8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment

November 9-12, 2008
Hilton Tokyo • Tokyo, Japan

Symposium Program
大豆の起原

大豆は野生のツルマメ（ノマメ）が改良されたもの。栽培の起原は中国の東北部あるいは華南とされています。司馬遷の『史記』（前漢の紀元前91年ころ成立）によれば、中国古代の伝説上皇帝“黃帝”が植えた五穀に大豆が含まれていたとされ、これが正しければ紀元前5000年以上前に栽培されていたことになります。

山梨県立博物館の研究では、日本にもすでに5000年ほど前の縄文時代に伝播していた痕跡があると言われています。（北杜市の酒呑場遺跡）

大豆の食べ方は、枝豆のように未熟豆をゆでて食べるほか、完熟豆を煮豆にしたり煎った豆をお漬けに使う以外は原形をとどめることなく加工され、納豆、豆乳、豆腐、湯葉、油揚げといった食品や、味噌・醤油などの調味料、さらには大豆を絞った油など、様々に用いられています。

The Origins of Soybeans

The progenitor of the modern soybean was a wild, vine-like plant called Glycine soja. It is generally believed that soybeans were originally cultivated in northeastern China or the Huanan region. According to the Records of the Grand Historian, the magnum opus of Sima Quan written from 109 BC to 91 BC, soybeans were one of the five grains cultivated by the legendary Chinese sovereign, the Yellow Emperor, which, if true, means that this crop has been being produced for more than 7,000 years.

According to research conducted by the Yamanashi Prefectural Museum, there is evidence that soybeans were already being propagated in Japan during the Jomon Era, some 5,000 years ago (reported from the Sakenomiba site Hokuto City, Yamanashi Prefecture).

There are many ways to eat soybeans, ranging from boiling immature beans, as in edamame, making boiled bean dishes, and roasting mature beans to produce a snack food, to processing them in ways that go beyond the original form of the bean, including food products such as natto, soy milk, tofu, yuba, and aburaage, seasonings such as miso and soy sauce, and soybean oil.
Welcome!

It is with great pleasure that we welcome you to the 8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment.

This international symposium has become the central meeting of interest to researchers investigating the health effects of soyfoods and soybean components. Soy continues to attract the attention of investigators throughout the world in a wide range of disciplines. Nearly 2,000 soy-related scientific health-focused articles are published annually. Furthermore, new technologies and improved methodology are better at allowing the scientific community to learn about the myriad ways that soy and soybean components affect biological systems. There is also increasing emphasis on understanding how differences among individuals affect their response to soy consumption. In fact, for the first time, there is an entire session at this symposium devoted to understanding the role that the production of equol – the bacterially-derived metabolite of the isoflavone daidzein, plays in the health effects of soy intake.

Importantly, this is also the first time since its inception in 1994, that the symposium is being held in Japan, a country that in many respects helped fuel scientific interest in soy. Of course, Japanese people have been consuming a wide range of soyfoods for centuries. But it was the low Japanese rates of such afflictions as heart disease and breast and prostate cancer, despite the high socioeconomic status of Japan, which raised the possibility that soyfoods might reduce risk of certain chronic diseases. In the final analysis however, it is only the results of clinical studies that allow definitive conclusions about health effects to be made. The 8th international symposium promises to be very exciting in this regard. The number of well-designed clinical studies to be presented is truly impressive.

Furthermore, it is very apparent that the number of soy research areas being investigated that will be discussed and debated at this symposium has greatly expanded. There will be more focus, for example, on cognitive function and possible reproductive and hormonal effects than at past meetings. In addition, quite a few studies will address some of the more hotly debated issues within the soy field - such as breast cancer and menopausal symptom relief. By attending this symposium, you will learn about this research long before it is published. Of course, it is during the discussion that some of the more interesting and important information is exchanged, so we encourage all of you to partake in this important part of the symposium.

In addition to the more than 30 speakers presenting original research, this symposium will allow for ample time to view and discuss the poster presentations. Be sure to take the opportunity to talk to investigators firsthand about their research. This is also a good time to discuss with colleagues possible future collaborations.

Finally, this symposium provides an excellent opportunity, during both the scientific and social events, to share ideas and to participate in discussions with leading experts. If you are new to this field it will be an opportunity to match names with faces. There will also be time to visit the sponsoring companies’ displays, providing an opportunity to learn about the types of products available for both experimental purposes and public use. Without the generous contributions of the sponsors, this symposium could not take place.

We look forward to welcoming you to this outstanding event.

Chairpersons

Shaw Watanabe
Director, National Institute of Health and Nutrition, Japan

Hideyuki Akaza
Professor and Deputy Director, Tsukuba University Hospital, Japan

Chisato Nagata
Professor, Gifu University Graduate School of Medicine, Japan

Kenneth D.R. Setchell
Professor, Department of Pathology and Laboratory Medicine, Cincinnati Children’s Hospital Medical Center, USA

Mark Messina
Adjunct Associate Professor, Loma Linda University and President, Nutrition Matters, Inc., USA

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Antitrust Policy

The American Oil Chemists’ Society (the “Society”) intends to strictly comply with the antitrust laws of the United States, all state governments, and any other relevant governing authority (the “Antitrust Laws”), and in furtherance of this intention, proclaims the following Antitrust Policy:

I. The Society shall not be used in a manner which violates the Antitrust Laws, and members of the Society, in their capacity as representatives of the Society, shall not tolerate, encourage or participate in any activity which could reasonably be expected to result in a violation of the Antitrust Laws.

II. This policy shall apply to all membership, board, committee and other meetings of the Society, and all events attended by individual members of the Society in their capacity as representatives of the Society.

III. The Society recognizes that the Antitrust Laws make certain activities between industry participants unlawful, and the Society expressly prohibits participation in such activities at any event which the Society holds or sponsors, or by any member of the Society at any event in which such member participates as a representative of the Society. Such prohibited activities include the following:

   a. Non-competition, territorial division, or operationally restrictive agreements;
   b. Boycotting, blacklisting, or unfavorable reporting; or
   c. Discussion of these and other prohibited matters, including the following:
      i. Price, price fixing, price calculation, or price changes;
      ii. Costs;
      iii. Terms or conditions of sales;
      iv. Quote decisions;
      v. Discounts;
      vi. Product or service offerings; or
      vii. Production or sales volume, capacity or plans.

IV. In the course of any event in which activities or discussion threaten to border on a prohibited matter, any member, officer, director, employee or representative of the Society present at such event in such capacity shall request that the activity or discussion be terminated immediately, and if such termination does not immediately occur, such person shall seek recordation of the problem if appropriate, shall cease all participation in the event, and shall report the matter to the Society at the earliest possible opportunity.

V. A copy of this Antitrust Policy shall be given at least annually to each officer, director, member, representative, or employee of the Society, or any other party participating in the Society, and the Antitrust Policy shall be readily available at all membership meetings.
The co-chairs for the 8th International Symposium on the Role of Soy in Health Promotion and Chronic Disease Prevention and Treatment would like to thank the following companies for their generous contributions. Without their assistance, this symposium would not have been possible.

Registration
4th Floor, Kiku Ballroom Lobby
Sunday, November 9 ............................................12:00–8:00 pm
Monday, November 10 ......................................7:30 am–3:00 pm
Tuesday, November 11 ......................................7:30 am–5:30 pm
Wednesday, November 12 ....................................7:30 am–1:00 pm

Sponsor Showcase
4th Floor, Kiku-en Room (Kiku Ballroom)
The Sponsor Showcase will feature tabletop displays highlighting the latest advances in soy research technologies as well as current soy products available for research and commercial use. This area will host all breaks and the dessert buffet on Monday.

Please note that although this area is open at the designated times below, the sponsors are only requested to be present during the dessert buffet and breaks.

Sunday, November 9 ..............................................2:00–6:00 pm
Monday, November 10 .....................................7:30 am–3:00 pm
Tuesday, November 11 .....................................7:30 am–6:30 pm
Wednesday, November 12 ...................................7:30–10:30 am

Attire
Business or business casual attire is appropriate for all symposium events.

Congratulations, Award Winners!

For Outstanding Contributions in Promoting Awareness of the Nutritional and Health Attributes of Soyfoods
Ms. Boon Yee Yeong
American Soybean Association, Singapore

For Outstanding Contributions to Increasing Scientific Understanding of the Health Effects of Soyfoods and Soybean Constituents
Johanna Lampe, PhD
Fred Hutchinson Cancer Research Center, Seattle, WA, USA
Mindy Kurzer, PhD
University of Minnesota, Minneapolis, MN, USA
Aedin Cassidy, PhD
University of East Anglia, Norwich, England
Shaw Watanabe, MD, PhD
National Institute of Health and Nutrition, Japan
Chisato Nagata, PhD
Gifu University, Japan

2008 Program

General Information

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PROGRAM SCHEDULE

All presentations will take place in the Kiku-yo/Kikka rooms. Each presentation time includes approximately 10 minutes of discussion.

Sunday, November 9

2:00 Opening Remarks.
Mark Messina, Nutrition Matters, USA
Shaw Watanabe, National Institute of Health and Nutrition, Japan
Daiji Ikeda, Otsuka Pharmaceutical Co., Ltd., Japan


3:10 Mood Effects of Soy Isoflavones in Older Adults: Preliminary Evidence of Interaction with Gender. C.E. Gleason1,2, J.H. Barnet2, C. Khosropour1, K.D.R. Setchell4, K. Walth4, and S. Asthana1,2. 1Section of Geriatrics, School of Medicine and Public Health, University of Wisconsin, USA, 2Madison VA GRECC, William S. Middleton Memorial VA, USA, 3Dept. of Biostatistics and Medical Informatics, University of Wisconsin, USA, 4Dept. of Pathology and Laboratory Medicine, Cincinnati Children’s Hospital Medical Center, USA.

3:30 Break.

4:00 Do Soy and Isoflavones Exert Hormonal Effects in Women? A Systematic Review and Meta-analysis. L. Hooper1, J.J. Ryder1, M.J. Kurzer1, J.W. Lampe1, M.J. Messina1, W.R. Phipps3, and A. Cassidy1, 1University of East Anglia, UK, 2University of Minnesota, USA, 3Fred Hutchinson Cancer Research Center, USA, 4Dept. of Pediatrics, University of Rochester, USA.


4:40 Isoflavone Supplements Containing Predominantly Genistein Reduce Hot Flashes. P. Williamson-Hughes1, M. Messina2, M. Empie2, and B. Flickinger2, 1Archers Daniels Midland Co., USA, 2Nutrition Matters, Inc., USA.

5:00 Effects of Genistein Aglycone on Endometrial Hyperplasia in Premenopausal Women: A Randomized Controlled Trial. A. Bitto1, D. Altavilla1, H. Marin2, R. D’Anna3, R. Granese3, D. Villani4, and F. Squadrito1, 1Dept. of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy, 2Dept. of Biochemical, Physiological and Nutritional Sciences, University of Messina, Italy, 3Dept. of Obstetrical and Gynecological Sciences, University of Messina, Italy, 4Dept. of Human Pathology, University of Messina, Italy.

5:20 Effect of Soy Food Products on Satiety, Food Intake and Subjective Sensations. L. Dye1, C. Lawton1, D. Camidge1, F. Crodën1, P. Lees1, S. DeVries2, and C. Debeuf2, 1University of Leeds, UK, 2Alpro NV, Belgium.

6:00–8:00 pm Welcome Reception
Yamato Room, 3rd Floor

Monday, November 10

Equol Session

9:00 Introduction.

9:05 Isoflavone Metabolism: The Key to Understanding the Health Effects of Soy. S. Watanabe, National Institute of Health and Nutrition, Japan.

9:20 Dietary and Developmental Factors Related to Equol Production and Stability. N. Brown, S. Summer, L. Zimmer-Nechemias, and K.D.R. Setchell, Dept. of Pathology and Laboratory Medicine, Cincinnati Children’s Hospital Medical Center, USA.

9:35 24hr Urinary Equol Excretion and Equol Producing Status in China. G. Keyou1, P. Wang2, B. Liu2, C. Donglian3, Y. Su1, K. Guo4, A. Onoda5, U. Tomomi5, S. Uchiyama5, P.-S. Wu5, and X. Li2, 1Chinese Nutrition Society, China, 2Peking University, China, 3Second Military Medical University, China, 4Sun Yat-sen University, China, 5Otsuka Pharmaceutical Co., Ltd., Japan, 6Otsuka (China) Investment Co., Ltd., China.

9:50 The Pharmacokinetic Behavior of Enantiomers of Equol in Healthy Adults. K.D.R. Setchell, Dept. of Pediatrics, Director of Clinical Mass Spectrometry, Cincinnati Children’s Hospital and Medical Center, USA.

10:05 S-Equol: Preclinical Studies Supporting its use as a Pharmaceutical Agent. R.L. Jackson1, R. Schwen1, and I. Merchenthaler2, 1Ausio Pharmaceuticals, LLC, USA, 2University of Maryland at Baltimore School of Medicine, USA.

10:20 Break.

10:45 Target Gene Analysis of Phytoestrogens and their Clinical Significance. T. Usui1, N. Sakane1, T. Tagami1, A. Shimatsu1, M. Naruse2, T. Ueno2, and S. Uchiyama2, 1Clinical Research Center, National Hospital Organization Kyoto Medical Center, Japan, 2Otsuka Pharmaceutical Co., Ltd., Japan.

11:00 Characteristics of Menopausal Symptoms of Japanese Women and the Possible Effects of Equol in Menopausal Health Care. T. Aso1,2, T. Ueno1, S. Uchiyama1, and M. Sakamoto1, 1Kyouno Hospital, Japan, 2Tokyo Medical and Dental University, Japan, 3Otsuka Pharmaceutical Co., Ltd., Saga Nutraceuticals Research Institute, Japan.

11:15 Equol Diminishes Tamoxifen-induced Endometrial Abnormalities in Sprague-Dawley Rats. K.A. Nicolau and A.I. Constantinou*, University of Cyprus, Cyprus.
2008 Program

11:30 **Equol Inhibits Prostate Cancer Cell Invasion and Metastasis.** K.A. Nicolaou, A.L. Skaltsounis, and A.I. Constantinou, University of Cyprus, Cyprus.

11:45 **Equol and Prostate Cancer Prevention in Humans.** H. Akaza, University of Japan, Japan.

12:00–1:00 pm

**Symposium Luncheon—Provided**
**Yamato & Katsura/Kasuga Rooms, 3rd Floor**

1:00–3:00 pm

**Dessert Buffet—Kiku-en Room, 4th Floor**
Sponsors Showcase
Poster Showcase

**Tuesday, November 11**

**Cancer Session**

8:55 **Opening Remarks.**

9:00 **Soy Food Intake and Breast Cancer Survival.** X.O. Shu, Y. Zheng, K. Gu, H. Cai, W. Zheng, and W. Lu, Vanderbilt Epidemiology Center, Vanderbilt University, USA.


10:00 **Modulation of Biomarkers of Growth and Differentiation in Breast Cancer by Soy Isoflavones.** O. Basturk, V. Adsay, M. Banerjee, L. Newman, D. Bouwman, D. Doerge, Z. Djuric, R. Parchment, A. Majumdar, F. Miller, F. Sarkar, and O. Kucuk, Dept. of Pathology, Memorial Sloan-Kettering Cancer Center, USA.

10:20 **Clinical Studies Show no Effects of Soy Protein or Isoflavones on Reproductive Hormones in Men: Results of a Meta-analysis.** J. Hamilton-Reeves, G. Vazquez, S. Duval, W. Phipps, M. Kurzer, and M.

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Messina\textsuperscript{4,5}, 1University of Minnesota, USA, 2College of St Catherine, USA, 3University of Rochester Medical Center, USA, 4Loma Linda University, USA, 5Nutrition Matters, USA.

10:40 Break.

11:00 Reduction of Adverse Events by Soy Isoflavones in Patients Undergoing External Beam Radiation Therapy for Prostate Cancer. I. Ahmad\textsuperscript{1}, J.D. Forman\textsuperscript{2}, F. Sarkar\textsuperscript{3}, G. Hillman\textsuperscript{4}, M. Banerjee\textsuperscript{4}, D. Doerge\textsuperscript{4}, E. Heath\textsuperscript{4}, U. Vaishampayan\textsuperscript{4}, M. Cher\textsuperscript{4}, and O. Kucuk\textsuperscript{4,5}, 1Karmanos Cancer Institute, Wayne State University, USA, 2University of Michigan, USA, 3National Toxicology Center, USA, 4Winship Cancer Institute, Emory University School of Medicine, USA.

11:20 Purified Isoflavones in Prostate Cancer. N. Kumar\textsuperscript{1,2}, J. Krisher\textsuperscript{1}, K. Besterman-Dahan\textsuperscript{2}, K. Allen\textsuperscript{2}, D. Riccardi\textsuperscript{2}, L. Kang\textsuperscript{2}, P. Xu\textsuperscript{1}, and J. Powsang\textsuperscript{1,2}, 1University of South Florida, USA, 2Moffitt Cancer Center, USA.

11:40 Repeated Oral Administration of Genistein Aglycone on Bone and Lipid Metabolism in Ovariectomized Rodents. H. Marini\textsuperscript{2}, R. D'Anna\textsuperscript{3}, and A. Bitto\textsuperscript{1}, 1Clinica di Gastroenterologia ed Epatologia, Università degli Studi di Perugia, Italy, 2Clinical and Mass Spectrometry, Department of Pathology and Laboratory Medicine Children's Hospital M.C, USA, 3DIMISEM, University of Southern California, Keck School of Medicine, USA.

12:00 Hematopoietic Progenitor Cells and Primary Lung Fibroblasts are Protected in vivo by Genistein against Radiation. R.M. Day\textsuperscript{1}, M. Barshishat-Kupper\textsuperscript{1}, S.R. Mog\textsuperscript{1}, O. Mungunskh\textsuperscript{1}, T.A. Davis\textsuperscript{2}, and M.R. Landauer\textsuperscript{1}, 1Dept. of Pharmacology, Uniformed Services University of the Health Sciences, USA, 2AFRRI, Uniformed Services Medical Research Center, USA.

12:20 Safety and Efficacy of Genistein Aglycone on Bone Metabolism and Some Predictors of Cardiovascular Risk: A 3-Year Follow-up Study. F. Squadrito\textsuperscript{1}, D. Altavilla\textsuperscript{1}, H. Marini\textsuperscript{2}, R. D’Anna\textsuperscript{3}, and A. Bitto\textsuperscript{1}, 1Dept. of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy, 2Dept. of Biochemical, Physiological and Nutritional Sciences, University of Messina, Italy, 3Dept. of Obstetrical and Gynecological Sciences, University of Messina, Italy.

12:40–2:00 pm Symposium Luncheon— Provided Yamato & Katsura/Kasuga Rooms, 3rd Floor

2:00 The Impact of Dietary Intake of Soy on the Risk of Cardiovascular Disease. Y. Kokubo, National Cardiovascular Center, Japan.

2:20 Comparative Bioactivities of Equol, Daidzein, and Genistein on Bone and Lipid Metabolism in Ovariectomized Rodents. M. Uehara\textsuperscript{1}, T. Ueno\textsuperscript{2}, S.I. Katsumata\textsuperscript{1}, K. Suzuki\textsuperscript{1}, and S. Uchiyama\textsuperscript{2}, 1Tokyo University of Agriculture, Tokyo, Japan, 2Saga Nutraceuticals Research Institute, Otsuka Pharmaceutical Co., Ltd., Japan.

2:40 Meta-Analysis Confirms Soy Protein’s Cholesterol Lowering Efficacy. P. Samuel\textsuperscript{1}, S. Zakharkin\textsuperscript{1}, E. Spitznagel\textsuperscript{2}, K. Greaves\textsuperscript{1}, D. Butteiger\textsuperscript{2}, and E. Kruit\textsuperscript{3,4}, 1Solae LLC, USA, 2Washington University in St. Louis, USA.


3:40 Break.

3:50 Equol and its Relation to Osteoporosis Prevention using Soy. F.M. Steinberg\textsuperscript{1}, S. Barnes\textsuperscript{2}, M.J. Murray\textsuperscript{3}, R.D. Lewis\textsuperscript{2}, J.G. Fischer\textsuperscript{4}, M.A. Cramer\textsuperscript{5}, P. Amato\textsuperscript{6}, R.L. Young\textsuperscript{6}, K.J. Ellis\textsuperscript{7}, R.S. Shyppalo\textsuperscript{8}, E.O. Smith\textsuperscript{8}, J.K. Fraley\textsuperscript{8}, and W.W. Wong\textsuperscript{3}, 1University of California, USA, 2University of Alabama, USA, 3Southern California Fertility Medical Center, USA, 4University of Georgia, USA, 5Oregon Health Sciences University, USA, 6Baylor College of Medicine, USA.

4:00 Soybean β-conglycinin Reduces a Risk of Visceral Fat Syndrome, So-called Metabolic Syndrome. M. Kohno\textsuperscript{1}, M. Hirotsuka\textsuperscript{1}, M. Kito\textsuperscript{2}, and Y. Matsuzawa\textsuperscript{3}, 3Food Science Research Institute, Fuji Oil Co., Ltd., Japan, 2Emeritus Professor of Kyoto University, Japan, 3Sumitomo Hospital, Japan.

4:40 Biological Effects of Pasta Containing Isoflavone Aglycons in Type 2 Diabetic Patients—A Double-Bind Randomized Crossover Study. E. Nardi\textsuperscript{1}, S. Asciutti\textsuperscript{2}, K.D.R. Setchell\textsuperscript{1,2}, D. Castellani\textsuperscript{1}, E. Floridi\textsuperscript{1}, A. Gherardi\textsuperscript{1}, N. Corazzi\textsuperscript{1}, V. Giuliano\textsuperscript{1}, M. Baldoni\textsuperscript{1}, S. Gizi\textsuperscript{1}, A. Morelli\textsuperscript{1}, G. Perilli\textsuperscript{1}, G. Di Matteo\textsuperscript{1}, F. Galli\textsuperscript{1} and C. Clerici\textsuperscript{1}, 1Clinica di Gastroenterologia ed Epatologia, Università degli Studi di Perugia, Italy, 2Clinical and Mass Spectrometry, Department of Pathology and Laboratory Medicine Children’s Hospital M.C, USA, 3DIMISEM, University of Perugia, Italy, 4Institute of Biochemistry, University of Perugia, Italy.

5:00 Gender-Specific Effects of Soy Isoflavones on Risk of Hip Fracture in the Singapore Chinese Health Study. W.-P. Koh\textsuperscript{1}, R. Wang\textsuperscript{2}, M.C. Yu\textsuperscript{2}, and A.H. Wu\textsuperscript{3}, 1Dept. of Community, Occupational and Family Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, 2Masonic Cancer Center, University of Minnesota, USA, 3Dept. of Preventive Medicine, University of Southern California, Keck School of Medicine, USA.

5:30–6:30 pm Dedicated Poster Viewing Reception
Visit with the authors.

Wednesday, November 12

Emerging Areas Research

8:55 Opening Remarks.

9:00 Transcriptome Analyses of the Effect of Soy Protein Intake. H. Kato\textsuperscript{1}, S. Tsuji\textsuperscript{2}, N. Tachibana\textsuperscript{2}, M. Kohno\textsuperscript{1}, K. Takamatsu\textsuperscript{1}, and K. Abe\textsuperscript{1}, 1Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan, 2Food
2008 Program

Science Research Institute, Fuji Oil Co., Ltd., Japan.

9:20 **Effect of Isoflavone on Ovariectomy-Induced Retardation in Hair Growth and Dermal Levels of Insulin-Like Growth Factor-I mRNA in Mice.** K. Okajima, N. Harada, and J. Zhao*, Dept. of Translational Medical Science Research, Nagoya City University Graduate School of Medical Sciences, Japan.

9:40 **Soy Isoflavones and Gastrointestinal Function.** K.D.R. Setchell, Dept. of Pediatrics, Director of Clinical Mass Spectrometry, Cincinnati Children’s Hospital and Medical Center, USA.

10:00 **Break.**

**General Topics**

10:30 **Effect of Soy Isoflavones in Spermatogenesis.** V. Unfer1, D. Bertoni1, M. Zacchê2, A. Serafini2, and E. Papaleo*2, 1AGUNCO Obstetric & Gynecology Centre, Italy, 2IVF Unit, Gynecologic-Obstetric Department, San Raffaele Hospital, Vita-salute University, Italy.

10:50 **Soy Protein Isolates of Varying Isoflavone Content do not Adversely Affect Semen Quality in Healthy Young Men.** L.K. Beaton1, B.L. Dillingham1, B.L. McVeigh1, J.W. Lampe2, and A.M. Duncan*1, 1Dept. of Human Health and Nutritional Sciences, University of Guelph, Canada, 2Fred Hutchinson Cancer Research Center, USA.

11:10 **Soy Foods do not Negatively Impact Mineral Balance or Bone Turnover in Young Women.** M.B. Reddy, Y. Zhou, and D.L. Alekel, Iowa State University, USA.

11:30 **Bioavailability of Calcium from Tempeh as Compared to Milk in Postmenopausal Malay Women.** H. Haron1,3, S. Shahar1, K. O’Brien2, A. Ismail3, L.S. Peng3, A. Azlan3, N. Kamaruddin4, and S. Abdul Rahman5, 1Universiti Kebangsaan Malaysia, Dept. of Nutrition & Dietetics, Faculty of Allied Health Sciences, Malaysia, 2Cornell University, Division of Nutritional Sciences, USA, 3Universiti Putra Malaysia, Dept. of Nutrition & Dietetics, Faculty of Medicine & Health Sciences, Malaysia, 4Universiti Kebangsaan Malaysia, Dept. of Medicine, Faculty of Medicine, Malaysia, 5Universiti Kebangsaan Malaysia, Food Science Programme, Faculty of Science and Technology, Malaysia.

11:50 **Spatial Working Memory is Improved with Soy Isoflavone Supplementation in Healthy Males.** A.J. Thorp1,2, N. Sinn1, J.D. Buckley1, A.M. Coates1, and P.R.C. Howe1, 1Nutritional Physiology Research Centre and ATN Centre for Metabolic Fitness, University of South Australia, Australia, 2School of Molecular and Biomedical Sciences, University of Adelaide, Australia.

12:10 **Closing Comments.**
Poster Presentations
Poster presentations are located in the Kiku Foyer.

Poster Presentations

Posters are available for viewing:
Monday, November 10 .................................7:30 am– 3:00 pm
Tuesday, November 11 .................................7:30 am– 6:30 pm
Wednesday, November 12 .............................7:30–10:30 am

A dedicated poster session will take place on Tuesday, 5:30–6:30 pm. This is your chance to talk to the investigators first-hand about their research.

Athletic Performance
1. Soy Protein Intake in Peptide Form Effectively Mitigates Exercise-Induced Muscle Damage. M. Maebuchi1, M. Samoto1, K. Masuda2, Y. Nakabou3, and M. Hirotsuka1,1Food Science Research Institute, Tsukuba Research and Development Center, Fuji Oil Co. Ltd., Japan, 2Dept. of Acupuncture and Moxibustion, Kansai University of Health Sciences, Japan, 3Graduate School of Health Science and Technology, Kawasaki University of Medical Welfare, Japan.

Bioavailability of Soybean Component
2. Isoflavone Content of Contemporary Soy Foods. Y. Morimoto, S. Suzuki, G. Maskarinec, and A.A. Franke, Cancer Research Center of Hawaii, USA.
3. Apparent Bioavailability of Isoflavones after Intake of Liquid and Solid Soy Foods. A.A. Franke1, B.M. Halm2,1, and L.A. Ashburn1, 1Cancer Research Center of Hawaii, USA, 2Kapi‘olani Medical Center for Women and Children, USA.

Cancer
1. Breast Cancer Cohort in Japan. Y. Mizota1, S. Yamamoto1, M. Iwasaki2, Y. Ohashi3, M. Ando4, and N. Shimoyma3, 1Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Japan, 2Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Japan, 3Dept. of Biostatistics, School of Public Health, University of Tokyo, Japan, 4Dept. of Breast and Oncology, National Cancer Center Hospital, Japan, 5Surgical Operation and Palliative Medicine Division, National Cancer Center Hospital, Japan.
2. Randomized Clinical Trial of the Action of Several Doses of Isoflavones in Localized Prostate Cancer. N. Kumar1,2, J. Krischer3, Ka. Besterman-Dahan4, K. Allen2, D. Riccardi2, L. Kang3, J. Powsang1, and P. Xu1, 1University of South Florida, USA, 2 Moffitt Cancer Center, USA.

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1. Daidzein, Soy Phytoestrogen, Selectively Ameliorates Obesity-Related Hypertension in Mice and Humans Without Affecting Other Metabolic Derangements. T. Furumoto1, D. Gotou1, S. Fuji2, and H. Tatsu3, 1Dept. of Cardiovascular Medicine Hokkaido University Graduate School of Medicine, Japan, 2Dept. of Molecular and Cellular Pathobiology and Therapeutics Nagoya City University Graduate School of Pharmaceutical Sciences, Japan.
4. Effects of Genistein on Human Pulmonary Artery Smooth Muscle Cells. Y.J. Suzuki, Georgetown University, USA.
5. Epigenetic Regulation of HMG-CoA Reductase and LDL Receptor Expression by the Soy Peptide, Lunasin, Provides a Mechanism for Lowering Cholesterol. A.F. Galvez1,2, F. Chunjiang2, and M. Kerley2, 1Center of Excellence for Nutritional Genomics, University of California, USA, 2Dept. of Animal Science, University of Missouri, USA.

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1. Dietary Soy Protein Suppresses the Diabetic Mediator RBP4 in Rats. C.W. Xiao1,2, C.M. Wood3, G. Leroux1, M.R. L’Abbé1, G.S. Gilani2, G.M. Cooke2,3, I. Curran2, D. Jin2, and R. Mehta2, 1Nutrition Research Division, Food Directorate, Health Products and Food Branch, Health Canada, Canada, 2Toxicology Research Division, Food Directorate, Health Products and Food Branch, Health Canada, Canada, 3Dept. of Cellular and Molecular Medicine, University of Ottawa, Canada.
2. Soy Isoflavone Inhibits TNF-α induced Downregulation of Adiponectin. M. Yanagisawa and T. Tsuda, College of Bioscience and Biotechnology, Chubu University, Japan.
3. Soy β-conglycinin Improves Insulin Sensitivity and Glucose Tolerance in Rats. N. Tachibana1, M. Kohno1, M. Hirotsuka1, and F. Horio1, 1Fuji Oil Co., Ltd., Japan, 2Nagoya University, Japan.
4. Influence of Soy Protein on Serum Lipids and Blood Glucose in Type 2 Diabetic Patients. A.M. Mahdavi, Tabriz University of Medical Sciences, Faculty of Health & Nutrition, Iran.
5. **Effect of Soy and its Components on Lipid Metabolism and Cardiovascular Risk Factors in Type 2 Diabetic Patients.** A.M. Mahdavi, Tabriz University of the Medical Sciences, Faculty of Health & Nutrition, Iran.

### Equol

1. **A Survey Study on Urinary Equol Excreters and Frequency of Equol Producer in Beijing, P.R. of China.** P. Wang1, A. Onoda2, T. Ueno3, S. Uchijama4, X. Li5, and P.-S. Wu6, 1Beijing University, China, 2Saga Nutraceuticals Research Institute, Japan, 3Otsuka Pharmaceutical Co., Ltd., China, 4Otsuka International Asia Arab Division, Otsuka Pharmaceutical Co., Ltd., Japan.

2. **24hr Urinary Equol Excretion and Equol Producing Status in Guangzhou, P.R. of China.** Y.X. Su1, K. Guo1, K. Onoda2, T. Ueno2, S. Uchiyama2, X. Li3, and P.-S. Wu4, 1Faculty of Nutrition, Public Health School of Sun Yat-sen University, Zhongshan, China, 2Saga Nutraceuticals Research Institute, Otsuka Pharmaceutical Co., Ltd., Japan, 4Otsuka (China) Investment Co., Ltd., China.

3. **Detection of the Equol-producing Bacterium Adlercreutzia equolifaciens in Human Feces by Nested PCR Method.** T. Maruo1, T. Toda1, C. Ito1, M. Sakamoto2, Y. Ishimi3, K. Yamada1, and Y. Benno2, 1Fujicco Co., Ltd., Japan, 2Microbe Division/Japan Collection of Microorganisms, RIKEN BioResource Center, Japan, 3Division of Nutritional Epidemiology, National Institute of Health and Nutrition, Japan.

4. **S-Equol Production from Glycitein by Rat Gut Microflora.** H. Ishida1, K. Ito1, C. Ito2, T. Toda2, and Y. Kiryu1, 1School of Pharmaceutical Science, University of Shizuoka, Japan, 2Fujicco Co., Ltd., Japan.

5. **Isolation and Identification of Equol-producing Bacterial Strains from Rat Feces.** H. Ishida1, K. Ito1, T. Maruo2, T. Toda2, and Y. Kiryu1, 1School of Pharmaceutical Science, University of Shizuoka, Japan, 2Fujicco Co., Ltd., Japan.

6. **Is It Possible to Assign Equol Producer Phenotype Based on Singlicate Blood Samples?** M. K. Melby, National Institute of Health and Nutrition, Japan.

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1. **Specification of Genomic Regions Associated with Isoflavones Content in Soybean Seeds using Recombinant Inbred Lines.** T. Yoshikawa1, D. Ogata1, Y. Okumoto1, M. Terai2, N. Yamada3, M. Terai4, T. Sayama1, T. Nakazaki1, K. Yagasaki1, T. Toda2, K. Yamada3, T. Yamada1, and T. Tanisaka1, 1Graduate School of Agriculture, Kyoto University, Japan, 2Nagano Chushin Agricultural Experiment Station, Japan, 3Fujicco Co., Ltd., Japan.

2. **Soymilk Can Reduce Oxidative Stress from Lactose Intolerant People.** C.-W. Chung, Central Research Institute, Dr. Chung’s Food Co., Ltd., Korea.

3. **Human Renin Inhibitory Activity in Miso, Soybean, and Minor Legumes.** S. Takahashi1, K. Hori1, H. Ogasawara1, M. Kumagai2, T. Watanabe2, and T. Gotoh3, 1Institute for Food and Brewing, Akita Prefectural Agriculture, Forestry, and Fisheries Research Center, Japan, 2Dept. of Engineering in Applied Chemistry, Japan.

### Immune Function

1. **Soy Isoflavone Intake and Risk of Cedar Pollinosis in Japanese Men and Women.** C. Nagata1, K. Nakamura1, T. Kawachi2, N. Takatsuka1, S. Obu2, and H. Shimizu3, 1Dept. of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Japan, 2Dept. of Prevention for Lifestyle-Related Diseases, Gifu University Graduate School of Medicine, Japan. 3Sakihai Institute, Japan

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1. **Preventive Effects of Isoflavone on Motor Dysfunctions of the Animal Model of Parkinson’s Disease in the Postmenopausal Period.** S. Kyuhou, Kansai Medical University, Japan.

2. **Comparison of Soy Isoflavone and Equol Supplements for Relieving Menopausal Symptoms.** S. Ishiwata1, S. Mizuno2, and S. Watanabe2, 1Atomi University, Japan, 2National Institute of Health and Nutrition, Japan.

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3. Daidzein-rich Isoflavone Aglycones are Potentially Effective in Reducing Hot Flashes in Menopausal Women. J.-R. Zhou, W. Pan, H. Ricciotti, L. Khaodhia, L. Li, M. Schickel, and G. Blackburn, Beth Israel Deaconess Medical Center, Harvard Medical School, USA.

Nonprotein/Isoflavone Components


2. Soybean Oil Enriched with Conjugated Linoleic-Lauric Acid Mixture. S. Tanrisever, Z. Gecioglu, H.A. Aksoy*, G. Ustun, and M. Tuter, Istanbul Technical University, Chemical Engineering Department, Turkey.

3. Dietary Soybean Oil Rich in Conjugated Linolenic Acid from Pomegranate Seed Oil. B. Ozdogan, B. Bilaloglu, D. Bashoyuk, G. Ustun*, H.A. Aksoy, and M. Tuter, Istanbul Technical University, Chemical Engineering Department, Turkey.

4. Dietary Soybean Oil Enriched with Conjugated Linolenic (CLNA) and Conjugated Linoleic (CLA) Acids. B. Ozak, M. Tuter*, G. Ustun, and H.A. Aksoy, Istanbul Technical University, Chemical Engineering Department, Turkey.

5. Production of Conjugated Linoleic Acid from Soybean and Sunflower Seed Oils by using Lactic Acid Bacteria. S. Ballikaya1, N. Aran*, and G. Ustun, Istanbul Technical University, Food Engineering Department, Turkey.

Obesity

1. Daidzein-rich Isoflavone Aglycones Improved High Fat-induced Metabolic Disorders in Ovariectomized Mice Fed a High-fat Diet. J.-R. Zhou1, W. Pan1,2, and G. Blackburn1, 


Reproduction

1. AglyMax Improves Implantation by Stimulating Secretion of Leukemia Inhibitory Factor (LIF) in Human Endometrial Epithelial Cells. A. Yanaihara1, J.-W. Xu2, N. Yasuii2, K. Ikeda3, W. Pan1-4, J. Watanabe5, M. Shiotani6, T. Miki7, and Y. Yamori8, Departments of Obstetrics and Gynecology, Showa University School of Medicine, Japan, Division of Pathophysiology, School of Pharmacy and Pharmaceutical Sciences, Mukogawa Women’s University, Japan, Nichimo Biotics Co., Ltd., Japan, Beth Israel Deaconess Medical Center at Harvard Medical School, USA, Hanabusa Women’s Clinic, Japan, Institute for World Health Development, Mukogawa Women’s University, Japan.

Safety Issues

1. Effects of Soy Isoflavone Extract on Thyroid Function in Postmenopausal Women. E.A.P. Nahas1, J. Nahas-Neto1, F.L. Orsatti1, and M. Messina2, 1Botucatu Medical School, UNESP-Sao Paulo State University, Brazil, 2School of Public Health, Loma Linda University, USA.

Skin Health


2. Effects of ImmuBalance on Atopic Dermatitis: Preclinical Study using Atopic NC/Nga Mice. A. Tanaka1, W. Pan2,3, N. Kingyo3, O. Keitaro1, and H. Matsuda1, 1Tokyo University of Agriculture and Technology, Japan, 2Beth Israel Deaconess Medical Center, USA, 3Nichimo Co., Ltd., Japan.
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3:40–4:00 pm.................Coffee Break
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Nichimo Biotics Co., Ltd. manufactures AglyMax, a daidzein-rich isoflavone aglycone ingredient made from koji fermented soy germ under patents obtained in Japan, U.S. and Europe. AglyMax has been researched extensively through collaborative-research projects with numerous universities and public research institutions including Beth Israel Deaconess Medical Center, Harvard Medical School, and many of the *in vitro*, *in vivo* and clinical studies have been published in medical journals in Japan, U.S., and England.

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Mood Effects of Soy Isoflavones in Older Adults: Preliminary Evidence of Interaction with Gender. C.E. Gleason1,2, J.H. Barnet3, K. Khosropour4, K.D.R. Setchell5, K. Walth6, and S. Asthana1,2,1. Section of Geriatrics, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin, USA, 2Madison VA GRECC, William S. Middleton Memorial VA, Madison, Wisconsin, USA, 3Dept. of Biostatistics and Medical Informatics, University of Wisconsin, Madison, Wisconsin, USA, 4Dept. of Pathology and Laboratory Medicine, Cincinnati Children’s Hospital Medical Center, and Dept. of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA.

Beneficial mood effects of soy isoﬂavones were found in middle-aged women and young adult men (Casini et al. 2006; File et al. 2001). However, isoﬂavones’ mood effects in older adults are unclear. We examined mood after 6 months’ treatment with 100mg/day Novasoy isoﬂavones vs. placebo in 30 cognitively healthy older adults (age 60 years; mean age=74 years; 50% women), hypothesizing that isoﬂavone treatment would result in better mood. Older adults on isoﬂavones demonstrated fewer symptoms on the POMS Depression/Subjective depression sub-scale (x^2=4.43; p=0.04), and trends for higher Vigor scores (x^2=3.58; p=0.06) compared to adults on placebo. Likewise, isoﬂavone-treated older adults demonstrated a trend for less depression on the GDS compared to placebo-treated subjects (x^2=3.62; p=0.06). An interaction of gender and treatment was found on the POMS Vigor scale; men on placebo demonstrated reduced vigor, whereas men on isoﬂavonos showed no change (x^2=4.97; p=0.03). Consistently, on the GDS with men on placebo reporting more depression symptoms compared to baseline, scores for men on isoﬂavonos did not change (x^2=4.08; p=0.04). In summary, these preliminary data support a possible beneﬁcial effect of soy isoﬂavones on mood in older adults and men in particular.

Acknowledgements: NIA K23 AG24302; NCRR M01 RR03186; Madison GRECC/Dept. of Veterans Affairs, ADM provided Novasoy® and placebo tablets.


Hormonal effects of soy isoﬂavones (SI) have been investigated in numerous trials with equivocal findings; several studies, but not all, observe effects on follicle-stimulating-hormone (FSH) and luteinizing-hormone (LH) in premenopausal-women (PREW) which might impact on fertility and ovulation while in postmenopausal-women (POSTW) some studies suggest soy increases estradiol levels with implications for breast cancer and osteoporosis. We systematically reviewed the effects of SI on estrogen and other hormones in PREW and POSTW. 47 studies were included; 11 for PREW (n=579), 35 for POSTW (n=1165), and 1 for peri-menopausal women (n=69). In PREW, SI consumption had no effect on total estradiol, estrone, or sex-hormone-binding-globulin (SHBG) levels but significantly reduced FSH and LH (using standarised mean differences (SMD), p=0.01 and 0.05 respectively) and increased menstrual cycle length (1.05 days; 95%CI; (0.13,1.97); 10 studies). In POSTW, a trend towards an increase in total estradiol was observed following SI (SMD p=0.07, 21 studies) but had no effect on other hormones. Source and dose had no effect, except for estradiol in POSTW following isoﬂavone extract consumption.

The clinical implications of these findings, if any, will be discussed.

Oral Presentation Abstracts

Please note: The following abstracts have not been edited for content. They appear as submitted by the authors.

Sunday Afternoon


Japanese females and males are holding the longest average life expectancy 86 and the second longest 79, respectively in the world. The average life-spans among developed countries are inversely related significantly with the age-adjusted mortality rates of coronary heart diseases (CHD) as demonstrated by our WHO-coordinated, CARDIAC Study covering 61 populations in 25 countries. This cross sectional multi-center survey on the association of dietary biomarkers such as 24-hour urinary isoﬂavone excretions (Iso) as the soy consumption demonstrated Iso were inversely related significantly with CHD, thus indicating the highest Iso in Japanese women may be contributory to their longest life-expectancy. Iso were also significantly inversely related with prostate cancer mortality in males and with breast cancer and all cancer mortalities in females. Randomized placebo-controlled intervention studies in Japanese living in Japan, Hawaii and Brazil, and in Scottish people and Australian Aboriginals showed that soy protein and/or isoﬂavone-fortiﬁed breads, jelly, juice, fermented soy soups etc, for 4 to 16 weeks as well as isoﬂavone tablets for 6 months reduced such risks as obesity, blood pressure, athero- genic index etc and increased bone density. “Well balanced meal once a day project ” by utilizing Japanese style lunch box containing low salted soy, fish, vegetables and rice without much fat also decreased the risks in 4 weeks. These results indicate Japanese food culture such as taking soy products daily, if applied world-wide through the creation of new soy products, will hopefully contribute to healthy longevity in the world.

Hormones, Menopause, and Mood


Epidemiological associations between soy intake and low rates of menopausal/ climacteric symptoms have been reported in Japanese populations. However, results from Western intervention studies on soy and menopause have been mixed. To understand these seemingly conﬂicting results, we will discuss the anthropology of menopause and its relationship to soy focusing on the following questions:

1. Does Japanese kônenki (climacteric) differ from Western menopause?
2. What are the symptoms of kônenki?
3. Does phytoestrogen intake/exposure influence the experience of kônenki?

The analysis draws on a longitudinal study of 140 Japanese women aged 45-55, who provided weekly blood samples with matched 24-hour dietary records for 6 months and completed a food frequency questionnaire and extensive questionnaires and interviews about health and menopause/ climacteric.

Using menopause as a case study, I explore issues of dietary intake versus exposure, timing and duration, developmental effects, and intetnal ecological factors influencing soy’s effects on health. Soy intake (estimated from dietary records) is negatively correlated with sweating symptoms, while soy exposure (estimated from dried blood spots) is negatively correlated with chilliness, the most common vasomotor symptom experienced by Japanese women.
Soy Isoflavones Improve Menopausal Symptoms—A Clinical Study Report. Martin Imhof¹, Dept. of Obstetrics and Gynecology, Humanis Clincium Korneuburg Vienna, Korneuburg/Vienna, Austria.

192 pre- to postmenopausal Caucasian women who suffered from vasomotor symptoms were recruited in 3 study centers for this randomized, double-blind, and placebo-controlled study. The effects of a daily intake of a soy extract preparation containing 100 mg of isoflavones or placebo on menopausal symptoms were assessed over a period of 12 weeks (part I), followed by a 12 week open observational period under verum (part II). Participants were keeping a diary on hot flushes and changes in the Greene Climacteric Scale (GCS) were evaluated. Safety parameters included haematology and biochemical parameters (including liver and thyroid function tests and hormonal levels), and vaginal cytology.

Results and Conclusions: Part I verum/placebo: All of the 3 main independent symptom measures of the GCS (psychological, physical, vasomotor) have been significantly improved (p<0.001). Hot flushes were reduced by 43.3% with verum, and by 30.8% with placebo (group difference p<0.001). Part II verum/verum: Hot flushes were further reduced to 67.8%. Neither for GCS nor hot flush data statistical significances between the former verum and placebo groups could be detected. Over the entire study period of 24 weeks, no changes were found for safety parameters and vaginal cytology. Soy extract with 100 mg of isoflavones per day safely and effectively reduces menopausal and vasomotor symptoms.

Isoflavone Supplements Containing Predominantly Genistein Reduce Hot Flashes. P. Williamson-Hughes¹, M. Messina², M. Emptie¹, and B. Flickinger¹. ¹Archer Daniels Midland, Co., Decatur, IL, USA, ²Nutrition Matters, Inc., Port Townsend, WA, USA.

Reviews and meta-analyses have evaluated isoflavone treatment of menopausal hot flushes. The majority of these reviews include various isoflavone sources, often without recognizing the amounts of specific isoflavones contained in study products. In 2006, we published a critical review of 11 studies utilizing well-characterized isoflavone-containing supplements which indicated efficacy was attributed to the isoflavone genistin. Six additional clinical studies have been published since our review. Of the 17 studies, 9 utilized predominantly genistin containing treatments, providing >15 milligrams of genistin (as aglycone equivalents). These studies (396 treated subjects) consistently reported a statistically significant reduction in hot flushes compared to control. The remaining 8 studies (364 treated subjects) used supplements containing relatively high daidzein and low genistin. Of these 8 studies, one reported a reduction in hot flushes, and another showed the high-daidzein treatment was only effective in women producing equol. Thus, our review clearly shows that high-genistin-containing supplements alleviate menopausal hot flushes. Furthermore, previous reviews which concluded isoflavones lack efficacy did so because of their failure to consider the specific isoflavone compositions of study products. Future studies should focus attention to the specific composition of isoflavone supplements.

Effects of Genistein Aglycone on Endometrial Hyperplasia in Premenopausal Women: A Randomized Controlled Trial. Alessandra Bitto¹, Domenica Altavilla¹, Herbert Marin², Rosario D’Anna³, Roberta Granese³, Daniela Villari⁴, and Francesco Squadrito⁵. ¹Dept. of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy, ²Dept. of Biochemical, Physiological, and Nutritional Sciences, University of Messina, Italy, ³Dept. of Obstetrical and Gynecological Sciences, University of Messina, Italy, ⁴Dept. of Human Pathology, University of Messina, Italy.

We performed a 6-month randomized placebo and progesterin controlled trial in premenopausal women with endometrial hyperplasia without cytological atypia. Women were 44–52 years, endometrium 4–12mm in the 10th day of menstruation and a symptomatological score of 3–5. Women were assigned to 3 arms: genistin aglycone (24; 54mg/day); norethisterone acetate (19; 10mg/day from day 16 to 25 of menstruation) and placebo (16). At 0 and 6 months a biopsy was taken. After 6 months in the genistin aglycone group, 42% had a significant and 33% a moderate relief of symptoms (mean reduction 65% and 40% respectively), while 25% of patients did not. Absence of hyperplasia was confirmed in 29%. Patients (47%) with norethisterone acetate had a significant symptom relief (mean reduction 70%), 32% had a moderate (mean reduction 38%), 21% had no changes. Absence of hyperplasia was confirmed in 31%. In the placebo only, 12% had a significant relief (mean reduction 50%), 6% had a moderate (mean reduction 30%), 62% had no change and 19% had a worsening. Absence of hyperplasia was confirmed in the 12%. Immunohistochemistry revealed a reduced expression of estrogen and progesterone receptors in patients under genistin with a complete regression. Genistin aglycone might be a new treatment for endometrial hyperplasia without atypia.

Obesity/Satiety

Effect of Soy Food Products on Satiety, Food Intake and Subjective Sensations. L. Dye¹, C. Lawton¹, D. Camidge¹, F. Croden¹, P. Lees¹, S. DeVries², and C. Debeuf². ¹University of Leeds, Leeds, UK, ²Alpro NV, Belgium.

The satiating effects of soy protein (SP) vs. non-soy protein (NSP) consumed in real meals at breakfast (400kcal) and lunch (1000kcal) were examined in 20 young healthy males (mean age 21 yrs., mean BMI 22kg/m²). Meals were matched on appearance, weight and macronutrient composition, varying in source of protein (both meals: Protein 20%; CHO 50%; Fat 30%). SP consumption at breakfast and lunch suppressed food intake at an ad libitum buffet dinner (p<0.05). The findings showed a greater satiating effect of SP meals compared to NSP equicaloric meals. This small but significant suppression of food intake of 172kcal (16%) could be beneficial for weight control. Total energy intake on the SP day (2975kcal) was 144kcal less than on the NSP day (3119kcal). Subjective measures of appetite showed that the SP breakfast was consistently more satiating than the NSP breakfast with similar trends at lunch. These effects on satiety are likely to be related to the higher fibre content of soy foods in combination with soy protein. There were few effects on mood or cognitive capacity which remained high throughout both test days. Overall the post meal palatability ratings of the SP and NSP test meals were high. The SP breakfast and lunch, produced greater mental alertness over the test day. Further studies are recommended to explore the mechanism and maintenance of these effects.

Acknowledgements: Alpro NV Belgium.

Monday Morning

Equol

Isoflavone Metabolism: The Key to Understanding the Health Effects of Soy. Shaw Watanabe, National Institute of Health and Nutrition, Japan.

The beneficial effects of isoflavones are widely supported by both experimental and epidemiological data. Equol, a metabolite of daidzein, is considered to be the most effective estrogen modifier in the body and

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has been shown to improve osteoporosis and climacteric syndrome. Only those individuals who have particular intestinal bacteria produce equol, however, and the rate of equol producers is reported to be about 20–30% among Caucasians and 30–50% among Japanese.

The biologically produced equol supplement by fermentation of soy germ using special lactococcus contains only the s-enantimer, which is more effective compared to the chemically synthesized racemic equol. We tried to confirm the pharmacokinetics and safety dose of equol supplement. Distinction of equol producer should also be clarified. Kontroversial results of randomized clinical studies could be explained by the equol productivity of individuals. The newly developed equol supplement should prove clinically useful as a selective estrogen modifier for climacteric women, especially for equol nonproducers. In addition, the antioxidant activity of equol may inhibit lipid peroxidation and reduce the risk of cardiovascular disease. Different physiological and/or pharmacological effects of isoflavones in both equol producer and non-producers need more studies.

Dietary and Developmental Factors Related to Equol Production and Stability. Nadine Brown*, Suzanne Summer, Linda Zimmer-Nechemias, and Kenneth Setchell, Dept. of Pathology and Laboratory Medicine, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA.

Equol, a non-steroidal estrogen of the isoflavone class, is an important metabolite of ingested soy isoflavones produced by bacteria that reside in the distal region of the gastrointestinal tract. For unknown reasons, only 20–30% of adults consuming soy foods produce equol, although the frequency of equol-production has been found to be much higher (50–60%) in Japanese adults and in vegetarians. Equol is also not produced by soy infant formula-fed infants before the age of 4 months consistent with an immaturity in bacterial colonization of their gastrointestinal tract. Equol can occur in two enantiomeric forms, but it is S-equol, that is exclusively produced by intestinal bacteria and unlike R-equol, which has negligible affinity for the estrogen receptors, S-equol has a high affinity for estrogen receptor ER-beta and thus can be classified as a selective estrogen receptor modulator. Several lines of evidence suggest that the ability to produce equol from ingested soy isoflavones may be associated with greater efficacy of diets containing soy foods, which led to the proposed “Equol Hypothesis” and awareness that these 2 distinct populations need defining in future dietary intervention studies.

Understanding the factors governing equol-production may facilitate defining strategies to enhance equol-production. In NIH funded studies, we have examined the production of equol after a soy food challenge in a cohort of 150 healthy adults, and examined possible correlations between equol production and dietary factors obtained by a 3-day dietary record. The proportion of equol producers was 26% for the cohort. No associations were observed between the ability to make equol and intakes of total fiber, soluble and insoluble fiber, total carbohydrates, total fat or saturated fat. In a follow-up study of 10 equol producers and 10 non-producers, equol production was found to be a relatively stable phenomenon as evidenced by repeated testing for equol at 6-month intervals over a 2-year period. Thus, it appears that spontaneous production of equol in non-equol producers rarely occurs.

The ontogeny of equol production has been examined in a longitudinal study of 90 infants following them from 6 months to 3 years of age to determine when equol first appears and whether differences in the type of early infant nutrition (breast milk, cows milk formula, or soy infant formula fed), or the composition of the post-weaning diet predisposes to the production of equol. Breast-feeding leads to differences in intestinal bacterial colonization and a lower pH compared with bottle-feeding, and this is could be expected to facilitate equol formation. In this longitudinal study, equol first appeared in the urine of infants from all 3 feeding regimens between 12 to 24 months of age. When these data are compared with historical data it indicates that the specific bacteria responsible for equol production colonize the intestinal tract and become active at the end of the first year of life.

Overall, these studies suggest that that the most important factor governing the ability to produce equol from soy foods by adults is the requirement of the presence of specific equol-producing bacteria and the composition of the diet appears to be a less relevant factor. Furthermore, our findings also confirm our earlier contention that equol-production is a relatively stable phenomenon.

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24hr Urinary Equol Excretion and Equol Producing Status in China. Ge Keyou*1, Peiyu Wang2, Baohua Liu2, Cai Donglian1, Yixiang Su1, Kaiping Guo4, Atsuko Onoda5, Ueno Tomomi3, Shigeto Uchiyama2, Po-Sheng Wu1, and Xueto Li6, 1Chinese Nutrition Society, China, 2Peking University, China, 3Second Military Medical University, China, 4Sun Yat-sen University, China, 5Otsuka Pharmaceutical Co., Ltd., Japan, 6Otsuka (China) Investment Co., Ltd., China.

Traditionally, soy foods have been frequently consumed in China, but no information is available about status of equol production and urinary excretion among them.

Our purpose of this study was to elucidate the percentage and the physiological range of 24hr urinary equol excretion in Chinese adults, and to elucidate the percentage of equol producers by soy isoflavone challenge test.

We collected blood sample and 24hr urine from 584 inhabitants
(294 men and 290 women, aged 20–74y) in Beijing, Shanghai, and Guangzhou in November 2007. They kept their ordinary diet and also recorded their diet during the 24hr urine collection. After 24hr urine collection, soy isoflavone challenge (41mg as aglycone) was done for 3 days. At 3rd day, 24hr urine was re-collected. The blood sample was subjected to biochemical and hormone tests. Urinary soy isoflavones and their metabolites were analyzed using a standard HPLC method.

In the first 24hr urine collection, frequency of urinary equol excretion was 23.4%. In 2nd 24hr urine collection after soy challenge, we confirmed the frequency of equol producer (54.9%).

Frequency of urinary equol excretion was increased by the soy challenge. Equol status did not affect concentration on serum sex and thyroid hormone.

**The Pharmacokinetic Behavior of Enantiomers of Equol in Healthy Adults.** K.D.R. Setchell, and N. Brown, Department of Pathology and Laboratory Medicine, Cincinnati Children’s Hospital Medical Center, University of Cincinnati, USA.

Equol, [7-hydroxy-3-(4′-hydroxyphenyl)-chroman], is a non-steroidal estrogen that was first discovered in the urine and plasma of humans following soy food consumption [1,2]. It was shown to be an important and stable metabolite of the soybean isoflavones, daidzein and daidzein, formed after initial hydrolysis of the β-glycoside followed by bacterial oxido-reduction of the furan ring [3]. Equol is not plant-based and is unique when compared with the soy isoflavones daidzein or genistein because it has a chiral center at C-3 of the furan ring and consequently exist as two distinct diastereoisomers [3]. More recent studies have confirmed that it is the S-equol enantiomer that is naturally formed by the action of bacteria [4]. R-equol is therefore a unique chemical entity as it is not derived from soy isoflavones. Interestingly, while both diastereoisomers antagonize the action of dihydrotestosterone without binding to the androgen receptor, S-equol is differs from R-equol in also showing selective affinity for the estrogen receptor, ERβ [5]. Both diastereoisomers are therefore of interest from a biological perspective and for their potential clinical actions. In order to study the pharmacokinetic behavior of these two enantiomers, we used a chiral catalyst to synthesize enantiomerically pure forms of the [13C] stable-labeled analogs of S- and R-equol and have then used these tracers to determine their pharmacokinetics. In a randomized crossover design study we administered as a single bolus oral dose, 20 mg of pure [13C]S-equol and [13C]R-equol to 12 healthy humans. Blood samples were obtained at frequent intervals over the next 48 h, and 12 h pooled urine collections were obtained for 3 days after administration of the tracers. Plasma and urinary [13C]R-equol and [13C]S-equol were measured by a newly developed and sensitive tandem mass spectrometry method. The plasma [13C]equol concentrations were plotted over time and established that both enantiomers were rapidly absorbed, attained high circulating plasma concentrations and the plasma elimination half-life (t1/2) was similar and in the range 4-6 h. Based on urinary [13C]equol excretion, the fractional absorption was found to be high indicating a high bioavailability and this contrasts previous findings for soy isoflavones daidzein or genistein, especially the latter which is poorly bioavailable. In summary, the pharmacokinetic behavior of these equol enantiomers was found to be similar in healthy adults. These data provide valuable information by which clinical studies of pure equol or equol supplements may be optimally designed.

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**References:**

**S-equol: Preclinical Studies Supporting its use as a Pharmaceutical Agent.** Richard L. Jackson*, 1, Rick Schwen, 1, and Istvan Merchenthaler, 2, 1Ausio Pharmaceuticals, LLC, Cincinnati, OH, USA, 2University of Maryland at Baltimore School of Medicine, Baltimore Maryland, Baltimore, MD, USA.

S-equol is the product of the gut biotransformation of daidzein, an isoflavone found in soy. Greater than 70% of Asians carry out this transformation, whereas people from other countries produce little or no S-equol. Being an S-equol producer has been shown to be associated with many health benefits, including reduced menopausal symptoms, prostate cancer, osteoporosis, cardiovascular diseases and diabetes. Based on these findings, Ausio Pharmaceuticals, LLC is developing S-equol as a pharmaceutical agent. The first clinical indications being developed are for vasomotor symptoms (VMS, hot flashes) in women and Benign Prostatic Hyperplasia (BPH, enlarged prostate) in men, and osteoporosis in both. The animal pharmacology studies support the development of S-equol for these clinical indications. Animal safety studies show that S-equol is not uterotrophic at the proposed clinical doses. S-equol is not genotoxic. Twenty-eight-day animal toxicity studies show that S-equol is safe with a large safety margin for human use. An IND has been filed with the FDA in the United States. This presentation will summarize the preclinical data that support the development of S-equol as a pharmaceutical product for the treatment of VMS and BPH.

**Target Gene Analysis of Phytoestrogens and their Clinical Significance.** Takeshi Usui*1, Naoki Sakane1, Tetsuya Tagami1, Akira Shimatsu1, Mitsuhide Naruse1, Tomomi Ueno2, and Shigeto Uchiyama2, 1Clinical Research Center, National Hospital Organization Kyoto Medical Center, Kyoto, Japan, 2Otuka Pharmaceutical Co., Ltd., Saga, Japan.

Genistein and daidzein are well characterized phytoestrogens rich in soy or soy-derived foods. These two isoflavones are considered to play an important role for various soy-related human health benefits such as prevention of osteoporosis or arteriosclerosis. Daidzein is metabolized to equol in most of the animals and some humans, and the equol is reported to be a stronger estrogenic compound. Individuals who can metabolize daidzein to equol (equol producers) might be more sensitive to soy intake than equol non-producers.

Here we studied the DNA microarray analysis of these phytoestrogens. DNA microarray analysis was done by using Agilent DNA microarray system and the regulated genes were analyzed by ConPath system. Some genes were differently regulated by each phytoestrogen.

We also studied the epidemiological approach to clarify the significance of equol producer in general population. We evaluated 360
Japanese participants for urine phytoestrogen levels. 25.3% of the total participants excreted measurable amount of equol (equol excreters). Equol excreters had less BMI, lower serum leptin levels, and lower serum high sensitive CRP levels than equol non-excreters, especially in females, suggesting favorable effects of equol on various metabolic disorders, especially in females. In conclusion, equol may play an important role on metabolic effects in human health.

Characteristics of Menopausal Symptoms of Japanese Women and the Possible Effects of Equol in Menopausal Health Care. Takeshi Aso*1,2, Tomomi Ueno3, Shigeto Uchiyama3, and Masaru Sakamoto 1, 1Kyoundo Hospital, Chiyoda-ku, Tokyo, Japan, 2Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan, 3Otsuka Pharmaceutical Co., Ltd., Saga Nutraceuticals Research Institute, Yoshinogari-cho, Saga, Japan.

Hormone replacement therapy (HRT) has been widely recognized as a potent evidence-based medicine (EBM ) for menopausal symptoms, but a large-scaled study in the United States (WHI) indicated increasing risks associated with the long-term HRT.

Soy has been suggested as an alternative remedy for disorders and diseases both peri- and post- menopause; however, the efficacy of the products has not been fully elucidated.

Recently, it was demonstrated that equol is an active metabolite of isoflavone which is generated from daidzein by intestinal bacteria, and approximately half of the Japanese population cannot produce equol. Some epidemiological studies in Japan showed that the menopausal symptoms of equol producers were milder than those of non-producers.

In order to investigate the physiological effects of equol on Japanese menopausal women of equol non-producers, an intervention trial (double-blind, placebo-controlled, parallel-group, comparative trial) was conducted. The adjusted tablets containing equol 0, 2, 6, and 10mg/day were ingested orally by 105 perimenopausal women for 12 weeks continuously. As a result, it was suggested that equol exhibited efficacy on improving menopausal symptoms of Japanese women. Thus, it seems to be possible to induce equol as a novel soybean-derived functional component in alternative remedy to control menopausal symptoms.

Equol Diminishes Tamoxifen-induced Endometrial Abnormalities in Sprague-Dawley Rats. Katerina Nicolaou and Andreas Constantinou*, University of Cyprus, Lefkosa, Lefkosa, Cyprus.

Tamoxifen is widely used to treat breast carcinoma in post-menopausal women. Previous studies have suggested an increased prevalence of endometrial carcinoma, hyperplasia and uterine polyps after treatment with tamoxifen. We have previously reported that the beneficial effects of soybeans against breast cancer are due to the daidzein metabolite equol. Our objective is to determine the effects of daidzein, alone or in combination with tamoxifen (TAM), in the rat endometrium. Within the stroma cells of the endometrium of Sprague-Dawley rats fed TAM-containing chow we have found increased oxidative DNA damage (as determined by increased 8-O-dG levels) and enhanced cell proliferation (increased PCNA) accompanied by decreased expression of the tumor suppressor protein PTEN when compared to rats fed the basal chow. While daidzein did not produce any significant changes in the above parameters, the combination of daidzein and TAM produced a significant reduction in DNA damage and PCNA levels and an increase in PTEN expression, restoring in this manner normal levels. These data demonstrate for the first time that the soy isoflavone daidzein may lower the risk of endometrial can-

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The Role of Soy

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The most severe adverse effects of tamoxifen. To identify the role of equol in the clinical setting.

Because of short T1/2 time of ingested equol it may not be useful to take

addition, our case-control study indicated that prostate cancer cohort

low incidence of prostate cancer compared to the Western peoples. In

including Japanese who have high consumption of soy foods show a very

decreases prostate volume of animal. Thus, equol may have an impor-
tability with dihydrotestosterone (DHT) and decreases its activity, and

preventing prostate cancer.

Equol Inhibits Prostate Cancer Cell Invasion and Metastasis.

K.A. Nicolaoul1, A.L. Skaltsounis2, and A.I. Constantinoùùù, 1University of Cyprus, Lefkosia, Lefkosia, Cyprus, 2University of Athens, Athens, Attiki, Greece.

Cancer metastasis requires controlled extracellular matrix degradation mediated by proteolytic enzymes like the urokinase-type plasminogen activator (u-PA)-plasminogen system.

Equol and Prostate Cancer Prevention in Humans.

Hideyuki Akaza, Department of Urology, University of Tsukuba, Ibaraki, Japan.

Results of the Prostate Cancer Prevention Trial (PCPT) which was performed under the sponsorship of NCI-USA including 18,000 healthy males had clearly demonstrated the efficacy of 5α-reductase inhibitor in preventing prostate cancer.

It is recently shown that equol, one of soy isoflavones, has binding ability with dihydrotestosterone (DHT) and decreases its activity, and decreases prostate volume of animal. Thus, equol may have an important role in the prevention of prostate cancer. As a fact, Asian residents including Japanese who have high consumption of soy foods show a very low incidence of prostate cancer compared to the Western peoples. In addition, our case-control study indicated that prostate cancer cohort shows lower % of equol producer compared to the control cohort. Because of short T1/2 time of ingested equol it may not be useful to take equol as a pill, instead may useful to change equol non-producer to pro-
ducer. At this time two important directions are thought in the study of equol in relation to prostate cancer prevention; one is to identify equol producing bacteria in the human intestinal bacteria, and the other one is to identify the role of equol in the clinical setting.

Tuesday Morning

Cancer Session

Soy Food Intake and Breast Cancer Survival. Xiao Ou Shu1, Ying Zheng2, Kai Gu3, Hui Cai3, Wei Zheng1, and Wei Lu2, 1Vanderbilt Epidemiology Center, Vanderbilt University, Nashville, TN, USA, 2Shanghai Center for Disease Control and Prevention, Shanghai, China.

Phytoestrogens are non-steroidal plant-derived compounds structurally similar to 17β-estriol. They possess weak estrogenic and anti-
estrogenic activities. Soy foods are the predominant source of isoflavones, 1 of the 2 major groups of phytoestrogens that humans obtain from diet. Isoflavones have been shown to compete with endogenous estrogens in the binding of estrogen receptors, increase the synthesis of sex-hormone-binding globulin, inhibit 17β-hydroxysteroid dehydrogenases, and have other anti-cancer properties. Therefore, it has been hypothesized that soy isoflavones may reduce risk of breast cancer and improve cancer prognosis. On the other hand, the estrogenic properties of isoflavones have also caused some concerns about its use among breast cancer patients. Furthermore, because soy isoflavones and tamoxifen share similarities in their ability to bind to estrogen receptors, it has been suspected that soy isoflavones may interact with tamoxifen and affect the efficacy of this widely-used adjuvant treatment for breast cancer. To investigate the effect of soy intake after cancer diagnosis on breast cancer prognosis, we analyzed data from a large, ongoing, population-based cohort study of breast cancer survivors, the Shanghai Breast Cancer Survival Study (SBCSS). The SBCSS includes 5,046 breast cancer patients who were identified through the Shanghai Cancer Registry and enrolled in the study between 2002 and 2007 approximately 6 months post-cancer diagnosis. Information on cancer diagnosis and treatment, lifestyle exposures after cancer diagnosis, and disease progression was collected via in-person interview at study recruitment and updated during follow-up surveys at 18, 36, and 60 months after cancer diagnosis. We did not find that soy food intake interacted with tamoxifen in relation to breast cancer survival. Both tamoxifen use and soy food intake were associated with better survival among breast cancer patients. Women who had used tamoxifen and had the highest soy food intake had the lowest risk of cancer-related death or cancer recurrence (HR=0.42, 95%CI=0.20-0.85) for women with ER/PR positive breast cancer as compared to non-

users of tamoxifen who had the lowest soy consumption). Our study provides the first epidemiological evidence indicating that soy food con-

sumption is safe and beneficial for breast cancer survivors.

Plasma Isoflavones and Fibroadenoma Risk in Women in Shanghai, China.

J.W. Lampe*1, S.C. Dijkstra1,2, R.M. Ray1, C. Wu1, W. Li1, D.L. Gao3, Y. Hu4, J. Shannon2, K. Wåhälä4, and D.B. Thomas1, 1Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 2Wageningen University, Wageningen, The Netherlands, 3Zhong Shan Hospital Cancer Center, Shanghai, China, 4Shi Dong Hospital, Shanghai, China, 5Oregon Health Sciences University, Portland, OR, USA, 6University of Helsinki, Helsinki, Finland.

Fibroadenomas (FA) are the most common benign breast neoplasms and account for up to 50% of breast biopsies. Although considered benign aberrations of normal lobular development, they use significant resources for diagnosis in order to rule out potential malignancies. Isoflavone exposure has been shown to be associated with fibrocystic conditions, but lit-
tle is known of its association with FA. We examined possible associations
between plasma genistein and daidzein concentrations and risk of FA in women in a breast self-examination trial in Shanghai, China, and diagnosed with FA (n=251) and in 1001 age-matched controls. Conditional logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CI). Isoflavone concentrations were inversely associated with risk of FA. Adjusted OR for the highest vs. the lowest quartile of plasma concentration were 0.37 for daidzein (0.16–0.88, p trend: 0.03) and 0.34 for genistein (0.15–0.78, p trend: 0.05). Median plasma concentrations for the lowest quartile were 2.9ng/mL for daidzein and 3.7ng/mL for genistein. For the highest quartile, median plasma values were 68.4ng/mL for daidzein and 130ng/mL for genistein. In conclusion, this study found an inverse association between plasma isoflavones and risk of FA in Chinese women. A role for isoflavones in modulating lobular development warrants further evaluation.

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Soy Isoflavone Supplementation and Breast Density in Postmenopausal Women. Gertraud Maskarinec1, Martijn Verheus1, Margaret A. Cramer2, Richard L. Lewis3, Michael J. Murray3, Francene M. Steinberg4, Ronald L. Young5, Paula Amato6, and William W. Wong7. 1Cancer Research Center of Hawaii, Honolulu, HI, USA, 2University of Georgia, Athens, GA, USA, 3Northern California Fertility Medical Center, Roseville, CA, USA, 4University of California, Davis, CA, USA, 5Baylor College of Medicine, Houston, TX, USA, 6Oregon Health & Science University, Portland, OR, USA.

Soy isoflavones may protect against breast cancer. Breast density, a marker for breast cancer risk, increases as a result of hormone replacement therapy. We examined the relation between isoflavone supplementation and breast density using the mammograms from 358 women who participated in the multi-site, randomized, double-blind, and placebo-controlled Osteoporosis Prevention Using Soy (OPUS) trial. The postmenopausal women were randomized so that 2/3 of the subjects received 80 or 120mg/d of isoflavones each and the remaining 1/3 received a placebo for 2 years. After digitizing annual mammograms, percent densities were assessed using a computer-assisted method. The reader was blinded to treatment and timing of mammograms. We applied mixed models to compare breast density by treatment, while considering the repeated measures and adjusting for baseline density and site. At baseline, the groups were similar in age (p = 0.56), body mass index (p = 0.40), and percent mammographic density (p = 0.31), but mean breast density differed by study site (p = 0.02). A model with all mammograms for 358 women did not show a significant treatment effect (p = 0.78). However, time was significant (p <0.001); breast density decreased by 1.6% per year across groups. Based on this 2-year trial, isoflavones do not modify breast density in postmenopausal women.

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Modulation of Biomarkers of Growth and Differentiation in Breast Cancer by Soy Isoflavones. Olca Basturk1, Volkkan Adsay2, M. osumi Banerje1, Lisa Newman3, David Bouwman2, Daniel Doerge4, Zora Djuric5, Ralph Parchment5, Adhip Majumdar5, Fred Miller6, Fazul Sarkar7, and Omer Kucuk4,4. 1Dept. of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, 2Dept. of Pathology, Emory University, Atlanta, GA, USA, 3University of Michigan, Ann Arbor, MI, USA, 4National Toxicology Center, Jefferson, AR, USA, 5Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA, 6Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA, USA.

Background: Epidemiologic studies suggest a role of soy in cancer prevention, and preclinical studies indicate that soy isoavonones (SI) act as potent modulators of various cellular pathways implicated in carcinogenesis. This study was undertaken to determine the effects of SI on neo-plastic and adjacent normal tissue in women with breast cancer.

Design: Sixty-four women with newly diagnosed DCIS or invasive ductal ca were randomly assigned to receive either placebo or oral SI 100 mg/day (50 mg genistean) for 3 wks before lumpectomy or mastectomy. All subjects had SI levels measured at baseline and after 3 weeks of intervention. The expression of bcl-2, Cyclin B1, Bax, Cx43, p21 and p FAK were analyzed by western blot and those of EGFR Related Protein (ERRP), Cx43, p-AKT, p-FAK, p21, Caspase-3 and Ki-67 were analyzed by immunohistochemistry.

Results: Western blot: There were significant decreases in Cx43 and p21 expression in the SI group compared to placebo in both benign (p = 0.0614, p = 0.0026) and tumor tissues (p = 0.0668, p = 0.0072). Similarly, the subjects with increase in genistein concentration had lower Cx43 and p21 expression compared to placebo in both benign (p = 0.0387, p = 0.0060) and tumor tissues (p = 0.0563, p = 0.0194). In addition, subjects in SI group had significantly lower bcl-2, Cyclin B1 and Bax concentrations compared to placebo in normal tissues (p = 0.0079, p = 0.0079, p = 0.0432) but not in tumor tissues. Similarly, the subjects with increase in genistein concentration had lower bcl-2 and Bax expression in benign tissue (p = 0.0282, p = 0.0433), but not in malignant tissue. This subgroup had also decreased Cyclin B1 and p FAK in the entire group (p = 0.0780, p = 0.05) but not statistically significant in the subgroups of benign and tumor tissues.

Immunohistochemistry: There were trends towards increase in ERPR and Cx43 (p = 0.593, p = 0.77) in malignant and benign parts of the tissue specimens in SI group A but rest of the biomarkers studied (p-AKT, p-FAK, p21, Caspase-3 and Ki-67) showed no statistically significant changes between the groups (p = 0.139, p = 0.167, p = 0.79, p = 0.844).

Conclusion: When administered at a dose of 100mg/day, SI down-regulated various molecules including Cx43 and p21. Further investigations are needed to determine whether this down-regulation is a dose-dependent phenomenon, and whether SI may become pro-estrogenic (rather than anti-estrogenic) at certain levels and thus may promote breast cancer rather than prevent it.

Clinical Studies Show No Effects of Soy Protein or Isoflavones on Reproductive Hormones in Men: Results of a Meta-analysis. J. Hamilton-Reeves2,1, G. Vazquez1, S. Duval3, W. Phipps1, M. Kurzer1, and M. Messina3,4. 1University of Minnesota, St. Paul, MN, USA, 2College of St Catherine, St. Paul, MN, USA, 3University of Rochester Medical Center, Rochester, NY, USA, 4Loma Linda University, Loma Linda, CA, USA, 5Nutrition Matters, Port Townsend, WA, USA.

The objective of this meta-analysis was to evaluate the effects of soy protein and isoflavone intake on testosterone, sex hormone binding globulin (SHBG), free testosterone, and free androgen index (FAI) in men, as reported in clinical trials. To identify appropriate intervention trials, the PUBMED database was searched through July 1, 2007 using the keywords soy, isoflavones, genistein, phytoestrogens, red clover, androgen, protein and isoflavone intake on testosterone, sex hormone binding globulin (SHBG), or calculated FAI was assessed. Clinical trials (parallel or crossover) and single-group studies were included. Twenty-nine trials involving 32 treatment groups were included. Regardless of statistical model, there were no significant effects of soy protein or isoflavone intake on total testosterone levels.
testosterone, SHBG, free testosterone, or FAI. The results of this meta-analysis suggest that neither soyfoods nor isoflavone supplements significantly affect bioavailable testosterone in men.

Acknowledgements: Soy Nutrition Institute for funding work on this manuscript.

Reduction of Adverse Events by Soy Isoflavones in Patients Undergoing External Beam Radiation Therapy for Prostate Cancer. *Itetakhar Ahmad, Jeffrey D. Forman, Fazul Sarkari, Gilda Hillman, Mosumi Banerjee, Daniel Doerge, Elisabeth Heath, Ulka Vaishampayan, Michael Cher, and Omer Kucuk.*

Purpose: Soy isoflavones (SI) sensitize prostate cancer (PrCa) cells to radiation therapy (RT) in preclinical studies. Since SI have antioxidant effects, they may also reduce the adverse effects of radiation therapy (RT). The study was designed to evaluate the effects of SI supplementation on acute toxicity (±6 months) observed after external beam RT in patients with PrCa.

Materials and Methods: Forty-two patients with PrCa were randomized to receive SI 100mg (Group 1) or placebo (Group 2) orally twice daily for 6 months beginning with the first day of RT which was prescribed to 73.8-77.5 Gy in 1.8-2.5 Gy fractions. One patient received combined neutrons and photons. All patients were treated between Nov. 2002 and Sept. 2006. Toxicity was assessed with quality of life questionnaires given to all patients at 3 and 6 months from the start of RT. There were 26 completed questionnaires at 3 months and 27 at 6 months. Group 1 consisted of 13 responses at 3 and 6 months and Group 2 consisted of 13 responses at 3 months and 14 responses at 6 months. PSA was recorded prior to the start of treatment and at 4 to 6 months from the start of RT.

Results: Median age for Group 1 was 60 yo and for Group 2 was 65 yo. T stage was 8 T1c, 3 T2a, and 2 T2b for Group 1 and 10 T1c, 2 T2a, and 1 T2b for Group 2. All patients were Gleason score 6 except two Gleason 7 patients in Group 2. At 3 months no difference in genitourinary symptoms were noted except for decreased dripping/leakage of urine in Group 1 (15.4% vs. 23.1%) and medium/big problem with urgency in Group 1 (30.8% vs. 0%). Gastrointestinal symptoms at 3 months were similar in both groups. Erectile function at 3 months was better in Group 1 in all respects. There was higher overall ability to have erections (69.2% vs. 61.5%), lower reduction in the ability to have erections (15.4% vs. 46.2%), and more with function same as or better than before RT (84.6% vs. 61.5%). At 6 months, genitourinary symptoms were similar in both groups except for less dripping/leakage of urine (7.7% vs. 28.4%) for Group 1. Gastrointestinal symptoms at 6 months showed decreased cramping or diarrhea in Group 1 (7.7% vs. 21.4%) and less pain with bowel movements (0% vs. 14.8%). Erectile function at 6 months showed Group 1 with better function. There was higher overall ability to have erections (77% vs. 57.1%), lower reduction in the ability to have erections (15.4% vs. 57.1%), and more with function same as or better than before RT (84.6% vs. 57.1%). Median pre-treatment PSA was 3.7 for Group 1 and 4.9 for Group 2. At 4-6 months, the median PSA for Group 1 was 0.9 and for Group 2 was 2.0 representing a PSA reduction of 75.7% and 59.2%, respectively.

Conclusions: These preliminary results suggest that SI taken in conjunction with RT may reduce urinary, gastrointestinal and sexual adverse effects observed in patients receiving external beam RT for PrCa.

Purified Isoflavones in Prostate Cancer. *Nagi Kumar,* 1,2 Jeffrey Krischer, Karen Besterman-Dahan, Kathy Allen, Diane Riccardi, Loveleen Kang, Ping Xu, and Julio Powsang 1,2

1University of South Florida, Tampa, Florida, USA, 2 Moffitt Cancer Center, Tampa, FL, USA.

Purpose: To evaluate the safety and effectiveness of purified isoflavones in prostate cancer. Methods: In this phase II randomized, double-blind, placebo-controlled trial, 53 eligible men with clinically localized prostate cancer (Gleason score 2-6) were supplemented with 80 mg of purified isoflavones or placebo for 12 weeks. Compliance to study agent, toxicity, changes in plasma isoflavones, serum PSA and steroid hormones were analyzed from baseline to 12 weeks. Results: Fifty subjects completed the 12-week intervention. Purified isoflavones significantly increased (P = < 0.001) plasma isoflavones in the isoflavone-treated group compared to placebo and produced no clinical toxicity. Mean serum PSA reduced from 6.26ng/dl (SD 5.03) to 5.40ng/dl (SD 2.71) in the treated arm compared to an increase observed in the placebo arm [6.56ng/dl (SD 4.62) to 7.00ng/dl (5.20)], although not statistically significant for this sample size and study period (P = 0.86). Modulation of serum sex hormone-binding globulin, total estradiol and testosterone in the isoflavone-treated group compared to men receiving placebo were non-significant. Conclusions: The study establishes the need to explore other potential mechanisms by which isoflavone modulates prostate cancer risk.

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Repeated Oral Administration of Genistein Enhances Recovery from Gamma Radiation Injury. *M.R. Landauer,* 1 T.A. Davis, 2 and S.R. Mog 1, 1AFRRI, Uniformed Services University, Bethesda, MD, USA, 2Naval Medical Research Center, Silver Spring, MD, USA.

Medical radiation countermeasures have applications in clinical oncology, space travel, radiation site cleanup and radiological terrorism. In the present studies, mice were pre-treated with oral genistein and exposed to a lethal dose (8.75 Gy @ 0.6 Gy/min) of cobalt-60 gamma radiation. Mice were gavaged with genistein for 4 or 6 days, either once a day (QD) with 5 mg/mouse, or twice a day (BID) with 5 mg/mouse. Mice that received genistein for 4 or 6 days QD had survival rates of 60% and 35%, respectively, and were not significantly different from the vehicle control group (30%). When gavaged BID for 4 or 6 days, survival rates for genistein-treated mice were 75% and 85%, respectively, significantly higher than vehicle-treated mice (30%). Based on the survival data, a separate group of mice were administered genistein (5mg/mouse, BID) for 6 days prior to 6 Gy irradiation and evaluated for hematological recovery. Mice treated with genistein had an increase in bone marrow cellularity and a more rapid recovery of white blood cells, neutrophils, platelets, red blood cells, and reticulocytes than time-matched vehicle-treated mice. These data indicate that oral administration of genistein prior to irradiation protects mice from lethal doses of radiation by resulting in accelerated recovery of bone marrow and reducing the severity of pancytopenia in irradiated mice.

Hematopoietic Progenitor Cells and Primary Lung Fibroblasts are Protected in vivo by Genistein against Radiation. *R.M. Day,* 1 M. Barshishat-Kupper, 2 S.R. Mog, 2, O. Mungunsukh, 1 T.A. Davis, 2 and M.R. Landauer, 2 Dept. of Pharmacology, Uniformed Services University of the Health Sciences, Bethesda, MD, USA, 2Armed Forces Radiobiology Research Institute, Uniformed Services University of the Health Sciences, Bethesda, MD, USA, 3Naval Medical Research Center, Silver Spring, MD, USA.
We previously showed that the soy isoflavone genistin protects against acute radiation injuries by preventing myelotoxicity. Hematopoietic stem cells (HSC) protection correlated with a transient pause of the cell cycle in the radioresistant G0/G1 phase by genistin. We also found that genistin prevented some radiation-induced alterations in protein expression in the lung. Here we examined genistin radioprotection of HSC and lung fibroblasts in C57BL/6J mice. A s.c. injection of vehicle (PEG-400) or genistin (200 mg/kg) was given 24h before sham irradiation or Total Body Irradiation (TBI, 7.75 Gy, 60Co). Non-irradiated groups were: No treatment, Vehicle, Genistin. TBI groups were: Radiation only, Vehicle + Radiation, Genistin + Radiation. HSC and first generation lung fibroblasts were analyzed for micronuclei 1h or 24h post-TBI. No differences were found among the non-irradiated groups. In the TBI treatment groups, genistin-treated mice had reduced micronuclei compared with radiation only and vehicle-treated mice in both HSC and lung fibroblasts. Thus, genistin administered 24h prior to TBI mitigates genotoxicity in bone marrow HSC and lung fibroblasts. Genistin protection against genotoxicity is likely part of the mechanism for genistin protection against acute and delayed radiation injuries.

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Bone/Cardiovascular Disease

Safety and Efficacy of Genistin Aglycone on Bone Metabolism and Some Predictors of Cardiovascular Risk: A 3-Year Follow-up Study. Francesco Squadrito*1, Domenica Altavilla1, Herbert Marin2, Rosario D’Anna3, and Alessandra Bitto1, 1Dept. of Nutritional Sciences, University of Messina, Italy, 2Dept. of Obstetrical and Gynecological Sciences, University of Messina, Italy, 3Dept. of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy. Context: Phytoestrogen genistin is an isoflavone found in low concentrations in soybeans and elevated amounts in certain soy-derived food, whereas genistin, the glucoside form of the aglycone genistein, is much more abundant in the unprocessed soybean. Genistin aglycone improves bone metabolism and has received wide attention over the last few years because of its potential preventive role for cardiovascular disease. However, questions about the long-term safety of genistin on reproductive tissues as well as its continued efficacy still remain.

Objective: We assessed the continued safety profile of genistin aglycone on breast and endometrium, and its effects on bone metabolism, and some predictors of cardiovascular risk after 3 years of therapy.

Design: The parent study was a randomized, double-blind, placebo-controlled trial involving 389 osteopenic, postmenopausal women for 24 months. Subsequently, a subcohort (138 patients) continued therapy for an additional year.

Patients and Interventions: Participants received 54 mg of genistin aglycone daily (n=71) or placebo (n=67). Both arms received calcium and vitamin D3 in therapeutic doses. Moreover, 4 weeks before randomization procedures and during our study, all patients received dietary instructions in an isocaloric fat-restricted diet.

Main Outcomes: Mammographic breast density or endometrial thickness, BRCA1 and BRCA2 expression was preserved while sister chromatid exchanges were reduced compared with placebo. BMD increases were greater with genistin for both femoral neck and lumbar spine compared to placebo. Genistin significantly reduced PYR, as well as serum CTX and sRANKL while increasing B-ALP, IGF-I and OPG levels. Moreover, genistin significantly decreased fasting glucose and insulin, HOMA-IR, fibrinogen and homocysteine. There were no differences in discomfort or adverse events between groups. Results on routine biochemical, liver function, and hematologic testing did not change over time in placebo or genistin recipients.

Conclusions: After 3 years of treatment, genistin plus calcium, vitamin D3 and a healthy diet exhibited a promising safety profile with positive effects on bone and some predictors of cardiovascular risk in a cohort of osteopenic, postmenopausal women.

The Impact of Dietary Intake of Soy on the Risk of Cardiovascular Disease. Yoshihiro Kokubo, National Cardiovascular Center, Suita, Osaka, Japan.

Soy has been proposed to reduce the risk of cardiovascular risk factors, but potential preventatives for cardiovascular disease (CVD) remain uncertain. Soy is the major source of isoflavones. Previous studies have shown that soy and isoflavones have associations for reducing high cholesterol levels, antioxidants, and estrogen-like effects. Isoflavones content is high in polyunsaturated fatty acid, fiber, vitamins, and minerals. In this congress, I would like to review the association between cardiovascular risk factors and soy or isoflavones, and then introduce the several prospective studies on the association between isoflavones and CVD. The impact of soy and isoflavones on the risk of CVD was performed for about 40 thousands Japanese who answered a food-frequency questionnaire without illness of CVD or cancer. After 12 years follow-up, we documented incidence of cerebral and myocardial infarctions (CI, n=587; MI, n=308), and CI and MI mortality (n=232). For women, the multivariable hazard ratios (HRs) in >5 times/week versus 0-2 times/week of soy intake were 0.64, 0.55, and 0.31 for risk of CI, MI, and CI and MI mortality. In women, the multivariable HRs for the highest versus the lowest quintiles of isoflavones were 0.35 and 0.37 for CI and MI, respectively. In conclusion, high isoflavones consumption was associated with the reduced risk of CVD in Japanese women, especially for postmenopausal women.


Previously, by using postmenopausal osteoporotic rodent models, we reported that equol might be directly involved with bone loss and hyperlipidemia. In the present study, for comparing the abilities of major isoflavones with an estrogen drug, the possible bioactivities of equol were investigated with regard to bone status and lipid and hormone levels.

Female rats were assigned to the following 10 groups: sham-operation (Sham), ovariectomy-control (Control), OVX + 0.05 or 0.25mg/kg/day Premarin (PRN0.05 or PRN0.25), OVX + 5 or 25mg/kg/day genistin (GNT5 or GNT25), OVX + 5 or 25mg/kg/day daidzein (DNZ5 or DZN25), and OVX + 5 or 25mg/kg/day s-equol (EQ5 or EQ25). Each compound was suspended in 0.5% CMC solution, and was orally administered to the rats for 28 days. Due to OVX, the weights of the body and adipose tissue and the urinary FSH and deoxypyrindoline levels were...
increased, but the administration of PRN, equol, or daidzein (DZN25) suppressed these increases; however, this effect was not exhibited by genistein. The uterine weight was reduced by OVX and restored by PRN. The femur dry weight that was decreased due to OVX was normalized by the administration of PRN, equol, or daidzein (DZN25). Furthermore, we conducted a similar study using OVX mice. These results suggest that the beneficial effects of equol on postmenopausal status were stronger than those of genistein and daidzein.

**Meta-Analysis Confirms Soy Protein's Cholesterol Lowering Efficacy.** Priscilla Samuel*, 1 Stanislav Zakharkin1, Ed Spitznagel2, Kathryn Greaves1, Dustie Butteiger1, and Elaine Krul1, 3 Solae LLC, Saint Louis, M.O, USA, 3 Washington University in St. Louis, Saint Louis, M.O, USA.

The goal of the analysis was to evaluate effect of soy protein on serum cholesterol levels. We identified 152 publications from Medline, recent reviews and meta-analyses on the relationship of soy protein and cholesterol reduction. Using FDA defined criteria, studies were evaluated and ranked, and 45 studies were included in meta-analysis. Changes in total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) (95% confidence intervals) were calculated using a random-effects model. Compared to control subjects, consumption of soy protein was associated with significant mean reductions in TC levels of 9.54mg/dL (7.03 to 12.05mg/dL) and LDL-C levels of 7.12mg/dL (5.80 to 8.45mg/dL). Subgroup analyses were performed separately for normocholesterolemics and hypercholesterolemics. Soy protein consumption reduced TC levels by 11.05mg/dL (8.00 to 14.11mg/dL) in hypercholesterolemics and by 4.24mg/dL (0.99 to 7.49mg/dL) in normocholesterolemics. The reduction in LDL-C levels in hypercholesterolemics was 8.71mg/dL (6.99 to 10.43mg/dL) and in normocholesterolemics was 5.10mg/dL (2.95 to 7.26mg/dL). All results were statistically significant. The stability and robustness of these estimates were confirmed by sensitivity analyses. In conclusion, the results of this meta-analysis continue to support a meaningful and statistically significant cholesterol reduction with the consumption of soy protein.


Recent growing interest in health and diet has led to an increased focus on soy foods and their functional components, e.g., isoflavones. In particular, equol, a gut bacterial metabolite of daidzein, appears to be an important bioactive metabolite of isoflavones because of its greater binding affinity to estrogen receptors when compared with that of parent compound.

Estrogen deficiency often increases the risk of postmenopausal syndromes such as osteoporosis, cardiovascular disease, and obesity. Estrogen deficiency also causes the skeleton to be less sensitive to mechanical force and decreases bone mass. In this regard, we examined the combined effects of isoflavones and walking exercise on bone loss in 136 postmenopausal Japanese women. The results showed that combined intervention of 75mg/d isoflavones (equivalent to 47mg/d of aglycone) and walking (45 min/d, 3 d/week) for 1 year showed a trend for a greater effect on BMI at total hip and Ward’s triangle region of the femur and fat accumulation than those of either alone. Furthermore, the preventive effects of isoflavones on bone loss and fat accumulation in the subjects depended on the individual’s equol producing capacity. Additionally, we found that a certain bacteria, Lactococcus 20-92 strain, which can produce equol from daidzin via daidzein, existed in the feces of the subjects.

**Equol and its Relation to Osteoporosis Prevention using Soy.** F.M. Steinberg*, 1 S. Barnes2, M. J. Murray3, R.D. Lewis1, J.G. Fischer4, M.A. Cramer5, P. Amato2, R.L. Young6, K.J. Ellis5, R.S. Shypalo6, E.O. Smith6, J.K. Frailey6, and W.W. Wong6, 1 University of California, Davis, CA, USA, 2 University of Alabama, Birmingham, AL, USA, 3 Northern California Fertility Medical Center, Roseville, CA, USA, 4 University of Georgia, Athens, GA USA, 5 Oregon Health Sciences University, Portland, OR, USA, 6 Baylor College of Medicine, Houston, TX, USA.

Soy is believed to have anti-osteoporotic properties, but the relationship to equol is unclear. To evaluate effects of soy isoflavones and metabolites on bone loss, 403 early postmenopausal women (54.0±4.0 y) were enrolled in an intent-to-treat, multi-site, 2-year, randomized, double-blind trial. Treatment groups were 1/3 placebo, 1/3 on 80mg/d soy hypocotyl isolsoflavones, and 1/3 on 120mg/d soy hypocotyl isolsoflavones, with 1,000mg/d of CaCO3 and daily multivitamin with 400 IU vitamin D. Bone mineral density (BMD) of the whole body (WB), hip and spine were measured at baseline and annually. Serum isoflavones and metabolites were analyzed by LC/MS 5 with equol production defined as 20 nmol/L. Bone turnover markers were also measured. Baseline characteristics were similar in all groups. Although a statistically significant protective effect on the decrease in WB BMD was observed with 120 mg/d soy isoflavones vs. placebo after 1y (p=0.027) and 2y (p=0.048), WB BMD was not correlated with serum equol at 1 or 2 y. Analysis of variance for equol producer status and WB BMD also was not statistically significant. Serum equol values ranged from 1.07±6080 nmol/L. In equol producers (30% of subjects at 1y) the mean equol concentration was 1009±1241 nmol/L, median 477 nmol/L. Preliminary results do not support an association of equol production status with maintenance of WB BMD.

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**Soybean β-conglycinin Reduces a Risk of Visceral Fat Syndrome, So-called Metabolic Syndrome.** Mitsutaka Kohno*, 1 Motohiko Hirotsuka2, Makoto Kito3, and Yuji Matsuzawa1, 1 Food Science Research Institute, Fuji Oil Co., Ltd., 1-Sumiyoshi, Izumisano, Osaka, Japan, 2 Emeritus Professor of Kyoto University, Kyoto, Japan, 3 Sumitomo Hospital, Osaka, Japan.

β-conglycinin is one of the major components of soy protein. In this study, we used randomized double-blind placebo-controlled designs to test the effect for obesity of dietary β-conglycinin, which was taken as the form of candy by human study. In order to measure visceral fat by means of CT scanning, 88 volunteers aged 26 to 69 years with body mass indices (BMI) between 25 and 30, and waist sizes over 85 cm (male) and 90 cm (female) being diagnosed as the warning sign of metabolic syndrome in Japan, participated in the study. The test period consisted of a 2-wk pre-evaluation phase for screening of the participants, a 20-wk consumption period and a 4-wk post-evaluation phase. Significant reductions were observed in not only visceral fat areas but body compositions (weight, BMI, body fat, body fat ratio and waist) in the β-conglycinin group, compared with the placebo (casein) group. The serum TG concentrations were significantly reduced in the β-conglycinin group by analysis of 26 subjects with TG concentrations above 150mg/dL at the start of the study, compared with the placebo group. Serum NEFA concentrations being closely related to visceral fat accumulation and insulin resistance reduced in the β-conglycinin group. These results show that β-conglycinin is an important food material for prevention and/or amelioration of visceral fat syndrome, so-called metabolic syndrome.
Biological Effects of Pasta Containing Isoflavone Aglycons in Type 2 Diabetic Patients—A Double-Blind Randomized Crossover Study. Elisabetta Nardi1, Stefania Asciutti1, Kenneth Setchell2, Danilo Castellani3, Emanuela Floridi1, Alessia Gherardi2, Nadia Corazzi1, Vittorio Giuliano1, Monia Baldoni2, Stefania Gizi2, Antonio Morelli1, Gabriele Perriello1, Giorgio Di Matteo3, Francesco Galli1 and Carlo Clerici1, 1Clinica di Gastroenterologia ed Endocrinologia, Università degli Studi di Perugia, Perugia, Italy, 2Clinical and Mass Spectrometry, Department of Pathology and Laboratory Medicine Children’s Hospital M.C., Cincinnati, Ohio, USA, 3DIMISEM, University of Perugia, Italy, 4Institute of Biochemistry, University of Perugia, Italy.

Cardiovascular complications cause the majority of diabetes-related deaths. The link between oxidative stress and increased cardiovascular events is represented by endothelial dysfunction. Isoflavones from soy have antioxidant capacity that contributes to protect cells from the damaging effects of reactive oxygen species. AIM: Evaluate the effects, in a double-blind randomized crossover placebo-controlled study, of a novel soy isoflavone pasta containing predominantly bioactive aglycon forms of isoflavones on oxidative stress and factors related to cardiovascular risk in adult Type 2 diabetics.

Materials and methods: Twenty patients (10M/10F) were randomized in 2 groups and given a daily serving (80g) of either soy germ pasta containing 33mg of isoflavone aglycons (Pasta+), or conventional pasta (Pasta-) lacking isoflavones, for a period of 4 weeks with a 4-wk washout and then the groups were crossed. Endothelial function was measured from brachial artery flow-mediated vasodilatation (VFM) with B-mode ultrasound and plasma GSH, Cys and Hcy by HPLC. Plasma F2-isoprostane analysis was performed by ELISA kit analysis, while total antioxidant capacity in plasma (TAC) was measured with the FRAP assay. Serum lipids, (total C, LDL-C, HDL-C, and triglycerides) were also measured.

Results: VFM increased from 5.4±4.8 to 10.2±7% (p=0.0005) when patients consumed Pasta+ and no change was observed with conventional pasta. The improvement in endothelial function accompanied significant reductions in both systolic and (123.8±15.3 to 126.2±21.1 mmHg; P=0.026) and diastolic (76.6±8.8 to 73.5±10.1 mmHg) only in patients consuming isoflavone-enriched pasta. Plasma GSH levels increased from 3.8±2.1 to 7.4±2.6 mM (p=0.002), and homocysteine decreased from 9.2±3.0 to 7.8±2.5 mM (p=0.017) only in the Pasta+ group. Plasma TAC increased from 874.0±185.4 to 952.8±177.3 mM (p=0.0002). There was no change in LDL-C, HDL-C, and a trend toward a decrease in triglycerides. Total C, which was not significantly elevated showed a decrease from 204.5±43.9 mg/dL to 199.6±46.1 mg/dL in patients using Pasta+ (p=0.025) and the level of oxidized LDL-C was significantly reduced (6.1±4.0 to 5.6±3.3 U/mL p=0.009) consistent with improvements in antioxidant status.

Conclusion: The presence of isoflavone aglycons in pasta improves endothelial function and ameliorates oxidative stress, important factors that reduce cardiovascular risk in patients with Type 2 diabetes.

Gender-Specific Effects of Soy Isoflavones on Risk of Hip Fracture in the Singapore Chinese Health Study. Woon-Puay Koh1, Renwei Wang2, Mimi C. Yu2, Anna H. Wu1, 1Department of Community, Occupational and Family Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; 2Masonic Cancer Center, University of Minnesota, Minneapolis, USA; 3Department of Preventive Medicine, University of Southern California, Keck School of Medicine, USA.

While there is some epidemiologic evidence that an increased intake of soy isoflavones may reduce risk of osteoporotic fractures in women, it is not known if this risk reduction also occurs in men. We examined the gender-specific effects of soy in relation to hip fracture risk in the Singapore Chinese Health Study, a prospective cohort of 63,257 middle-aged and elderly Chinese living in Singapore. At recruitment between 1993 and 1998, each subject was administered a validated semi-quantitative food frequency questionnaire covering 165 food and beverage items, as well as questions on medical history and lifestyle factors. As of 31 Dec 2006, 969 incident hip fracture cases were identified via linkage with hospital discharge databases and verified with medical records. The mean age of fracture was 71.4 (standard deviation (SD)=7.5) years among the 276 males cases, and 72.8 (SD=6.9) years among the 693 female cases. In both genders, hip fracture risk was positively associated with smoking and decreased with increasing body mass index. Using Cox regression and adjusting for other covariates, we found that hip fracture risk was reduced significantly in association with increased isoflavone intake among women in a dose-dependent manner (p for trend=0.0008); the relative risk (RR) for the highest versus lowest quartile was 0.73 (95% confidence interval (CI)=0.59-0.89). Conversely, soy intake was unrelated to hip fracture risk among men (p for trend=0.836); adjusted RR for highest versus lowest quartile of intake was 1.01 (95% CI=0.70-1.45). These results suggest that isoflavone supplementation is only beneficial in the prevention of osteoporosis in women but not in men.

Wednesday Morning

Emerging Areas Research

Transcriptome Analyses of the Effect of Soy Protein Intake. Hisanori Kato1, Shinosuke Tsuji1, Nobuhiko Tachibana2, Mitsutaka Kohno2, Kiyoharu Takamatsu2, and Keiko Abe3, 1Graduate School of Agricultural and Life Sciences, The University of Tokyo, Tokyo, Japan, 2Food Science Research Institute, Fuji Oil Co., Ltd., Izumisano, Japan.

Recent methodological advances for molecular biology and bioinformatics have enabled today’s scientists to obtain a comprehensive view of the response of cells and organisms to external stimuli including foods and food components. Transcriptome analyses using DNA microarrays stand out among omics technologies for their high-throughput feature. We used this technology to assess the effects of soy protein ingestion at the level of holistic gene expression under various feeding conditions. First, rats were fed on a soy protein diet or a casein diet (control) for 8 weeks, and the gene expression profiles in the respective livers were obtained. The expression levels of over a hundred genes were shown to be significantly different. Changes in enzyme genes for lipid metabolism and energy metabolism were particularly striking, and likely to underlie the known beneficial effects of soy protein. Next, to determine whether the effects of soy protein are maintained in the presence of other dietary proteins, we examined hepatic gene expression profiles of rats fed various mixed-protein diets. Soy protein retained at least part of its beneficial effects even when ingested in combination with other proteins. These results are indicative of the usefulness of the DNA microarray as a tool box to evaluate the function of dietary proteins and to have an insight into the mechanism(s) of the functionality.

Effect of Isoflavone on Ovariectomy-Induced Retardation in Hair Growth and Dermal Levels of Insulin-Like Growth Factor-I mRNA in Mice. Kenji Okajima, Naoko Harada, and Juan Zhao, Dept. of Translational Medical Science Research, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

Insulin-like growth factor-I (IGF-I) plays an important role in hair growth. We previously reported that sensory neuron activation leading to
Soy Isoflavones and Gastrointestinal Function. K.D.R. Setchell1, S. Asciutti2, and C. Clerici1, 2Department of Pathology and Laboratory Medicine, Cincinnati Children’s Hospital Medical Center, University of Cincinnati, USA and 2Clinica di Gastroenterologia ed Epatologia, University of Perugia, Italy; 3Dipartimento di Medicina Interna, Scienze Endocrinometaboliche, University of Perugia, Italy.

Gastroparesis is a symptomatic chronic disorder of the stomach that is characterized by delayed gastric emptying of solid foods in the absence of any mechanical obstruction. It occurs in 30 - 40% of all patients with type 2 diabetes and is associated with upper gastrointestinal symptoms that include chronic and recurrent abdominal pain, discomfort, nausea, and vomiting. In most cases the etiology is unknown but is related to the enteric nervous system and gastric smooth muscle dysfunction. Delayed gastric emptying compromises the pharmacokinetics of orally administered drugs by altering their rate of absorption, and can also lead to alterations in glycemia control. There is currently no effective therapy for treating patients with delayed gastric emptying since the withdrawal of the prokinetic drug, cisapride.

Given the selective affinity of soy isoflavones for estrogen receptor ERα, and the fact that ERα is localized to the enteric neurons and to the external muscularis of the stomach we questioned whether soy isoflavones could play some physiological role in the stomach by potentially regulating gastric motility. This area of our research followed anecdotal observations from clinical trials (1) of a newly developed soy germ pasta containing predominantly isoflavones in aglycon form that this soy isoflavone-enriched food seemed to result in less fullness and bloating compared with pasta that did not contain isoflavones. For this reason we investigated the effect of regular consumption of this soy isoflavone-enriched pasta on gastric function.

In a double-blind, cross-over, placebo-controlled study of type 2 diabetic patients adhering to the ADA standard diet but with documented delayed gastric emptying we investigated the influence of isoflavone aglycons on gastric emptying time (2). Patients were randomized into two groups and fed complete diets that included a daily 80g-portion of either soy germ-enriched pasta (containing 33 mg of isoflavones), or conventional pasta for 8 weeks followed by a 4 week wash-out period before crossed-over. Gastric emptying time was measured using the [13C]octanoic acid breath test before and after the treatment periods. The inclusion of soy isoflavone-enriched pasta in the diet led to a significant (p<0.05) acceleration in gastric emptying time when compared with baseline values (t1/2 161.2 ± 55.4 min vs 112.6 ± 35.3 min) and a normalization of the delayed gastric emptying in these patients. By contrast conventional pasta lacking isoflavones had no effect on gastric emptying. Importantly, postprandial serum glucose and insulin levels were not adversely affected by the acceleration in gastric emptying.

In a separate study to probe the possible mechanism of action of isoflavones in the stomach, we performed endoscopy to obtain gastric mucosal biopsies from healthy subjects after consuming isoflavone-rich pasta and normal pasta. We examined the expression of 11,000 human genes using microarray analysis and found that the expression of 58 genes, many which contained estrogen response elements (ERE) were significantly and beneficially modulated by the presence of isoflavones in the pasta, and these included classes of genes involved in gastric function and oxidative stress. Our finding that the gene PTDGS, which encodes for prostaglandin D2 synthase, an enzyme responsible for the synthesis of prostaglandin F2α, was up-regulated five-fold, as measured by quantitative RTPCR, by soy isoflavone-enriched pasta provides a rationale mechanism for the improvement in gastric emptying time in patients with gastroparesis. We speculate that isoflavone aglycons, when coming in contact with the gastric mucosa, accelerate gastric emptying by an effect on prostaglandin synthesis which leads to smooth muscle contraction.

In conclusion, pasta enriched with isoflavone aglycons improves gastric emptying time in type 2 diabetes patients with delayed gastric emptying, therefore warranting consideration as a potential therapeutic tool for the reduction or relief of symptoms associated with diabetic gastroparesis.

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General Topics
Effect of Soy Isoflavones in Spermatogenesis. V. Unfer1, D. Berton1, M. Zacchê2, A. Serafini1, and E. Papaleo2, 1AGUNCO Obstetric & Gynecology Centre, Rome, Italy, 2IVF Unit, Gynecologic-Obstetric Dept., San Raffaele Hospital, Vita-salute University, Milan, Italy.

Some evidence indicates that estrogens may be involved in the regulation of spermatogenesis. We hypothesized that SI exert estrogen-like effects in men and have an impact on spermatogenesis. The aim of this study was to evaluate the effects of different doses of SI in normospermic men. In this 3-month study, 20 volunteers were randomized into 3 different groups; groups A, B, and C received 160, 320, or 480 mg/day SI, respectively. The SI profile of the supplement was as follows: 40% to 45% genistein, 40% to 45% daidzein and 10% to 20% glycitein. Semen analysis was conducted at baseline and after 3 months of treatment. When compared to baseline, there were no statistically significant differences in ejaculated volume, sperm concentration, count and motility of spermatozoa in men given SI. Although estrogens are thought to be involved in the regulation of spermatogenesis and SI exert estrogen-like effects under certain experimental conditions, the results of this pilot study show that SI have no effects on these processes in normospermic men. Nevertheless, our group has previously shown that in men with altered spermiogenesis due to a defect in local estrogen production, SI administration can have a therapeutic benefit. It is reassuring that SI do not adversely affect spermatogenesis in healthy men. More research is needed to fully understand the potential therapeutic role of SI in oligoastenospermic men.
Soy Protein Isolates of Varying Isoflavone Content do not Adversely Affect Semen Quality in Healthy Young Men. Laura K. Beaton1, Barbara L. Dillingham1, Brianne L. M McVeigh1, Johanna W. Lampe2, and Alison M. Duncan*1, 1Dept. of Human Health and Nutritional Sciences, University of Guelph, Guelph, ON, Canada, 2Fred Hutchinson Cancer Research Center, Seattle, WA, USA.

Background: Despite documented health benefits of soy isoflavones, there is concern regarding potential adverse effects on male fertility. Human studies examining effects of soy isoflavones on male reproductive health are limited. The purpose of this study was to determine the effects of soy protein of varying isoflavone content on parameters of semen quality in healthy young men.

Methods and results: In a randomized crossover design, 32 healthy men (age: 27.5±5.67 years, BMI: 25.4±3.14 kg/m2) supplemented their diets with milk protein isolate (MPI), low-isoflavone soy protein isolate (low-iso SPI; 1.64±0.19 mg aglycone iso/day) and high-isoflavone SPI (high-iso SPI; 61.7±7.35 mg aglycone iso/day) for 57 days each, separated by 28-day washout periods. Twenty-four-hour urine samples collected on days 54-56 of each treatment period indicated that excretion of isoflavones was significantly higher following consumption of high-iso SPI compared with low-iso SPI and MPI. Analysis of semen samples collected on days 1 and 57 of each treatment period revealed no significant effects of low- or high-iso SPI on semen parameters including semen volume, sperm concentration, sperm count, total motile sperm count, sperm motility or sperm morphology, when compared with MPI.

Conclusion: Results of this study demonstrate that consumption of SPI of low- or high-isoflavone content for a period of 57 days does not adversely affect semen quality in healthy adult males.

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Soy Foods do not Negatively Impact Mineral Balance or Bone Turnover in Young Women. M. B. Reddy1, Y. Zhou, and D.L. Alekel, Iowa State University, Ames, IA, USA.

Soy foods have health benefits, but concern has arisen regarding mineral balance because soy is high in phytate. We hypothesized 3 servings of soy foods (~20 g protein) daily for 10 wk would not affect iron or zinc status in women of childbearing age. We excluded women with chronic disease, smokers, anemia, pregnancy, and/or irregular menstrual cycles. Subjects 18-28 years were randomly assigned to either soy (n=31) or meat (n=32) group. The soy group was instructed not to consume additional soy foods and control group not to consume >1 serving/day of animal foods. We collected blood and 3 day dietary records at baseline and after treatment. Subjects ate their meals 3 days/week at our research unit and carried out frozen meals (soy or control) to consume at home the other days. Subjects consumed study-provided soy- or dairy-based milk and yogurt daily. At baseline, iron status, serum zinc, or bone turnover markers were not different between groups; 13 of 63 subjects had iron deficiency (serum ferritin <12ng/mL). After treatment, we observed no significant change in serum ferritin, iron, zinc, hemoglobin, or bone turnover markers between groups. Our results indicated that incorporating 2-3 servings/d of soy foods containing ~20 g protein had no detrimental effect on bone turnover markers, iron status, or zinc status in women at-risk for these mineral deficiencies.


Bioavailability of Calcium from Tempeh as Compared to Milk in Postmenopausal Malay Women. Hasniah Haron1,2,3, Suzana Shahar1, Kimberly O’Brien2, Amin Ismail1, Loh Su Peng3, Azrina Azlan1, NorAzmi Kamaruddin1, and Suriiah Abdul Rahman2, 1Universiti Kebangsaan Malaysia, Dept. of Nutrition & Dietetics, 2Universiti Putra Malaysia, Dept. of Nutrition & Dietetics, Faculty of Medicine & Health Sciences, 43400, Serdang, Malaysia, 3Universiti Kebangsaan Malaysia, Dept. of Medicine, Faculty of Medicine, Jalan Yaacob Latif, Bandar Tun Razak, Cheras 56000 Kuala Lumpur, Malaysia, 4Universiti Kebangsaan Malaysia, Food Science Programme, Faculty of Science and Technology, 43600 Bangi, Selangor, Malaysia.

Postmenopausal women in Malaysia typically consume only 30-60% of the 1000mg/day which is the Malaysian RNI for this age group. This may due to traditional dietary habits and non-milk based diet. Thus, an understanding of calcium bioavailability from traditional soy foods like tempeh is important in this population. To assess its bioavailability as a calcium source, fractional calcium absorption from tempeh was determined in 26 healthy postmenopausal Malay women and compared to that observed from milk using dual stable isotope approach in a randomized cross-over design. Subjects consumed the same calcium load (130mg Ca) from either milk or tempeh with a one-month washout period between each test meal. 44Ca (0.036mg/kg) was administered intravenously to subjects prior to oral administration of 44Ca (0.272mg/kg) in milk. For the tempeh study, oral 44Ca (0.272mg/kg) was consumed in deionized water at the midpoint of the ingestion of the tempeh test meal. All urine from subjects was collected for 24h post-dosing in 8h pools. Fractional calcium absorption was determined as the relative recovery of the oral to the intravenous stable calcium isotope recovered in the 24h urine pool using magnetic sector TIM S. Average fractional calcium absorption from tempeh (36.85±10.62%) was not significantly different (P>0.05) from that observed from milk (34.28±8.60%).

Acknowledgements: IAEA provided stable isotopes.
Role of Soy

Poster Presentation Abstracts

Please note: The following abstracts have not been edited for content. They appear as submitted by the authors.

Athletic Performance

Soy Protein Intake in Peptide Form Effectively Mitigates Exercise-Induced Muscle Damage. Motohiro Maebuchi1, Masahiko Samoto1, Kenichi Masuda2, Yoshihiro Nakabou1, and Motohiro Hirotsuka1. Food Science Research Institute, Tsukuba Research and Development Center, Fuji Oil Co. Ltd., Japan, 2Dept. of Acupuncture and Moxibustion, Kansai University of Health Sciences, Japan, 3Graduate School of Health Science and Technology, Kawasaki University of Medical Welfare, Japan.

In this study, we compared the intestinal absorption from different sources with the same amino acid composition (protein, peptide, and amino acid mixture) by measuring changes in serum concentration of various amino acids. Peptides used in this study were prepared by enzymatic digestion of 11S globulin (a major component of soy protein). Subjects were asked to drink beverages containing each of the following 3 different preparations: 11S globulin, 11S peptide, and an amino acid mixture of equivalent composition. Our results suggest that the ingestion of hydrolyzed soy protein results in faster and more efficient absorption than the consumption of protein or amino acid mixtures in healthy adult men.

In addition, we demonstrated the effects of the intake of soy-peptide on exercise-induced muscle damage. Serum creatine phosphokinase activity was used as an indicator of muscle damage. Immediate ingestion of 11S peptide after exercise resulted in a significant decrease of serum creatine phosphokinase activity at 18 hours post-exercise compared with placebo. Furthermore, the effect was significantly superior to the performance of 11S globulin. These results suggest that soy protein intake in peptide form effectively mitigates exercise-induced muscle damage.

Bioavailability of Soybean Component

Effect of Cholesterol on Plasma and Cecal Isoflavonoids in Daidzein-supplemented Mice. Motoki Tamura*, Hiroyuki Nakagawa, Fukatsu Tomoka, and Iwami Takashi, National Food Research Institute, Tsukuba, Ibaraki, Japan.

We investigated the effects of cholesterol on the plasma cholesterol, plasma isoflavonoids, and cecal isoflavonoids of mice fed a diet supplemented with daidzein. Male mice were randomly divided into 3 groups, which were fed a cholesterol-daidzein (CDA), cholesterol-sodium cholate-daidzein (CCDA), or daidzein (DA) diet for 60 d. Plasma cholesterol concentrations were measured by enzyme methods. Plasma daidzein and equol metabolites were measured by high-performance liquid chromatography (HPLC). Cecal daidzein and equol present as aglycon in the cecum were also measured by HPLC. Plasma equol concentrations were significantly higher in the DA group than in the CDA group and the CCDA group. However, there were no significant differences in the daidzein concentrations. The cecal equol concentration was significantly higher in the DA group than in the CDA group and the CCDA group.

Isoflavone Content of Contemporary Soy Foods. Yukiko Morimoto*, Shana Suzuki, Gertraud Maskarinec, and Adrian A. Franke, Cancer Research Center of Hawaii, Honolulu, HI, USA.

With increasing attention to the potential health benefits of soy foods, a wide range of traditional and contemporary soy food products are currently sold in the market in the United States. We analyzed 16 commercial soy food products found in local grocery stores in Honolulu, Hawaii, including tempeh, soy bars, soy nut butter, tofu hot dog, and soy ice cream. We measured total and individual isoflavone (daidzein, genistein, glycitein, and their conjugates and aglycones) levels as a surrogate for the actual soy/soy isolate content using high-pressure liquid chromatography with photo diode-array detection. Total isoflavone levels ranged from 37 μg/g (tofu jerky) to 2085 μg/g (soya granules) with a mean of 121 μg/g. When converted to common serving sizes, the total isoflavone levels ranged from negligible to moderate to very high (1.0 mg per serving for tofu jerky to 34.7 mg per serving for soy yogurt to 90.7 mg per serving for soya granules) as compared to a traditional soy food (45.7 mg per serving for tempeh). These results show that contemporary, soy-based products contain varying amounts of soy and isoflavones. It may not be appropriate to categorize some of these products as soy products because of their low isoflavone content. This type of information should be offered to consumers who use these products in an effort to increase their soy intake as part of a healthy diet.

Apparent Bioavailability of Isoflavonoids after Intake of Liquid and Solid Soy Foods. A.A. Franke1,2, B.M. Halm2,3, and L.A. Ashburn1,2, Cancer Research Center of Hawaii, Honolulu, Hawaii, USA, 3Kapi‘olani Medical Center for Women and Children, Honolulu, Hawaii, USA.

Isoflavone (IFL) intake may provide numerous health benefits. Additional evidence from our recent controlled soy intervention studies confirmed that urinary IFL excretion (UIE) provides a reliable surrogate for systemic IFL exposure. This allows UIE to be used as a dependable measure of ‘apparent bioavailability’ (AB).

We investigated the AB of IFLs in 14 healthy adults consuming 2 liquid and 2 solid soy foods in a cross-over designed study with an average 1 week wash-out period. Volunteers consumed the foods during a self-selected breakfast which was kept identical for all 4 soy items (95.2 g milk, 12.6 g protein in one cup of water, 12.7 g health bar, and 13.6 lightly salted/roasted soy nuts; on average 23.7 mg IFLs, 88-96% glycosides, by HPLC analysis). This avoided confounding of results by foods consumed together with the soy items. All urine was collected immediately before and 2, 8, 24, and 26 hours after soy intake. Data are presented that show AB differences between the test foods and that allow determination of urine collection periods needed to detect significant AB differences in future studies.

Studies with soy foods should consider IFL bioavailability related issues closely to avoid IFL accumulation caused by repeated dosing before completion of the wash-out period.

Acknowledgements: We thank genuinely the dedicated participants, and the support by Physician’s Pharmaceuticals and NIH grant RR020890.

Cancer

Breast Cancer Cohort in Japan. Yuri Mizota1, Seiichiro Yamamoto1, Motoki Iwasaki3, Yasuo Ohashi1, Masashi Ando2, and Naoto Shimoyama3, 1Cancer Information Services and Surveillance Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan, 2Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan, 3Dept. of
Biostatistics, School of Public Health, University of Tokyo, Tokyo, Japan; Dept. of Breast and Oncology, National Cancer Center Hospital, Tokyo, Japan; Surgical Operation and Palliative Medicine Division, National Cancer Center Hospital, Tokyo, Japan.

Although there is growing epidemiologic studies to investigate the etiological role of lifestyle factors on female breast cancer, few studies have examined the association between lifestyle factors and breast cancer recurrence and survival. To investigate the influence of lifestyle factors such as diet and physical activity, and use of complementary/alternative medicine on prognosis including the quality of life, recurrence, and survival of patients with breast cancer, we designed a large-scale cohort study of breast cancer patients in Japan. Among many lifestyle factors examined, we are especially interested in the effect of soy and isoflavones on breast cancer prognosis.

The planned sample size is 10,000 breast cancer patients. Main part of this study is being conducted as a collaborative study with several clinical trials. Participant’s information on clinical factors, treatment, and follow-up will be obtained from the clinical trials. A self-administered questionnaire will be delivered to subjects before, immediately after, or 1 or 5 years after surgery, and their responses will be employed as baseline data. Blood samples are also to be collected. The primary endpoint is disease-free survival. The secondary endpoints are overall survival and the health-related quality of life. Follow-up period will be 5 years after the last participant enrollment.

Randomized Clinical Trial of the Action of Several Doses of Isoflavones in Localized Prostate Cancer, Nagi Kumar1,2, Jeffrey Krischer3, Karen Besterman-Dahan4, Kathy Allen5, Diane Riccardi2, Loveleen Kang2, Julio Powsang6, and Ping Xu7, 1University of South Florida, Tampa, Florida, USA, 2Moffitt Cancer Center, Tampa, Florida, USA.

Purpose: The purpose of this trial was to evaluate the safety and effective dose of isoflavones to be used in future clinical trials for prostate cancer prevention.

Methods: Forty-five eligible men were supplemented with 40, 60 and 80 mgs of purified isoflavones or no supplement from biopsy to prostatectomy. Compliance to study agent, toxicity, changes in plasma isoflavones, serum steroid hormones, PSA and tissue Ki-67 were analyzed from baseline to completion of study. Results: Forty-four subjects completed the study with duration of intervention of 30 (+/-3) days. Significant increases in plasma isoflavones with treatment for all doses compared to controls was observed with no toxicity. Significant increases in serum total estradiol, stabilization of serum PSA, free testosterone, decreased tissue Ki-67% was observed in the 40 mgs isoflavone-treated arm compared to all other treatment arms and controls without producing toxicity nor increasing serum testosterone levels. Conclusions: Based on criteria of safety and modulation of intermediate-endpoint biomarkers, 40 mgs of purified isoflavones may be the best dose to be used in a future definitive, larger phase II clinical trial to evaluate purified soy isoflavones to be employed as baseline data.

A self-administered questionnaire will be delivered to subjects before, immediately after, or 1 or 5 years after surgery, and their responses will be employed as baseline data. Blood samples are also to be collected. The primary endpoint is disease-free survival. The secondary endpoints are overall survival and the health-related quality of life. The follow-up period will be 5 years after the last participant enrollment.

Acknowledgements: The research study was funded by the National Institute of Health–National Cancer Institute U10 CA81920.

Epigenetic Regulation of Chemopreventive Genes by the Soy Peptide, Lunasin, A.F. Galvez*, J. del Rosario, P. Tripathi, K. Dawson, and R.L. Rodriguez, Center of Excellence for Nutritional Genomics, University of California, Davis, CA 95616, USA.

Lunasin is a chromatin-binding soy peptide with anti-cancer properties. Microarray analysis of lunasin-treated prostate cells under basal conditions shows that lunasin upregulates expression of chemopreventive genes but only in non-malignant cells. Using histone acetylase (HAT) assay and acid-extracted histones as template, lunasin specifically binds to deacetylated Lysine 8 (Lys8) of histone H4, changing the structural conformation of the H4 N-terminal tail to allow increased acetylation of Lysine 16 (Lys16) by HAT enzymes p300, Hat1 and PCAF. Acetylation of H4-Lys16 is the major histone modification involved in chromatin decondensation and subsequent gene expression. However, when recombinant histone H4 (hyponoacetylated H4) is used as template in HAT assays, the only secondary co-activator, PCAF, can acetylate Lys16. We also showed that the CpG island promoter of the pro-apoptosis, thrombospondin 1 gene (THBS1) in the malignant cell line (RWPE-2), is DNA hypermethylated and shows loss of H4-Lys16 acetylation compared to the non-malignant cell line (RWPE-1). The deacetylation, DNA hypermethylation and the consequent loss of H4-Lys16 acetylation in promoters of chemopreventive genes can help explain the inability of lunasin to upregulate chemopreventive genes in malignant cells.

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Cardiovascular Disease

Daidzein, Soy Phytoestrogen, Selectively Ameliorates Obesity-Related Hypertension in Mice and Humans Without Affecting Other Metabolic Derangements. T. Furumoto*, D. Goto*, S. Fujii*, and H. Tsutsui*, 1Dept. of Cardiovascular Medicine Hokkaido University Graduate School of Medicine, Sapporo, Japan, 2Dept. of Molecular and Cellular Pathobiology and Therapeutics Nagoya City University Graduate School of Pharmaceutical Sciences, Nagoya, Japan.

Obesity is correlated with metabolic disorders such as hypertension and insulin resistance. To determine whether supplementation of soy phytoestrogen is appropriate for the treatment of obesity we examined daidzein on the metabolic disorders in genetically obese mice and obese hypertensives. (1) Male obese mice and their lean littermates at 18 weeks of age were fed soy-free diet with vehicle or daidzein supplementation for 10 days. Obese mice exhibited significant increases in systolic blood pressure (BP) (150mmHg vs. lean 127, p<0.05). Daidzein supplementation significantly decreased systolic BP in obese mice (132mmHg, p<0.05) without affecting fasting plasma glucose, insulin and cholesterol. Markedly increased mRNA expression of tumor necrosis factor-α in abdominal adipose tissue in obese mice was reduced. (2) Daidzein-rich isoflavones aglycone (Agly Max) was given to Japanese obese hypertensives (n=8, mean age=57) for 8 weeks. After treatment, systolic BP was markedly decreased (156mmHg to 141, p<0.05). Diastolic BP was also decreased without changing other metabolic disorders.

These results suggest that daidzein rapidly ameliorated hypertension in obese without changing other metabolic derangements. Selective reduction of BP by soy phytoestrogen may provide novel therapeutic strategy for the effective treatment of obesity-related hypertension.


When provided concurrently with soy protein for 1-3 months, soy isoflavones exert synergistic or additive cholesterol-lowering effects. This meta-analysis was performed to evaluate the effects of extracted soy isoflavones alone (not ingested concurrently with soy protein) on total and LDL cholesterol. MEDLINE (1966-2007), EMBASE (1966-2007), CEN-
TRAL (1966-2007), ICHUSHI (1983-2008), and CNKI (1979-2007) were searched for randomized placebo-controlled trials published in English, Japanese, and Chinese, describing the changes in lipid profiles in adult humans resulting from ingestion of extracted soy isoflavones for 1-3 months. Reference lists of relevant systematic reviews and meta-analyses were hand-searched. Meta-analysis of 10 and 9 trials with usable information using REVMan found that an average of 70 mg soy isoflavones/day (27-132 mg, as the aglycone form) alone had a non-significant effect on total [0.01 mmol/L (95% CI: -0.12, 0.14); P = 0.86] and LDL [0.03 mmol/L (95% CI: -0.11, 0.16); P = 0.71] cholesterol in menopausal women, respectively. It is concluded that ingestion of about 70 mg extracted soy isoflavones/day alone for 1-3 months does not improve total and LDL cholesterol levels in normocholesterolemic menopausal women; further studies are needed to verify the effects of extracted soy isoflavones.

Molecular Modeling Studies: Potential Binding of Soy Protein 7S Globulin Subunits to Human LDL Receptor. L. Fernando*, L. Buehler, D. Hecht, and R. Bakhiet, Southwestern College, Chula Vista, CA, USA.

Soybean 7S Globulin subunits have been associated with a decrease in cholesterol in both in vitro and in vivo studies. One possible mechanism could be binding of the protein or its digested fragments to the LDL receptor. In order to explore the feasibility of this hypothesis, molecular modeling experiments were performed using homology modeling software (MOE, Chemical Computing Group, Inc.) and protein-protein docking software (FTDock, RPScore & Multidock from Biomolecular Modeling Laboratory, Imperial Cancer Research Fund). In these studies, a homology model was generated for the 7S globulin. The LDL receptor binding site was also obtained from the Protein Data Bank (IN7D.pdb). From these docking studies it was observed that the homology model bound to several sites of the extra-cellular region of the LDL receptor.

Effects of Genistein on Human Pulmonary Artery Smooth Muscle Cells. Y.J. Suzuki*, Georgetown University, Washington, DC, USA.

Pulmonary hypertension is a devastating disease without cure. It is characterized by increased pulmonary vascular resistance in part due to thickening of pulmonary vascular walls via increased growth of smooth muscle cells (SMC). Thus, strategies to inhibit growth and promote death of pulmonary artery SMC should have therapeutic potential for the treatment of this disease. An isoflavone compound, genistein, has been considered in apoptosis-based therapy for cancer, in which unwanted cells are killed via apoptosis. Such approach may be also useful to eliminate SMC and regress pulmonary vascular thickness. Genistein may also affect signal transduction pathways for pulmonary artery SMC growth. Recently, genistein was reported to attenuate the development of pulmonary hypertension in rats. In the present study, effects of genistein on cultured human pulmonary artery SMC were examined. Pharmacologic doses of genistein caused sustained phosphorylation of ERK MAP kinase and inhibited transient ERK phosphorylation, which promotes cell growth, induced by serotonin, a major mediator of pulmonary vascular thickening. Genistein also promoted oxidative stress as indicated by the formation of protein carbonylation, which may promote cell death signal. Thus, genistein may be effective in suppressing growth of pulmonary artery SMC and pulmonary hypertension.

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Epigenetic Regulation of HMG-CoA Reductase and LDL Receptor Expression by the Soy Peptide, Lunasin, Provides a Mechanism for Lowering Cholesterol. A.F. Galvez*1,2, F. Chunjiang3, and M. Kerley2, 1Center of Excellence for Nutritional Genomics, University of California, Davis, CA 95616, USA, 2Dept. of Animal Science, University of Missouri, Columbia, MO 65211, USA.

The soy peptide, lunasin, binds to hypoacyetylated chromatin and inhibits acetylation of histone H3 by PCAF histone acetylase. Transcriptional regulation of HMG CoA reductase (HMG) and LDL receptor (LDL-R) by Sterol Regulatory Element Binding Proteins (SREBP) requires the selective recruitment of different co-regulatory factors, CREB/CBP for HM G and Sp1 for LDL-R. CBP interacts with the activation domain of SREBP and associates with PCAF to acetylate histone H3, which is required for SREBP-regulated transcriptional activation of HMG.

By inhibiting H3 acetylation by PCAF, lunasin significantly reduces HM G expression by 50% in HepG2 cells grown in cholesterol-free media. In contrast, LDL-R expression increases by 60%, due to the coordinate increase in expression of its co-transcriptional activator, Sp1. RT-PCR experiments show the corresponding decrease of HM G and the increase of LDL-R and Sp1 mRNAs in lunasin-treated HepG2 cells. Hence, lunasin reduces cholesterol levels by directly inhibiting gene expression of HM G, leading to lower cholesterol biosynthesis and by increasing LDL-R expression, which enhances clearance of plasma LDL cholesterol. A dietary intervention study has been initiated using formulated lunasin-enriched soy protein and casein basal diets on C57/B6 mice to determine cholesterol lowering effects of lunasin in vivo.


One possible mechanism to lower circulating cholesterol, a key benefit of soy in the diet, is to bind bile acids (BA) in the digestive tract. Cholesterol is the precursor of bile acids which are used in digestion to emulsify fat and aid in lipid uptake. BAs are effectively reabsorbed back into the body, however, an accepted mechanism to lower cholesterol is to reduce the BA reabsorption (increase BA excretion). BA excretion results in a decrease in serum cholesterol levels as the liver upregulates its uptake of plasma cholesterol for BA synthesis. Solae has an in vitro BA binding assay (BABA) that quickly measures soy's bile acid binding capacity and has shown that a Solae soy protein isolate, SPI, effectively binds BAs. Solae SPI has also been shown to lower circulating cholesterol in the male Syrian hamster, an accepted animal model of human lipid metabolism. BABA has been used to isolate the active component in soy and determine a molecular mechanism for soy's ability to reduce cholesterol. Solae SPI binds bile acids in our in vitro assay and this agrees with the increase in fecal BAs seen in hamsters suggesting that one of the mechanisms by which soy protein lowers cholesterol is via bile acid binding. We are currently fractionating Solae SPI to determine the molecular BA binding motifs in soy protein responsible for its inherent cholesterol lowering activity.

Diabetes

Dietary Soy Protein Suppresses the Diabetic Mediator RBP4 in Rats. C.W. Xiao1,2,3, C.M. Wood1, G. Leroux1, M.R. L'Abbé1, G.S. Gilani3, G.M. Cooke2,3, I. Curran4, D. Jin5, and R. M ehta2, 1Nutrition Research Division, Food Directorate, Health Products and Food Branch, Health Canada, Ottawa, Ontario, Canada, 2Toxicology Research Division, Food Directorate, Health Products and Food Branch, Health Canada, Ottawa, Ontario, Canada, 3Dept. of Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada.
Lowering retinol binding protein 4 (RBP4) has recently been suggested as a new strategy for treating Type 2 diabetes because of its key role in mediating insulin resistance. Soy intake decreases incidence of obesity, diabetes and cardiovascular diseases. This study was conducted to examine the effect of soy protein isolate (SPI) and isoflavones (ISF) on lipid levels and RBP4 gene expression. Sprague-Dawley rats were fed either 20% casein or alcohol-washed SPI or SPI plus ISF (SPI+ISF) for 70 or 310 days. SPI markedly decreased plasma RBP4 levels in female rats, but had no effect in male rats compared to casein. Added ISF slightly reduced plasma RBP4 in male rats but had no additional effect in female rats. Adipose RBP4 protein content in female rats fed SPI or SPI+ISF for 310 days were significantly lower than those fed casein; however, the mRNA abundance was similar. Plasma total cholesterol and triglyceride (TG) levels were significantly lower in female rats fed SPI-based diets for 310 days compared to the casein diet, but were not different in male rats. Hepatic cholesterol and TG contents were markedly higher in males than in females fed casein, and were lowered by dietary SPI in male rats, but less affected in female rats. Overall, these results suggest that intake of soy protein lowers the lipid levels and decrease the diabetic mediator RBP4 protein; however the effect appears to be gender-dependent.

**Soy Isoflavone Inhibits TNF-α induced Downregulation of Adiponectin.** Masayoshi Yanagisawa* and Takanori Tsuda, College of Bioscience and Biotechnology, Chubu University, Kasugai, Aichi 487-8501, Japan.

Adiponectin is one of the most important adipocytokines for insulin sensitivity, and is specifically and highly expressed in adipocytes. In this study, we demonstrated that soy isoflavone (genistein, daidzein) and its metabolite (equol) significantly inhibited TNF-α induced downregulation of adiponectin expression in 3T3-L1 adipocytes. Interestingly, these compounds did not activate PPARγ transcriptional activity, indicating that the inhibitory effect is not due to transactivation of PPARγ-mediated upregulation of adiponectin. Recent studies show that MAPK (JNK) signaling is involved in regulation of adiponectin expression. The pre-treatment of genistein significantly inhibited TNF-α induced JNK activation which is involved in adiponectin expression. On the other hand, the administration of daidzein did not inhibit TNF-α induced JNK activation. These data suggest that genistein and daidzein can significantly inhibit TNF-α mediated downregulation of adiponectin in adipocytes via different mechanism, and soy isoflavone has a unique therapeutic potential that may possibly be able to be used to regulate the adipocyte function.

Acknowledgements: This study was supported in part by Fuji Foundation of Protein Research.

**Soy β-conglycinin Improves Insulin Sensitivity and Glucose Tolerance in Rats.** N. Tachibana*, M. Kohno, M. Hirotsuka, and F. Hiroto, Fuji Oil Co., Ltd., Izumisano-shi, Osaka, Japan. 1Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan.

We previously found that beta-conglycinin (β-CG), a major constituent of soy protein, has serum triglyceride(TG)-lowering effect and anti-obesity effect in rats. Thinking the mechanism of this β-CG action, we have the hypothesis that β-CG might lower the serum TG and glucose concentrations by improving insulin action. Therefore, the purpose of the present study was to examine the effect of β-CG on glucose tolerance and insulin sensitivity in rats.

Twenty-week-old male Wistar rats were divided into 3 groups, and fed the diet containing either casein, soy protein isolate (SPI), or β-CG for 4 weeks. Rats in the β-CG or SPI group had a significantly lower blood glucose concentration at 15min during oral glucose tolerance test (OGTT) compared with that in the casein group. The area under curve (AUC) of blood glucose concentration during OGTT in the β-CG group was significantly lower than in the other groups. In insulin tolerance test, blood glucose disposal rate in the β-CG group was higher compared with the casein group. Furthermore, feeding β-CG significantly increased the serum adiponectin concentration and decreased the serum TG concentration compared with casein or SPI.

These results indicate that β-CG improves glucose tolerance and insulin sensitivity compared with casein, and support that β-CG might lower the serum TG concentration by improving insulin sensitivity.

**Influence of Soy Protein on Serum Lipids and Blood Glucose in Type 2 Diabetic Patients.** Aida Malek M. Ahdavi*, Tabriz University of Medical Sciences-Faculty of Health & Nutrition, Tabriz-Iran.

Objective: An increasing body of literature suggests that soy protein has favorable effects on various chronic and metabolic diseases like cardiovascular disease and diabetes. The object of this study is to investigate the effect of soy protein on serum lipids and blood glucose in Type 2 diabetic patients.

Methods: Thirty diabetic patients aged 30-70 years old were sampled randomly and recommended to consume 25 grams soy powder daily for 3 months. Soy consumption and dietary patterns of the patients were under control during the study period and were assessed by food frequency questionnaire. Blood samples were collected at the end of the 3rd month and biochemical parameters were compared with the base.

Results: In this study, soy consumption lead to the significant decrease in blood glucose (P<0.02) and HbA1c (P<0.001). At the end of the study, compared to the base, serum cholesterol and triglycerides decreased significantly (6% and 15% respectively, P<0.01). Changes in LDL-cholesterol, HDL-cholesterol, blood pressure and body weight were not significant.

Conclusion: Consumption of 25 grams soy protein daily for 3 months leads to the significant decrease in fasting blood glucose, HbA1c, serum cholesterol and triglycerides in Type 2 diabetic patients.

Acknowledgements: I am very thankful to the patients.

**Effect of Soy and its Components on Lipid Metabolism and Cardiovascular Risk Factors in Type 2 Diabetic Patients.** Aida Malek M. Ahdavi*, Tabriz University of the Medical Sciences-Faculty of Health & Nutrition, Tabriz, Iran.

Objective: The object of this study is to investigate the effect of soy and its components on lipid metabolism and cardiovascular risk factors in Type 2 diabetics.

Methods: We conducted an electronic search of MEDLINE, Cochrane Library Database, and ScienceDirect.

Results: Soy consumption in Type 2 diabetics results in 0.22mmol/l decrease in total cholesterol, 0.21mmol/l decrease in LDL-cholesterol, 0.1mmol/l decrease in triglycerides and 0.04mmol/l increase in HDL-cholesterol. Soy consumption results in 14% decrease in serum homocystein and 16.7±9.0 mmHg decrease in blood pressure.

Conclusion: We conclude that soy protein has an important role in decreasing free fatty acids, total cholesterol, triglycerides, LDL-cholesterol and in increasing HDL-cholesterol in Type 2 diabetic patients. The main mechanism of this effect is mediated by SREBP (Sterol Regulatory Element Binding Protein). Isoflavones of soy protein also lead to the increase in fatty acid oxidation and decrease in lipogenesis. Soy protein increases the nitric-oxide synthase activity and decreases the release of the PGH2 and therefore is beneficial in decreasing blood pressure. Therefore, soy as an important food source can have a considerable effect in decreasing cardiovascular risk factors in Type 2 diabetic patients.
Equol
A Survey Study on Urinary Equol Excreters and Frequency of Equol Producer in Beijing, P.R. of China. Peiyu Wang1, Baohua Liu1, Atsuko Onoda2, Tomomi Ueno2, Shigeto Uchiyama2, Xuetuo Liu3, and Po-Sheng Wu4, 1Faculty of Nutrition, Public Health School of Sun Yat-sen University, Zhongshan, Guangzhou, China, 2Saga Nutraceuticals Research Institute, Kanzaki-gun, Saga, Japan, 3Otsuka (China) Investment Co., Ltd., Beijing, China, 4Otsuka International Asia Arab Division, Otsuka Pharmaceutical Co., Ltd., Chuo-ku, Osaka, Japan.

Traditionally, soy foods have been frequently consumed among Chinese people, but no information is available about status of equol production and urinary excretion among them.

Our purpose of this study was to elucidate the percentage and the physiological range of urinary equol excretion in Beijing, and to elucidate the frequency of equol producers by soy isoflavone challenge test.

We collected 24hr urine from 201 inhabitants (100 men and 101 women, aged 20-72y) in Beijing City in November 2007. They keep their ordinary diet and also recorded their diet during the 24hr urine collection. After 24hr urine collection, soy isoflavone challenge (41mg isoflavone aglycone) was done for 3 days. At 3rd day of soy isoflavone challenge, 24hr urine was re-collected. Urinary soy isoflavones and their metabolites were analyzed using a standard High Performance Liquid Chromatography (HPLC) method.

In 24hr urine collection on their regular diet, frequency of urinary equol excretion was 26.7% in female, 26.9% in men and 26.8% in total, respectively. In 2nd 24hr urine collection after soy isoflavone challenge, we confirmed the frequency of equol producer. Frequency of urinary equol excretion increased by the soy isoflavone challenge. 26.8% of Chinese adults in Beijing City were detected equol excretion in urine under the usual lifestyle. However, equol-producing potential was higher.

24hr Urinary Equol Excretion and Equol Producing Status in Guangzhou, P.R. of China. Yi Xiang Su1, Kaiping Guo1, Atsuko Onoda2, Tomomi Ueno2, Shigeto Uchiyama2, Xuetuo Liu3, and Po-Sheng Wu4, 1Faculty of Nutrition, Public Health School of Sun Yat-sen University, Zhongshan, Guangzhou, China, 2Saga Nutraceuticals Research Institute, Otsuka Pharmaceutical Co., Ltd., Kanzaki-gun, Saga, Japan, 3Otsuka (China) Investment Co., Ltd., Beijing, China, 4Otsuka International Asia Arab Division, Otsuka Pharmaceutical Co., Ltd., Chuo-ku, Osaka, Japan.

Objective: To assess 24hr urinary equol excretion and frequency of equol producers in Chinese adults in Guangzhou, P.R. of China.

Methods: Food intake record and 24hr urine were collected from 205 volunteers recruited in Guangzhou. 102 female and 103 male, aged 20-60y were studied. After 24hr urine collection, soy challenge (24mg isoflavone) was done for 3days. At 3rd day of soy challenge, 24hr urine was re-collected. Urinary soy isoflavones and their metabolites were analyzed using a standard High Performance Liquid Chromatography (HPLC) method.

Results: In the first 24hr urine collection, frequency of urinary equol excretion was 15.7% in female, 12.6% in men and 14.2% in total, respectively. In 2nd 24hr urine collection after soy challenge, we confirmed the frequency of equol producer. Frequency of urinary equol excretion increased by the soy challenge.

Conclusion: 14.2% of Chinese adults in Guangzhou were detected equol excretion in urine under the usual lifestyle. However, equol-producing potential was higher.

Detection of the Equol-producing Bacterium Adlercreutzia equolifaciens in Human Feces by Nested PCR Method.

Equol Producer in Beijing, P.R. of China. Toshinari Maruo1,2, Yoshihisa Toda1, Chiaki Ito2, Mitsu Sakamoto2, Yoshiko Ishimi3, Katsushige Yamada1, and Yoshimi Benno2, 1Fujico Co., Ltd., 6-13-4 Minatojima-nakamachi, Chuo-ku, Kobe, Hyogo 650-8558, Japan, 2Microbe Division/Japan Collection of Microorganisms, RIKEN BioResource Center, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan, 3Division of Nutritional Epidemiology, National Institute of Health and Nutrition, 1-23-1 Toyama, Shinjuku-ku, Tokyo, 162-8636, Japan.

Background: Equol, a metabolite of soy isoflavone daidzein, has been growing interest for many researchers. Recently, we isolated an equol-producing bacterium and proposed new genus, Adlercreutzia equolifaciens. However, there is a lack of information on the occurrence of it in the human intestine. In this study, nested PCR technique with the specific primers for A. equolifaciens was developed and tested for the detection of it in human feces.

Methods: Two primer pairs for A. equolifaciens were designed based on their 16S rRNA gene sequences. The specificity of the nested PCR was tested with some closely related species. DNA samples were prepared from the feces of 52 Japanese postmenopausal women (26 subjects were equol-producers) and subjected to the nested PCR.

Results: Nested PCR detected A. equolifaciens in 14 of 52 fecal samples. Ten of 14 PCR positive subjects were equol-producers, but other 4 subjects were equol-nonproducers. Four PCR bacterial strains were isolated from human feces of an equol-nonproducer (male, 28 years old) by using the nested PCR. They had no equol-producing activity, but one selected strain was identified as A. equolifaciens based on its 16S rRNA gene sequence.

Conclusion: These results suggest that A. equolifaciens may partially contribute to the equol production of human, but all strains do not always have equol-producing activity.
Isolation and Identification of Equol-producing Bacterial Strains from Rat Feces. Hitoshi Ishida*, 1 Koshiro Ito 1, Toshinari Maruo 3, Toshiya Toda 3, and Yosuke Kiyu 4, 1 School of Pharmaceutical Science, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan, 2 Fujico Co., Ltd., 6-13-4 M Inatomiya-nakamachi, Chuo-ku, Kobe, Hyogo 650-8558, Japan.

Background: Recently, there has been great interest in effects of S-equol, a metabolite of daidzein produced by intestinal flora, because it is known to be the most effective in stimulating an estrogenic response among soy isoflavones and their metabolites. Although there have been extensive efforts on isolation of a single bacterium capable of producing equol, there have been few reports. In the proceeding paper, we demonstrated that glycine is microbially transformed into S-equol by rat gut microflora.

Objective: This study was aimed to isolate and identify equol producing bacteria from SD-rat feces.

Methods: Isolation of bacteria capable of producing equol was carried out from feces of SD-rat. Isoflavones in the cultures were analyzed by using chiral phase HPLC and MS/M/MS spectrometry.

Results: Three strains (H1, H2 and H3) capable of producing S-equol from daidzein were isolated. Moreover, they can also produce S-equol from 6-hydroxydaidzein. On the basis of the 16S rRNA gene sequence analysis, strain H1 and H2 were identified as Adlercreutzia equolifaciens that was recently characterized as equol-producing baceterium isolated from human feces.

Conclusion: Our results provided the first account of conversion of 6-hydroxydaidzein to S-equol by bacterial strains from animals. These strains are probably important to the improvement of animal performance.

Is It Possible to Assign Equol Producer Phenotype Based on Singlicate Blood Samples? Melissa K. Melby*, National Institute of Health and Nutrition, Shinjuku, Tokyo, Japan.

Background: Isoflavone pharmacokinetic studies have generally sampled frequently during the 0-12 hours post-ingestion window, and subsequently every 12 hours. Debates about the indubility of equol producer (EqP) ability may due to sampling in inappropriate pharmacokinetic windows.

Objective: To characterize the complete pharmacokinetics of equol and assess whether and how EqP phenotype could be assigned using singlicate serum samples.

Design: Using finger-prick dried blood spots, a detailed pharmacokinetic case study was performed using 20mg daidzein aglycone equivalents. Subsequently, a pharmacokinetic study (N=10) with sampling every 2-3 hours following 4mg daidzein ingestion was performed.

To examine dose-response and maximal background concentrations in equol non-producers (EqNPs), a high IF study (N=7) was conducted with samples collected at baseline, 3 stages following 1 month intake of; (1) 38.5mg/day, (2) 77.0mg/day; (3) 115.4mg/day daidzein aglycone equivalents; and post one-month washout period.

Results: Four of 10 participants were EqPs (41%) in the pharmacokinetic study. Serum equol peaked between 13-22 hrs following isoflavone intake. A 22N threshold clearly distinguished between samples collected from EqPs and EqNPs 12-24 hours post-ingestion. Following high isoflavone intake, no dose response in equol concentrations was observed in EqNPs and maximal concentration of 30N was observed at baseline.

Conclusions: An absolute cutoff between 22–30N could be used to assign EqP phenotype based on singlicate serum samples, as long as samples are collected in the 12-24 hour post-ingestion window. Possible mis-assignment of EqPs as EqNPs may result from sampling during inappropriate pharmacokinetic windows (0-13 hours or more than 22 hours post-ingestion of daidzein).

General Topics


Soy products contain isoflavones that have been beneficial for the prevention and treatment of several human diseases including breast and prostate cancers, osteoporosis and also menopausal symptoms of women. To breed a cultivar with desirable isoflavones content, it is important to disclose the genetic control of their content. This study aimed to identify quantitative trait loci (QTL) for isoflavones content in soybean seeds. The 94 recombinant inbred lines (RILs) from the cross between “Peking” and “Tamahohame” were planted at Nagano, Kyoto, and Osaka. Isoflavones contents of seeds were determined by high performance liquid chromatography (HPLC), and the genetic map was constructed using 314 polymorphic SSR markers. The interactions between genotypes and locations for isoflavones contents were analyzed by ANOVA. As a result of QTL analysis for the total isoflavones contents and the contents of daidzein, glycine and genistein, a total of 25 QTLs were found. Three QTLs for the total isoflavones contents were commonly observed in 3 locations. The DNA markers closely linked to those 3 QTLs must be useful for developing soybean varieties with desirable amounts of isoflavones in the seeds.

Soy Milk Can Reduce Oxidative Stress from Lactose Intolerant People. Chai-Won Chung*, Central Research Institute, Dr. Chung’s Food Co., Ltd., Cheongju-si, Chungcheongbuk-do, Korea.

Lactose, found in mammalian milks, must be decomposed into galactose and glucose by lactase to be absorbed by body. Approximately 70% of the world’s population and 75% of Korean adults is lactose mal-digestion. Undigested lactase produces short-chain fatty acids, carbon dioxide and hydrogen gas by colon microflora. They can be risk factors to diabetes and some cancers by oxidative stress. In these clinical studies, effects of soy milk intake to lactose intolerant people were investigated.

In study I, people were loaded either 50g of lactose or 25g of galactose and glucose each daily for 5 days, then measured changes of antioxidant activity. In study II, 77 college students–lactose intolerant or tolerant as a control–ingested cow or soymilk for 4 weeks, then were measured for state of lipid peroxidation, DNA damage and activity of antioxidant enzyme. Malondialdehyde and urine 8-OHdG level of red blood cell were increased significantly in lactose loaded group in study I. Study II showed that lipid peroxidation and antioxidant enzyme activity were not changed, but DNA damage was decreased in lactose intolerant-soy milk group. However, in lactose intolerant-milk group, lipid peroxidation and DNA damage increased and glutathione peroxidase decreased. In conclusion, these studies showed that soy milk intake represented positive effect on antioxidant system for lactose intolerant people.

Human Renin Inhibitory Activity in Miso, Soybean, and Minor Legumes. Saori Takahashi*, Kazuyuki Hori*, Hironobu Ogasawara1, Masanori Kumagai1, Takayuki Watanabe1, and 1 School of Health and Nutrition, Shinjuku, Tokyo, Japan.
Takeshi Gotoh, 1, Insitute for Food and Brewing, Akita Prefectural Agriculture, Forestry, and Fisheries Research Center, Akita, Japan, 2Dept. of Engineering in Applied Chemistry, Akita, Japan.

Renin catalyzes the liberation of angiotensin I (AI) from angiotensinogen. Angiotensin converting enzyme (ACE) cleaves C-termi-
nus dipeptide from AI to produce active peptide angiotensin II (AII). All raises blood pressure by vasoconstriction as well as stimulation of the synthesis and release of aldosterone. Thus, renin is a key enzyme of RAS. ACE has been used as a target enzyme in RAS for screening inhibitors of its simple assay method; however, renin is a rate-limiting enzyme in RAS, so it was not used because the measurement is very complicated. In the present study, we expressed recombinant human renin in Escherichia coli cells, refolded and activated by trypsin. Using the recombinant human renin as a target enzyme, we screened the renin inhibitory activity in fer-
mented soybean paste (miso) and found that soybean, the major ingre-
dient of miso, had renin inhibitory activity. Moreover, the effects of minor legume (legumes except soybean and peanut) extracts on human renin activity were investigated. We used 15 minor legumes including 6 gen-
era and found that they had renin inhibitory activity. Partial clustering analysis of the inhibitory data showed that minor legumes could be clas-
sified into 2 groups according to their renin inhibitory activity.

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Immune Function

Soy Isoflavone Intake and Risk of Cedar Pollinosis in Japanese Men and Women. Chisato Nagata1, Kozue Nakamura1, Toshiaki Kawachi1, Naoyoshi Takatsuka1, Shino Oba2, and Hiroyuki Shimizu1, 2, 1Dept. of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan, 2Dept. of Prevention for Lifestyle-Related Diseases, Gifu University Graduate School of Medicine, Gifu, Japan, 3Sakihai Institute, Japan.

Although soy isoflavone has been suggested to have both immune-
enhancing and immune-suppressive effects, the effects of soy isoflavone intake on allergic disorders are unclear. We aimed to prospectively exami-
ne the relationship between soy isoflavone intake and risk of cedar polli-
nosis, the most common seasonal allergic rhinitis in Japan, in a population-based cohort. Each subject’s usual diet, including soy isoflavone intake, was determined with the use of a validated food-fre-
quency questionnaire at baseline. A total of 11,229 persons who were 35 to 69 years old and had no history of cancer or allergic diseases at the baseline responded to a follow-up questionnaire asking about 4 symp-
toms related to cedar pollinosis. During the 10-year follow-up, 931 of these subjects reported that they had cedar pollinosis. There was no sig-
nificant association between soy isoflavone intake and risk of cedar polli-
nosis in men and women after controlling for covariates. For the highest, compared with the lowest quartile of soy isoflavone intake, hazard ratios were 1.07 (95% CI: 0.81-1.42) in men and 0.89 (95% CI: 0.68-1.15) in women. These data did not support an association between soy isoflavone intake and risk of cedar pollinosis.

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Menopausal Symptoms

Preventive Effects of Isoflavone on Motor Dysfunctions of the Animal Model of Parkinson’s Disease in the Postmenopausal Period. Shin-ichi Kyuhou*, Kansai Medical University, Moriguchi, Osaka, Japan.

In Parkinson’s disease (PD), dopaminergic neurons in the substantia nigra pars compacta (SNc) degenerate. It has already been found that estrogen has potential neuroprotective effects on the dopaminergic neu-
rons in the SNc. However, estrogen replacement after menopause has many risks such as cancers. As a natural alternative to estrogen, isoflavone is a good candidate for treatment because isoflavone has estrogen activ-
ities. The present study investigated the preventive effects of isoflavone on the motor dysfunctions of PD. In ovariectomized rats, unilateral injection of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle (MFB) induced motor dysfunctions in the forelimbs on the side contralat-
eral to the lesions assessed by cylinder and step tests. Pretreatment of
gein, an isoflavone, significantly preserved the motor dysfunctions. Morphologically, tyrosine hydroxylase (TH) positive neurons in the SNc were markedly reduced after injection of 6-OHDA into the MFB. Treatment of
gein significantly prevented the reduction of the TH positive neu-
rns. TH positive nerve terminals and dopamine transporter expression in the striatum were also preserved after genistein administration.

Taken together, isoflavone is suggested to serve to prevent PD in
the post-menopausal women.

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Isoflavone supplements may provide an alternative to estrogen for relief of menopausal symptoms. However, intervention studies with soy isoflavones showed inconclusive results. The clinical effectiveness of soy iso-
flavones for menopausal symptoms may be different by the metabo-
lishing ability from daidzein to equol. Our previous study indicated that
equil producers have less menopausal symptoms. This study compared the effectiveness of isoflavone and equol supplements for menopausal symptom.

We conducted a 12 week randomized, double-blind, placebo-con-
trolled trial by isoflavone (60mg or 120mg per day) supplements for 94 menopausal women in 2005, and by equol (10mg or 30mg per day) sup-
plements for 134 menopausal women in 2006. The subjects to compare the effectiveness of isoflavone and equol supplements for relieving menopausal symptoms were 65 women who participated in both trials. Menopausal symptom score was self-reported in the questionnaire at the baseline and the end of the treatment in both trials.

Of 65 women, 15 were pre-menopausal (age 47±5yrs), 11 were peri-menopausal (age 51±4yrs), and 39 were post-menopausal (age 53±3yrs). At the baseline, total menopausal symptom score varied by menopausal status and by equol producer status (41.5% producers).

In equol non-producers, equol supplement seemed to reduce menopausal symptoms more than isoflavone supplement.

Daidzein-rich Isoflavone Glycones are Potentially Effective in Reducing Hot Flashes in Menopausal Women. J.-R. Zhou*, W. Pan, H. Ricciotti, L. Khadoihar, L. Li, M. Schickel, and G. Blackburn, Beth Israel Deaconess Medical Center, Harvard Medical School, USA.
The aim of this study was to determine the effect of daidzein-rich isoflavone aglycones (AglyMax) on hot flash symptoms in menopausal women. It was a randomized, double-blind, placebo-controlled trial of menopausal women, aged 38 to 60 years, who experienced 5–14 hot flashes per day. A total of 190 menopausal women were randomized to receive a placebo, 40 or 60 mg/day of AglyMax for 12 weeks. The primary outcome was the mean changes from baseline to week 12 in the frequency of hot flashes. The secondary outcomes included changes in menopause-specific quality of life. A total of 142 (75%) women completed the study. AglyMax treatments (40 and 60 mg/day) improved hot flash frequency and severity equally, therefore these 2 groups were combined for analysis. Comparing with the placebo group (n=45), the AglyMax group (n=97) had a significantly reduced mean daily hot flash frequency, reducing hot flash frequency by 52% at 12 weeks (P=0.048). AglyMax group did not have any significant changes in endogenous sex hormones or thyroid hormones. Menopause-specific quality of life was non-significantly improved in AglyMax treatment group. The study suggests that AglyMax supplementation may be an effective and acceptable alternative to hormone treatment for menopausal hot flashes without apparent side effects.

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Nonprotein/Isoflavone Components


The aim of this study was to evaluate the effect of soy dietary fiber on diarrhea and constipation. Sprague-Dawley male rats were divided into 3 groups and fed AIN-93G containing 50 g/kg α-cellulose (CON), 59.6 g/kg soybean fiber (SF) or 55.6 g/kg chicory fiber (CF). To induce diarrhea, the magnesium citrate-phenolphthalein solution was used and the loperamide solution was used to induce constipation. Fecal weight and water content were measured to evaluate the effect of fiber on diarrhea and constipation. In the diarrhea-inducing study, fecal water content was significantly reduced in the SF group. In the constipation-inducing study, there were no significant differences among the 3 groups in both fecal weight and water content. Our study showed that soy dietary fiber has an effect of alleviating diarrhea. Therefore, it may be suggested that soy dietary fiber could be used as a medical food in patients suffering from diarrhea.


Conjugated linoleic acid (CLA) is a mixture of positional and geometric isomers of linoleic acid containing conjugated double bonds at C10 and C12 or C9 and C11. Predominant CLA isomers are cis 9, trans 11, and trans 10, cis 12 CLA. CLA has physiological benefits on cancer risk, immune response and atherosclerosis. Therefore, the consumption of CLA-enriched foods like structured lipids (SLs) is desirable. Soybean oil which has essential fatty acids, linoleic and linolenic acids has also good nutritional profile. Lauric acid (C12) has a higher antiviral and antibacterial activity than other medium-chain fatty acids.

In this study to improve the health benefits of soybean oil (SO), lipase catalyzed acidolysis of SO with a mixture of CLA and lauric acid (LaA) was performed using Lipoyzme TL IM (Thermomyces lanuginosa) lipase at 50°C.

The effects of substrates mole ratio and the reaction time on the incorporation of CLA and LaA into SO, acidolysis reactions were carried out for 1-6h taking the mole ratios of SO: total fatty acids (FA) 1:3-1:5 using 10% (wt/g substrates) of enzyme. Soybean oil containing 29.2% of CLA and 18% LaA was obtained at 1:5 molar ratio of SO:FA, 10% of enzyme and 1h of reaction time. Thus obtained CLA and LaA-rich SL from soybean oil would be used as a dietary oil in the formulation of healthy food products.


Soybean oil is rich in 2 essential fatty acids: linoleic and linolenic acids. These acids aid the body’s absorption of vital nutrients and are required for human health. Conjugated linolenic acids (CLNA) is the collective term for a mixture of conjugated positional and geometric isomers of octadecatrienoic fatty acids. The pomegranate (Punica granatum) seed oil contains 64–88% of CLNA, mainly punicic acid. CLNA potentially have beneficial effects on human health by reducing visceral lipids and enhancing immune response and preventing metabolic disorders of Type 2 diabetes.

In this study, the health benefits of soybean oil were enhanced with the incorporation of CLNA into triacylglycerols. Acidolysis reactions were conducted between soybean oil (SO) and pomegranate oil fatty acids (PFA) having 80.0% of CLNA with Lipoyzme TL IM (Thermomyces lanuginosa) lipase.

To see the effects of substrates mole ratio, enzyme amount and the reaction time on the incorporation of CLNA into SO, series of acidolysis reactions were carried out for 1-6h taking the mole ratios of SO:PFA 1:3-1:5 and using 10-20% (wt/g substrates) of enzyme. Soybean oil containing 45% of CLNA was obtained at 1:5 molar ratio of SO:PFA, 20% of enzyme and 3h of reaction time. Thus, obtained CLNA-rich soybean oil would be used as a dietary oil in the formulation of healthy food products.

Dietary Soybean Oil Enriched with Conjugated Linolenic (CLNA) and Conjugated Linoleic (CLA) Acids. B. Ozak, M. Tuter*, G. Ustun, and H.A. Aksoy, Istanbul Technical University, Chemical Engineering Dept., Maslak, Istanbul, Turkey.

Soybean oil is a very healthy food ingredient despite the bad publicity regarding fats and oils in general. The major unsaturated fatty acids in soybean oil triglycerides are linolenic acid, linoleic acid and oleic acid. These acids are required for human health. Conjugated linoleic acids (CLA) is the collective term for a mixture of conjugated positional and geometric isomers of octadecadienoic fatty acids. Conjugated linolenic acids (CLNA) is the collective term for a mixture of conjugated positional and geometric isomers of octadecatrienoic fatty acids. CLA and CLNA potentially have beneficial effects on human health.

In this study the health benefits of soybean oil was enhanced with the incorporation of CLNA and CLA into triacylglycerols. CLNA is obtained from pomegranate (Punica granatum) seed oil. Acidolysis reactions were conducted between soybean oil (SO), pomegranate oil fatty acids (PFA) having 80.0% of CLNA and CLA with Lipoyzme TL IM (Thermomyces lanuginosa) lipase.

To see the effects of substrates mole ratio and the reaction time on the incorporation of CLNA and CLA into SO, series of acidolysis reactions were carried out for 1-5h taking the mole ratios of SO:PFA 1:1; 5:1-1:2:5:2:5 and using 10% (wt/g substrates) of enzyme. Soybean oil containing 17.2% of CLNA and 25.2% CLA was obtained at 1:2.5:2.5 molar ratio of SO:PFA:CLA, 3h of reaction time.
Production of Conjugated Linoleic Acid from Soybean and Sunflower Seed Oils by using Lactic Acid Bacteria. S. Balikayaa, N. Arana, and G. Ustunb, 1Istanbul Technical University, Food Engineering Dept., Maslak, 34469, Turkey, 2Istanbul Technical University, Chemical Engineering Dept., Maslak, 34469, Turkey.

Conjugated linoleic acids (CLA) belong to the family of positional and geometric isomers of octadecadienoic acid. Animal studies demonstrated that CLA inhibits tumourigenesis and metastases, reduces sensitivity to allergens, decreases accumulation of body fat, and exhibits inhibitory effect on arteriosclerosis in test animals.

CLA synthesis from linoleic acid hydrolyzed from linoleic acid rich oils such as soybean and sunflower seed oils was studied by using 10 different isolates of lactic acid bacteria (LAB) in MRS Broth containing 12% (w/v) skim milk powder and hydrolyzed soybean or sunflower seed oils. Lactobacillus plantarum was found to be the most suitable bacterium among LAB tested. Experiments were conducted by adding hydrolyzed oils to culture media within the range of 100, 150 and 200 μL. The maximum CLA levels of 1.44% and 1.52% were obtained in the presence of 150 μL hydrolyzed soybean and sunflower seed oils, respectively. It has been observed that CLA yield increased after adjusting the pH of culture media approximately to 6.0 during 12h of incubation period. The results indicated that similar CLA yields were obtained with soybean and sunflower seed oils and that the use of pure linoleic acid did not increase CLA synthesis when compared with sunflower and soybean oil.

Osteoporosis

Effects of Dietary High Carbohydrate on Equol Production and Bone Mass in Ovariectomized Mice Treated with Daidzein. Yuko Tousen, Junko Ezaki, Furumiko Abe, and Yoshiko Ishimi, Nutritional Epidemiology Program, National Institute of Health and Nutrition, Shinjuku-ku, Tokyo, Japan.

Soybean isoflavones are considered to prevent bone loss by acting as selective estrogen receptor modulators in estrogen-deficient status. Daidzein, a major isoflavones, is metabolized to equol by gut microflora, and the metabolite exhibits a stronger estrogenic activity than daidzein. Epidemiological study has suggested that a diet rich in carbohydrates stimulates equol production. In this context, we examined the effects of high carbohydrate diet on conversion of daidzein into equol and on bone metabolism in ovariectomized (OVX) mice. After undergoing OVX or sham operation, ddY mice were randomly divided to 6 groups; sham-operation (Sham), OVX, OVX + 17β-estradiol (E2), OVX + 0.1% daidzein diet (Dz), OVX + high carbohydrate diet (HC) and OVX + 0.1% daidzein + HC diet (Dz + HC) groups. The diets were prepared according to the AIN-93G formulation. After 6 wk, the blood and femora were sampled immediately. Bone mineral density (BMD) of the distal femur was significantly lower in the OVX group than in the sham group, however, a significant difference was not observed between Dz and Dz + HC groups. A significant difference in plasma equol levels was not found between Dz and Dz + HC group. These results suggest that the effect of high carbohydrate diet on equol production is not well characterized in OVX animal model and requires further investigation.

Obesity

Daidzein-rich Isoflavone Aglycones Improved High Fat-induced Metabolic Disorders in Ovariectomized Mice Fed a High-fat Diet. J.-R. Zhou, W. Pan, and G. Blackburn, 1Beth Israel Deaconess Medical Center, Harvard Medical School, USA, 2Nichimo, Co., Japan.

The objective of this study was to determine the effect of daidzein-rich isoflavone aglycones (AglyMax) on high fat (HF)-induced body weight gain and insulin resistance in ovariectomized mice. Female C57BL/6 mice (6 wk) were either ovariectomized (OVX, n=24) or sham-operated (n=16), and were respectively randomized into 3 and 2 of the 5 experimental groups: (i) Sham: the normal diet with 10% of the energy from fat; (ii) HF-sham: the HF diet with 60% of the energy from fat; (iii) OVX-HF: the HF diet; (iv) OVX-HF and low-dose AglyMax (0.12% of the diet); or (v) OVX-HF and high-dose AglyMax (0.5% of the diet). Food intake and body weight were measured 3 times weekly. At 12 weeks, the average body weight gain in HF-sham mice was 239% of that in the Sham mice (P<0.001). The average body weight gain in OVX mice was 139% of that in the HF-sham mice (P<0.001). Mice treated with AglyMax at 0.12% and 0.5% of the diets had reduced body weight gains by 12.7% (P=0.08) and 39.0% (P<0.001) respectively, compared with the OVX-HF group. OVX mice treated with AglyMax had improved insulin sensitivity as measured by glucose tolerance test and insulin tolerance test. Our results suggest that dietary supplementation with AglyMax may be effective in improving HF-induced metabolic disorders.

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Reproduction

Aglymax Improves Implantation by Stimulating Secretion of Leukemia Inhibitory Factor (LIF) in Human Endometrial Epithelial Cells. Atsushi Yanaihara, Jin-Wen Xu, Naomi Yasui, Katsumi Ikeda, Weijun Pan, June Watanabe, M. asahide Shiotani, Tomohiro Miiki, and Yukio Yamori, Dpts. of Obstetrics and Gynecology, Showa University School of Medicine, Tokyo, Japan, 2Division of Pathophysiology, School of Pharmacy and Pharmaceutical Sciences, M ukogawa Women’s University, Nishinomiya, 663-8179, Japan, 3Nichimo Biotics Co., Ltd., Tokyo 140-0002, Japan, 4Department of Obstetrics and Gynecology, School of Medicine, Showa University, Tokyo, 142-8555, Japan, 5Department of Pathophysiology, School of Pharmacy and Pharmaceutical Sciences, M ukogawa Women’s University, Nishinomiya, 663-8179, Japan, 6Institute for World Health Development, M ukogawa Women’s University, Nishinomiya, 663-8179, Japan.

LIF is one of the most important cytokines on implantation in the uterus. The effects of isoflavones on uterine biology at the molecular level remains unexplored. We verify the hypothesis that isoflavones induce secretion of LIF in human endometrial epithelial cells. AglyMax, genistein, and equol display bioavailability in regulating the secretion of LIF and TGF-β determined by using ELISA kits in Ishikawa cells. AglyMax and equol induced LIF and TGF-β1 secretion. Genistein displayed a similar effect. The accelerated secretion of LIF and TGF-β1 was blocked by MEK1/2 inhibitor, and p38 MAP kinase inhibitor. On the other hand, incubation of Ishikawa cells with AglyMax for 9 days caused the increase in glycodelin expression assayed by Western blotting and immunocytochemistry staining. PKA inhibitor attenuated this glycoprotein expression.
tein expression. In separated primary endometrial epithelial cells at the follicular phase or luteal phase from health subjects, AglyMax effectively stimulated phosphorylation of ERK1/2 and p38 MAP kinase and induced LIF, TGF-β secretion at the follicular phase, and enhanced phosphorylation of PKA and expression of glycolin at the luteal phase. Our findings suggest that AglyMax may alter the uterine expression of estrogen-responsive genes, and advance the timing of implantation within lower isoflavone levels.

Safety Issues

Effects of Soy Isoflavone Extract on Thyroid Function in Postmenopausal Women. E.A.P. Nahas+1, J. Nahas-Neto1, F.L. Orsatti1, and M. Messina2, Botucatu Medical School, UNESP-Sao Paulo State University, Botucatu, Sao Paulo, Brazil, 2School of Public Health, Loma Linda University, Loma Linda, CA, USA.

Objective: to investigate the effects of soy isoflavone on thyroid function in postmenopausal women.

Methods: In this randomized, placebo-controlled study, a total of 80 Brazilian women (mean age:55.1 years) were randomized to receive: 250mg of standardized soy extract, a total of 100mg/day of isoflavone (n=40) or placebo (n=40). Exclusion criteria included: chronic gastrointestinal or thyroid diseases, and users of hormone therapy. Serum thyroid stimulating hormone (TSH) and free thyroxine (T4) were measured at baseline and 10-months. The plasma levels of isoflavones were measured to assess compliance. The ANOVA for repeated measure was used in the statistical analysis.

Results: In the isoflavone group, at baseline and 10 months, TSH (mIU/ml) levels were 2.54+/-1.4 and 2.58+/-1.3; T4 (ng/dl) levels were 1.24+/-0.16 and 1.27+/-0.25, respectively. In the placebo group, TSH levels were 2.10+/-1.3 and 2.58+/-1.7; T4 levels were 1.28+/-0.20 and 1.34+/-0.22, respectively. No significant differences in these parameters were observed between groups. However, in the placebo group, TSH mean values were significantly increased after 10 months (p<0.05). The subjects given soy isoflavone showed significantly higher detectable levels of isoflavones than those in the placebo group.

Conclusions: The soy isoflavone extract does not exerted effects on thyroid function in postmenopausal women.

Skin Health

Relationship between Equol Producer and Skin Condition in Japanese Premenopausal Women. Tomomi Ueno*1, Atsuko Onoda3, Yasuhiro Abiru1, Shigeto Uchiyama1, and Taisuke Seki2, 1Saga Nutraceuticals Research Institute, Otsuka Pharmaceutical Co., Ltd., Kanzaki-gun, Saga, Japan, 2Seki Dermatological Clinic, Toyama, Toyama, Japan.

Equol, which is the bacterial metabolite of daidzein, is a stronger estrogenic or anti-estrogenic compound. Equol have beneficial effects on osteoporosis, hyperlipidemia, and breast cancer. It has been reported that there is an individual difference in the equol metabolism. There are 50% equol producers in middle-aged Japanese. However, the past research reported that Japanese younger women and men were low frequency equol producers (H. Akaza, Jpn J Clin Oncol, 2004).

On the other hand, estrogen increases skin thickness and improves skin moisture of facial skin. Equol seems to inhibit 5alpha-reductase activity, the conversion of testosterone to dihydrotestosterone which causes acne. Therefore, we hypothesized that equol has a beneficial influence on skin condition. However, effects of equol on the facial skin were still not clear. We tried to investigate about rate of equol producer and relationship between equol producer and acne, skin moisture.

Ninety-six premenopausal women (case: 48 patients of acne, control; 48 normal skin women) were recruited, rate of equol producer was 29.2%. Relationship between equol and acne was not able to clarify. However, skin moisture in equol producer was higher than in non-producer.

These results suggest that equol has beneficial effects on skin moisture. Further intervention study is necessary to determine effects of equol ingestion on equol non-producer.

Effects of ImmuBalance on Atopic Dermatitis: Preclinical Study using Atopic NC/Nga Mice. Akane Tanaka*1, Weijun Pan2,3, Nobuyuki Kingyo3, Ohmori Keitaro1, and Hiroshi Matsuda1, 1Tokyo University of Agriculture and Technology, Japan, 2Beth Israel Deaconess Medical Center, USA, 3Nichimo Co., Ltd., Japan.

Effect of probiotics on the prevention of early atopic diseases has been indicated recently. Particularly, fermented soy product downregulated peanut-specific response in peanut-allergic mice. ImmuBalance, which is a koji fungus (Aspergillus oryzae) and lactobacteria soybean fermentation product, is suggested to have beneficial effect for the regulation of an immune system in allergic conditions. Thus, we examined whether ImmuBalance had preventive effect on atopic dermatitis (AD) using an AD model, NC/Nga mice. NC/Nga mice with AD were fed ImmuBalance containing (2%) or regular (control) chow for 2 weeks. Clinical skin severity scores, transepidermal water loss (TEWL), scratching behavior in a fixed period were determined. In ImmuBalance-applied mice, clinical skin conditions were gradually ameliorated, and at the end of the experiment, clinical scores in the ImmuBalance-applied group were significantly reduced as compared to the control group as well as the result from TEWL examination. Scratching behavior in a control group was increased according to the progress of dermatitis; on the other hand, it was unchanged before and after the experiment in an ImmuBalance-applied group. Further examination might take place, but these results indicate that ImmuBalance may have some beneficial effects on improvement of established AD without side effects.
大 豆と地球環境

国連食糧農業機関は現在、地球の土地の 1/3 が牧畜と家畜用飼料の生産に使われていると報告しています。牛肉 1 キログラムを得るためには、7 〜 11 キログラムの飼料となる穀物が必要と言われています。しかし、そのまま穀物が人々の直接の食べ物になるなら、世界の食糧問題と環境問題は大きく解決に近づきます。

（東京大学生産技術研究所教授神大貴著『世界の水危機、日本の水問題』より）

大豆食は、肉食に替わるたんぱく質の補給源となることから、食糧問題や環境問題の鍵を握ると注目を集めています。

Soybeans and the environment

According to a report published by the Food and Agriculture Organization of the United Nations, one third of the earth's entire land surface is used for grazing or to produce animal feed. It is said that cattle require seven to eleven kilos of grain in order to generate one kilogram of beef. Were this grain to be directly consumed by humans it would bring the world substantially closer to resolving its food and environmental problems.

- From World Water Crisis and Japanese Water Resource Issues by Taikan Oki, Professor at the Institute of Industrial Science, the University of Tokyo.

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2008 年 8 月末現在
Sunday, November 9, 2008

12:00–8:00 pm .......................... Registration ............................................ Kiku Ballroom Lobby, 4th Floor
2:00–2:15 pm .......................... Opening Remarks .................................. Kiku-yo/Kikka Rooms, 4th Floor
2:00–6:00 pm .......................... Sponsor Showcase/Posters .......................... Kiku-en Room, 4th Floor
2:15–5:40 pm .......................... Oral Presentations ............................... Kiku-yo/Kikka Rooms, 4th Floor
3:30–4:00 pm .......................... Break .................................................. Kiku-en Room, 4th Floor
6:00–8:00 pm .......................... Welcome Reception ......................... Yamato Room, 3rd Floor

Monday, November 10, 2008

7:30 am–3:00 pm .......................... Registration ............................................. Kiku Ballroom Lobby, 4th Floor
7:30 am–3:00 pm .......................... Sponsor Showcase/Posters .......................... Kiku-en Room, 4th Floor
9:00 am–12:00 pm .......................... Oral Presentations ............................... Kiku-yo/Kikka Rooms, 4th Floor
10:20–10:45 am .......................... Break .................................................. Kiku-en Room/Kika Foyer, 4th Floor
12:00 pm–1:00 pm .......................... Luncheon .......................................... Yamato & Katsura/Kasuga Rooms, 3rd Floor
12:00 pm–1:00 pm .......................... Dessert Buffet ........................ Kiku-en Room/Kika Foyer, 4th Floor

Symposium concludes early to give attendees the afternoon at their leisure.

Tuesday, November 11, 2008

7:30 am–5:30 pm .......................... Registration ............................................. Kiku Ballroom Lobby, 4th Floor
7:30 am–6:30 pm .......................... Sponsor Showcase/Posters .......................... Kiku-en Room, 4th Floor
8:55 am–12:20 pm .......................... Oral Presentations ............................... Kiku-yo/Kikka Rooms, 4th Floor
10:40–11:00 am .......................... Break .................................................. Kiku-en Room/Kika Foyer, 4th Floor
12:40–2:00 pm .......................... Luncheon .......................................... Yamato & Katsura/Kasuga Rooms, 3rd Floor
2:00–5:20 pm .......................... Oral Presentations .................................. Kiku-yo/Kikka Rooms, 4th Floor
3:40–4:00 pm .......................... Break .................................................. Kiku-en Room/Kika Foyer, 4th Floor
5:30–6:30 pm .......................... Dedicated Poster Viewing Reception .... Kika Foyer, 4th Floor
6:30–8:30 pm .......................... Dinner ................................................ Yamato Room, 3rd Floor

Special Event Sponsored by Soy Nutrition Institute Japan

Wednesday, November 12, 2008

7:30 am–1:00 pm .......................... Registration ............................................. Kiku Ballroom Lobby, 4th Floor
7:30 am–10:30 am .......................... Sponsor Showcase/Posters .......................... Kiku-en Room, 4th Floor
8:55 am–12:20 pm .......................... Oral Presentations ............................... Kiku-yo/Kikka Rooms, 4th Floor
10:00–10:30 am .......................... Break .................................................. Kiku-en Room/Kika Foyer, 4th Floor