetes mellitus (T2DM) and the metabolic syndrome. A previous study found that palm fruit juice (PFJ) delayed or prevented diabetes and in some cases even reversed its early stages in young NRs. However, the molecular mechanisms by which PFJ exerts these anti-diabetic effects are unknown. In this study, the transcriptomic effects of PFJ were studied in young male NRs, using microarray gene expression analysis.

METHODS: Three-week-old weanling NRs were fed either a high-carbohydrate diet (%En from carbohydrate/fat/protein = 70:10:20, 16.7 kJ/g; n = 8) or the same high-carbohydrate diet supplemented with PFJ (415 ml of

13,000-ppm gallic acid equivalent (GAE) for a final concentration of 5.4 g GAE per kg diet or 2.7 g per 2000 kcal; n = 8). Livers were obtained from these NRs for microarray gene expression analysis using Illumina MouseRef-8 Version 2 Expression BeadChips. Microarray data were analysed along with the physiological parameters of diabetes.

RESULTS: Compared to the control group, 71 genes were up-regulated while 108 were down-regulated in the group supplemented with PFJ. Among hepatic genes up-regulated were apolipoproteins related to high-density lipoproteins (HDL) and genes involved in hepatic detoxification, while those down-regulated were related to insulin signalling and fibrosis.

CONCLUSION: The results obtained suggest that the anti-diabetic effects of PFJ may be due to mechanisms other than an increase in insulin secretion.

KEYWORDS: Palm fruit juice, Oil palm phenolics, Antioxidants, Diabetes, Metabolic syndrome, Gene expression, Nile rat

"Palm Fruit Bioactives augment expression of Tyrosine Hydroxylase in the Nile Grass Rat basal ganglia and alter the colonic microbiome." Weinberg RP, Koledova VV, Subramaniam A, Schneider K, Artamonova A, Sambanthamurthi R, Hayes KC, Sinskey AJ, Rha C.

Abstract

Tyrosine hydroxylase (TH) catalyzes the hydroxylation of L-tyrosine to L-DOPA. This is the rate-limiting step in the biosynthesis of the catecholamines - dopamine (DA), norepinephrine (NE), and epinephrine (EP). Catecholamines (CA) play a key role as neurotransmitters and hormones. Aberrant levels of CA are associated with multiple medical conditions, including Parkinson's disease. Palm Fruit Bioactives (PFB) significantly increased the levels of tyrosine hydroxylase in the brain of the Nile Grass rat (NGR), a novel and potentially significant finding, unique to PFB among known botanical sources. Increases were most pronounced in the basal ganglia, including the caudate-putamen, striatum and substantia nigra. The NGR represents an animal model of diet-induced Type 2 Diabetes Mellitus (T2DM), exhibiting hyperglycemia, hyperinsulinemia, and insulin resistance associated with hyperphagia and accelerated postweaning weight gain induced by a high-carbohydrate diet (hiCHO). The PFB-induced increase of TH in the basal ganglia of the NGR was documented by immuno-histochemical staining (IHC). This increase in TH occurred equally in both diabetes-susceptible and diabetes-resistant NGR fed a hiCHO. PFB also stimulated growth of the colon microbiota evidenced by an increase in cecal weight and altered microbiome. The metabolites of colon microbiota, e.g. short-chain fatty acids, may influence the brain and behavior significantly.

"Amelioration of Abdominal Obesity by LowMolecular-Weight Polyphenol (Oligonol) from Lychee." 2009;1(4): 341–348 Journal of Functional Foods Nishihira J., et al.

Abstract:

Topic Can Oligonol® have an effect on metabolic syndrome by reducing visceral fat obesity?

BACKGROUND: It has been reported that adipocytes (fat cells) generate reactive oxygen species (ROS), and that the increased oxidative stress in adipocytes might be a cause of obesity-associated metabolic syndrome. Previous research provides evidence that polyphenols could improve obesity, lipid metabolism and glucose metabolism.

STUDY TYPE: Human clinical intervention trial Study Design Randomized double-blind, placebo-controlled: Participants took either Oligonol® or placebo twice a day for 10 weeks. Physical and hematological examinations as well as CT scan of abdomen were carried out at baseline (control) and after 10 weeks. Subjects 14 male, 4 female volunteers with abdominal circumference over 85 cm

DOSAGE: 100 mg Oligonol®

RESULTS: Oligonol® supplementation resulted in the following significant changes compared with control: • Decrease in body weight, abdominal circum-ference and visceral fat. • Improved insulin resistance was improved by Oligonol® in conjunction with elevation of serum adiponectin, a hormone that is an independent risk factor for metabolic syndrome.

CONCLUSION: "These results suggest that Oligonol® ameliorates metabolic syndrome by reducing visceral fat obesity.

"Effect of Lychee Fruit Extract (Oligonol) on Peripheral Circulation, a Pilot Study Skin Thermography Demonstrates Vasodilation Effects of Polyphenol." 2014 July; 6(7) Natural Medicine Journal Kitadate K, Aoyagi K, Homma K.

Abstract:

TOPIC: What is the effect of Oligonol on peripheral circulation measured as skin temperature changes by infrared thermography?

BACKGROUND: A trial to assess the effect of Oligonol on peripheral circulation was compared with a placebo in healthy adults. The underlying mechanism for Oligonol's effect on circulation may be a result of increased nitric oxide (NO) production. Previous studies have indicated that polyphenols might regulate NO production by the

protein kinase C-dependent nicotinamide adenine dinucleotide phosphateoxidase activation pathway. A NO-dependent mechanism is further supported by the previous finding that Oligonol enhanced NO production by regulating phosphorylation and dephosphorylation of endothelial NO synthase (eNOS) 28. The effect of Oligonol on NO production was investigated in bradykinin-stimulated vascular endothelial cells under high-glucose conditions. Oligonol prevented the impairment of eNOS activity induced by high glucose through reversing altered eNOS phosphorylation status. Briefly, when endothelial cells were stimulated by bradykinin (30 nm) and cultured in a medium with a high concentration of glucose, NO production was decreased. However, the reduction was recovered by treatment with Oligonol.

STUDY TYPE: A single-blind, placebo-controlled crossover human intervention trial

STUDY DESIGN: The effect of Oligonol on peripheral circulation was measured as skin temperature changes by infrared thermography. Six healthy subjects (3 male, 3 female; 28–40 years old; body mass index < 25) were supplemented with 50 mg of Oligonol and a placebo (malt extract, dextrin) alternatively on different days. Subjects fasted for 12 hours prior the test and changed into clothing designed for skin thermography measurement. Subjects were asked to stay calm and rest for 60 minutes in a temperature-controlled room (room temperature 26° C ± 1° C, humidity 50%) prior to oral administration of the samples. Thermographic measurements of changes in skin temperature were completed immediately before the oral dose and every 30 minutes after for up to 120 minutes. The areas of interest for the thermographic measurements were the neck, shoulder, and right palm. A paired t-test was used to determine skin temperature differences within subjects between time periods. Welch's t-test was used to compare skin temperature between groups. A level of $p = .05$ was recognized as statistically significant. Values are presented as mean and standard error of the mean.

SUBJECTS: Six healthy subjects (3 male, 3 female; 28–40 years of age)

DOSAGE: 50 mg Results Thirty minutes following Oligonol ingestion, thermographic measurements showed a significant temperature increase in the right palm in the Oligonol group compared with the placebo group. Temperature changes between groups were significantly different at 30 minutes and 60 minutes. The temperature remained significantly above base line levels for up to 120 minutes in the Oligonol group. While thermographic measurements of the neck and shoulder trended toward an increase in temperature in the Oligonol group compared with placebo, there were no significant differences between groups. Within each treatment group, the temperature increased and remained significantly above the base line temperature through 120 minutes. The results showed a significant elevation of body surface temperature in the beforeand-after thermographs in the palms of all subjects in the Oligonol group, which suggests peripheral blood flow improvement in healthy people. The results of thermographic measurements of the neck and shoulder showed no significant differences between groups. However, there was a significant increase in both groups compared with the base line.

CONCLUSION: Oligonol improves peripheral circulation as measured by skin temperature changes using infrared thermography. The elevation in temperature is thought to be a result of the increase of the blood through the vascular smooth muscle, resulting from polyphenol-enhanced NO production in the vascular endothelium. This mechanism may underlie the beneficial vascular health effects of Oligonol. Further studies with increased sample size are warranted

"Effect of Oligonol in Increasing Peripheral Body Temperature." Amino Up Chemical Co., Ltd., Japan, R & D Division. 2007

Abstract:

TOPIC: Can Oligonol® increase peripheral body temperature? Background People suffering from cold hands and feet are more likely individuals with some kind of blood circulation disorder.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Cross-over study: Thermographic measurements to measure changes in skin temperature were performed on subjects before supplementation with Oligonol® and 30, 60, 90 and 120 minutes following supplementation.

SUBJECTS: 5 healthy sedentary male volunteers

DOSAGE: 50 or 100 mg Oligonol®

RESULTS: Thermographic measurements verified an increase of peripheral body temperature 30 minutes after intake of 50 or 100 mg Oligonol® and lasting for more than 2 hours.

CONCLUSION: "This study suggests that a dose of 50 mg of Oligonol® might have improving effects on blood circulation.

"Effect of Lychee-Derived Low-Molecular-Weight Polyphenol (Oligonol) on Post-Prandial Hyperglycemia and Metabolic Syndrome Hyperglycemia." Presented at the 4th International Conference on Polyphenols and Health (ICPH2009) Nishihira J., et al.

Abstract:

TOPIC: Can Oligonol® suppress or moderate excessive elevation of blood glucose levels after a meal?

BACKGROUND: Post prandial hyperglycemia is recognized as a cardiovascular risk factor in both diabetic and the general population. Animal studies have suggested that Oligonol® has a potential to suppress postprandial hyperglycemia.

STUDY TYPE: Human intervention trial Study Design Randomized double-blind, placebo controlled crossover: Subjects were supplemented with Oligonol® or placebo prior to food intake. Blood glucose was measured before and after food intake and every 30 minutes for 2 hours.

SUBJECTS: 12 male volunteers with fasting blood sugar more than 100 mg/dl Dosage 600 mg Oligonol®

RESULTS: Oligonol® supplementation resulted in: • No side effects, such as abdominal discomfort or diarrhea. • Suppression or delay of peak glucose level, in 4 cases out of 6. • Minimal change of blood glucose level in 1 case. • Increase of blood glucose level in 1 case.

CONCLUSION: "Oligonol® suppressed, but not in all cases, postprandial hyperglycemia. From current data and published literatures, it is assumed that Oligonol® may function as α-glucosidase inhibitor and/or α-amylase inhibitor. The current results encourage us to proceed to further studies on this effect of Oligonol® on border-line diabetic subjects.

"Effect of Lychee Polyphenol on Postprandial Serum Lipid Responses in Healthy Human Subjects." Presented at 15th International Symposium on Atherosclerosis June 2009

Abstract:

TOPIC: Can Oligonol® reduce postprandial hyperlipidemia in healthy individuals?

BACKGROUND: Post prandial hyperlipidemia is recognized as a cardiovascular risk factor in both diabetic and the general population. Animal studies have suggested that Oligonol® has a potential to suppress postprandial hyperlipidemia.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Three-way cross-over study: Subjects ingested 15 grams of mayonnaise with and without lychee fruit polyphenols (LFP) or oligomerized lychee fruit polyphenols (OLFP). Fasting and postprandial triglycerides (TG) and cholesterol concentrations were measured, as well as serum remnant-like particle cholesterol (RLPC), apolipoprotein B48 (ApoB48) and free fatty acid concentrations (FFA)

SUBJECTS: 9 healthy male volunteers

DOSAGE: 500 mg lychee fruit polyphenols or 500 mg oligomerized lychee fruit polyphenols Results LFP and OLFP supplementation following fat load resulted in the following changes compared with control: • Lower serum TG response to fat load. • Significant decreased chylomicron TG response. • The time for reaching maximum level of serum TG, chylomicron TG, RLP-C and ApoB48 was delayed.

CONCLUSION: "This study indicated that lychee polyphenol supplementation could inhibit the fat absorption and improve postprandial hyperlipidemia in healthy subjects

"The Inhibitory Effect of Oligonol on MMP Activation." Presented at the 18th International Congress on Nutrition and Integrative Medicine (ICNIM) July 2010 Kishimoto Y., et al

TOPIC: Does Oligonol® supplementation affect MMP activity following fat intake?

BACKGROUND: Matrix metalloproteinase (MMP) plays an important role in the initiation and progression of atherosclerosis.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Three-way crossover: Subjects ingested 15 grams of mayonnaise with or without lychee fruit polyphenols (LFP) or Oligonol®. Plasma MMP-2 activity was measured following food intake.

SUBJECTS: 9 healthy male volunteers Dosage 500 mg Oligonol® or 500 mg LFP Results Oligonol® significantly suppressed postprandial MMP-activation.

CONCLUSION: "This study suggested that Oligonol® might play a preventative role in atherosclerosis because of the inhibition effects on MMP activation."

"Effect of Oligonol on Risk Factors in Atherosclerosis." Presented at the 18th International Congress on Nutrition and Integrative Medicine (ICNIM) Tani M., et al.

TOPIC: Can Oligonol® supplementation affect postprandial serum lipid response in healthy individuals?

BACKGROUND: Postprandial hyperlipidemia and MMP activation play an important role in pathogenesis of atherosclerosis.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Cross-over study: Subjects ingested 15 grams of mayonnaise with or without Oligonol®. Serum triglyceride (TG) response and MMP-9 activity was measured.

SUBJECTS: 9 healthy male volunteers

DOSAGE: 500 mg Oligonol®

RESULTS: Oligonol® supplementation following fat load resulted in the following changes compared with control: • Lower serum TG response to fat load. • Significant decreased chylomicron TG response. • The time for reaching maximum level of serum TG, chylomicron TG, was delayed. • Postprandial MMP activation was suppressed.

CONCLUSION: "These results suggested that Oligonol® may play a preventative role of atherosclerosis because of improving postprandial hyperlipidemia.

"Oligonol Supplementation Attenuates Body Temperature and the Circulating Levels of Prostaglandin E2 and Cyclooxygenase-2 After Heat Stress in Humans." 2013 16(4): 318–23 Journal of Medicinal Foods Shin Y., et al.

TOPIC: What effect does Oligonol supplementation have on circulating levels of prostaglandin E2 (PGE2), cyclooxygenase-2 (COX-2) enzymes, and body temperature after heat stress in 17 healthy human male volunteers?

BACKGROUND: Oligonol is an optimized phenolic product containing catechin-type monomers and oligomers (dimers, trimers, and tetramers) of proanthocyanidin that are easily absorbed. Oligonol, a phenolic extract from lychee fruit with green tea polyphenols, has been reported to have antioxidant and anti-inflammatory effects. Supplementation with Oligonol decreases serum concentrations of cortisol, IL-1β, and IL-6, which are fever-related hormones or cytokines released after heat stress, therefore, it is thought that it has an antipyretic or fever-reducing potential. Prostaglandin E2 is the principal mediator of fever and exerts its fever-inducing action by binding to receptors on thermoregulatory neurons in the anterior hypothalamus. PGE2 is formed in most cells from cyclooxygenase-mediated metabolism of arachidonic acid. COX-2 enzymes and production of PGE2 are involved in causing febrile and inflammatory responses. Cytokines are chemical messengers found in the circulation and help mediate fever and inflammation caused by heat stress. Interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), are cytokines involved in PGE2 production in response to fever. Transcription factors, such as nuclear factor-kappa β and signal transducer and activator of transcription 3, are activated by these cytokines and lead to the induction of COX-2, which mediates fever production. This study investigated the effect of Oligonol supplementation on circulating levels of inflammatory factors prostaglandin E2 and cyclooxygenase-2. It also checked the body temperature after heat stress in 17 healthy human male volunteers (age range 21.6–22.1 years old). The experiments were performed using a chamber with automated climate control at 26.0° C and a relative humidity of 60%–63.0%. Study Type A double-blind crossover-design human intervention study

STUDY DESIGN: Subjects ingested 100 mg of Oligonol in a beverage or a placebo before half-body immersion into hot water at 42° C for 30 minutes. Tympanic and skin temperatures were measured and mean body temperatures were calculated. Serum concentrations of PGE2 and COX-2 were analyzed before, immediately after, and 60 minutes after immersion in the hot water. All experiments were conducted in a thermoneutral climate chamber (26° C ± 0.5° C, 60% ± 3% relative humidity, and < 1 m/sec air velocity) from 2 to 5 p.m. Upon arrival at the climate chamber, the subjects wore short pants and sat in a chair in a relaxed posture for 60 minutes to become conditioned to the chamber climate before the commencement of the experiments. After 60 minutes of rest, heat load was applied to each subject via immersion of half of their body into a hot water bath of 42º C ± 0.5º C for 30 minutes. Measurements were taken at rest, immediately after immersion, and 60 minutes after. Subjects drank 0.5 L of the Oligonol beverage or the placebo beverage 1 hour before the immersion.

SUBJECTS: 17 healthy males 21 to 22 years old

Dosage: 100 mg

RESULTS: Oligonol intake significantly prevented elevation of tympanic temperature (difference of 0.17° C after heat stress, $p < .05$; 0.17° C at 60 minutes, $p < .05$) and mean body temperatures (temperature difference: 0.18° C at post, $p < .05$; 0.15° C at re-60, $p < .05$), and lowered concentrations of serum PGE2 (increased by 13.3% vs. 29.6% at post, $p < .05$) and COX-2 (increased by 15.6% vs. 21.8% at post, $p < .05$) compared with placebo beverage.

CONCLUSION: The results suggest that Oligonol suppresses increases in body temperature under heat stress, and this is associated with decreases in serum levels of the inflammatory mediators PGE2 and COX-2 enzymes.

"Effects of Oligonol, an Oligomerized Polyphenol Formulated from Lychee Fruit, on Serum Concentration and Urinary Excretion of Uric Acid." 2010;3(1):13–16 Anti-Inflammatory Properties Journal of Functional Foods Moriawaki Y., et al.

TOPIC: Does Oligonol® have an effect on uric acid metabolism and therefore be used as an effective treatment or prevention of gout or hyperuricemia? Background High serum uric acid levels lead to an increased risk for gout and epidemiological studies suggest that polyphenols from cherries and those found in wine might play a role in reducing serum concentration of uric acid. High levels of serum uric acid (hyperuricemia) increase the risk for gout.

STUDY TYPE: Human clinical intervention trial

STUDY DESIGN: Open-label controlled: serum uric acid concentration and uric acid excretion were measured at baseline and three more times following Oligonol® supplementation. Subjects served as their own control by repeating the experiment 2 weeks later with no supplementation.

SUBJECTS: 6 healthy male volunteers

DOSAGE: 600 mg Oligonol®

RESULTS: Oligonol® supplementation resulted in the following significant changes compared with baseline and compared with control period: • Decreased serum and urinary uric acid excretion at 0.5, 1.5, and 2.5 hours after administration. • Fractional uric acid clearance was also decreased over the entire experimental period. In addition, an in vitro experiment showed that Oligonol® inhibited xanthine oxidase activity in a dosedependent manner.

CONCLUSION: "Together, these results suggest Oligonol® lowers serum concentration of uric acid through

inhibition of xanthine oxidase, and may be effective for prevention and treatment of hyperuricemia and/or gout.

"Clinical Study on the Improvement Effect of Oligonol in Skin." Amino Up Chemical Co., Ltd., Japan. January 2007

TOPIC: Can the oral supplementation of Oligonol® affect the skin?

BACKGROUND: Antioxidant supplementation has been correlated with improved skin condition due to the ability to prevent free radical damage to skin.

STUDY TYPE: Human intervention trial
STUDY DESIGN: Open-label controlled: Participants were supplemented with Oligonol® twice per day for 12 weeks. Using a Robo Skin Analyzer, pigment deposits (freckles) and wrinkles in the eye angle were evaluated. In addition, participants responded to a questionnaire regarding their skin condition.

SUBJECTS: 17 female volunteers between 26 and 60 years of age.

DOSAGE: 100 mg Oligonol® twice per day Results After 12 weeks of supplementation with Oligonol®, the following results were reported: • Improvement tendency of pigmentary deposits (higher than 10% reduction) in 29% of the subjects. • Reduction of the skin age (estimated age). • Improvement tendency of the wrinkles in eye area (higher than 10% reduction) in 47% of cases. • Results were more visible in participants who were over 40-years-old. • 50% of participants reported noticeable improvement of skin condition, especially in reduction of skin roughness and improving wrinkles.

CONCLUSION: "Based on analysis with Robo Skin Analyzer it was possible to verify an improvement in pigmentary deposits and wrinkles in the eye angle. In addition many responses to the questionnaire expressed improvement of skin condition.

"Anti-Aging Effect of Novel Low Molecular Polyphenol "Cysteinyl-Oligo-Proanthocyanidin." August 2008 Presented at the 16th International Congress on Nutrition and Integrative Medicine (ICNIM) Tsuboi T., et al.

TOPIC: Can topical application of Oligonol®-CS improve skin parameters associated with aging?

BACKGROUND: Polyphenols proved to have antiallergic, antioxidative, antibacterial, and anti viral effects in in-vitro studies, but their high molecular weight made them less penetrable to the skin and cells. Oligonol®-CS contains low molecular weight oligomers, resulting in higher skin permeability.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Oligonol®-CS solution was used topically twice a day on left half of face, while a placebo was used on right half of face. Skin parameters such as skin elasticity, effect on noticeable pores, pigmentation, moisture and oil content, and wrinkles were measured at baseline and after 2 months.

SUBJECTS: 5 volunteers

DOSAGE: 10% Oligonol®-CS

RESULTS: In vivo and in vitro data reported that Oligonol®-CS: • Possessed strong UV protection activity and antioxidative activity. • Prevented Maillard reaction and inhibited MMP-1 production which helped protect the collagen and elastin damage in the skin leading to the improvement of skin wrinkles and skin elasticity. • Improved wrinkles and pigmentation. • Reduced skin thickness in Oligonol®-CS applied area compared with placebo. and these results can be attributed to the improvement of barrier function. • Noticeably improved pores. • Contributed strong antioxidative and UV protection resulting in improvement of pigmentation.

CONCLUSION: "Based on these findings, Oligonol®-CS can be used as an active cosmetic ingredient with various functional activities for future cosmetic product development.

"Effects of Oligonol Supplementation on the Appearance of Skin Photo-Aging, Wrinkles, Hyperpigmentation and Lentigines." March 2010 Presented at Experimental Biology Annual Meeting Mackenzie R.

TOPIC: Can oral supplementation with Oligonol® positively affect the appearance of skin photo-aging, wrinkling, hyperpigmentation and lentigines (liver spots)?

BACKGROUND: Oligonol® has well-documented effects on oxidative stress prevention, which can translate directly to skin improvement.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Open-label controlled pilot. Subjects were supplemented with Oligonol® twice daily for 3 months.

SUBJECTS: 19 healthy sedentary male volunteers. Various parameters of skin health were performed using high resolution photography (DermaLite) and optical profilometry as well as serum CRP levels (C-reactive protein, an inflammatory marker).

DOSAGE: 100 mg Oligonol® twice daily

RESULTS: After 3 months, Oligonol® supplementation resulted in: • Decreased CRP in 54.5% of participants. • Decrease in fine lines in 72.7% of participants based on blind evaluation of DermaLite photographs by trained observers. • Reduction of deep wrinkles and sleep wrinkles in 18.2% of participants. • Consistent lightening and brightening of complexion, along with less redness, blotchiness, freckles and brown-pigmented blotches.

CONCLUSION: "The outcome confirmed known positive effects to skin health."

"Supplementation with a Flavanol-rich Lychee Fruit Extract Influences the Inflammatory Status of Young Athletes." 2011 Phytotherapy Research Nishizawa M., et al.

TOPIC: Can Oligonol® supplementation have an effect on inflammation and tissue damage in athletes during intense exercise?

BACKGROUND: Exercise has acute and chronic effects on inflammatory response. These effects can be measured by the release of inflammatory cytokines, such as interleukin (IL)-6. Plasma IL-6 increases during physical exercise and muscle contraction also induces the production of IL-6 as a myokine. Myokines are a subclass of cytokines that are produced, expressed and released by muscle fibers and exert either paracrine or endocrine effects.

STUDY TYPE: Human clinical intervention trial

STUDY DESIGN: Randomized, placebo-controlled double blind: Subjects received 100 mg daily of Oligonol® (50 mg twice per day) or a placebo daily for 2 months. All subjects performed identical high-intensity training for 2 months. A 2-month training program was designed by a qualified trainer and consisted of repeated training and rest cycles with running at low intensity (50%), medium intensity (13%), and high intensity (37%). Each subject ran a total of 800–1000 km during the training period. Various outcome parameters were measured in the morning before training period (baseline), 1 month (mid-training) and 2 months (post-training).

SUBJECTS: 20 young male long distance runners

DOSAGE: 100 mg Oligonol®

RESULTS: Two months of Oligonol® supplementation resulted in: • The resting heart rate was not significantly different between the two groups at baseline. However, the resting heart rate gradually decreased in the Oligonol® group and was significantly lower post-training than in the placebo group. • White blood cell count was significantly lower at posttraining in the Oligonol® group than in the placebo group. • Hemoglobin, hematocrit and mean corpuscular hemoglobin were significantly lower at mid training in the Oligonol® group than in the placebo group, although significant differences were not observed at post-training. • The percent

decrease in the IL-6 level from pre-training to midtraining (mid/pre) was significantly smaller in the Oligonol® group than in the placebo group. • The percent increase of the cytokine TGF-1 from baseline to post training was significantly greater in the Oligonol® group than in the placebo group.

CONCLUSION: "Flavanol-rich lychee fruit extract (FRLFE) seems to protect against exercise-induced oxidative stress and tissue damage and may be useful as a dietary supplement for regular exercisers. Further studies will help us elucidate the mechanism of action of FRLFE during exercise."

"Oligomerized lychee fruit extract (OLFE) and a mixture of vitamin C and vitamin E for endurance capacity in a double blind randomized controlled trial." 2012; 50(2): 106-113 Journal of Clinical Biochemistry and Nutrition Kang S., et al.

TOPIC: Can Oligonol® supplementation have an effect on exercise endurance capacity and how does it compare with vitamin C and E supplementation?

BACKGROUND: Several studies have presented evidence that exercise can increase Reactive Oxygen Species (ROS) production and that exercise-induced oxidative stress can cause muscle fatigue. While several animal studies have found that antioxidant supplements delay muscle fatigue and improve exercise performance, the clinical efficacy of antioxidants remains uncertain.

STUDY TYPE: Human clinical intervention trial

STUDY DESIGN: Randomized, placebo-controlled double blind: Subjects received 200 mg daily of Oligonol® (50 mg twice per day), a mixture of 800 mg vitamin C and 320 IU vitamin E, or a placebo daily for 30 days.

SUBJECTS: 70 regularly exercising males. Various parameters of exercise endurance were measured at baseline and at the end of 30 days.

DOSAGE: 200 mg Oligonol®

RESULTS: 30 days of Oligonol® supplementation resulted in: • Running times to exhaustion at 80% HRmax were measured and the change from baseline to after supplementation increased only in the Oligonol® group. • Endurance capacity was measured by the anaerobic threshold (AT). After supplementation, the Oligonol® group showed a significant increase in their anaerobic threshold, by 7.4% , whereas the vitamin and placebo groups showed no significant changes. • The initially observed increase in lactase dehydrogenase (used to screen for tissue damage) after the treadmill test for the Oligonol® group at baseline was reduced after 30 days of supplementation by over one-fourth of the initial observation.

CONCLUSION: "The increase in the submaximal running time and the AT, without a change in the VO2max value, and the decrease in the exercise-induced amplification of the LDH suggest Oligonol® as a possible enhancer of the endurance capacity

"The Effects of Oligonol Intake on Cortisol and Related Cytokines in Healthy Young Men." 2010; 4(3): 203-207 Nutrition Research and Practice Lee JB., et al.

TOPIC: Does Oligonol® have an anti-inflammatory effect following exercise-induced stress?

BACKGROUND: Exercise has acute and chronic effects on systemic immunity and inflammatory response. These effects can be measured by changes in serum levels of the stress hormone cortisol and the release of inflammatory cytokines, such as interleukin (IL)-6 and IL-1β. These responses are remarkably similar to those induced by infection, sepsis, or trauma.

STUDY TYPE: Human clinical intervention trial

STUDY DESIGN: Randomized, placebo-controlled: Each subject received 0.5 L water with Oligonol® or a placebo daily for 4 weeks. The body composition, white blood cell (WBC) and differential counts as well as the serum cortisol, IL-1β, and IL-6 concentrations were measured before and after Oligonol® intake.

SUBJECTS: 19 healthy sedentary male volunteers

DOSAGE: 100 mg Oligonol®

RESULTS: Four weeks of Oligonol® supplementation resulted in: • Significant decreases in serum cortisol concentration and levels of IL-6 and IL-1β were significantly decreased with Oligonol® intake compared to before treatment. • The rate of increase of these factors after exercise was decreased compared with the placebo group.

CONCLUSION: "These results suggest that oral Oligonol® intake for 4 weeks had a significant effect on inhibition of inflammatory markers in healthy young men."

"Oxidative Stress to Acute Hypobaric-Hypoxia and Antioxidant Ability of Oligonol." 2010; 30:118–124 Japanese Journal of Mountain Medicine Nagasawa J., et al.

TOPIC: Does Oligonol® supplementation have an effect on hypobaric/hypoxic oxidative stress?

BACKGROUND: Oxidative stress disorders cause or induce various diseases. Oxidative stress is increased during exposure to high altitude/hypoxic environments.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Single-blind, placebo controlled: 2-week supplementation of Oligonol® followed by physical activity under hypobaric/hypoxic stress conditions (616 hPa, 12.8% oxygen). Various parameters of oxidative

stress were measured at rest and after exercise at 80% HRmax.

SUBJECTS: 10 men Dosage 200 mg Oligonol®

RESULTS: Following two week supplementation with Oligonol®, the following results were reported: • Significant increase in plasma erythropoietin and salivary cortisol levels in both placebo and treatment group, but levels tended to be lower in the Oligonol® group. • Oligonol® group demonstrated significantly lower levels of serum MDA-LDL concentrations and hydroxyl radical production levels.

CONCLUSION: "Antioxidant administration shows significant antioxidant power with exercise load.

"Effect of Oligonol Supplementation on Oxidative Stress and Antioxidant Capacity Following High-Intensity Intermittent Sprint Cycle Exercise. September 2009." Presented at the 64th the Japanese Society of Physical Fitness and Sports Medicine Kusakabe M., et al.

TOPIC: Can Oligonol® supplementation effect oxidative stress and antioxidant capacity following high-intensity exercise?

BACKGROUND: Increased aerobic metabolism during exercise is a potential source of oxidative stress. Antioxidant supplements offer protection against the oxidative stress of exercise.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Randomized, placebo-controlled trial: participants were supplemented with either Oligonol® or a placebo for 2 weeks. After 2 weeks, subjects performed intermittent sprint cycle exercise for 20 sets (7-second maximal pedaling with 53 second recovery). Oxygen uptake and heart rate were measured continuously during exercise. Various parameters for oxidative stress were measured before exercise (baseline), immediately after exercise, and again 1 hour after exercise.

SUBJECTS: 18 male volunteers

DOSAGE: 200 mg Oligonol®

RESULTS: The following changes were reported in the Oligonol® group compared with placebo group: • Significant increase in oxygen uptake during exercise. • Significant decrease in serum LDL concentration. Conclusion "Oligonol® supplementation increases oxygen uptake during exercise. It seems likely that supplementation might reduce oxidative stress during rest and exercise in spite of no change in antioxidant capacity."

"The Supplementation of Oligonol, the New Lychee Fruit-Derived Polyphenol Converting Into a Low-Molecular Form, Has a Positive Effect on Fatigue During Regular Track-and-Field Training in Young Athletes." 2008; 13(4):93-99 Advances in Exercise and Sports Physiology Ohno H., et al.

TOPIC: Can Oligonol® supplementation affect subjective mood states (fatigue and pain) and oxidative stress following athletic training?

BACKGROUND: Increased aerobic metabolism during exercise is a potential source of oxidative stress. Antioxidant supplements offer protection against the oxidative stress of exercise. In addition, the relationship between training distance and mood has been found to follow a dose-dependent pattern — mood progressively worsening as training load increases.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Randomized Single-Blind placebo-controlled crossover: Subjects were supplemented with either placebo or Oligonol® for 26 days (Period 1). Their supplementation was switched for the next 26 days (Period 2). During the two periods, the training protocol consisted of 3 hour track-and-field training 5 times/ week. Subjects completed three questionnaires before training began, and at the end of each period. In addition, urine samples were submitted and various parameters on oxidative stress were measured.

SUBJECTS: 24 male and 22 female athletes

DOSAGE: 200 mg Oligonol®

RESULTS: The following changes were reported for Oligonol® supplementation compared with placebo: • RPE (Ratings of Perceived Exertion) responses during training were significantly lower in both groups, suggesting Oligonol® intake caused the subjects to feel less fatigued. • Tendency to attenuate the feeling of pain (muscular, lumbago and menstrual) followed by a change for the worse for group that discontinued Oligonol® midway through training.

CONCLUSION: "The results suggest that Oligonol® supplementation in young athletes has significant subjective positive effects particularly on fatigue during training and thus may contribute to the maintenance of good conditioning."

"Development of Oligonol rich candy and the effect on the oral cavity." July 2014 Presented at the 22nd International Congress on Nutrition and Integrative Medicine (ICNIM) Matsukawa T., et al.

TOPIC: What is the effect of a candy made with Oligonol, a polyphenol-rich extract of lychee fruit, on bad breath and Candida albicans population in the mouths of human subjects?

BACKGROUND: A candy has been formulated with a low-molecular-weight proanthocyanidin-type polyphenol derived from lychees and known as Oligonol. It has been proven that this confection can be utilized for preventive and therapeutic use in oral candidiasis models as demonstrated both in vitro and in vivo. Oligonol is formulated as a major component of the candy and has shown antibacterial activity against E. coli, MRSA, C. albicans, etc. This bioactive antimicrobial property is expected to aid in the prevention of oral candidiasis and in the improvement of oral cavity health to reduce the risk of developing periodontitis and milder conditions such as bad breath.

STUDY TYPE: Human clinical intervention study

STUDY DESIGN: The investigators studied the effect of Oligonol-rich candy, containing a concentration of Oligonol, in the oral cavity in 20 middle-aged and elderly people in good health. Ten subjects consumed 3 Oligonol-rich candies daily for a week, and another 10 subjects consumed placebo candies instead during the same period. Following a 2-week wash-out phase after administration of the test substance, a crossover study was conducted. The study was conducted as a doubleblind test after being approved by an ethics committee. Mouth rinses were collected 4 times before and after each test. Halitosis was measured by hand-held device. A questionnaire was given after each test.

SUBJECTS: 20 middle-aged and elderly people in good health

DOSAGE: Not reported

RESULTS: A comprehensive analysis of the results was created from the total viable bacterial count in the mouth rinse, from the reported degree of halitosis, and from the questionnaire. It was revealed that the Oligonolrich candy significantly decreased the count of C. albicans in live form in the 8 subjects who had more than 4,000 CFU of C. albicans before the study. Bad breath significantly improved for all 20 subjects and the questionnaire results showed that the Oligonol-rich candy improves halitosis and a discomfort index of a “sticky” mouth environment.

CONCLUSION: The results of this study demonstrate that Oligonolenriched candy is useful for oral hygiene practice in healthy people for daily use.

“Bioequivalence Study of Oligonol.” Amino Up Chemical Co., Ltd., Japan. June 13, 2007

TOPIC: Is Oligonol® absorbed and does it improve blood antioxidant capacity when ingested orally in hard capsule or dissolved in a drink?

BACKGROUND: In vitro antioxidant assays cannot be extrapolated to guarantee absorption and improved blood antioxidant capacity. Human clinical trials are required to show bioavailability.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Open-label controlled: Subjects were divided up into groups by age and various forms of Oligonol® were ingested: 200mg hard capsule with water 200mg hard capsule (intake with black tea) 200mg dissolved in bottled water 200mg dissolved in black tea 200mg dissolved in sports drink 200mg dissolved in carbonated drink Blood samples were taken before the intake, 1, 2, 4, 6 and 8 hours following intake. Total serum polyphenol concentration and serum antioxidant activity by TEAC were measured.

SUBJECTS: 34 volunteers

DOSAGE: 200 mg Oligonol®

RESULTS: During the period of the study: • Serum polyphenol concentration was almost double for Oligonol® dissolved in water compared with hard capsule. Maximum polyphenol content was reached in 2 hours for both cases. • Same results were seen with Oligonol® dissolved in black tea versus Oligonol® hard capsule taken with black tea — almost double the polyphenol concentration of serum, but speed of absorption was the same. • Oligonol® dissolved in black tea had higher serum polyphenol concentration than other drinks. • Serum antioxidant activity was 1.5 times higher for Oligonol® taken in dissolved in water compared to hard capsule taken with water. Tmax was reached in 2 hours for both cases. • Same results were seen with Oligonol® dissolved in black tea versus Oligonol® hard capsule taken with black tea — about 1.5 times the serum antioxidant capacity, but speed of absorption was the same.

"Absorption of Flavonols from a Novel Lychee Fruit Extract Rich in Flavonoids, and Effects on Membrane Stability and Oxidant Defense in Experimental Animals and Healthy Human Adults." 2008;2(T5.79) Polyphenols Communications Hackman R., et al.

TOPIC: Is Oligonol® absorbed and bioavailable and is it more bioavailable than lychee fruit extract (LFE)?

BACKGROUND: In order for flavonols to be absorbed, longer-chain flavonols need to be degraded into flavonol monomers or procyanidin dimers, as longer-chain procyanidins appear too large to be absorbed intact. Oligonol® is produced from lychee fruit extract whose procyanidins have been deoligomerized into monomers and dimers.

STUDY TYPE: Human intervention trial

STUDY DESIGN: Randomized parallel group: Participants consumed either unprocessed LFE or Oligonol® as a single dose. Blood was collected at 0, 2, 4, and 6 hours. Participants continued to consume supplements for 90 days and blood was collected again. Total polyphenol content of blood serum was measured.

SUBJECTS: 37 healthy volunteers

DOSAGE: 100 mg Oligonol® versus 100 mg LFE

RESULTS: Serum polyphenol concentration was significantly higher in Oligonol® group than in LFE group over the 6-hour test period.

CONCLUSION: "This data supports the concept that appropriately processed lychee fruit extract is well absorbed and may be useful as a flavonoid-rich dietary supplement.

"Suppressive Effect of Depolymerized Product "Oligonol" for Reactive Oxygen in Humans." November 2007 Presented at the 3rd International Conference on Polyphenols and Health Aoyagi K., et al.

TOPIC: Does Oligonol® supplementation diminish oxidative stress and is it superior to lychee fruit polyphenols (LFP) in reducing oxidative stress?

BACKGROUND: Oxidative stress has been thought of as a cause of aging, cancer or vascular disturbance. Creatinine is a physiological substance that distributes almost equally in the body. The oxidative product of creatinine can be measured by hydroxyl radicals (CTLs) in urine, and the ratio between creatol and creatinine is a good marker of oxidative stress.

STUDY TYPE: Human clinical intervention trial

STUDY DESIGN: Two way crossover study. Oxidative stress was measured by creatol/creatinine ratio in plasma at baseline and after 4 hours, 1 month and 3 months following Oligonol® supplementation. Subjects repeated study using lychee fruit polyphenols (LFP).

SUBJECTS: 43 healthy volunteers and 12 presymptomatic volunteers (high baseline oxidative stress levels)

DOSAGE: 100, 200 and 400 mg Oligonol® or LFP

RESULTS: Oligonol® supplementation was effective in lowering oxidative stress of initially-high-score subjects. For the initially-low-score subjects, Oligonol® increased oxidative score. Oligonol® had a superior effect compared with LFP.

CONCLUSION: "Oligonol® may have the oxidative stress-modulating effect by normalizing various statuses of oxidative stress."

"A Phase I Multiple Dose Trial of the Safety of Oligonol, a Novel Polyphenol Oligomer, in Healthy Volunteers." 2008 Spierings E, et al.

TOPIC: Is Oligonol® safe for human consumption?

BACKGROUND: The health claims for functional foods and the identification of their active functional ingredients mandates the documentation of any potential toxicity they may present. Phase 1 clinical trials are used to make the initial safety assessment of compounds with potential medical uses.

STUDY TYPE: Phase I Clinical Trial

STUDY DESIGN: Open-label controlled: Oligonol® was orally administered to healthy subjects twice per day for 14 days. Its effect on various laboratory parameters assessing safety were measured at 7-day intervals. Adverse events were monitored at 7-day intervals.

SUBJECTS: 30 healthy male and female volunteers

DOSAGE: 600 mg Oligonol® (300 mg twice per day)

RESULTS: Laboratory measurements and adverse effects reported after 7 and 14 days of supplementation with Oligonol®: • No abnormalities in the laboratory parameters between baseline and the final visit. • There were no changes in the EKG or in the urine analysis between the visits. • There was no difference found in serum LPO between baseline and the final visit. • 21 subjects (70%) reported no adverse symptoms during the trial at the interim or final assessment. • 3 subjects (10%) had abdominal discomfort and bloating at both interim and final visits, but none dropped out. • 17% of subjects reported other transient symptoms at either the interim or the final visit.

CONCLUSION: “This data supports previous data in animals and human beings that shows Oligonol® is a safe, well-tolerated nutritional supplement.”

“Oligonol 3-month Clinical Safety Study.” Amino Up Chemical Co., Ltd., Japan

TOPIC: Is Oligonol® safe for human consumption?

BACKGROUND: The health claims for functional foods and the identification of their active functional ingredients mandates the documentation of any potential toxicity they may present. Phase 1 clinical trials are used to make the initial safety assessment of compounds with potential medical uses.

STUDY TYPE: Safety assessment

STUDY DESIGN: Open-label: Volunteers were supplemented with 400 mg/day for 92 days. Oligonol® and general blood biochemical analysis was conducted before intake and at day 30 and day 92. Adverse events were monitored.

SUBJECTS: 6 healthy volunteers

DOSAGE: 400 mg Oligonol® (200 mg taken twice per day)

RESULTS: During the period of the study: • No significant adverse event was reported. • One of the volunteers experienced a transient mild symptom of diarrhea. This symptom disappeared spontaneously without specific treatment after one week. Therefore it was determined that it was not related to a side effect. • The general biochemical analysis showed no adverse event in liver and kidney functions.

CONCLUSION: “Based on these findings, it can be assumed that Oligonol® is safe as food.”