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Dr. Jeffrey Bland's Professional Publications

Endocrinology. 2019 Jan 1;160(1):143-155. doi: 10.1210/en.2018-00711.

[Bitter Taste Receptor Ligand Improves Metabolic and Reproductive Functions in a Murine Model of PCOS.](#)

Wu S¹, Xue P¹, Grayson N², Bland JS², Wolfe A¹.

Abstract

Polycystic ovary syndrome (PCOS) results from functional ovarian hyperandrogenism due to dysregulation of androgen secretion. Cultured theca cells from polycystic ovaries of women with the most common form of PCOS overexpress most androgen producing enzymes, particularly CYP450c17. In this study, a murine model was used of PCOS induced by chronic feeding with a high-fat diet that exhibits the reproductive, hyperandrogenic, and metabolic constellation of PCOS symptoms seen in women. Oral administration of KDT501, a hops-derived bitter taste receptor (Tas2R 108) isohumulone ligand resulted in resolution of PCOS-associated endocrine and metabolic disturbances and restored reproductive function. Pioglitazone, a PPAR γ agonist, also improved metabolic and reproductive function, though not to the same degree as KDT501. Specifically, treatment of the murine PCOS model with KDT501 resulted in reduced testosterone and androstenedione levels in the absence of significant changes in LH or FSH, improved glucose tolerance and lipid metabolism, and reduced hepatic lipid infiltration and adiposity. There was significant improvement in estrous cyclicity and an increase in the number of ovarian corpora lutea, indicative of improved reproductive function after exposure to KDT501. Finally, ex vivo exposure of murine ovaries to KDT501 attenuated androgen production and ovarian expression of CYP450c17. Interestingly, the ovaries expressed Tas2R 108, suggesting a potential regulation of ovarian steroidogenesis through this chemosensory receptor family. In summary, a therapeutic strategy for PCOS possibly could include direct influences on ovarian steroidogenesis that are independent of gonadotrophic hormone regulation.

PMID: 30418546

Mol Metab. 2018 Oct;16:76-87. doi: 10.1016/j.molmet.2018.07.013. Epub 2018 Aug 4.

[Intestinal bitter taste receptor activation alters hormone secretion and imparts metabolic benefits.](#)

Kok BP¹, Galmozzi A¹, Littlejohn NK¹, Albert V¹, Godio C¹, Kim W¹, Kim SM¹, Bland JS², Grayson N², Fang M³, Meyerhof W⁴, Siuzdak G³, Srinivasan S¹, Behrens M⁵, Saez E⁶.

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Abstract

OBJECTIVES:

Extracts of the hops plant have been shown to reduce weight and insulin resistance in rodents and humans, but elucidation of the mechanisms responsible for these benefits has been hindered by the use of heterogeneous hops-derived mixtures. Because hop extracts are used as flavoring agents for their bitter properties, we hypothesized that bitter taste receptors (Tas2rs) could be mediating their beneficial effects in metabolic disease. Studies have shown that exposure of cultured enteroendocrine cells to bitter tastants can stimulate release of hormones, including glucagon-like peptide 1 (GLP-1). These findings have led to the suggestion that activation of Tas2rs may be of benefit in diabetes, but this tenet has not been tested. Here, we have assessed the ability of a pure derivative of a hops isohumulone with anti-diabetic properties, KDT501, to signal through Tas2rs. We have further used this compound as a tool to systematically assess the impact of bitter taste receptor activation in obesity-diabetes.

METHODS:

KDT501 was tested in a panel of bitter taste receptor signaling assays. Diet-induced obese mice (DIO) were dosed orally with KDT501 and acute effects on glucose homeostasis determined. A wide range of metabolic parameters were evaluated in DIO mice chronically treated with KDT501 to establish the full impact of activating gut bitter taste signaling.

RESULTS:

We show that KDT501 signals through Tas2r108, one of 35 mouse Tas2rs. In DIO mice, acute treatment stimulated GLP-1 secretion and enhanced glucose tolerance. Chronic treatment caused weight and fat mass loss, increased energy expenditure, enhanced glucose tolerance and insulin sensitivity, normalized plasma lipids, and induced broad suppression of inflammatory markers. Chronic KDT501 treatment altered enteroendocrine hormone levels and bile acid homeostasis and stimulated sustained GLP-1 release. Combined treatment with a dipeptidyl peptidase IV inhibitor amplified the incretin-based benefits of this pure isohumulone.

CONCLUSIONS:

Activation of Tas2r108 in the gut results in a remodeling of enteroendocrine hormone release and bile

acid metabolism that ameliorates multiple features of metabolic syndrome. Targeting extraoral bitter taste receptors may be useful in metabolic disease.

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PMCID: PMC6158035

PMID: 30120064

J Endocr Soc. 2017 Apr 21;1(6):650-659. doi: 10.1210/js.2017-00202. eCollection 2017 Jun 1.

[Effects of KDT501 on Metabolic Parameters in Insulin-Resistant Prediabetic Humans.](#)

Kern PA¹, Finlin BS¹, Ross D², Boyechko T², Zhu B¹, Grayson N³, Sims R³, Bland JS³.

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2. Center for Clinical and Translational Sciences, University of Kentucky, Lexington, Kentucky 40536.
3. KinDex Pharmaceuticals, Seattle, Washington 98104.

Abstract

Context:

KDT501 is an isohumulone drug that has demonstrated beneficial effects on metabolic parameters in mice.

Objective:

This study was intended to examine potential improvements in metabolism in humans.

Design and Setting:

Changes in carbohydrate and lipid metabolism, along with inflammatory markers, were evaluated in prediabetic humans in a clinical research center.

Participants:

Nine obese patients participated. All had prediabetes or normal glucose tolerance plus three features of metabolic syndrome.

Intervention:

All participants were treated with escalating doses of KDT501 to a maximum dose of 1000 mg every 12 hours for a total of 28 days.

Outcome Measures:

Changes in carbohydrate metabolism were measured with oral glucose tolerance, homeostatic model of insulin resistance, and euglycemic clamp; changes in plasma lipids and response to a lipid tolerance test; and changes in plasma inflammatory markers.

Results:

The drug was well tolerated. After KDT501 treatment, plasma triglycerides were reduced at 4 hours during a lipid tolerance test. Furthermore, plasma adiponectin and high-molecular-weight adiponectin increased significantly, and plasma tumor necrosis factor- α decreased significantly. There were no significant changes in oral glucose tolerance test results or insulin sensitivity measures.

Conclusions:

Despite the small sample size and the short duration of therapy, KDT501 administration reduced measures of systemic inflammation and improved postmeal plasma triglyceride levels, which may be beneficial in participants with insulin resistance or metabolic syndrome.

PMCID: PMC5686568

PMID: 29264518

Adv Med. 2017;2017:1718957. doi: 10.1155/2017/1718957. Epub 2017 Oct 15.

[A Systems Medicine Approach: Translating Emerging Science into Individualized Wellness.](#)

Bland JS¹, Minich DM^{2,3}, Eck BM⁴.

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2. Institute for Functional Medicine, Federal Way, WA, USA.
3. University of Western States, Portland, OR, USA.
4. Metagenics, Inc., Aliso Viejo, CA, USA.

Abstract

In today's aging society, more people are living with lifestyle-related noncommunicable diseases (NCDs) such as cardiovascular disease, type 2 diabetes, obesity, and cancer. Numerous opinion-leader organizations recommend lifestyle medicine as the first-line approach in NCD prevention and treatment. However, there is a strong need for a personalized approach as "one-size-fits-all" public health recommendations have been insufficient in addressing the interindividual differences in the diverse populations. Advancement in systems biology and the "omics" technologies has allowed comprehensive analysis of how complex biological systems are impacted upon external perturbations (e.g., nutrition and exercise), and therefore is gradually pushing personalized lifestyle medicine toward reality. Clinicians and healthcare practitioners have a unique opportunity in advocating lifestyle medicine because patients

see them as a reliable source of advice. However, there are still numerous technical and logistic challenges to overcome before personal "big data" can be translated into actionable and clinically relevant solutions. Clinicians are also facing various issues prior to bringing personalized lifestyle medicine to their practice. Nevertheless, emerging ground-breaking research projects have given us a glimpse of how systems thinking and computational methods may lead to personalized health advice. It is important that all stakeholders work together to create the needed paradigm shift in healthcare before the rising epidemic of NCDs overwhelm the society, the economy, and the dated health system.

PMCID: PMC5661085

PMID: 29164177

Front Endocrinol (Lausanne). 2017 Sep 29;8:255. doi: 10.3389/fendo.2017.00255. eCollection 2017.

[The Influence of a KDT501, a Novel Isohumulone, on Adipocyte Function in Humans.](#)

Finlin BS¹, Zhu B¹, Kok BP², Godio C², Westgate PM³, Grayson N⁴, Sims R⁴, Bland JS⁴, Saez E², Kern PA¹.

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3. College of Public Health, University of Kentucky, Lexington, KY, United States.
4. Kindex Pharmaceuticals, Seattle, WA, United States.

Abstract

OBJECTIVE:

In a phase II clinical trial in nine obese, insulin-resistant humans, we observed that treatment with KDT501, a novel isohumulone drug, increased total and high-molecular weight (HMW) adiponectin in plasma. The objective was to determine whether KDT501 increased adiponectin secretion from subcutaneous white adipose tissue (SC WAT) and the underlying mechanism(s).

METHODS:

Nine obese participants with either prediabetes or with normal glucose tolerance plus three features of metabolic syndrome were part of the study. SC WAT biopsies were performed before and after 28 days of KDT501 treatment in a clinical research setting. In addition, a cold stimulus was used to induce thermogenic gene expression. Adiponectin secretion was measured, and gene expression of 130 genes involved in adipose tissue function was determined. The effect of KDT501 on adipocyte mitochondrial function was analyzed *in vitro*.

RESULTS:

SC WAT explants secreted more total and HMW adiponectin after KDT501 treatment ($P < 0.05$). After KDT501 treatment, a number of genes involved in thermogenesis and lipolysis were induced by cold ($P < 0.05$). KDT501 also potentiated β -adrenergic signaling ($P < 0.001$) and enhanced mitochondrial function in adipocytes ($P < 0.001$).

CONCLUSION:

KDT501 induced adiponectin secretion posttranscriptionally and increased gene expression of thermogenic and lipolytic genes in response to cold stimulation. These beneficial effects on SC WAT may be explained by the ability of KDT501 to potentiate β -adrenergic signaling and enhance mitochondrial function in adipocytes.

CLINICAL TRIAL REGISTRATION:

<https://www.ClinicalTrials.gov>, ID number: [NCT02444910](https://www.ClinicalTrials.gov/ct2/show/study/NCT02444910).

PMCID: PMC5626816

PMID: 29033896

Integr Med (Encinitas). 2017 Feb;16(1):22-25.

[Defining *Function* in the Functional Medicine Model.](#)

Bland J¹.

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Abstract

In the functional medicine model, the word *function* is aligned with the evolving understanding that disease is an endpoint and function is a process. Function can move both forward and backward. The vector of change in function through time is, in part, determined by the unique interaction of an individual's genome with their environment, diet, and lifestyle. The functional medicine model for health care is concerned less with what we call the *dysfunction* or *disease*, and more about the dynamic processes that resulted in the person's dysfunction. The previous concept of functional somatic syndromes as psychosomatic in origin has now been replaced with a new concept of function that is rooted in the emerging 21st-century understanding of systems network-enabled biology.

PMCID: PMC5312741

PMID: 28223904

Integr Med (Encinitas). 2017 Feb;16(1):12-13.

[Creating Health in America, One Person at a Time: A Message for Incoming President Trump.](#)

Bland J.

PMCID: PMC5312737

PMID: 28223900

Integr Med (Encinitas). 2016 Dec;15(6):14-16.

[Kidney Disease: Personalized Lifestyle Health Care Makes a Big Difference.](#)

Bland J¹.

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Abstract

We cannot solve the kidney disease problem through the building of more dialysis centers or by providing a greater number of kidney transplants. We must find a way to implement effective lifestyle management programs if we truly want to bend the curve and decrease the prevalence of kidney disease. The solution to the chronic kidney disease challenge lies in the skilled application of personalized lifestyle health care. Achieving this goal represents a tremendous opportunity for multidisciplinary collaboration and integration.

PMCID: PMC5312831

PMID: 28223892

Integr Med (Encinitas). 2016 Oct;15(5):14-16.

[Intestinal Microbiome, *Akkermansia muciniphila*, and Medical Nutrition Therapy.](#)

Bland J¹.

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25 years. Dr Bland is the cofounder of the Institute for Functional Medicine (IFM) and is chairman emeritus of IFM's Board of Directors. He is the author of the 2014 book *The Disease Delusion: Conquering the Causes of Chronic Illness for a Healthier, Longer, and Happier Life*.

Abstract

The gastrointestinal microbiome has become a topic of great interest in medicine in recent years. Genomic sequencing can now be done at a fraction of the cost of a few years ago, and this has allowed for the development and compilation of an extensive amount of data related to the species diversity of the human gastrointestinal microbiome.¹ Studies have demonstrated that the intestinal microbiome is sensitive to the composition of the diet.² It is also recognized that the composition of the microbiome can be altered rapidly in response to dietary changes, stress, chemical exposure, and exercise.³ Both the expanded understanding of the composition of the human microbiome and the ability to measure it through genomic analysis of the stool have resulted in clinicians frequently wanting to know what actionable conclusions can be taken away from an analysis of the gastrointestinal microbiome.

PMCID: PMC5145007

PMID: 27980489

Integr Med (Encinitas). 2016 Aug;15(4):19-22.

[The Gut Mucosal Firewall and Functional Medicine.](#)

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Abstract

The evidence is strong: Protection and restoration of the intestinal firewall is of primary importance in many patients suffering from a wide range of chronic diseases. The functional medicine approach to evaluation and treatment of problems associated with compromised integrity of the intestinal firewall represents a successful application of the systems biology approach to the management of chronic disease.

PMCID: PMC4991645

PMID: 27574489

Integr Med (Encinitas). 2016 Jun;15(3):16-8.

[Where Is Health Care Headed?](#)

Bland J¹.

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Abstract

Looking at the trends, developments, and discoveries points us toward the future, but it is only when we consider these in the context of our understanding about the origins of disease that we can truly gain a clearer view of where health care is headed. This is the view that moves us from a focus on the diagnosis and treatment of a disease to an understanding of the origin of the alteration in function in the individual. This change in both perspective and understanding of the origin of disease is what will lead us to a systems approach to health care that delivers personalized and precision care that is based on the inherent rehabilitative power that resides within the genome.

PMCID: PMC4982642

PMID: 27547161

Integr Med (Encinitas). 2016 Apr;15(2):12-4.

[Mild Cognitive Impairment, Neurodegeneration, and Personalized Lifestyle Medicine.](#)

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Abstract

The takeaway message of this advancing science surrounding the causes and treatment of neurodegenerative diseases is to recognize MCI symptoms early and intervene with a comprehensive, multifaceted, personalized lifestyle medicine program that is designed to improve neurological function and built on the components described above. The present evidence suggests this approach represents the best medicine available today for beating back the rising tide of cognitive impairment and neurodegeneration.

PMCID: PMC4898276

PMID: 27330484

Integr Med (Encinitas). 2016 Mar;15(1):14-6.

[When Is a Rare Disease Not so Rare? Implications for Medical Nutrition Therapy.](#)

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PMCID: PMC4818062

PMID: 27053929

Integr Med (Encinitas). 2015 Dec;14(6):14-6.

[When Is a Disease a "Disease"?](#)

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PMCID: PMC4718199

PMID: 26807065

Integr Med (Encinitas). 2015 Oct;14(5):18-20.

[Functional Medicine: An Operating System for Integrative Medicine.](#)

Bland J¹.

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1. Jeffrey Bland, PhD is the chairman emeritus of the Institute for Functional Medicine, and he is the

founder and president of the Personalized Lifestyle Medicine Institute.

PMCID: PMC4712869

PMID: 26770161

PLoS One. 2014 Jan 30;9(1):e87848. doi: 10.1371/journal.pone.0087848. eCollection 2014.

[KDT501, a derivative from hops, normalizes glucose metabolism and body weight in rodent models of diabetes.](#)

Konda VR¹, Desai A¹, Darland G¹, Grayson N¹, Bland JS¹.

Author information:

1. KinDex Therapeutics, LLC, Seattle, Washington, United States of America.

Abstract

AIMS/HYPOTHESIS:

We developed KDT501, a novel substituted 1,3-cyclopentadione chemically derived from hop extracts, and evaluated it in various in vitro and in vivo models of diabetes and insulin sensitivity.

METHODS:

KDT501 was evaluated for anti-inflammatory effects in monocyte/macrophage cells; agonistic activity for peroxisome proliferator-activated receptors (PPAR); lipogenesis and gene expression profile in human subcutaneous adipocytes. Body composition, glucose, insulin sensitivity, and lipids were assessed in diet-induced obesity (DIO) mice and Zucker Diabetic Fatty (ZDF) rats after oral administration.

RESULTS:

KDT501 mediated lipogenesis in 3T3L1 and human subcutaneous adipocytes; however, the gene expression profile of KDT501 differed from that of the full PPAR γ agonist rosiglitazone, suggesting that KDT501 has pleiotropic biological activities. In addition, KDT501 showed only modest, partial PPAR γ agonist activity and exhibited anti-inflammatory effects in monocytes/macrophages that were not observed with rosiglitazone. In a DIO mouse model, oral administration of KDT501 significantly reduced fed blood glucose, glucose/insulin AUC following an oral glucose bolus, and body fat. In ZDF rats, oral administration of KDT501 significantly reduced fed glucose, fasting plasma glucose, and glucose AUC after an oral glucose bolus. Significant, dose-dependent reductions of plasma hemoglobin A1c, weight gain, total cholesterol, and triglycerides were also observed in animals receiving KDT501.

CONCLUSION:

These results indicate that KDT501 produces a unique anti-diabetic profile that is distinct in its spectrum of pharmacological effects and biological mechanism from both metformin and pioglitazone. KDT501

may thus constitute a novel therapeutic agent for the treatment of Type 2 diabetes and associated conditions.

PMCID: PMC3907559

PMID: 24498211

ScientificWorldJournal. 2013 Jun 26;2013:129841. doi: 10.1155/2013/129841. Print 2013.

[Personalized lifestyle medicine: relevance for nutrition and lifestyle recommendations.](#)

Minich DM¹, Bland JS.

Author information:

1. Personalized Lifestyle Medicine Institute, 800 Fifth Avenue, Suite 4100, Seattle, WA 98104, USA.

Abstract

Public health recommendations for lifestyle modification, including diet and physical activity, have been widely disseminated for the prevention and treatment of disease. These guidelines are intended for the overall population without significant consideration for the individual with respect to one's genes and environment. Personalized lifestyle medicine is a newly developed term that refers to an approach to medicine in which an individual's health metrics from point-of-care diagnostics are used to develop lifestyle medicine-oriented therapeutic strategies for improving individual health outcomes in managing chronic disease. Examples of the application of personalized lifestyle medicine to patient care include the identification of genetic variants through laboratory tests and/or functional biomarkers for the purpose of designing patient-specific prescriptions for diet, exercise, stress, and environment. Personalized lifestyle medicine can provide solutions to chronic health problems by harnessing innovative and evolving technologies based on recent discoveries in genomics, epigenetics, systems biology, life and behavioral sciences, and diagnostics and clinical medicine. A comprehensive, personalized approach to medicine is required to promote the safety of therapeutics and reduce the cost of chronic disease. Personalized lifestyle medicine may provide a novel means of addressing a patient's health by empowering them with information they need to regain control of their health.

PMCID: PMC3710624

PMID: 23878520

Altern Ther Health Med. 2013;19 Suppl 1:50-5.

[Jeffrey Bland, Phd, FACN, FACB: heart disease, inflammation, and the revolution in health care. Interview by Craig Gustafson.](#)

Bland J.

PMID: 24734271

Nutr Res Pract. 2012 Oct;6(5):405-13. doi: 10.4162/nrp.2012.6.5.405. Epub 2012 Oct 31.

[Optimized mixture of hops rho iso-alpha acids-rich extract and acacia proanthocyanidins-rich extract reduces insulin resistance in 3T3-L1 adipocytes and improves glucose and insulin control in db/db mice.](#)

Tripp ML¹, Darland G, Konda VR, Pacioretty LM, Chang JL, Bland JS, Babish JG.

Author information:

1. MetaProteomics LLC, 9770 44 Ave. NW, Ste 100, Gig Harbor, WA 98332, USA.

Abstract

Rho iso-alpha acids-rich extract (RIAA) from *Humulus lupulus* (hops) and proanthocyanidins-rich extracts (PAC) from *Acacia nilotica* exert anti-inflammatory and anti-diabetic activity in vitro and in vivo. We hypothesized that a combination of these two extracts would exert enhanced effects in vitro on inflammatory markers and insulin signaling, and on nonfasting glucose and insulin in db/db mice. Over 49 tested combinations, RIAA:PAC at 5:1 (6.25 µg/mL) exhibited the greatest reductions in TNF α -stimulated lipolysis and IL-6 release in 3T3-L1 adipocytes, comparable to 5 µg/mL troglitazone. Pretreatment of 3T3-L1 adipocytes with this combination (5 µg/mL) also led to a 3-fold increase in insulin-stimulated glucose uptake that was comparable to 5 µg/mL pioglitazone or 901 µg/mL aspirin. Finally, db/db mice fed with RIAA:PAC at 5:1 (100 mg/kg) for 7 days resulted in 22% decrease in nonfasting glucose and 19% decrease in insulin that was comparable to 0.5 mg/kg rosiglitazone and better than 100 mg/kg metformin. RIAA:PAC mixture may have the potential to be an alternative when conventional therapy is undesirable or ineffective, and future research exploring its long-term clinical application is warranted.

PMCID: PMC3506871

PMID: 23198019

Nutrition. 2013 Jan;29(1):276-83. doi: 10.1016/j.nut.2012.05.004. Epub 2012 Sep 15.

[META060 protects against diet-induced obesity and insulin resistance in a high-fat-diet fed mouse.](#)

Vroegrijk IO¹, van Diepen JA, van den Berg SA, Romijn JA, Havekes LM, van Dijk KW, Darland G, Konda V, Tripp ML, Bland JS, Voshol PJ.

Author information:

1. Department of General Internal Medicine, Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, The Netherlands.

Abstract

OBJECTIVE:

We investigated whether a reduced iso- α acid derived from an extract of *Humulus lupulus* L., META060,

had an effect on weight gain, body composition, and metabolism in a high-fat-diet (HFD) fed mouse model.

METHODS:

Weight gain was monitored for up to 20 wk in mice receiving a low-fat diet, an HFD, or an HFD supplemented with META060 or rosiglitazone. Body composition was determined using dual-energy x-ray absorptiometric analysis. Indirect calorimetric measurements were performed to investigate the energy balance in the mice, and oral glucose tolerance tests were administered to examine the effect of META060 on the glycemic response.

RESULTS:

The HFD-fed mice administered META060 for 14 wk had a significantly lower mean weight than HFD-fed mice (30.58 ± 0.5 versus 37.88 ± 0.7 g, $P < 0.05$). Indirect calorimetric measurements showed an increased metabolic flexibility in mice supplemented with META060. In addition, glucose tolerance was improved, comparable to the effects of rosiglitazone treatment.

CONCLUSIONS:

META060 has potential therapeutic value for managing obesity and insulin resistance, and further research into the mechanism of action is warranted.

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PMID: 22985971

Glob Adv Health Med. 2012 Sep;1(4):84-91. doi: 10.7453/gahmj.2012.1.4.012.

[The Effects of Tetrahydro-iso-alpha Acids and Niacin on Monocyte-Endothelial Cell Interactions and Flow-mediated Vasodilation.](#)

Lamb JJ¹, Konda VR, Desai A, Bland JS, Tripp ML.

Author information:

1. Joseph Lamb, MD, is director, Intramural Clinical Research at Metagenics, Gig Harbor, Washington; adjunct faculty, Institute for Functional Medicine, Gig Harbor; and medical director, KinDex Therapeutics, Seattle, Washington.

Abstract

Niacin favorably modifies cardiovascular risk factors but is associated with flushing and shows limited benefit in improving endothelial function. We investigated whether combining anti-inflammatory tetrahydro-iso-alpha acids (THIAA) from hops with niacin would improve endothelial function. We hypothesized that the THIAA+niacin combination would demonstrate benefits not seen with niacin alone. In an in vitro model, a THIAA+niacin mixture inhibited several TNF- α -induced cytokines in human

aortic endothelial cells and in human monocytic cells and was significantly more efficacious than niacin alone. Subsequently, the effect of 125 mg THIAA and 500 mg niacin on endothelial-regulated flow-mediated vasodilation (FMD) was explored in a pilot study of 11 dyslipidemic volunteers. The 12-week treatment (2 tablets/day) resulted in a clinically relevant FMD increase compared to a trend toward an FMD decrease with placebo; the between-arm difference was statistically significant. THIAA+niacin treatment also improved total cholesterol, low-density lipoprotein cholesterol, and uric acid. No significant improvement in these parameters was observed with placebo. High-sensitivity C-reactive protein was significantly increased only in the placebo arm. Nutritional support with a THIAA+niacin combination may provide benefits for endothelial function in those with dyslipidemia.

PMCID: PMC3833516

PMID: 24278836

J Sep Sci. 2012 May;35(9):1183-9. doi: 10.1002/jssc.201101109.

[Isolation of bitter acids from hops \(*Humulus lupulus* L.\) using countercurrent chromatography.](#)

Dahlberg CJ¹, Harris G, Urban J, Tripp ML, Bland JS, Carroll BJ.

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Abstract

Commercially available hops (*Humulus lupulus* L.) bitter acid extracts contain a mixture of three major congeners (co-, n-, and ad-) in addition to cis/trans diastereomers for each congener. Individual isomerized α -acids were obtained by the consecutive application of two separate countercurrent chromatography methods. First, individual isomerized α -acid congeners as a mixture of cis/trans diastereomers were obtained using a solvent system consisting of hexane and aqueous buffer. The second purification, capable of separating cis/trans diastereomers, was accomplished using a quaternary solvent system; an alternative procedure using α -cyclodextrin followed by countercurrent chromatography was also investigated. The NaBH(4) reduction of the purified isomerized α -acid compounds followed by countercurrent chromatography purification resulted in individual α iso α -acids (>95%). Similarly, catalytic hydrogenation of the purified isomerized α -acid compounds followed by countercurrent chromatography purification produced individual tetrahydro isomerized α -acids (>95%). Reported herein is a widely applicable approach that focuses on three critical variables--solvent system composition, pH, and buffer-to-sample ratio--that enable the efficient purification of individual bitter acids (>95%) from commercially available hops extracts.

© 2012 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

PMID: 22689494

Atherosclerosis. 2012 Jul;223(1):130-6. doi: 10.1016/j.atherosclerosis.2012.05.004. Epub 2012 May 15.

[META060 attenuates TNF- \$\alpha\$ -activated inflammation, endothelial-monocyte interactions, and matrix metalloproteinase-9 expression, and inhibits NF- \$\kappa\$ B and AP-1 in THP-1 monocytes.](#)

Desai A¹, Darland G, Bland JS, Tripp ML, Konda VR.

Author information:

1. Metagenics, Inc., Gig Harbor, WA 98332, USA.

Abstract

BACKGROUND:

Cytokine-induced monocyte-endothelial interaction and vascular inflammation play a critical role in atherogenesis. A modified hop extract, META060, was identified as an inhibitor of inflammatory mediators in human rheumatoid arthritis synovial fibroblasts.

OBJECTIVE:

To determine how META060 may impact the initial stages of atherosclerosis, we investigated the effects of META060 in endothelial and monocyte cell models.

METHODS:

and results: TNF- α (10 ng/mL)-activated human monocytic THP-1 cells adhered to human aortic endothelial cells (HAECs); pre-treatment of cells with META060 (10 μ g/mL) significantly inhibited cell adhesion. META060 (1-20 μ g/mL) inhibited TNF- α -induced expression of inflammatory mediators including IL-1 β , MCP-1 and RANTES in HAECs and THP-1 cells. TNF- α - or LPS-mediated MMP-9 protein levels (measured by an immunoassay) and enzyme activity (determined by zymography) were inhibited by META060 in a dose-dependent manner. Data from transcription factor screening assays showed that META060 selectively inhibited NF- κ B and AP-1 in THP-1 cells, suggesting that META060 regulated inflammatory markers through gene regulation.

CONCLUSION:

META060 inhibited monocyte-endothelial cell interactions and suppressed multiple biomarkers of inflammation in both a monocytic cell line and an endothelial cell line. MMP-9 expression and activity also were inhibited. These effects resulted in part from META060's inhibition of transcription factors NF- κ B and AP-1. META060 may have beneficial effects for prevention or treatment of cardiovascular diseases by ameliorating inflammation and plaque destabilization, which are hallmarks of atherosclerosis.

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PMID: 22658256

Glob Adv Health Med. 2012 May;1(2):38-45. doi: 10.7453/gahmj.2012.1.2.009.

[The Heart and Medicine: Exploring the Interconnectedness of Cardiometabolic-related Concerns Through a Systems Biology Approach.](#)

Lamb J¹, Bland J.

Author information:

1. Joseph Lamb, MD, is director, Intramural Clinical Research, Metagenics, Gig Harbor, Washington; adjunct faculty, Institute for Functional Medicine, Gig Harbor; and medical director, KinDex Therapeutics, Seattle, Washington.

Abstract

Patients do not just wake up one morning with cardiac disease. Instead there is an extended preclinical phase during which lifestyle choices determine outcome. Recent advances in our understanding of oxidative stress, endocrine signaling, immune/inflammatory balance, and energy production illuminate opportunities for efficacious intervention. A thorough exploration of these pathophysiologies will allow physicians the opportunity to offer their patients a journey away from illness and disease to optimal wellness.

PMCID: PMC3833496

PMID: 24278817

Nutr Res. 2011 May;31(5):347-55. doi: 10.1016/j.nutres.2011.03.016. Epub 2011 Apr 29.

[Nutritional supplementation of hop rho iso-alpha acids, berberine, vitamin D?, and vitamin K? produces a favorable bone biomarker profile supporting healthy bone metabolism in postmenopausal women with metabolic syndrome.](#)

Lamb JJ¹, Holick MF, Lerman RH, Konda VR, Minich DM, Desai A, Chen TC, Austin M, Kornberg J, Chang JL, Hsi A, Bland JS, Tripp ML.

Author information:

1. MetaProteomics, LLC, a subsidiary of Metagenics, Inc., Gig Harbor, WA 98332, USA.

Abstract

Metabolic syndrome poses additional risk for postmenopausal women who are already at risk for osteoporosis. We hypothesized that a nutritional supplement containing anti-inflammatory phytochemicals and essential bone nutrients would produce a favorable bone biomarker profile in postmenopausal women with metabolic syndrome. In this 14-week, randomized trial, 51 women were instructed to consume a modified Mediterranean-style, low-glycemic-load diet and to engage in aerobic exercise. Those in the intervention arm (n = 25) additionally received 200 mg hop rho iso-alpha acids, 100 mg berberine sulfate trihydrate, 500 IU vitamin D?, and 500 ?g vitamin K? twice daily. Forty-five women completed the study. Baseline nutrient intake did not differ between arms. Compared with baseline, the intervention arm exhibited an approximate 25% mean decrease (P < .001) in serum

osteocalcin (indicative of bone turnover), whereas the placebo arm exhibited a 21% increase ($P = .003$). Serum 25-hydroxyvitamin D increased 23% ($P = .001$) in the intervention arm and decreased 12% ($P = .03$) in the placebo arm. The between-arm differences for osteocalcin and 25-hydroxyvitamin D were statistically significant. Serum insulin-like growth factor I was statistically increased in both arms, but the between-arm differences were not statistically significant. Subanalysis showed that among those in the highest tertile of baseline insulin-like growth factor I, the intervention arm exhibited a significant increase in amino-terminal propeptide of type I collagen, whereas the placebo arm showed a significant decrease at 14 weeks. Treatment with rho iso-alpha acids, berberine, vitamin D?, and vitamin K? produced a more favorable bone biomarker profile indicative of healthy bone metabolism in postmenopausal women with metabolic syndrome.

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PMID: 21636012

J Clin Lipidol. 2010 Jan-Feb;4(1):59-68. doi: 10.1016/j.jacl.2009.11.002. Epub 2009 Dec 3.

[Subjects with elevated LDL cholesterol and metabolic syndrome benefit from supplementation with soy protein, phytosterols, hops rho iso-alpha acids, and Acacia nilotica proanthocyanidins.](#)

Lerman RH¹, Minich DM, Darland G, Lamb JJ, Chang JL, Hsi A, Bland JS, Tripp ML.

Author information:

1. Functional Medicine Research Center, MetaProteomics, LLC, 9770 44th Avenue NW, Ste 100, Gig Harbor, WA 98332, USA.

Abstract

BACKGROUND:

Metabolic syndrome is associated with increased cardiovascular disease (CVD) risk, a risk that is significantly increased when accompanied by elevated low-density lipoprotein cholesterol (LDL-C). Whereas lifestyle therapies are the initial intervention of choice for both of these risk factors, it has not been clearly determined that this approach is efficacious when they occur concomitantly.

OBJECTIVE:

To evaluate effects of supplementing a lifestyle program with a medical food and nutraceutical in individuals with metabolic syndrome and elevated LDL-C.

METHODS:

We conducted a subgroup analysis of a 12-week, randomized trial in adults with metabolic syndrome; data from those with LDL-C ≥ 160 mg/dL were analyzed. Control-arm subjects were instructed to consume a modified Mediterranean-style, low-glycemic-load diet (MED, $n = 12$). Treatment-arm subjects received a phytochemical-enhanced diet (PED, $n = 12$) consisting of the same low-glycemic-load diet

plus a medical food containing soy protein and plant sterols and a nutraceutical containing hops rho iso-alpha acids and acacia proanthocyanidins. All subjects received identical aerobic exercise counseling.

RESULTS:

At 12 weeks, mean weight loss did not differ between arms. However, the PED arm exhibited greater improvement than the MED arm ($P < .05$) in total cholesterol, LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), cholesterol/HDL-C, triglyceride/HDL-C, apolipoprotein (apo) B, apo B/apo A-1, homocysteine, total LDL particle number, and large HDL particle number. All individuals in the PED arm but only one third in the MED arm achieved LDL-C levels < 160 mg/dL.

CONCLUSION:

Individuals at high CVD risk benefit from a soy/phytosterol containing medical food and phytochemical supplemented lifestyle program.

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PMID: 21122628

J Nutr Metab. 2010;2010. pii: 467316. doi: 10.1155/2010/467316. Epub 2010 May 18.

[Hop and Acacia Phytochemicals Decreased Lipotoxicity in 3T3-L1 Adipocytes, db/db Mice, and Individuals with Metabolic Syndrome.](#)

Minich DM¹, Lerman RH, Darland G, Babish JG, Pacioretty LM, Bland JS, Tripp ML.

Author information:

1. Department of Research & Development, MetaProteomics, LLC, 9770 44th Avenue NW, Suite 100, Gig Harbor, WA 98332, USA.

Abstract

The plant-based compounds rho-iso-alpha acids (RIAA) from *Humulus lupulus* (hops) and proanthocyanidins (PAC) from *Acacia nilotica* have been shown to modulate insulin signaling in vitro. We investigated their effects on triglyceride (TG) deposition in 3T3-L1 adipocytes, glucose and insulin in obese mouse models, and metabolic syndrome markers in adults with metabolic syndrome. The combination of RIAA and PAC synergistically increased TG content and adiponectin secretion in 3T3-L1 adipocytes under hyperinsulinemic conditions and reduced glucose or insulin in obese mice. In a clinical trial, tablets containing 100 mg RIAA and 500 mg PAC or placebo were administered to metabolic syndrome subjects (3 tablets/day, $n = 35$; 6 tablets/day, $n = 34$; or placebo, $n = 35$) for 12 weeks. Compared to placebo, subjects taking 3 tablets daily showed greater reductions in TG, TG : HDL, fasting insulin, and HOMA scores. The combination of RIAA : PAC at 1 : 5 (wt : wt) favorably modulates dysregulated lipids in insulin resistance and metabolic syndrome.

PMCID: PMC2915809

PMID: 20721358

J Med Food. 2010 Jun;13(3):535-47. doi: 10.1089/jmf.2009.0110.

[Antidiabetic screening of commercial botanical products in 3T3-L1 adipocytes and db/db mice.](#)

Babish JG¹, Pacioretty LM, Bland JS, Minich DM, Hu J, Tripp ML.

Author information:

1. Bionexus, Ithaca, New York 14850, USA.

Abstract

Numerous botanicals are purported to improve glucose metabolism and diabetic risk factors with varying degrees of supportive evidence. We investigated 203 commercially available botanical products representing 90 unique botanical species for effects on lipogenic activity in differentiating 3T3-L1 adipocytes. Anti-inflammatory activity of 21 of these products was further assessed in tumor necrosis factor alpha (TNFalpha)-stimulated, mature 3T3-L1 adipocytes. From these results, rho-isoalpa acids, Acacia nilotica bark, fennel, and wasabi were tested in the db/db mouse model. Fifty-nine percent of the 90 unique botanicals increased adipogenesis as did the standard troglitazone relative to the solvent controls. Botanical species with the greatest percentage of positive products were Centella asiatica, Panax quinquefolius, and Phyllanthus amarus at 100%, Vitis vinifera at 80%, Humulus lupulus at 71%, Aloe barbadensis at 66%, and Momordica charantia, Phaseolus vulgaris, and Punica granatum at 60%. All 21 subset samples inhibited TNFalpha-stimulated free fatty acid release and attenuated TNFalpha inhibition of adiponectin secretion. Both rho-isoalpa acids and A. nilotica reduced nonfasting glucose in the db/db mouse model, whereas A. nilotica also decreased nonfasting insulin levels. A post hoc analysis of the screening results indicated that the positive predictive value of the lipogenesis assay alone was 72%, while adding the criterion of a positive response in the anti-inflammatory assays increased this figure to 82%. Moreover, this large-scale evaluation demonstrates that antidiabetic, in vitro efficacy of botanicals is more a function of manufacturing or quality control differences than the presence of marker compounds and further underscores the need to develop functional as well as analytical bases for standardization of dietary supplements.

PMID: 20521979

Altern Ther Health Med. 2010 May-Jun;16(3):54-7.

[Cancers as systemic functional diseases, Part 2: clinical implications.](#)

Bland J¹.

Author information:

1. Institute for Functional Medicine, Gig Harbor, Washington, USA.

PMID: 20486625

Arthritis Rheum. 2010 Jun;62(6):1683-92. doi: 10.1002/art.27441.

[META060 inhibits osteoclastogenesis and matrix metalloproteinases in vitro and reduces bone and cartilage degradation in a mouse model of rheumatoid arthritis.](#)

Konda VR¹, Desai A, Darland G, Bland JS, Tripp ML.

Author information:

1. MetaProteomics, LLC, Gig Harbor, Washington 98332, USA.

Abstract

OBJECTIVE:

The multikinase inhibitor META060 has been shown to inhibit NF-kappaB activation and expression of markers of inflammation. This study was undertaken to investigate the effect of META060 on biomarkers associated with bone and cartilage degradation in vitro and its antiinflammatory efficacy in vivo in both acute and chronic inflammation models.

METHODS:

Glycogen synthase kinase 3beta (GSK3beta)-dependent beta-catenin phosphorylation was evaluated in RAW 264.7 macrophages to assess kinase inhibition. The inhibition of osteoclastogenesis and tartrate-resistant acid phosphatase (TRAP) activity was evaluated in RANKL-treated RAW 264.7 cells. The inhibition of interleukin-1beta (IL-1beta)-mediated markers of inflammation was analyzed in human rheumatoid arthritis synovial fibroblasts (RASFs). Mice with carrageenan-induced acute inflammation and collagen-induced arthritis (CIA) were used to assess efficacy.

RESULTS:

META060 inhibited the activity of kinases (spleen tyrosine kinase [Syk], Bruton's tyrosine kinase [Btk], phosphatidylinositol 3-kinase [PI 3-kinase], and GSK3) associated with RA and inhibited beta-catenin phosphorylation. META060 inhibited osteoclastogenesis, as indicated by decreased transformation of RAW 264.7 cells to osteoclasts and reduced TRAP activity, and inhibited IL-1beta-activated prostaglandin E(2), matrix metalloproteinase 3, IL-6, IL-8, and monocyte chemoattractant protein 1 in RASFs. In mice with acute inflammation, oral administration of META060 reduced paw swelling similar to the effect of aspirin. In mice with CIA, META060 significantly reduced the arthritis index and decreased bone, joint, and cartilage degradation. Serum IL-6 concentrations in these mice were inhibited in a dose-dependent manner.

CONCLUSION:

Our findings indicate that META060 reduces swelling in a model of acute inflammation and inhibits bone and cartilage destruction in a model of chronic inflammation. Its efficacy is associated with the inhibition of multiple protein kinases, including Syk, Btk, PI 3-kinase, and GSK3. These results warrant further clinical testing of META060 for its therapeutic potential in the treatment of inflammatory diseases.

PMID: 20201075

J Bone Miner Metab. 2010 May;28(3):342-50. doi: 10.1007/s00774-009-0141-z. Epub 2009 Dec 19.

[Hop rho iso-alpha acids, berberine, vitamin D3 and vitamin K1 favorably impact biomarkers of bone turnover in postmenopausal women in a 14-week trial.](#)

Holick MF¹, Lamb JJ, Lerman RH, Konda VR, Darland G, Minich DM, Desai A, Chen TC, Austin M, Kornberg J, Chang JL, Hsi A, Bland JS, Tripp ML.

Author information:

1. Boston University School of Medicine, Boston, MA, USA.

Abstract

Osteoporosis is a major health issue facing postmenopausal women. Increased production of pro-inflammatory cytokines resulting from declining estrogen leads to increased bone resorption. Nutrition can have a positive impact on osteoporosis prevention and amelioration. The objective of this study was to investigate the impact of targeted phytochemicals and nutrients essential for bone health on bone turnover markers in healthy postmenopausal women. In this 14-week, single-blinded, 2-arm placebo-controlled pilot study, all women were instructed to consume a modified Mediterranean-style low-glycemic-load diet and to engage in limited aerobic exercise; 17 randomized to the placebo and 16 to the treatment arm (receiving 200 mg hop rho iso-alpha acids, 100 mg berberine sulfate trihydrate, 500 IU vitamin D(3) and 500 microg vitamin K(1), twice daily). Thirty-two women completed the study. Baseline nutrient intake did not differ between arms. At 14 weeks, the treatment arm exhibited an estimated 31% mean reduction ($P = 0.02$) in serum osteocalcin (a marker of bone turnover), whereas the placebo arm exhibited a 19% increase ($P = 0.03$) compared to baseline. Serum 25-hydroxyvitamin D (25(OH)D) increased by 13% ($P = 0.24$) in the treatment arm and decreased by 25% ($P < 0.01$) in the placebo arm. The between-arm differences for OC and 25(OH)D were statistically significant. Serum IGF-I was increased in both arms, but the increase was more significant in the treatment arm at 14 weeks ($P < 0.01$). Treatment with hop rho iso-alpha acids, berberine sulfate trihydrate, vitamin D(3) and vitamin K(1) produced a more favorable bone biomarker profile that supports a healthy bone metabolism.

PMID: 20024591

J Inflamm (Lond). 2009 Aug 27;6:26. doi: 10.1186/1476-9255-6-26.

[Rho iso-alpha acids from hops inhibit the GSK-3/NF-kappaB pathway and reduce inflammatory markers associated with bone and cartilage degradation.](#)

Konda VR¹, Desai A, Darland G, Bland JS, Tripp ML.

Author information:

1. MetaProteomics Nutrigenomics Research Center (a subsidiary of Metagenics, Inc), 9770 44th Avenue N,W,, Gig Harbor, WA, 98332, USA.

Abstract

BACKGROUND:

Rho iso-alpha acids (RIAA) from hops have been shown to have anti-inflammatory properties. To understand the mechanisms, we evaluated the effect of RIAA in cell signaling pathways and inflammatory markers using various in vitro models. We also investigated their therapeutic effect in mice with collagen-induced arthritis.

METHODS:

The LPS-stimulated RAW 264.7 macrophages were used to evaluate the effect of RIAA on the NF-kappaB and MAPK signaling pathways; phosphorylation of ERK1/2, p38 and JNK was assessed by western blotting and NF-kappaB binding by electrophoretic mobility shift assays. Effect on the NF-kappaB activity was evaluated by the luciferase reporter assays in LPS-stimulated RAW 264.7 cells. GSK-3alpha/beta kinase activity was measured in cell-free assays. The inhibitory effect of RIAA on inflammatory markers was assessed by measuring nitric oxide in LPS-stimulated RAW 264.7 cells, RANKL-mediated TRAP activity in transformed osteoclasts, and TNF-alpha/IL-1beta-mediated MMP-13 expression in SW1353 cells. Mice with collagen-induced arthritis were fed with RIAA for 2 weeks. Symptoms of joint swelling, arthritic index and joint damage were assessed.

RESULTS:

RIAA selectively inhibited the NF-kappaB pathway while having no effect on ERK1/2, p38 and JNK phosphorylation in LPS-stimulated RAW 264.7 cells. RIAA also inhibited GSK-3alpha/beta kinase activity and GSK-3beta dependent phosphorylation of beta-catenin in RAW 264.7 cells. In addition, RIAA inhibited NF-kappaB-mediated inflammatory markers in various cell models, including nitric oxide in LPS-stimulated RAW 264.7 cells, RANKL-mediated TRAP activity in transformed osteoclasts, and TNF-alpha/IL-1beta-mediated MMP-13 expression in SW1353 human chondrosarcoma cells. Finally, in a mouse model of collagen-induced arthritis, RIAA ameliorated joint damage as evidenced by significant reduction of the arthritis index and histology score; at 250 mg/kg-body weight, RIAA had efficacy similar to that of 20 mg/kg-body weight of celecoxib.

CONCLUSION:

RIAA may have potential as an anti-inflammatory therapeutic.

PMCID: PMC2743673

PMID: 19712471

Metab Syndr Relat Disord. 2009 Jun;7(3):187-92. doi: 10.1089/met.2008.0051.

[A science-based, clinically tested dietary approach for the metabolic syndrome.](#)

Schiltz B¹, Minich DM, Lerman RH, Lamb JJ, Tripp ML, Bland JS.

Author information:

1. Functional Medicine Research Center, MetaProteomics, LLC, Gig Harbor, Washington 98332, USA.

Abstract

During the last decade, great strides have been made to delineate the importance of diet in the prevention and treatment of the metabolic syndrome. Dietary recommendations have emphasized a low-fat ("antiatherogenic") diet as the first-line therapeutic approach. However, the complex etiology of the metabolic syndrome would seem to necessitate tailored dietary approaches beyond simple macronutrient modification. Current data have revealed varying biological effects of individual macronutrients within the same category, suggesting that adjusting dietary macronutrient percentages without considering their physiological impact may not be adequate. The concepts of glycemic index and glycemic load support the need for differentiation between various types of carbohydrates. Additionally, significant evidence to date indicates that metabolic syndrome biomarkers improve with dietary patterns rich in phytochemical complexity (e.g., Mediterranean diet). Taking these aspects into account, we designed a specific dietary approach consisting of foods found in the popularized Mediterranean diet, modified to include only those items that are low in glycemic load and grains (gluten) and are antiinflammatory. Initially based on scientific literature, this food plan has since been tested and adapted in our clinic over the past decade. This paper describes the rationale of the dietary program and provides an overview of data on its efficacy in individuals with metabolic syndrome.

PMID: 19450142

Inflamm Res. 2009 May;58(5):229-34. doi: 10.1007/s00011-008-8162-y.

[META060 inhibits multiple kinases in the NF-kappaB pathway and suppresses LPS--mediated inflammation in vitro and ex vivo.](#)

Desai A¹, Konda VR, Darland G, Austin M, Prabhu KS, Bland JS, Carroll BJ, Tripp ML.

Author information:

1. MetaProteomics Nutrigenomics Research Center, a subsidiary of Metagenics, Inc., Gig Harbor, WA 98332, USA.

Abstract

OBJECTIVE:

We investigated whether a novel candidate META060 targeted the inflammatory signal transduction without affecting constitutive COX-2 enzymatic activity in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. We also investigated its bioavailability in humans and its anti-inflammatory effect ex vivo.

METHODS:

We measured prostaglandin E(2), nitric oxide, TNFalpha and IL-6 by ELISA, COX-2 protein by Western

blot, NF-kappaB nuclear binding by electrophoretic mobility shift assays, and NF-kappaB activation by luciferase assay. Kinase inhibitions were measured by cell-free assays. Bioavailability was tested in 4 human subjects consuming 940 mg META060. LPS-activated TNFalpha and IL-6 were measured in peripheral blood mononuclear cells (PBMC) isolated from 1 subject up to 6 hours post administration.

RESULTS:

META060 dose-dependently inhibited prostaglandin E(2) and nitric oxide formation, COX-2 abundance, and NF-kappaB activation. In cell-free assays, META060 inhibited multiple kinases in the NF-kappaB signaling pathway, including BTK, PI3K, and GSK3. META060 was detected in the plasma of the subjects; isolated PBMC were resistant to LPS-stimulated TNFalpha and IL-6 production.

CONCLUSION:

Without inhibiting COX-2 enzyme, META060 reduces the inflammation by inhibiting multiple kinases involved in NF-kappaB pathway, and may have potential as a safe anti-inflammatory therapeutic.

PMID: 19169645

Altern Ther Health Med. 2008 Nov-Dec;14(6):20-1.

[Autism: asking the right questions to find the right answers.](#)

Bland J.

Erratum in

Altern Ther Health Med. 2009 Jan-Feb;15(1):14.

PMID: 19043933

Altern Ther Health Med. 2008 Sep-Oct;14(5):12-4.

[The future of nutritional pharmacology.](#)

Bland J.

PMID: 18780579

Nutr Rev. 2008 Aug;66(8):429-44. doi: 10.1111/j.1753-4887.2008.00075.x.

[Dietary management of the metabolic syndrome beyond macronutrients.](#)

Minich DM¹, Bland JS.

Author information:

1. Functional Medicine Research Center, MetaProteomics, LLC, Gig Harbor, Washington 98332, USA.

Abstract

Due to the complexity of chronic conditions like the metabolic syndrome (MetS), tailored dietary approaches beyond macronutrient ratio modification may be necessary to effectively address metabolic measures. Mounting data on whole foods-based, phytochemical-abundant dietary patterns, such as the Mediterranean diet, reveal that they contain constituents, such as phytochemicals, that may be beneficial for treating MetS. The role of food-based phytochemicals on underlying mechanisms of MetS, specifically as they impact insulin signaling, has yet to be investigated thoroughly. This review discusses various dietary approaches for MetS, with a focus on certain foods and dietary phytochemicals known to impact insulin signaling.

PMID: 18667004

Altern Ther Health Med. 2008 Jul-Aug;14(4):18-21.

[The importance of functional biomarkers in the management of chronic illness.](#)

Bland J.

PMID: 18616065

Altern Ther Health Med. 2008 May-Jun;14(3):18-20.

[Systems biology, functional medicine, and folates.](#)

Bland J.

PMID: 18517101

Altern Ther Health Med. 2008 Mar-Apr;14(2):16-8.

[Does complementary and alternative medicine represent only placebo therapies?](#)

Bland J.

PMID: 18383985

Phytochemistry. 2008 May;69(7):1534-47. doi: 10.1016/j.phytochem.2008.02.001. Epub 2008 Mar 20.

[Safety, efficacy and anti-inflammatory activity of rho iso-alpha-acids from hops.](#)

Hall AJ¹, Babish JG, Darland GK, Carroll BJ, Konda VR, Lerman RH, Bland JS, Tripp ML.

Author information:

1. Metagenics/MetaProteomics Nutrigenomics Research Center, Gig Harbor, WA 98332, USA.

Abstract

A defined mixture of rho iso-alpha-acids (RIAA), a modified hop extract, was evaluated for anti-inflammatory efficacy and safety. RIAA inhibited LPS-stimulated PGE(2) formation with >200-fold selectivity of COX-2 (IC(50)=1.3 microg/ml) over COX-1 (IC(50)>289 microg/ml). This occurred only when RIAA was added prior to, but not post, LPS stimulation. Consistent with this observation, RIAA produced no physiologically relevant, direct inhibition of COX-1 or COX-2 peroxidase activity. This suggests that RIAA inhibits inducible but not constitutive COX-2. In support, we found RIAA showed minimal PGE(2) inhibition (IC(50)=21 mug/ml) relative to celecoxib (IC(50)=0.024 microg/ml), aspirin (IC(50)=0.52 microg/ml) or ibuprofen (IC(50)=0.57 microg/ml) in the AGS gastric mucosal model, where COX-1 and -2 are expressed constitutively. Taken together these results predict RIAA may have lower potential for gastrointestinal and cardiovascular toxicity observed with COX enzyme inhibitors. Following confirmation of bioavailable RIAA administered orally, gastrointestinal safety was assessed using the fecal calprotectin biomarker in a 14-day human clinical study; RIAA (900 mg/day) produced no change compared to naproxen (1000 mg/day), which increased fecal calprotectin 200%. Cardiovascular safety was addressed by PGI-M measurements where RIAA (1000 mg) did not reduce PGI-M or affect the urinary PGI-M/TXB(2) ratio. Drug interaction potential was evaluated against six major CYPs; of relevance, RIAA inhibited CYP2C9. Toxicity was assessed in a 21-day oral, mouse subchronic toxicity study where no dose dependent histopathological effects were noted. Clinically, RIAA (1000 mg/day) produced a 54% reduction in WOMAC Global scores in a 6-week, open-label trial of human subjects exhibiting knee osteoarthritis.

PMID: 18358504

Altern Ther Health Med. 2008 Jan-Feb;14(1):14-6.

[Functional somatic syndromes, stress pathologies, and epigenetics.](#)

Bland J.

PMID: 18251316

Can J Physiol Pharmacol. 2007 Sep;85(9):872-83.

[Clinical safety and efficacy of NG440: a novel combination of rho iso-alpha acids from hops, rosemary, and oleanolic acid for inflammatory conditions.](#)

Minich DM¹, Bland JS, Katke J, Darland G, Hall A, Lerman RH, Lamb J, Carroll B, Tripp M.

Author information:

1. Functional Medicine Research Center, division of MetaProteomics, LLC., 9770 44th Avenue NW, Suite 100, Gig Harbor, WA 98332, USA.

Abstract

In this report, we examine the clinical safety and efficacy of NG440, a phytochemical-based antiinflammatory formula consisting of a combination of rho iso-alpha acids from hops, rosemary, and oleanolic acid. In a previous study, we demonstrated that NG440 significantly decreased pain by 50% in patients with osteoarthritis. Consistent with these data, results from a multicentre trial indicate that NG440 reduced pain scores in patients with joint discomfort, as measured by VAS (visual analog scale) methodology. As demonstrated in an ex vivo clinical study, these effects on pain relief may be due to reduced inflammatory cytokine production including lower prostaglandin E2 formation. Finally, strong data exist to suggest that NG440 is a safe formula for human consumption. Animal toxicity data revealed no adverse effects of NG440 at dosages ≤ 250 mg.kg⁻¹.day⁻¹ for 21 days. Furthermore, human trial data suggest that NG440 does not negatively impact cardiovascular and gastrointestinal markers normally affected by selective COX-2 enzyme inhibitors, including platelet function, blood pressure, blood cell count, or fecal calprotectin, a measure of gastrointestinal injury. In conclusion, NG440 may serve as a safe and efficacious alternative in some areas where specific COX-2 inhibitors have been traditionally used.

PMID: 18066133

Altern Ther Health Med. 2007 Jul-Aug;13(4):62-5.

[Acid-alkaline balance: role in chronic disease and detoxification.](#)

Minich DM¹, Bland JS.

Author information:

1. Information Integration and Innovation at Metagenics, Inc, Gig Harbor, Wash, USA.

Abstract

In conclusion, the increasing dietary acid load in the contemporary diet can lead to a disruption in acid-alkaline homeostasis in various body compartments and eventually result in chronic disease through repeated borrowing of the body's alkaline reserves. Adjustment of tissue alkalinity, particularly within the kidney proximal tubules, can lead to the more effective excretion of toxins from the body. Metabolic detoxification using a high vegetable diet in conjunction with supplementation of an effective alkalizing compound, such as potassium citrate, may shift the body's reserves to become more alkaline.

PMID: 17658124

Nutr Rev. 2007 Jun;65(6 Pt 1):259-67.

[A review of the clinical efficacy and safety of cruciferous vegetable phytochemicals.](#)

Minich DM¹, Bland JS.

Author information:

1. Metagenics, Inc., Department of Research and Development, Gig Harbor, Washington 98332, USA.

Abstract

Supplementation with the crucifer-derived phytochemicals indole-3-carbinol (I3C) and 3,3'-diindolylmethane (DIM) has been an area of active interest due to their role in estrogen metabolism. This review addresses the debate about which cruciferous compound to use clinically by evaluating their efficacy and safety. Significantly more clinical trials are available for I3C than for DIM. I3C leads to beneficial shifts in hormone markers, and limited evidence suggests that DIM may result in a similar effect. More research in humans is needed to further address whether DIM poses any safety risk. Current data do not suggest that DIM provides enhanced clinical benefits over I3C.

PMID: 17605302

Altern Ther Health Med. 2007 Mar-Apr;13(2):S85-7.

[Managing biotransformation: introduction and overview.](#)

Bland J¹.

Author information:

1. Metagenics, Inc., Gig Harbor, WA, USA.

PMID: 17405682

Prostaglandins Leukot Essent Fatty Acids. 2006 Jul;75(1):9-17. Epub 2006 Jun 27.

[Gastric mucosal cell model for estimating relative gastrointestinal toxicity of non-steroidal anti-inflammatory drugs.](#)

Hall AJ¹, Tripp M, Howell T, Darland G, Bland JS, Babish JG.

Author information:

1. Metagenics, 9770 44th Avenue, Gig Harbor, WA 98332, USA.

Abstract

The study objective was to characterize the AGS human gastric mucosal cell line as a model for estimating gastrointestinal toxicity of COX-inhibiting compounds. Rofecoxib, celecoxib, nimesulide, ibuprofen, indomethacin, aspirin, salicylic acid, naproxen and acetaminophen were tested for inhibition of COX-2-mediated prostaglandin E2 synthesis in A549 and AGS cells. The IC50 ratio AGS/A549 was calculated as an estimate of the therapeutic index (TI) for gastrointestinal toxicity. Calculated IC50 values of non-steroidal anti-inflammatory drugs (NSAIDs) in A549 cells were in excellent agreement with published values ($r = 0.996$; $P < 0.005$). Calcium ionophore induction of arachidonic acid release in AGS cells provided TI similar to those using platelets and A549 cells ($r = 0.918$; $P < 0.01$). The AGS/A549 model exhibited lower TI than the platelet/A549 model. Spearman ranking correlated clinical NSAID gastropathy with lower AGS TI values. The AGS cell line has excellent potential to serve as a model for assessing the gastrointestinal effects of COX-inhibiting compounds.

PMID: 16806870

Nutrition. 2006 Feb;22(2):104-13.

[Effect of a low glycemic index diet with soy protein and phytosterols on CVD risk factors in postmenopausal women.](#)

Lukaczer D¹, Liska DJ, Lerman RH, Darland G, Schiltz B, Tripp M, Bland JS.

Author information:

1. Functional Medicine Research Center, Metagenics, Inc., Gig Harbor, Washington, USA.

Abstract

OBJECTIVES:

Cardiovascular disease (CVD) is the leading cause of death in women. Hyperlipidemia is a major risk factor for CVD, but research suggests that metabolic syndrome and type 2 diabetes are also key factors in CVD in postmenopausal women. Most dietary programs, however, focus only on hyperlipidemia and not on insulin resistance associated with diabetes and metabolic syndrome. This 12-wk trial compared the effects of a dietary program combining a low glycemic index diet with a functional food delivering 30 g of soy protein and 4 g of phytosterols per day (LGID) with a standard dietary program (American Heart Association Step 1 diet; AHAD) in postmenopausal women.

METHODS:

Fifty-nine postmenopausal women (average age 54.6 y, range 44-65 y) with a body mass index of 27 to 39 kg/m² were randomly assigned to the LGID or the AHAD program for 12 wk. Total caloric intake and exercise were matched in each arm.

RESULTS:

Twenty-seven women completed the LGID program, and 26 completed the AHAD program. The participants on the LGID program showed statistically significant decreases in total cholesterol (15.8%, $P = 0.0036$ between-group comparison), low-density lipoprotein cholesterol (14.8%, $P = 0.004$ between-group comparison), and triacylglycerol (44.8%, $P = 0.006$ between-group comparison). In addition, significant improvements were observed in ratios of total to high-density lipoprotein cholesterol and of triacylglycerol to high-density lipoprotein cholesterol, blood pressure, and Framingham risk assessment for coronary heart disease compared with the AHAD program.

CONCLUSIONS:

A significantly greater improvement was observed in CVD risk factors in postmenopausal women on the LGID program (incorporating 30 g of soy protein and 4 g of phytosterols per day) than with a standard therapy.

PMID: 16459222

Phytother Res. 2005 Oct;19(10):864-9.

[A pilot trial evaluating Meta050, a proprietary combination of reduced iso-alpha acids, rosemary extract and oleanolic acid in patients with arthritis and fibromyalgia.](#)

Lukaczer D¹, Darland G, Tripp M, Liska D, Lerman RH, Schiltz B, Bland JS.

Author information:

1. Clinical Research at the Functional Medicine Research Center, Gig Harbor, WA 98332, USA.

Abstract

The aim of this open-label, 8-week observational trial was to investigate the efficacy of Meta050 (a proprietary, standardized combination of reduced iso-alpha-acids from hops, rosemary extract and oleanolic acid) on pain in patients with rheumatic disease. Osteoarthritis, rheumatoid arthritis and fibromyalgia patients were given 440 mg Meta050 three times a day for 4 weeks, which was changed to 880 mg twice a day for the subsequent 4 weeks in the majority of patients. Pain and condition-specific symptoms were assessed using a standard visual analog scale (VAS), an abridged arthritis impact measurement scale (AIMS2) and the fibromyalgia impact questionnaire. Fifty-four subjects with rheumatic disease completed the trial. Following treatment, a statistically significant decrease in pain of 50% and 40% was observed in arthritis subjects using the VAS ($p < 0.0001$; Wilcoxon-ranked sums) and AIMS2 ($p < 0.0001$), respectively. Fibromyalgia subject scores did not significantly improve. A decreasing trend of C-reactive protein, a marker for inflammation, was also observed in those subjects who presented with elevated C-reactive protein. No serious side effects were observed. These observations suggest that Meta050 at a dosage of 440 mg three times a day has a beneficial effect on pain in arthritis subjects.

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PMID: 16261517

Altern Ther Health Med. 2005 Sep-Oct;11(5):60-5.

[Clinical effects of a proprietary combination isoflavone nutritional supplement in menopausal women: a pilot trial.](#)

Lukaczer D¹, Darland G, Tripp M, Liska D, Lerman RH, Schiltz B, Bland JS.

Author information:

1. Metagenics Inc, Functional Medicine Research Center, Gig Harbor, WA, USA.

Abstract

BACKGROUND:

As they reach menopause, a majority of women living in Westernized countries experience climacteric symptoms. Hormone replacement therapy (HRT) has been used to remediate these symptoms. Recent studies, however, have suggested that HRT may increase the risk of developing breast cancer and cardiovascular disease (CVD). Therefore, many women are looking for alternative treatment options.

PURPOSE:

This trial was a pilot study to assess the effect of a nutritional supplement containing isoflavones from kudzu and red clover, along with other targeted nutrients on menopausal symptoms and markers of breast cancer and CVD risk. Twenty-five menopausal women suffering from severe hot flashes and night sweats completed a 12-week intervention using this combination isoflavone nutritional supplement.

RESULTS:

We observed a 46% decrease in reported hot flashes, from an average of 9.7 to 5.2 per day. Quality of life, as assessed by the standardized Greene Questionnaire, showed similar improvement. Two markers of CVD risk, the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol and homocysteine, showed modest improvement. A proposed marker of breast cancer risk, the ratio of 2-hydroxyestrone to 16 alpha-hydroxyestrone, also showed a statistically significant improvement.

CONCLUSIONS:

The results of this pilot trial suggests that this combination isoflavone nutritional supplement may significantly relieve the most troubling symptoms of menopause, as well as confer some chemopreventive and cardioprotective benefits.

PMID: 16189949

Altern Ther Health Med. 2005 Mar-Apr;11(2):20-2.

[Alternative therapies--a moving target.](#)

Bland J¹.

Author information:

1. Institute for Functional Medicine.

PMID: 15819445

Altern Ther Health Med. 2004 Sep-Oct;10(5):74-81.

[Jeffrey S. Bland, PhD, FACN, CNS: functional medicine pioneer.](#)

Bland JS.

PMID: 15478789

J Gerontol A Biol Sci Med Sci. 2004 Jun;59(6):B560-7.

[Biomarkers of aging: from primitive organisms to humans.](#)

Butler RN¹, Sprott R, Warner H, Bland J, Feuers R, Forster M, Fillit H, Harman SM, Hewitt M, Hyman M, Johnson K, Kligman E, McClearn G, Nelson J, Richardson A, Sonntag W, Weindruch R, Wolf N.

Author information:

1. International Longevity Center-USA, 60 E. 86th St., New York, NY 10028, USA.

Abstract

Leading biologists and clinicians interested in aging convened to discuss biomarkers of aging. The goals were to come to a consensus, construct an agenda for future research, and make appropriate recommendations to policy makers and the public-at-large. While there was not total agreement on all issues, they addressed a number of questions, among them whether biomarkers can be identified and used to measure the physiological age of any individual within a population, given emerging information about aging and new technological advances. The hurdles to establishing informative biomarkers include the biological variation between individuals that makes generalizations difficult; the overlapping of aging and disease processes; uncertainty regarding benign versus pathogenic age-related changes; the point at which a process begins to do damage to the organism, and, if so, when does it occur; and when to distinguish critical damage from noncritical damage. Finally, and significantly, it is difficult to obtain funding for this research.

PMID: 15215265

Altern Ther Health Med. 1998 Jul;4(4):42-8.

[The use of complementary medicine for healthy aging.](#)

Bland JS¹.

Author information:

1. HealthComm International, Inc, Harbor, Wash., USA.

Abstract

By the year 2020, twenty percent of the US population will be aged 65 years or older. The greatest growth in numbers will be among those aged 85 years or older. If the healthcare demands of this group match those of their parents, it will place an extraordinary burden on funding for medical services. By promoting healthy aging, complementary medicine practitioners can improve the cost-effectiveness of healthcare delivery. A scientifically based complementary medicine program to promote healthy aging includes (1) diet and nutritional tailoring, (2) nutrient enhancement to meet specific individual needs, (3) exercise training, (4) stress management, (5) promotion of structural integrity, (6) environmental adjustment, (7) counseling on purposeful living, and (8) normalizing intercellular communication. The program described in this article incorporates these features and focuses on the following modifiable

factors of unhealthy aging: altered mitochondrial function and oxidative stress, increased protein glycation, chronic inflammation, defects in methylation, reduced detoxification ability, and altered immunity.

PMID: 9656500

Altern Med Rev. 1998 Jun;3(3):170.

[The pro-oxidant and antioxidant effects of vitamin C.](#)

Bland JS.

PMID: 9630733

Altern Med Rev. 1998 Feb;3(1):40-53.

[AIDS wasting syndrome as an enterometabolic disorder: the gut hypothesis.](#)

Kaminski M Jr¹, Weil S, Bland J, Jan P.

Author information:

1. FUHS/Chicago Medical School, USA.

Abstract

There is an interesting relationship between the HIV virus, the health of the gastrointestinal tract, and AIDS wasting syndrome, involving Tumor Necrosis Factor alpha (TNF alpha), specific and non-specific immunity in the gut, gut permeability, and oxidative stress. It is hypothesized that the progression of HIV to full-blown AIDS may be impacted by maintaining a healthy gut. A therapeutic protocol which decreases oxidative stress, inhibits TNF alpha, enhances phase I and II liver detoxification, and improves specific and non-specific immunity in the gut should be part of a therapeutic protocol for HIV-infected individuals. Through a better understanding of the pathophysiology of HIV advancing to AIDS, the practitioner can develop a treatment strategy of nutritional and lifestyle changes which could theoretically prevent an HIV infection from advancing to full-blown AIDS.

PMID: 9600025

Altern Ther Health Med. 1996 Nov;2(6):73-6.

[Phytonutrition, phytotherapy, and phytopharmacology.](#)

Bland JS¹.

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1. HealthComm International Inc, Gig Harbor, Wash., USA.

Abstract

All families of plant food are known to contain phytonutrients, that is, unique substances produced during the natural course of plant growth and development that are specific to each plant's genes and environment. The term phytonutrition refers to the role of these substances in cultural food practices and cuisines worldwide in supporting health. In addition to their phytonutritive role, phytonutrients have a phytotherapeutic role, acting as modifiers of physiological function. The consumption of 30 to 50 mg per day of soy isoflavones in the traditional Japanese diet and the ability of this diet to help lower the incidence of breast cancer among Japanese women is an example of phytotherapeutic effect. The dividing line between phytonutrition and phytotherapy has blurred with the discovery that certain food components can not only modify physiological function but also aid in medical practices such as drug delivery. Naringenin, for example, the 4',5',7-hydroxyflavanone found exclusively in grapefruit, can slow hepatic detoxification of prescription drugs like cyclosporine and thus potentially help prevent rejection of transplanted organs. Natural and synthetic phytonutrients may differ significantly in their effect on physiological function owing to stereoisomeric composition. The potential of specific phytochemicals to promote health must be carefully evaluated with the same risk-benefit model traditionally used to assess concentrated levels of any substance placed into the body.

PMID: 8942046

Altern Ther Health Med. 1995 Nov 1;1(5):62-71.

[a Medical Food-Supplemented Detoxification Program in the Management of Chronic Health Problems](#)

Bland JS, Barrager E, Reedy RG, Bland K.

Abstract

Objective * To evaluate the effectiveness of a medical food-supplemented detoxification program versus a hypoallergenic, calorie-controlled diet alone in the management of symptoms in chronically ill patients. **Design** * Outcome-focused study of patient response to dietary interventions. **Setting** * Clinical outpatient research facility. **Patients** * 106 chronically ill patients. **Intervention** * A medical food supplement designed to provide nutritional support for gastrointestinal healing and hepatic detoxification in addition to an oligoantigenic, calorie-controlled diet, versus an oligoantigenic, calorie-controlled diet alone. **Results** * The 84 patients in the experimental group, who consumed the medical food supplement, had a 52% reduction in symptoms over 10 weeks as measured by the Metabolic Screening Questionnaire. In comparison, the 22 patients on the control diet had only a 22% reduction of symptoms. Symptom reduction in the intervention group occurred concomitantly with the normalization of hepatic phase I cytochrome P450 activity in relation to phase II glycine conjugation detoxification function measured before and after intervention. The intervention group also had a statistically significant increase in urinary sulfate-to-creatinine ratio after treatment, suggesting improved reserves of sulfur-conjugating nutrients and glutathione status. Enhanced nutrient absorption after intervention was implied by the increased absorption and urinary excretion of mannitol after the 10 weeks of therapy, although the results were only marginally significant. **Conclusions** * These results suggest that this supplemental medical food program may provide an important adjunctive therapy for the management of many complex symptoms associated with the chronically ill.

PMID: 9359760

Altern Ther Health Med. 1995 Sep;1(4):75-6.

[Diet and prostate problems.](#)

Bland JS¹.

Author information:

1. HealthComm International, Inc., Gig Harbor, Wash., USA.

PMID: 9359811

Altern Ther Health Med. 1995 May;1(2):22-7.

[Psychoneuro-nutritional medicine: an advancing paradigm.](#)

Bland JS¹.

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1. HealthComm International, Inc., Gig Harbor, Wash., USA.

Abstract

Recent research has led to the evolution of an important clinical relationship among psychology, neurobiochemistry, and nutrition. The result has been the development of the multidisciplinary field of psychoneuro-nutritional medicine. The successful application of this medical model to mental health problems ranging from behavior disorders in children to cognitive/emotional disorders in adults has opened the door to new lower-technology, cost-effective approaches to improving functional neurobiochemistry. This review describes the psychoneuro-nutritional medicine model and its application to a variety of biobehaviorally related health problems.

PMID: 9359782

N Engl J Med. 1992 Jan 16;326(3):200; author reply 201-2.

[Relation of meat, fat, and fiber intake to the risk of colon cancer in women.](#)

Bland JS.

Comment on

[Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women.](#) [N Engl J Med. 1990]

PMID: 1309269

J Manipulative Physiol Ther. 1989 Apr;12(2):113-9.

[Evaluation and clinical significance of appendicular skeletal assessment by radiographic photodensitometry.](#)

Bland JS¹, Brooks DH, Kent DJ, Fisher WH.

Author information:

1. HealthComm, Inc., Gig Harbor, WA 98335.

Abstract

"Senile" or age-related bone loss affects cortical and trabecular bone and may be detected in the appendicular as well as the axial skeleton. This study presents radiographic photodensitometry as a precise and sensitive technique for evaluating appendicular skeletal status. Data from reproducibility studies indicate that the coefficient of variation for the technology is between 1.9% and 4.5% for the three bones analyzed. Evaluation of age-related changes in bone mass for over 800 subjects demonstrated a decline in mass vs. age after the fourth decade in women, with the slope of the decline being very similar to that seen in CT longitudinal studies. Applied serially to a patient over time, the technology identifies changes in bone mass and may be used to evaluate the response to intervention therapy.

PMID: 2654315

J Pedod. 1984 Summer;8(4):319-36.

[Childhood nutrition and oral diseases.](#)

Bland J.

PMID: 6594494

Int J Radiat Biol Relat Stud Phys Chem Med. 1981 Jul;40(1):19-29.

[Actions of gamma-radiation on resealed erythrocyte ghosts. A comparison with intact erythrocytes and a study of the effects of oxygen.](#)

Kong S, Davison AJ, Bland J.

Abstract

With respect to both permeability and inactivation of membranous GAPDH, ghosts were more susceptible than erythrocytes to free radicals produced in the gamma-irradiation of aqueous solutions. The rate of increase in the permeability of irradiated ghosts was immeasurably greater than that of irradiated erythrocytes, while the rate of inactivation of GAPDH was 21-fold greater. The sensitivity of ghosts to radiation damage was affected strongly by the presence of oxygen during irradiation. In the presence of air, the rates of increase of permeability and inactivation of GAPDH were 2.8- and 1.5-fold of those in the

presence of N₂. The use of buffer saturated with oxygen accelerated the aerobic rates of increase of permeability and inactivation of GAPDH by 60- and 2.7-fold. These results indicate that inactivation of GAPDH is somewhat sensitive to oxygen, particularly at high concentration of oxygen. Nevertheless, in air or under nitrogen, the rate of enzymic inactivation was almost an order of magnitude greater than that of increase of permeability, indicating that the former is much more sensitive to irradiation. The major mechanism of the oxygen effect observed is the ability of oxygen to increase the branching of the free radical chain reactions which propagate damage after initiation within the membrane.

PMID: 6973550

J Am Dent Assoc. 1980 Jul;101(1):12, 14.

[Hair analysis of trace minerals.](#)

Bland J.

PMID: 6930429

Physiol Chem Phys. 1978;10(2):145-52.

[Effect of tocopherol on photooxidation rate of human erythrocyte membrane in vitro.](#)

Bland J, Canfield W, Kennedy T, Vincent J, Wells R.

Abstract

Study indicates that tocopherol's ability to prevent erythrocyte photohemolysis is a result of selective chemical trapping of the photooxidation-generated oxidant, singlet oxygen, before it can cause peroxidation of the essential unsaturated lipids in the erythrocyte membrane. The data provide fundamental information that support the purported clinical efficacy of tocopherol in the treatment of congenital erythrocyte membrane oxyhemolysis.

PMID: 724810

Physiol Chem Phys. 1975;7(1):69-85.

[Effect of alpha-tocopherol on the rate of photohemolysis of human erythrocytes.](#)

Bland J, Madden P, Herbert EJ.

Abstract

The results of this study demonstrate that alpha-tocopherol has a significant ability in vivo to prohibit the production of cholesterol hydroperoxide in the erythrocyte membrane, and also significantly reduce the degree of cell membrane deformation upon exposure of the blood to light and oxygen (photooxygenation conditions). This study suggests that alpha-tocopherol prohibits the production of cholesterol

hydroperoxide in the membrane which if produced leads to a weakened membrane observed as a "budded" cell in the electron micrographs.

PMID: 1129378p>