

**College of Health Sciences
Research Grant Proposal 2016
Required Cover Sheet**

Faculty Name: Mary Onysko

College unit: Pharmacy

Title of Research Project:

Pilot Study to Evaluate the Efficacy of Fenugreek Furostanolic Saponin to Improve Metabolic Parameters in Obese Subjects

Budget Request: \$ 7,500

Signature statement: I understand that acceptance of a CHS grant award obligates me to an oral presentation of the funded research at a future CHS “Grand Rounds” research day and submission of a report to the CHS research committee outlining the findings of the research and timeline for manuscript and/or grant submission within 18 months of grant funding date.

Signature



Date: 3/3/16

Office/cell phone: 303-788-3172

Email: monysko@uwoyo.edu

(total word count 1454)

2. INTRODUCTION

Type 2 diabetes (T2DM) is an emerging worldwide health problem [1-3]. A major reason for the increased prevalence of T2DM is the growing epidemic of obesity [4]. Insulin resistance, characterized by an impaired responsiveness of the body to insulin, is a pre-diabetic stage in the transition from obesity to full-blown T2DM, which affects an estimated 80 million Americans [6-7]. Early identification and treatment of prediabetes can delay the progression to full-blown diabetes. However, pharmacological agents that improve the sensitivity of insulin are somewhat limited [8]. The development of pharmacological strategies to target prediabetes therefore remains a mounting challenge.

Recent clinical studies suggest that the extract of the spice fenugreek reduces fasting and post-prandial blood glucose and glycated hemoglobin [9-12]. Furostanolic saponins (FS) from fenugreek has been recently shown to have an excellent safety profile and possess antidiabetic properties [13-14]. To this end, my collaborator has begun a pilot clinical study in Laramie to determine the metabolic effect of FS in overweight/obese insulin-resistant human subjects. However, given the demographics and population of Laramie, a major deterrent for the study is limited subject enrollment, especially those that meet the inclusion criteria.

As an Ambulatory Care Clinical Pharmacist at the Swedish Family Medicine Residency Clinic, I treat and counsel a large population of prediabetic subjects on a routine basis. This lends to an opportunity to expand the pilot study as a multi-center study. Accordingly, the specific aim of the proposed study is to determine the efficacy of FS to improve glucose tolerance and insulin sensitivity in insulin-resistant, overweight/obese subjects. We propose to employ a randomized, double blind, placebo controlled pilot clinical study to evaluate the effect of oral supplementation with FS on glucose tolerance (oral glucose tolerance study), insulin resistance (hemostatic model assessment of insulin resistance or HOMA-IR, C-proteins), redox status (total antioxidant capacity, glutathione, 8-isoprostane, 13-hydroxyoctadecadienoic acid) and inflammatory markers (interleukin-6, tumor-necrosis factor- α , C-reactive proteins), serum lipids and adiponectin. Our central hypothesis is that supplementation with FS improves metabolic parameters in overweight/obese subjects. Successful completion of this proposal will provide a strong, evidence-based framework for the development of FS as adjunct for therapy or prophylaxis of diabetes and related conditions.

3. APPROACH

Study subjects and design:

Following informed consent, health-screening, and satisfaction of inclusion/exclusion criteria, 30 research participants will be randomly assigned to receive either placebo (microcrystalline cellulose) or FS (500 mg twice daily) capsules for a period of 12 weeks. FS will be prepared by solvent extraction and column purification and formulated into capsules by Cepham Inc., (Piscataway, NJ). Overweight or obese (body mass index greater than 25kg/m²) male and female subjects aged 18-59 who satisfy ONE of the following inclusion criteria will be

included in the study: i) Fasting blood glucose >100 mg/dL ii) Fasting insulin level >9.0 uIU/mL. iii) Hemoglobin A1C (HbA1c) >5.6% iv) 2h-post-challenge glucose level of 125mg/dL [15, 16] v) HOMA-IR >2.5 Subjects diagnosed with diabetes, pregnancy, coronary artery disease, concurrent use of any medications, and other known chronic diseases will be excluded. The subjects will be randomized via a computer generated allocation sequence.

Insulin sensitivity and oral glucose tolerance test (OGTT):

At baseline and at the end of the treatment period, fasted subjects will consume 75g of dextrose dissolved in 250 mL of water over a 10 min period. Venous blood (~10 mL) will be sampled at time 0 and at 2h following ingestion to determine the concentrations of blood glucose, insulin, HbA1c, serum lipids, C-reactive proteins will be analyzed by ELISA. HOMA-IR will be calculated according to the formula: fasting insulin ($\mu\text{U/L}$) x fasting glucose (nmol/L)/22.5.

Anthropometry and body composition:

Height and weight will be determined using a stadiometer and physician's scale. Waist circumference will be measured midway between the lateral lower rib margin and the iliac crest. Diastolic and systolic blood pressure will be measured twice, 1 min apart after a 5-min rest period, on the non-dominant arm while participants are seated.

Oxidative stress markers and serum adiponectin:

Plasma samples will be shipped by overnight fedex to the lab of Dr. Nair where the blood samples will be analyzed. Plasma concentrations of 8-iso-PGF 2α , 13-HODE, and protein carbonyls will be quantified by colorimetric ELISA (Enzo Life Sciences International). The ratio of reduced glutathione to oxidized glutathione will be determined as described previously [15]. Plasma total radical-trapping antioxidant parameter (TRAP) will be measured using Total Antioxidant Capacity Assay kit (Northwest Life Science Specialties). Plasma ferric reducing antioxidant power (FRAP) will be determined using a colorimetric detection kit (Arbor Assays) [16,17].

Statistical analysis:

Statistical analyses will be performed by using SPSS for Windows software (version 17.0) and R version 3.1.3. When appropriate, we will describe patient characteristics using means \pm SEMs for continuous variables and proportions \pm SEP (Standard Error of Proportions) for categorical variables. Baseline differences in these variables between placebo and treatment groups will be evaluated by Student's t-test for independent samples. When distributional assumptions are not met, intervals will be constructed via non-parametric bootstrap. Differences in post intervention outcome measures between the placebo and treatment groups will be evaluated by ANCOVA with the pretreatment values as covariates. Significance will be set at $p < 0.05$. Power calculations for the determination of required sample sizes were not performed due to the lack of preliminary data for estimating variability. However, previously published studies suggest that a sample size of 30 (2 groups of 15) will be sufficient to identify significant differences in the primary outcomes ($\alpha = 0.05$; power = 90%) [18-22].

Anticipated results, potential pitfalls and alternative strategies:

We *anticipate* that compared to daily ingestion of placebo, daily ingestion of FS will result in one or all of the following changes: i) improved glucose tolerance evidenced by lower post-glucose challenge blood glucose levels ii) improved insulin sensitivity, evidenced as lower HbA1c, decline in HOMA-IR index and an attenuated C-peptide level iii) Improvement in lipid profile – evidenced by lower levels of serum low-density-lipoprotein cholesterol and a higher levels of high-density lipoprotein iv) increased TRAP and FRAP, lower protein carbonyl levels,

increase in the ratio of reduced glutathione to oxidized glutathione vi) reduction in serum 8-iso-PGF2 α and 13-HODE, TNF α , IL-6, and v) increase in adiponectin levels. Results in favor of our hypothesis would support the further development of fenugreek FS as an agent to treat cardiometabolic conditions. In an unlikely event that we do not see any difference, we would have to conclude that either the test agent does not alter cardiometabolic parameters or alternatively at the dose studied. A potential shortcoming without approach is that the HOMA-IR which is derived from fasting insulin levels primarily reflects hepatic insulin sensitivity and not necessarily peripheral insulin sensitivity [23]. If we observe inconsistencies in HOMA-IR index, we will use the serum obtained at 2h OGTT to calculate Matsuda index which is a combined indicator of both hepatic and peripheral insulin sensitivity [24].

PROJECT TIMELINE

Date	Task
May-Jun, 2016	IRB application
July-Oct, 2016	Subject recruitment, screening, enrollment, randomization, intervention
Oct - Jan, 2017	Continue treatment, subject review and refill every 4 weeks
Jan-Apr, 2017	Post-treatment blood draw, OGTT, blood analysis
May-Jun, 2017	Data analysis, manuscript preparation, data presentation at AACP or ADA Meeting; Prepare extramural grant application

4. SIGNIFICANCE

In 2010, the prevalence of insulin resistance among adults 20 years or older was >35%, which amounts to an estimated 80 million of Americans with prediabetes [25]. Early intervention of pre-diabetes can substantially delay the progression to full-blown diabetes. Diet and exercise have beneficial effects in slowing the progression of the disease, although adherence and patient acceptability is often a problem in the general population [26]. Drugs such as metformin and thiazolidinediones can counter insulin resistance but are known to cause significant side effects that limit their use [27]. Therefore, identifying and characterizing pharmacological agents to treat obesity and related conditions assumes importance. A large proportion of the US population use nutritional dietary supplements, either alone or as an adjunct to conventional agents to treat diabetes or delay its onset [28-30]. However, despite such wide acceptance, systematic studies in humans using the active components of natural products (vis-à-vis crude extract) to establish causality are lacking. The outcome of these studies will potentially lead to the characterization of a novel plant-based drug candidate, with established safety profile, that can improve insulin sensitivity in obese subjects and delay the onset of T2DM.

5. FUTURE PLANS

As a clinical pharmacist in the ambulatory care facility a vast majority of my patients are obese and diabetic. Characterizing novel treatment strategies aimed at prediabetes is therefore an area of research interest that I propose to develop. The data obtained from these studies will be used as preliminary studies for a proposal to be submitted to the NIH in response to the RFA-AT-16-001 (Phased Innovation Award for Exploratory Clinical Trials and Studies of Natural Products in NCCIH High Priority Research Topics) or similar funding requests to the American Diabetes Association and American Heart Association.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Mary Onysko	POSITION TITLE Clinical Associate Professor of Pharmacy Practice		
eRA COMMONS USER NAME (credential, e.g., agency login) monysko			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
Oregon State University/Oregon Health and Science University	PharmD	6/2006	Pharmacy
Ambulatory Care Specialty Residency		7/2007	Pharmacy

A. Positions and Employment

July 2013-present	Clinical Associate Professor of Pharmacy Practice, University of Wyoming
Aug 2007-July 2013	Clinical Associate Professor of Pharmacy Practice, University of Wyoming
July 2006-July 2007	Pharmacy Resident, Providence Physician Division, Providence Health and Services Portland, Oregon

Honors/Awards 2012 Pharmacy Practice Faculty of the Year

Professional Memberships: American Society of Health Systems Pharmacy (ASHP); American College of Clinical Pharmacy (ACCP) ; American College of Clinical Pharmacy (ACCP)

B. Selected Peer-Reviewed Publications *(These are the featured publications and research from my co-investigator, Dr. Nair. I do not have any publications specifically related to this application):*

Relevant (in terms of the methods and concepts being used) to the current application (in chronological order):

1. Ceylan-Isik AF, **Sreejayan N**, Ren J: Endoplasmic reticulum chaperon tauroursodeoxycholic acid alleviates obesity-induced myocardial contractile dysfunction. *J Mol Cell Cardiol* 50:107-116, 2011
2. **Nair, S.**, Ren J: Autophagy and cardiovascular aging: Lesson learned from rapamycin. *Cell Cycle*. 2012; 11: 11 (review article)
3. Hua Y, Zhang Y, Dolence J, Shi GP, Ren J, **Nair S.**: Cathepsin K Knockout Mitigates High-Fat Diet-Induced Cardiac Hypertrophy and Contractile Dysfunction. *Diabetes*, 62: 498-509, 2013
4. Xu X, Hua Y, **Sreejayan N**, Zhang Y, Ren J: Akt2 knockout preserves cardiac function in high-fat diet-induced obesity by rescuing cardiac autophagosome maturation. *J Mol Cell Biol*. 5:61-63, 2013
5. Panzhinskiy E, Hua Y, Culver B, **Nair S.**: Endoplasmic reticulum stress up-regulates protein-tyrosine phosphatase 1B expression and impairs glucose uptake in cultured myotubes. *Diabetologia*, 16: 598-608, 2013

Additional publications of mine (Dr. Onysko) in chronological order:

1. McBryde M., Vandiver JW., **Onysko M.** Transitions of care in medical education: A compilation of effective teaching methods. *Family Medicine*. Accepted for publication October 12, 2015. In press.
2. **Onysko M.**, Legerski P. (student author), Potthoff J. (student author), Erlandson M. “Targeting neuropathic pain: Consider these alternatives” – *Journal of Family Practice* 2015 Aug;64(8):470-475.
3. Mlodinow S., **Onysko M.**, Vandiver J., Hunter M., Mahvan T. “Statin adverse effects: Sorting out the evidence” *Journal of Family Practice* 2014 Sep;63(9):497-506.
4. Reeder CD, **Onysko M.** “Does weight loss as a result of surgery increase libido in men with low sex drive?” *Evidence-Based Practice* 2014;17(8)E16.
5. Winslow B., **Onysko M.**, Thompson K., Caldwell K., Ehlers G., “Common Questions About *Clostridium difficile* Infection” *American Family Physician* 2014;89(6):437-442.
6. Vandiver JW., Faulkner D., Erlandson M., **Onysko M.** “Is a novel anticoagulant right for your patient?” *Journal of Family Practice* 2014;63(1):22-8.
7. O’Day J.(student author), **Onysko M.** “Are ACE inhibitors effective in preventing diabetic nephropathy in type 2 diabetics without proteinuria?” *Evidence-Based Practice* 2014;17(1)14.
8. **Onysko M.**, Rutten M.(student author), “Are postmenopausal women taking calcium supplementation at an increased risk of myocardial infarction?” *Evidence-Based Practice* 2013;17(10)11-12.
9. Leach K., **Onysko M.** “How common is tachysystole with fetal heart rate abnormalities when inducing labor with misoprostol?” *Evidence-Based Practice* 2013;16(9)14.
10. Mah N., **Onysko M.** “In a patient with hyperlipidemia, what target triglyceride level should be used to eliminate the risk of pancreatitis?” *Evidence-Based Practice* 2013;16(8)10.
11. Darrow P., **Onysko M.**, Hunter M. “How long should anticoagulation be continued in a patient with a DVT” *Evidence-Based Practice* 2013;16(8)8.
12. Underdahl J. (student author), Burch J., **Onysko M.** “Is there any harm to using diuretics in patients with chronic kidney disease?” *Evidence-Based Practice* 2013;16(6)12.
13. Engelhardt M.(student author), Burch J., **Onysko M.** “Can imipramine be used for attention deficit disorder?” *Evidence-Based Practice* 2012;15(12)17-18.
14. Salvesson L., **Onysko M.** “How common are allergic reactions to topical antibiotics?” *Evidence-Based Practice* 2012;15(11)13.
15. **Onysko M.**, Burch J. “Current standards and future treatments of rheumatoid arthritis” *Formulary* 2012;47:359-368.
16. Reece M., Winslow B., **Onysko M.** “Is massage effective for relieving pain from minor back and neck trauma?” *Evidence-Based Practice* 2012;15(8)9.
17. Darnell J. (student author), **Onysko M.**, Hunter M. “In patients taking warfarin, what are the risks of adding supplemental fish oil?” *Evidence-Based Practice* 2012;15(6)11-12.
18. Bradley A.(student author), Hunter M., **Onysko M.** “What are the benefits of Omega-3s in pregnancy?” *Evidence-Based Practice* 2012;15(2)10.
19. Hunter M., **Onysko M.** “What is the most effective first-line medical treatment of patients with primary Raynaud’s phenomenon?” *Evidence-Based Practice* 2012;15(1)8-9.
20. Winslow B., **Onysko M.**, Stob C., Hazlewood K. “The Treatment of Alzheimer’s Disease” *American Family Physician*. 2011;83(12)1403-1412.

21. Maxwell J, Winslow B, **Onysko M**. “Does the uric acid level provide diagnostic information in patients with hyponatremia who are taking a diuretic?” Evidence-Based Practice 2011;14(7)9.
22. Lange T.(student author), Hunter M, **Onysko M**, Winslow B. “Denosumab (Prolia®) for osteoporosis” Evidence-Based Practice 2011;14(1)1-2.
23. Hunter M, **Onysko M**. “Is there a difference in the absorption of omega-3 fatty acids from different sources?” Evidence-Based Practice 2011;14(1)10-11.

C. Research Support None

D. PROPOSED BUDGET:

	Item	Unit Price	Total
1.	IRB costs	250.00	250.00
2.	Subject compensation (gift card) For completing the study \$100 x 30 If not qualified: \$15 x 20	3000.00 300.00	3300.00
3.	Chemicals, reagents, consumables Eliza's for insulin, kits for measuring oxidative stress (pre and post intervention)	1500.00	3500.00
4.	Shipping costs	450.00	450.00
	Total		7500.00

BUDGET JUSTIFICATION:

1. Dollar 250 is the cost of filing IRB at Swedish Medical Center (I have already registered with their IRB site and am preparing the proposal.)
2. We plan on enrolling 30 subjects and giving each subject an Amazon gift card of \$100 value as a compensation. However, we estimate about 20 subjects who may not qualify after the initial blood draw who will be given a \$15 gift card for their participation
3. Consumables: Dollar 3500 has been budgeted for glucose testing and ELISA kits for insulin, oxidative stress assay, adiponectin, serum lipids and chemicals for GSH/GSSG quantification.
4. Shipping: Dollar 450 has been budgeted for costs towards shipping the samples to Laramie.

BIBLIOGRAPHY:

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2. Novotny R, Fialkowski MK, Li F, Paulino Y, Vargo D, Jim R, Coleman P, Bersamin A, Nigg CR, Leon Guerrero RT, Deenik J, Kim JH, Wilkens LR. Systematic Review of Prevalence of Young Child Overweight and Obesity in the United States-Affiliated Pacific Region Compared With the 48 Contiguous States: The Children's Healthy Living Program. *Am J Public Health* 2015;105:e22-e35.
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8. Kinch MS, Umlauf S, Plummer M. An analysis of FDA-approved drugs for metabolic diseases. *Drug Discov Today* 2015.
9. Neelakantan N, Narayanan M, de Souza RJ, van Dam RM. Effect of fenugreek (*Trigonella foenum-graecum* L.) intake on glycemia: a meta-analysis of clinical trials. *Nutr J* 2014;13:7.
10. Suksomboon N, Poolsup N, Boonkaew S, Suthisisang CC. Meta-analysis of the effect of herbal supplement on glycemic control in type 2 diabetes. *J Ethnopharmacol* 2011;137:1328-33.
11. Fuller S, Stephens JM. Diosgenin, 4-Hydroxyisoleucine, and Fiber from Fenugreek: Mechanisms of Actions and Potential Effects on Metabolic Syndrome. *Adv Nutr* 2015;6:189-97.
12. Mathern JR, Raatz SK, Thomas W, Slavin JL. Effect of fenugreek fiber on satiety, blood glucose and insulin response and energy intake in obese subjects. *Phytother Res* 2009;23:1543-8.
13. Swaroop A, Bagchi M, Kumar P, Preuss HG, Tiwari K, Marone PA, Bagchi D. Safety, efficacy and toxicological evaluation of a novel, patented anti-diabetic extract of *Trigonella Foenum-Graecum* seed extract (Fenfurol). *Toxicol Mech Methods* 2014;24:495-503.
14. Hua Y, Ren SY, Guo R, Rogers O, Nair RP, Bagchi D, Swaroop A, Nair S. Furostanolic saponins from *Trigonella foenum-graecum* alleviate diet-induced glucose intolerance and hepatic fat accumulation. *Mol Nutr Food Res*. 2015; 59: 2094-100.
15. Li SY, Du M, Dolence EK, Fang CX, Mayer GE, Ceylan-Isik AF, LaCour KH, Yang X, Wilbert CJ, Sreejayan N, Ren J. Aging induces cardiac diastolic dysfunction, oxidative stress, accumulation of advanced glycation endproducts and protein modification. *Aging Cell* 2005;4:57-64.

16. Fabbrini E, Serafini M, Colic Baric I, Hazen SL, Klein S. Effect of plasma uric acid on antioxidant capacity, oxidative stress, and insulin sensitivity in obese subjects. *Diabetes* 2014;63:976-81.
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18. Krysiak R, Okrzesik J, Okopien B. The effect of short-term metformin treatment on plasma prolactin levels in bromocriptine-treated patients with hyperprolactinaemia and impaired glucose tolerance: a pilot study. *Endocrine* 2014.
19. Bjorndal B, Strand E, Gjerde J, Bohov P, Svardal A, Diehl BW, Innis SM, Berger A, Berge RK. Phospholipids from herring roe improve plasma lipids and glucose tolerance in healthy, young adults. *Lipids Health Dis* 2014;13:82.
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23. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *Am J Physiol Endocrinol Metab* 2008;294:E15-26.
24. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care* 1999;22:1462-70.
25. <http://diabetesniddk.nih.gov/dm/pubs/statistics/#Pre-diabetesY20> (accessed on Feb 12, 2016).
26. Vitolins MZ, Anderson AM, Delahanty L, Raynor H, Miller GD, Mobley C, Reeves R, Yamamoto M, Champagne C, Wing RR, Mayer-Davis E, Look ARG. Action for Health in Diabetes (Look AHEAD) trial: baseline evaluation of selected nutrients and food group intake. *J Am Diet Assoc* 2009;109:1367-75.
27. Liao EP. Management of type 2 diabetes: new and future developments in treatment. *Am J Med* 2012;125:S2-3.
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Report of Previous CHS Funding

No previous CHS funding.

Thursday, March 03, 2016

Mary Onysko, PharmD, BCPS
Clinical Associate Professor of Pharmacy Practice
University of Wyoming School of Pharmacy
Swedish Family Medicine Residency
191 E. Orchard Road #200
Littleton, Colorado 80121

Dear Mary,

I am happy that you are planning on submitting a proposal for the CHS- faculty grant initiative. Although you had started your IRB submission at Swedish in January, you were unable to complete the process as we did not have a committed funding for this project. Getting this funding would help us to complete the planned studies. As you are aware, we have begun part of the study here, but due to the demographics of Laramie we have had difficulties recruiting subjects who satisfied our inclusion criteria. An obvious advantage you have in your practice site is that you see a number of subjects every day who would qualify to participate in the study. Also, being in a medical center, unlike us you have the support staff, lab facilities and residents which are great help in furthering this project. All in all, I am excited that we are able to do our study as a multi-centered trial which would be a strong validation of our findings. I believe this would also strengthen any manuscripts that may arise from the study. Once we obtain sufficient preliminary data I would suggest that we submit a joint proposal to the NIH's Exploratory Clinical Trials and Studies of Natural Products in NCCIH and the American Diabetes Association's Research Grant for Clinical Trials

As you have indicated in your proposal, my lab is well set to perform the biochemical and clinical analysis of the serum samples. We have the serum samples from our studies here and it would be interesting to compare the parameters from your cohort to those of ours. As a collaborator I would be glad to commit 10% of my time on your project.

I look forward to collaborating with you.

Sincerely,



Sreejayan Nair, PhD
Professor of Pharmacology
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sreejay@uwyo.edu