Winning Abstracts from the
3rd Annual
Natural Supplements Research Competition

Scripps Center for Integrative Medicine
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Report on the Research Awards from the 3rd Annual Natural Supplements Research Competition

ROBERT ALAN BONAKDAR, M.D.*

The 3rd annual Natural Supplements Research Competition was hosted by the Scripps Center for Integrative Medicine on January 18–20, 2006, in La Jolla, CA, and took place as part of the conference “Natural Supplements: An Evidence Based Update.” This Continuing Medical Education conference, which was cosponsored by the Scripps Clinic and the University of California at San Diego (both in La Jolla) brought together a group of more than 400 health care providers to discuss emerging trends in the field of dietary supplements. The research presentations took place throughout the weekend of the conference with accepted posters that were eligible for awards in three categories:

III. Original Clinical Research
III. Basic Sciences / Review / Case Studies
III. Student

The posters were judged by a multidisciplinary team in areas including originality, study design, interpretation, and relevance to the conference theme. All participants received book prizes including The Review of Natural Products 4th Edition† by Facts and Comparisons Publishing. The top posters in each category received cash prizes of up to $1,000 with sponsorship by American Specialty Health (San Diego, CA). Posters accepted included international entries as well as those from botanical research centers including Bastyr University, Kenmore, WA. This year’s competition also had greater participation by students, residents, and fellows thanks to tuition scholarships provided by American Specialty Health.

A brief overview of the research winners as well abstracts are presented below. The next Natural Supplements Research Competition will take place in conjunction with the 4th annual Natural Supplements: An Evidence Based Update conference January 19–21, 2007 in La Jolla, CA. Further information, including research entry forms can be obtained at www.Scrippsintegrativemedicine.org

FIRST PLACE

First- and second-place awards in the original research categories were garnered by Jay Udani, M.D., the medical director of the Northridge Hospital Integrative Medicine Program, Northridge, CA, and affiliated with Medicus Research, also in Northridge. He and his colleagues looked at innovative natural supplement approaches for hyperlipidemia and glycemic control. In the first study a randomized double-blinded placebo-controlled crossover design was utilized to test a “healthy cookie” that contained 8 g of soluble fiber and more than 2 g of plant sterols. The healthy cookie demonstrated a significant reduction in total and low-density lipoprotein cholesterol and fasting glucose compared to placebo.

The second-place study examined the ability of additive natural supplements in modifying the glycemic index (GI). In this trial the addition of a white kidney bean extract (Phaseolus vulgaris) by Phase2® (Pharmachem Laboratories, Kearny, NJ) in increasing doses to white bread was able to decrease its GI. The mechanism appears to be related to α-amylase inhibition and, as Dr. Udani concluded, this provides “a novel and potentially effective method for reducing the GI of existing foods without modifying their ingredient profiles.”

The third-place award was presented to Karyn Purvis, Ph.D., and colleagues at the TCU Institute of Child Development, who examined the use of amino acids as a novel approach for treating children with behavioral disorders. Based upon urinary neurochemical markers, subjects were treated with targeted amino acid therapy.Upon follow-up testing, the amino acid group had significant improvement in behavioral assessments and in several neurochemical markers compared to placebo. The researchers concluded that, in this high-risk group, the targeted amino acids had an apparent ability to modulate “high levels of excitatory neurotransmitters (NTs) (e.g., phenylethylamine [PEA], glu-
tamate) combined with low levels of inhibitory NT (e.g., serotonin, gamma-aminobutyric acid).”

**CATEGORY II**

Several promising areas of basic research emerged as well as insight on the discussion about and recommendation of dietary supplements. Ryan B. Bradley, N.D., of Bastyr University and Erica B. Oberg, N.D., of the University of Washington (Seattle) took first place for their work on “Algorithmic Naturopathic Treatment of Type 2 Diabetes: An Evidence-Based Approach.” Their collaborative efforts examine the evidence-based integration of various natural supplements including chromium, vanadium, coenzyme Q-10, ginseng (Panax quinquefolius), gymnema (Gymnema sylvestre), and cinnamon (Cinnamomum cassii) for treating diabetes. As the authors noted, “[A]s with all polypharmacy, natural or otherwise, a risk–benefit analysis should underly clinical recommendations.”

The second-place award was given to Debra Bemis, Ph.D., and colleagues at the Columbia University Medical Center, New York, NY, for their examination of a combination phyto–anti-inflammatory, Zyflamend® (New Chapter, Inc., Battleboro, VT) for treating prostate cancer. The product contains a combination of herbal products with anti-inflammatory actions including turmeric (Curcuma longa), ginger (Zingiber officinalis), holy basil (Ocimum sanctum), and green tea (Camellia sinensis). In this in vitro study, Zyflamend inhibited cell growth and induced apoptosis via cyclooxygenase-independent mechanism(s) potentially involving modulation of several cell-signaling proteins (p21, p21AR, pStat3, and pPKCα/β).

The third-place award in this category came from researchers at the Nicholas Piramal Research Centre in Mumbai, India, whose laboratory work examined the anti-inflammatory potential of the traditional Indian herb Mundi (Sphaeranthus indicus). A specific extract of Mundi was utilized in various in vitro and in vivo models of inflammation including synovial cells obtained from patients with rheumatoid arthritis (RA) who were undergoing knee-replacement surgery. In these models, Mundi was found to inhibit tumor-necrosis factor (TNF)–α as well as other proinflammatory cytokines (interleukin [IL]–1 β, IL-6, and IL-8) in a dose-dependent fashion while demonstrating a low toxicity profile in the in vivo model. Because of these preliminary results, the authors suggested that this botanical agent may have clinical promise for treating RA.

**CATEGORY III**

Winners in the student (both degree members of residency programs) category included Michael Kurisu, D.O., of the University of California at San Diego, whose poster provided a timely review of the role of a specific butterbur (Petasites hybridus) formulation, Petadolax® (Weber & Weber International GmbH & Co. KG–USA, Windermere, FL) for preventing migraine headaches. Butterbur, which has been recommended for hundreds of years for treating inflammatory, allergic, and respiratory disorders has received recent attention because of several trials demonstrating significant benefit over placebo when the herb was taken for migraine headache, typically at 150 mg per day. Melanie Fiorella, M.D., also of the University of California at San Diego, asked the question: “Does the dose of isoflavonoids predict the efficacy of soy products in the treatment of hot flashes?” There has been much controversy regarding soy’s (Glycine max) potential in this setting with conjecture regarding the isoflavone type and content which may predict soy’s benefit in this setting. The review of 18 randomized controlled trials found a positive correlation between improvements in hot flashes and products with a high proportion of the isoflavone genestin.

Overall, the 3rd annual research competition provided several areas of innovation in the use of natural supplements from the in vitro area of promise to well-controlled clinical trials that may influence practice. What is equally important is that the work of Drs. Bradley and Oberg, who examined how integration of multiple natural supplements can be performed in an evidence-based fashion. Similarly, Dr. Fiorella reminded us that not all supplements are created alike and thus require identification of specific brands and dosages that may have the best potential to benefit patients. Careful analyses like this underlie the “art” that is needed in deciphering and incorporating the “science” in our clinical recommendations. The next stage of integration, which examines the potential risk–benefit for incorporating natural therapies with conventional care, is eagerly awaited.

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Category I, First Place

A SOLUBLE FIBER AND PLANT STEROL–CONTAINING COOKIE FOR LOWERING CHOLESTEROL: A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED STUDY.

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Background: The inverse association between plasma cholesterol and coronary risk (including cardiovascular mortality) has been well-established in the literature. Two effective components of nutritional therapy for lowering cholesterol include plant sterols and soluble fiber. The objective of this study was to assess the effects of the addition of soluble fiber (8 g) and plant sterols (2.6 g) (SFPS)-containing cookies compared with placebo cookies on a population with mild-to-moderately elevated cholesterol.

Methods/design: A randomized double-blind, placebo-controlled crossover study of 33 moderately hyperlipidemic (mean total cholesterol 211.1 mg/dL; range 158.4–297.3; and mean LDL [low-density lipoprotein] 127.9 mg/dL; range 80.3 to 195.1) subjects was performed. The subjects (11 male and 22 female) aged 35–65 with a BMI [body–mass index] between 25 and 35 kg/m2, were randomly assigned to treatment with the SFPS cookies or placebo cookies for 4 weeks. After completing the first 4 weeks, subjects were washed out for 4 weeks after which they were placed on the other cookies. Subjects continued their normal diet and exercise regimens during the entire study.

Results: Statistically significant reductions were seen in favor of the SFPS cookies compared with the placebo cookies in total cholesterol (203 ± 30 versus 217 ± 28, p = 0.006); LDL cholesterol (120 ± 30 versus 133 ± 27, p = 0.008); and fasting glucose (91 ± 10 versus 95 ± 8, p = 0.045). Intake of the SFPS cookies resulted in an increase in LDL peak diameter compared to the placebo cookies (27.57 ± 0.06 nm versus 27.35 ± 0.08 nm, p = 0.038). No significant differences were observed in weight, triglycerides, or HDL between the two groups.

Conclusion: Moderately hyperlipidemic subjects were able to significantly reduce their total cholesterol, LDL cholesterol, and fasting glucose while increasing their LDL particle size when consuming soluble-fiber and plant-sterol–containing cookies compared with placebo cookies. The SFPS cookie appears to be a novel and effective potential adjunct to other lifestyle and pharmacological interventions for reducing the cardiovascular risks of elevated serum cholesterol.

Category I, Second Place

A NOVEL METHOD OF LOWERING THE GLYCEMIC INDEX OF WHITE BREAD USING A PROPRIETARY WHITE BEAN EXTRACT.

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Background: The Phase2® (manufactured by Medicus Research) product is a water-extract of a white kidney bean (Phaseolus vulgaris) and has been shown to inhibit the digestive enzyme α-amylase, which is responsible for the digestion of complex carbohydrates. Slowing this digestive process may lower the glycemic index (GI) of certain foods. Prior research has demonstrated that lower GI diets are associated with a lower risk of diabetes and heart disease and may lower cholesterol and HbA1c. The objective of this study was to assess the effects of the addition of Phase2 on the glycemic index of commercially available white bread.

Methods/Design: An open-label, 6-arm crossover study with 13 randomized subjects. Standardized GI testing (following the published Food and Agriculture Organization (FAO) methodology) was performed on Wonder Brand White Bread with and without the addition of Phase2 capsules and powder, each in dosages of 1500 mg, 2000 mg, and 3000 mg.

Results: Clinically meaningful reductions in the GI of Wonder Brand White Bread were seen at all dosages and formulations except the 1500-mg capsule dose. These reductions reached statistical significance with 3000 mg of Phase2 in powder form (−20.23 or 39.07%, p = 0.0228).

Conclusion: The GI of Wonder Brand White Bread was significantly reduced by the addition of 3000 mg of the Phase2 brand white bean extract in powder form with other dosages and formulations trending toward significance. With the appropriate dose and formulation, the Phase2 white bean extract appears to be a novel and potentially effective method for reducing the GI of existing foods without modifying their ingredient profiles. Given the potential health benefits of a low GI diet, further study of Phase2 at adequate dosage / formulation combinations with other high-GI foods should be considered.

Category I, Third Place

AN EXPERIMENTAL EVALUATION OF TARGETED AMINO ACID THERAPY WITH AT-RISK CHILDREN

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Purpose: In this preliminary investigation we explored the efficacy of targeted amino acid therapy (TAAT) with adopted children at risk for serious behavior disorders. These special-needs adopted children can be especially difficult to treat using behavioral and/or pharmacological approaches and often present ongoing challenges for parents and the professionals who treat them.

Methods: Fifty-seven families, with a total of 97 children, were recruited through local support groups for adoptive parents. Approximately half of the children (48) had received one or more clinical diagnoses. Families were randomly assigned to either a treatment group (TG) or to a delayed-treatment control group (CG). Seventy-eight children had complete data, with noncompletion rates being approximately equal across the two treatment groups. There were 44 children (14 girls, 30 boys, average age 10.0 years) in the TG, and 34 children (14 girls, 20 boys, average age = 9.7 years) in the CG. The treatment consisted of amino-acid supplements designed to provide nutritional support for serotonin and GABA [gamma-aminobutyric acid] production. Data were collected once in mid-July and once in mid-September. Children provided morning urine samples, and parents completed the Achenbach’s Child Behavior Checklist (CBCL) at both timepoints. Urine samples were assayed for eight neurotransmitters (NTs): epinephrine, norepinephrine (NE), dopamine, serotonin, GABA, glutamate, phenylethylamine (PEA), and histamine.

Results: Data were analyzed using repeated measures multivariate analysis of variance (MANOVA) and ANOVA (analysis of variance). The TG showed significant improvements, relative to the CG, on four of eight NT assays—epinephrine (2% versus 53%), serotonin (+148% versus +9%), GABA (+21 versus 19%), and PEA (+8% versus +40%)—and on six of eleven CBCL subscales—Anxiety/De-
pression (29% versus 3%), Thought Problems (33% versus 13%), Attention Problems (18% versus 1%), Aggressive Behavior (21% versus 5%), Other Problems (23% versus +1%) and Externalizing Behaviors (22% versus 6%). Regression analyses suggested that PEA played an especially important role in the patterns of change, especially with regard to Thought Problems and Other Problems.

Conclusions. These improvements, resulting from a brief 2-month intervention, suggest that TAAT has considerable promise as an intervention for behaviorally disordered children. NT pretesting revealed that this group of children had high levels of excitatory NT (e.g., PEA, glutamate) combined with low levels of inhibitory NT (e.g., serotonin, GABA), and this information was crucial in targeting the nutritional intervention to the children’s greatest need.

Category II, First Place

ALGORITHMIC NATUROPATHIC TREATMENT OF TYPE 2 DIABETES: AN EVIDENCE-BASED APPROACH

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Background: The Naturopathic Medicine Research Agenda (NMRA) selected type 2 diabetes as a model condition in which to critically evaluate the promise of naturopathic medicine in health care. Available research demonstrates naturopathic physicians utilize evidence-based CAM treatments in their approach to type 2 diabetes, which are combined in a health care delivery style unique to naturopathic philosophy. Treatments include guideline-supported therapeutic lifestyle change (TLC) as “foundational treatment” plus bioactive/functional foods, nutritional/botanical supplements, and therapeutic techniques to affect behavioral modification. Although the level and quality of evidence varies among practices, and from one supplement to another, the totality of evidence for CAM in diabetes deserves attention. In this poster, the authors present their experience with the development of an evidence-based, clinical algorithm directing the use of nutritional and botanical medicines based on their known mechanisms of action in diabetes.

Methods: A thorough review of published clinical trials on CAM therapies plus recognized clinical evaluation strategies were combined with available descriptive data on current naturopathic clinical practices to develop initial treatment algorithms. The resulting algorithms underwent peer review and refinement following a Delphi protocol by leaders in naturopathic medicine research plus clinicians with diabetes specialization.

Results: The resulting algorithms used clinical decision points based on measures of glycemic control (hemoglobin A1c), insulin resistance (HOMA-IR), beta-cell reserve (HOMA-BR), presence of diabetic complications, and select nutritional assessments to make stepwise recommendations for nutritional (e.g., chromium, vanadium, coenzyme Q10, antioxidants, carnitine, magnesium, vitamin D, etc.) and botanical medicines (e.g., Panax quinquefolius, Gymnema sylvestre, Cinnamomum cassia, Camellia sinensis, Trigonil foenecus-graecum, etc.). Recommendations are based on level of evidence and are presented according to mechanism of action (e.g., insulin sensitizer, beta-cell protectant, antioxidant, etc.) in the algorithms.

Conclusions: Through careful analysis of the totality of data on nutritional and botanical treatments and direction by recognized clinical markers of disease status, an evidence-based clinical treatment approach using nutritional and botanical medicines is achievable. The use of algorithmic models appears to be an effective approach to accurately capture the unique aspects of a CAM system of medicine while providing a point of comparison with conventional treatment approaches. As with all polypharmacy, natural or otherwise, a risk–benefit analysis should underly clinical recommendations.

Category II, Second Place

ZYFLAMEND®, A UNIQUE HERBAL PREPARATION WITH NONSELECTIVE COX INHIBITORY ACTIVITY, INDUCES APOPTOSIS OF PROSTATE CANCER CELLS INDEPENDENTLY OF COX-2

Bemis D, Capodice J, Buttyan R, Katz A
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Introduction and Objectives: Cyclooxygenases (COX) inhibitors have suppressive effects on several types of cancer cells, including prostate cancer. This study considers COX inhibitory activity of a unique anti-inflammatory herbal preparation (Zyflamend®, New Chapter, Inc., Battleboro, VT), and analyzes its effects on the human prostate cancer cell line, LNCaP. Zyflamend is comprised of supercritical CO2 extracts from ten herbs: rosemary (Rosmarinus officinalis); turmeric (Curcuma longa); ginger (Zingiber officinale), holy basil (Ocimum sanctum); green tea (Camellia sinensis); hu zhang (Polygonum cuspidatum); Chinese goldthread (Coptis chinensis); barberry (Berberis vulgaris); oregano (Origanum vulgare); and baikal skullcap (Scutellaria baicalensis). Each of these herbs have been reported to have significant COX-2 inhibitory activity, general anti-inflammatory, or antioxidant activities in either the crude extract or in compounds present within the herbs.

Methods: COX inhibitory activity was determined by a spectrophotometric-based assay using purified ovine COX-1 and COX-2 enzymes. In vitro cell growth and apoptosis were assessed by cell counting, Western blot detection of poly(ADP-ribose)polymerase (PARP) cleavage, and measurement of caspase-3 activity in treated and control cell extracts. Effects on expression of the cell signaling proteins, p21, AR, p-PKCα/βII, and p-Stat3 were determined by Western blotting. Phosphorylation status of several signal-transduction phosphoproteins was profiled via high-throughput phosphoprotein screening assay in treated and control cells. RT-PCR was utilized to determine COX-2 mRNA levels in LNCaP, PC-3, and CWR 22Rv1 human prostate cancer cell lines.

Results: Zyflamend dramatically decreased COX-1 and COX-2 enzymatic activity. Elevated p21 expression coincided with attenuated cell growth following treatment of LNCaPs with Zyflamend. PARP cleavage fragments were evident and caspase-3 activity was up-regulated indicating Zyflamend induced apoptosis in LNCaPs. Androgen receptor protein levels declined by 40%, and decreases were observed in the phosphorylated (active) forms of Stat3 and PKCα/βII following treatment.

Conclusions: As we confirmed, the lack of COX-2 expression in LNCaPs, our data suggests that Zyflamend inhibits cell growth and induces apoptosis via COX-independent mechanism(s) potentially involving enhanced expression of p21 and reduction of AR, pStat3 and pPKCα/βII. Additionally, we believe LNCaP cells provide a unique model to further study the observed COX-independent activities of COX-2 inhibitors.

Category II, Third Place

SPHAERANTHUS INDICUS—A PRO-INFLAMMATORY CYTOKINE INHIBITOR HERB AS A POTENTIAL CANDIDATE FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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Purpose: The misery caused by rheumatoid arthritis (RA), a chronic, systemic, articular inflammatory disorder has been known to [humanity] from time immemorial. The role of proinflammatory
cytokines such as tumor necrosis factor-α (TNF-α), IL-1, IL-6, and IL-8 in initiating an autoimmune reaction to produce rheumatoid synovitis followed by joint destruction in RA has also come to light. Sphaeranthus indicus (known as Goarakhandi or Mundi in India) is a well-known medicinal herb that could possess immunomodulatory action. To assess this, certain in vitro and in vivo tests have been conducted to demonstrate the possible role of S. indicus in preventing rheumatoid arthritis.

**Methods:** Alcoholic extracts of fruiting and flowering heads of S. indicus and a phytoactive were evaluated using an in vitro screening model of inflammation, specifically directed toward inhibition of TNF-α. The alcoholic extract and phytoactive were studied at eight different concentrations in lipopolysaccharides (LPS)–induced TNF-α, IL-1β, IL-6, and IL-8 release in hPBMCs as well as synovial cells obtained from RA patients undergoing knee replacement surgery. In vivo studies were also undertaken by using LPS–induced TNF-α inhibition in a BALB/c mouse model with oral administration of 100 mg/kg of extract of S. indicus to evaluate its efficacy in TNF-α inhibition.

**Results:** The content of the phytoactive in an extract of S. indicus is 5%–7% by HPLC (high-performance liquid chromatography). It showed a dose-dependent inhibition of LPS-induced TNF-α release and other proinflammatory cytokines by hPBMCs after 5 hour-incubation and was nontoxic at the doses tested. The IC50 of the phytoactive for TNF-α inhibition was 0.18 μg/mL. An extract of S. indicus showed a dose-dependent inhibition of LPS-induced TNF-α, IL-1β, IL-6, and IL-8 inhibition in synovial cells after a 10-hour incubation. According to an evaluation of in vivo findings, the extract of S. indicus inhibited TNF-α release after an LPS challenge in BALB/c mice at 100 mg/kg body weight.

**Conclusion:** The S. indicus extract profoundly inhibits TNF-α and other proinflammatory cytokines in various in vitro and in vivo assays and suggests that this botanical agent may indeed have clinical efficacy in treatment of RA. The phytoactive present in S. indicus also shows promising TNF-α inhibitory activity, which could be studied further and then developed as a prospective NCA candidate in RA.

**Category III, Student Winner**

**A REVIEW OF THE SAFETY AND EFFICACY OF PETA- SITES HYBRIDUS (BUTTERBUR) EXTRACT FOR PRO- PHYLAXIS OF MIGRAINE HEADACHES**

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**Introduction:** Butterbur, Petasites hybridus, is a native European perennial shrub that flourishes along banks and streams. An extract of Petasites root has been used for medicinal purposes since ancient times and is currently being applied to a variety of conditions including migraine headaches. The extract is marketed, under the name of Petadolax® (Weber & Weber International GmbH & Co., KG—USA, Windmere, FL) in the United States, United Kingdom, and Germany.

**Objective:** To review the available published clinical evidence for the use of butterbur extract for the prophylaxis of migraine headaches.

**Study design / methods:** A review of the published clinical trials of the use of butterbur extract for the prophylaxis of migraine headaches. Literature searches, and reference lists, as well as manufacturers were used for the most relevant and recent publications.

**Results:** RCT [randomized controlled trial] # 1: Grossman et. al 2001, Two-arm double blind study, N = 60. Length = 12 weeks. 50 mg of Petadolax versus placebo. The active treatment was more effective in the reduction of migraine attacks. An independent re-analysis in 2003 demonstrated a responder rate of 45% and a decrease of migraine attack frequency per month by 52% (p = 0.0024). RCT #2: Lipton et. al. 2004, Three-arm double blind study, N = 245, Length = 4 months. 50 mg, 75 mg, and a placebo given b.i.d. Migraine attack frequency was reduced by 48% for the dose of 75 mg (p = 0.0012). Responder rate = 68%. The 50 mg b.i.d. dosing was not significantly more effective than placebo.

**Study # 3: Pohtm et. et. al. 2005, Prospective open-label study.** N = 108. Length = 4 months. Dose = 50 to 150 mg. Responder rate = 74% in the children and 86% in the adolescents. Seventy seven percent of total patients reported a reduction in migraine attack frequency of at least 50%.

**Safety study: Danesch et. et. al. 2003, An independent study on the safety of butterbur root extract using animal studies, clinical trials, surveillance, and pharmacovigilance.** Conclusions were: No toxicity or severe adverse effects with excellent tolerability with the most common side-effect being mild eructations. An importance was stressed on standardizing an extract of butterbur.

**Conclusion:** The use of the butterbur extract, Petadolax, was well-tolerated with minimal GI (gastrointestinal) side-effects and led to a decrease of 50% migraine attack frequency per month in the adult as well as the pediatric populations. Effective dose ranging between 100 and 150 mg per day. Future research should focus on long term placebo controlled trials utilizing dose response in varied headache populations.

**Category III Student Category Runner-Up**

**SOY SUPPLEMENTS FOR HOT FLASHES: DOES DOSE AND COMPOSITION MATTER?**

M. Fiorella  
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**Objective:** To assess whether the dose and composition of soy supplements are a factor in their effectiveness to decrease hot flashes in menopausal women.

**Background:** While estrogen remains the most effective treatment for the relief of hot flashes, women have been turning to “natural” therapies since the Women’s Health Initiative reported the risks associated with estrogen therapy. Soy has held promise as a natural therapy since studies demonstrated a link between the soy-based Asian diet and low rates of menopausal symptoms in Asian women. However, studies have provided conflicting answers to the question, “is soy effective in alleviating hot flashes?” Data analysis is complicated by large variations in study parameters and quality, and there have been differing views among recent review authors. One concluded soy supplements’ efficacy is dependent on a woman’s baseline hot flash severity, another that soy is ineffective. This review evaluates whether the dose and composition of the supplement studied is a factor in whether soy alleviates hot flashes.

**Methods:** Major databases were searched using key words related to soy, isoflavones, and menopause. Exclusion criteria were participants with breast cancer and isoflavones from sources other than soy. The studies were assigned a quality rating. They were then grouped according to positive or negative outcome and compared for patient characteristics, study design, and soy product used.

**Results:** Eighteen randomized-controlled trials (RCTs) and two abstracts were compared resulting in eight studies that did not show a benefit of soy and ten that did. Poor statistical quality and lack of descriptive detail limited the comparisons. Of the detailed, high-quality studies, there was a positive correlation between improvements in hot flashes and products with a high proportion of the isoflavone genistein.

**Conclusion:** Soy supplements with a high proportion of the isoflavone genistein appear to be beneficial in reducing hot flash number and severity. Further studies are needed to look at how these results correlate with recommending a soy-based diet.