Supplementation of Conventional Therapy with the Novel Grain Salba (*Salvia hispanica L.*) Improves Major and Emerging Cardiovascular Risk Factors in Type 2 Diabetes: Results of a Randomized Controlled Trial

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Running title: Salba improves CVD risk factors in diabetes

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**ABSTRACT**

**OBJECTIVE:** To determine whether addition of Salba (*Salvia hispanica L.*), a novel whole-grain, rich in fiber, alpha-linolenic acid (ALA) and minerals, to conventional treatment is associated with improvement in major and emerging cardiovascular risk factors in individuals with type 2 diabetes.

**RESEARCH DESIGN AND METHODS:** Using a single-blind, crossover design, subjects were randomly assigned to receive either 37±4 g/day of Salba or wheat bran for 12 weeks while maintained on their conventional diabetes therapies. Twenty well-controlled subjects with type 2 diabetes (11M:9F; age 64±8 years; BMI 28±4 kg/m²; A1C 6.8±0.9%) completed the study. Setting: outpatient clinic (Risk Factor Modification Center, St. Michael’s Hospital, Toronto, Canada).

**RESULTS:** Compared to control, Salba reduced systolic blood pressure (SBP) by 6.3±4 mmHg (p<0.001), hs-CRP (mg/L) by 40±1.6% (p=0.04), and vonWillebrand factor (vWF) by 21±0.3% (p=0.03), with significant decreases in A1C and fibrinogen in relation to the Salba baseline but not with control. There were no changes in safety parameters including liver, kidney and haemostatic function or body weight. Both plasma ALA and EPA PUFA levels were increased two-fold (p<0.05) while consuming Salba.

**CONCLUSIONS:** Long-term supplementation with Salba attenuated a major cardiovascular risk factor (SBP) and emerging factors (hs-CRP and vWF) safely beyond conventional therapy, while maintaining good glycemic and lipid control in people with well-controlled type 2 diabetes.

**Clinical Trial Registration:** ClinicalTrials.gov Identifier: NCT00362011.

**Abbreviations:** PUFA, polyunsaturated fatty acids; ALA, alpha-linolenic acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio, EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
Diabetes mellitus is a highly prevalent and heterogeneous condition, with cardiometabolic implications that can be improved by tight glycemic control. An aggressive reduction in major risk factors (RF) for cardiovascular disease (CVD) such as elevated blood pressure and dyslipidemia as well as emerging RF including pro-inflammatory and prothrombotic markers is recommended. However, despite an armamentarium of medications and lifestyle therapy, these goals are often difficult to achieve, placing people with diabetes at increased CVD risk. New treatment modalities to complement existing interventions are therefore of great interest, including dietary interventions for primary prevention or as a possible therapeutic option which may confer benefits beyond currently recommended conventional therapies.

There is growing evidence that whole-grains may play an important role in prevention of chronic disease. Collective endorsement of whole-grains by major health agencies around the world, including the Food & Drug Administration (FDA) approved health claim (1), is based on large epidemiological and prospective population studies that suggest a strong inverse relationship between increased consumption of whole-grain foods and reduced risk of diabetes and CVD (2). Populations that consume three or more servings per day may benefit from the cardioprotective benefits of whole-grain. It is however unknown which of the constituents of whole-grain is responsible for the benefit. Phyto-protective constituents, including dietary fiber, antioxidants, minerals and vitamins have been suggested but the physiological mechanisms of the cardioprotective effects are still poorly understood. The main sources of whole-grains in the diet are bread and breakfast cereals, which are relatively nutrient depleted foods due to aggressive industrial processing. Introduction of new varieties of whole-grain should be encouraged in order for the general public to best adhere to effective health strategies that promote whole-grain consumption. Furthermore, well-controlled intervention studies are required to provide information about the link of the specific nutrients from whole-grains to cardiovascular health.

Salba is a new generation of whole-grain produced by Salba Corporation S.A., Buenos Aires, Argentina, and cultivated by selective breeding (Agisalba S.A., Ica, Peru). Salba is a white color variety from the original herbaceous plant *Salvia hispanica* L., which is over 90 per cent black grain and is known as a “running food” and used as both food and remedy by the ancient Aztecs. Salba is a pleasant tasting grain which can easily be incorporated into a variety of baked products or just sprinkled onto yogurt, salad, soup etc. With its rich nutrient composition compared to most whole-grains currently recommended, Salba represents the highest whole food source of dietary fiber and the n-3 polyunsaturated fatty acid (PUFA) – alpha-linolenic acid (ALA) – in nature. In addition, it is an exceptionally rich source of vegetable protein, calcium, magnesium, iron and antioxidants (i.e. total antioxidant capacity is 70 per gram of Salba).

As all these nutrients have been implicated in lowering CVD risks, and as they occur naturally in Salba, we hypothesized that simple addition of Salba to conventional treatment may reduce CVD risk factors when added to the diet of individuals with well controlled type 2 diabetes.
RESEARCH DESIGN AND METHODS

Participants

The study was approved by the St. Michael’s Hospital ethics review board. Eligible participants gave written informed consent. Eligibility criteria included: documented type 2 diabetes for at least 6 month duration without clinically manifest complications, age 18-75 years, non-pregnant, metabolically stable (A1C 6.0-8.5%, fasting plasma glucose (FPG) 6.4-8.5 mmol/L), and not taking insulin, dietary fiber supplements, ALA supplements, fish oil or consuming cold-water fish more than 3 times per week. Subjects were instructed not to change their lifestyle and level of physical activity during the study.

Assuming a 35% attrition rate and a two-tailed $\alpha=0.05$ and $1-\beta=80\%$ to detect a 0.8% difference in A1C with a standard deviation (SD) of 0.8%, sample size calculations indicated that 27 participants needed to be enrolled to yield 19 participants for final analysis.

Treatments

The supplements were provided both in ground form and in specially formulated breads which were similar in appearance. Both the test and control intervention food were matched for energy and total dietary fiber. Salba was obtained from Salba Nutritional Solutions, Inc. (Toronto, Canada) and the wheat bran control from the American Association of Cereal Chemists (St. Paul, MN, USA). The Salba and control breads were prepared in a bakery using a standardized recipe and methodology. The ground supplements (Salba and control) were matched in appearance and were provided in opaque containers. Subjects were instructed to keep the bread and supplements in the refrigerator to minimize possible oxidation of the n-3 fats. Supplements were provided at a level of 15g/1000 Kcal intake, and were calculated according to subject’s individual daily energy requirements as estimated by the Harrison-Benedict equation multiplied by a “very light” activity factor of 1.3 and verified with the initial three-day dietary record. Control supplements contained wheat bran which is considered to be lipid neutral and has little effect on glucose tolerance (3).

Conventional therapy

Salba or control supplements were added to conventional therapy. Dietitians instructed the participants to consume a diet that followed the Canadian Diabetes Association (CDA) nutrition recommendations (4). The targeted macronutrient profile of carbohydrate:protein:fat was approximately 55%:15%:30%, with an emphasis on low-glycemic index carbohydrate sources, 25-35 g total fiber, $\leq10\%$ sugars, and less than 10% saturated fatty acids (SFA). To monitor compliance, dietary data were analyzed at weeks 0 and 12 for energy, macro- and micronutrients. Three-day food records were analyzed by using Food Processor Nutrition Analysis software, version 7.1 (ESHA Research, Salem, OR). Participants were also instructed to maintain their usual therapy (type and dose) of oral hypoglycemic, antihypertensive, or lipid-lowering medications. Salba or control supplements were added to this combination of a diet that followed CDA nutrition recommendations and usual therapy. By mimicking the macronutrient profile of the background CDA diets, the control supplements were designed to act as an extension of the diets.

Study design

The study used a randomized, placebo-controlled, single-blind, crossover design with four distinct periods, in which subjects acted as their own controls. Participants began with a run-in phase for at least two weeks to adjust to a healthy diet and to stabilize baseline parameters. Half of the participants were then randomized to either
the Salba or control treatment for the first of two 12-week treatment arms. This period was followed by a 4-6 week washout phase to mitigate carryover effects. For the second treatment phase, participants were crossed-over to the alternate treatment. During each treatment phase, participants attended the clinic every two weeks to have anthropometric and clinical measurements taken, submit symptom diary and three-day dietary records, receive new treatment foods, return unused bread and ground supplements, and have an interview with the dietitian and principal investigator. At weeks 0 and 12, fasting blood samples were collected.

Throughout the trial, an independent research assistant maintained the blinding of packages, labels, and diet randomization. Randomization was achieved using a computer generated random number table.

Participants were excluded if during the course of the study there were any changes to their regular antihypertensive, lipid-lowering, or oral hypoglycemic medications, consumed less than 50% of the study supplements or had a significant weight change over the course of the study, defined as >3 kg/3 months.

**Outcomes**

There were three levels of outcome measures - efficacy, safety, and compliance - for which separate models were constructed. Efficacy measures of glycemic control (A1C, FPG, and fasting plasma insulin (FPI)), blood pressure (systolic (SBP) and diastolic (DBP) office blood pressure), lipids (total cholesterol (TC), LDL, HDL, triglycerides (TG), and emerging risk factors for CVD (high-sensitivity C-reactive protein (hs-CRP), fibrinogen, VonWillebrand factor (vWF), and Factor VIII). Safety measures included markers of hepatic (aspartate aminotransferase (AST), alanine aminotransferase (ALT)), renal (serum urea and creatinine), and haemostatic (prothrombin time (PT), partial thromboplastin time (PTT), International normalized ratio (INR)) function. Finally, compliance measures included body weight change, quantity of returned bread and ground Salba supplements at follow-up visits, lifestyle adherence (dietary profiles and body weight) and plasma fatty acids.

**Measurements and analyses**

Office BP measurements were performed as described previously (5), with the cuff secured around the participant’s non-dominant arm. Samples for A1C and hepatic, renal, and hemostatic function were analyzed directly by St. Michael’s Hospital Core laboratory. Plasma A1C was determined using ion-exchange HPLC (Diamat HPLC, Bio-Rad Laboratories Ltd, Mississauga, Canada). PT and PTT were determined using appropriate reagents and automatic clot timers. INR was derived according to the formula: (patient PT/ mean normal PT)\[\text{Internal Sensitivity Index}\]. Serum ALT and AST were determined enzymatically. Serum creatinine and urea were determined by standard methods. Plasma glucose and insulin analyses were performed by the glucose oxidase and double antibody radioimmunoassay methods, respectively. Plasma total lipids were analyzed by gas liquid chromatography (6).

**Statistical methods**

Statistical analyses were performed using NCSS 2000 (NCSS statistical software, Kaysville, Utah). Comparisons of within- and between-treatment differences in compliance, efficacy, and safety outcomes were assessed using repeated measures GLM ANCOVA adjusted for sex, age, and sequence. Results were expressed as mean ± SD and significance was set at p<0.05. The Newman-Keuls procedure was used post hoc to adjust for multiple comparisons. Between treatment end results were adjusted for baseline values. Percent
changes for each variable are based on the calculation for each individual subject’s percent change. All comparisons were adjusted for age, sex, weight, BMI, use of cholesterol and hypotensive medications, aspirin, and oral hypoglycemic agents.

**RESULTS**

Forty-four subjects with type 2 diabetes were screened and 27 eligible subjects were enrolled in the study. Exclusions during Salba treatment and control were equal. Reasons for dropouts during the protocol included medication changes (n=3), refusal to continue (n=3), and increased gastrointestinal side effects (n=2). Final analysis included 20 patients with type 2 diabetes, 11 males and 9 females, (mean±SD): age 64±8 years, BMI 28±4 kg/m$^2$, and A1C 6.8±0.9%. Medication treatment received concomitantly by the participants was single or combined oral hypoglycemic agents (10 subjects on insulin secretagogues, nine on metformin, one on pioglitazone), four subjects were on HMG-CoA reductase inhibitors (three on atorvastatin and one on simvastatin), three were on low-dose aspirin, nine were on antihypertensive agents (four on ACE inhibitors, three on beta-blockers, two on calcium channel blockers). Participants who had a change in their medications were excluded from the final analysis.

**Compliance**

Within- and between-treatment differences in markers of compliance were assessed for both Salba and control treatment. Neither the proportion of supplements (cumulative bread and ground supplement) consumed over the 12 weeks between Salba and control (82±24% vs. 85±6%) nor body weight change from week 0 to week 12 (0.25±0.42 kg vs. 0.18±0.37 kg) was significantly different between Salba and control. Further proof of compliance is supported by the results of plasma total fatty acids analysis assessed at the end of each treatment. After 12 weeks of consuming Salba the participants had approximately double the plasma level of ALA (2.5±0.3% vs. 1.2±0.1%, p<0.05) and eicosapentaenoic acid (EPA) (0.18±0.03% vs. 0.09±0.02%; p=0.006), when compared to control.

**Diet**

Analysis of the three-day dietary records showed that participants maintained the diets they were instructed to follow. The addition of Salba to a healthy diet changed the macronutrient intakes between Salba and placebo treatment with respect to the percent of calories from carbohydrate and fat. In the Salba group the dietary profile was 45:21:34 (% calories from CHO:PRO:FAT) whereas the control diet was 54:19:27. Both total fat and PUFA were significantly higher in the Salba treatment than control (p<0.001) at the expense of CHO, which was significantly lower in the Salba group than control (p<0.001). The monounsaturated fatty acid (MUFA) content of the Salba phase was higher at p=0.04. As expected, the n-3 PUFA intake was also significantly higher and reached 7.4±4.3 g/day compared to 1.1±0.8 g/day on control (p<0.001). The mineral intakes were not significantly different except for magnesium which was significantly higher (p=0.03) on the Salba (612±149 mg) due to the high content of Mg in Salba compared to control (424±167 mg).

**Efficacy Parameters**

**Major CVD risk factors: Blood Pressure, A1C, Fasting Glucose, Insulin and Serum Lipids.** Compared to baseline, SBP dropped on the Salba treatment by 6.3±4.2 mmHg (p<0.001) to an average of 123±16 mmHg. DBP dropped by 3±1.3 mmHg on the Salba treatment but did not reach statistical significance (Table 1). On the control diet, the SBP increased by 7±1.17 mmHg and the DBP increased by 3.14±1.12 mmHg; as a result, both achieving statistical significance.
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at p<0.05, with 20±1% reduction for SBP and 7% DBP between Salba and the control. Mean measures of glycemic control at the end of the Salba phase (A1C, FBG and FBI) were not statistically different when compared to the end of the control phase (Table 1). No significant difference was observed comparing change from baseline in any parameter on the control phase. Fasting plasma blood glucose and insulin levels were approximately 3% lower after treatment with Salba but this did not reach significance. A1C was significantly reduced from baseline during the Salba treatment (p=0.02) but not when compared to control.

Blood lipids were not different comparing Salba to control treatment in any measured parameter (TG, LDL, HDL, TC) (Table 1). Baseline lipids were within targets as set by the 2006 Clinical Practice guidelines (7) with the exception of LDL which was marginally elevated (primary target LDL-C ≤2.0 mmol/L).

Emerging CVD Risk Factors: Coagulation and Inflammatory markers.

On the Salba treatment, fibrinogen level significantly decreased over the 12 weeks from 3.52±0.76g/L to 3.37±0.61g/L (p=0.03) but was not significantly different from control (Table 1). At the end of the Salba phase, vWF was significantly lower than control (p=0.03), while Factor VIII was reduced by 23%, although this did not reach statistical significance (p<0.06) when compared to control. Low-grade body inflammation measured by hs-CRP was not significantly different from baseline in the Salba phase (-7%, p=0.24) but increased significantly (33%) during the control phase (p=0.01) and was significantly higher at the end of the control phase compared to the end of the Salba phase (40%, p=0.04).

Safety

Mean INR, PT and PTT did not change over the 12 weeks of the study period on either the Salba or the control treatments (data not shown). Mean values of blood urea nitrogen and creatinine, both measurements of kidney function, were not significantly different. AST and ALT, measures of liver function, also did not change. Both baseline and post-intervention values were within normal ranges as set by St. Michael’s Hospital Core Laboratory.

CONCLUSIONS

This study demonstrated that a 12-week dietary supplementation with the novel whole-grain Salvia hispanica L. (Salba) was associated with attenuated systolic BP and the emerging risk factors (hs-CRP and vWF) in people with type 2 diabetes, controlled on diet and oral hypoglycemic agents.

An increasing body of evidence from epidemiological observational studies suggests a strong inverse relationship between consumption of whole-grain and the risk of diabetes and CVD (8). Many components of whole-grains, including complex carbohydrates, vegetable protein, n-3 PUFA, dietary fiber, minerals, antioxidants, and their combined effects could be responsible for this reduction. However, controlled interventional studies supporting health claims for whole-grain are scarce. Therefore, our study was designed to determine if the novel whole-grain Salba could reduce CVD risk factors when added to usual care of individuals with well controlled type 2 diabetes. To our knowledge, this is one of the first long-term randomized controlled trials (RCT) to demonstrate a simultaneous reduction of major and emerging CVD RF in an intervention using whole-grain in well-controlled diabetes.

All subjects in the study consumed more than 50% of supplements and were compliant with the treatment diet. Twelve-week dietary supplementation with 37±4 g/day of Salba (7 g/day ALA) resulted in a
two-fold elevation in plasma phospholipid EPA, with no change of docosahexaenoic acid (DHA), compared to control. Similar changes were observed in another study (9) where dietary supplementation of 9.5 g ALA per day during 3 months resulted in 87% increase in plasma total lipid EPA compared to control. A parallel 1.7 g/day EPA+DHA supplementation elevated plasma phospholipid EPA almost similarly, by 79% (9).

This study demonstrated the safety of adding 37 g of *Salvia hispanica* to a traditional healthy diet and conventional therapy. Although Salba has been used for many years in the diets of Aztecs in Mexico with no apparent side effects, there was a concern that a high amount of n-3 PUFA could alter the eicosanoids produced leading to an adverse effect on clotting factors. High doses of n-3 PUFA have been implicated in altered bleeding and clotting time (10). However, coagulation, liver enzymes and kidney function were not significantly affected by the addition of Salba in our study.

**Major cardiovascular RF**

Despite the fact that our acute pilot study demonstrated that bread made with Salba reduced postprandial glucose and insulinemia (11), there were no long-term beneficial effects of Salba treatment on fasting blood glucose and insulin. Although a significant change was seen across Salba treatment in A1C, this was not significant when compared to control presumably due to the already optimal baseline glycemic control (A1C=6.8±0.9%) achieved by subjects’ underlying diabetes therapy. Many factors in Salba may be responsible for this moderate glycemic lowering effect. Salba contains 36% of its weight as fiber, of which only 4 g are soluble fiber but of a very high viscosity. The viscous mucilage formed when fiber from Salba is exposed to water and human digesta might be one of the main factors potentially thought to affect glycemic control. Factors in Salba that may act against good glycemic control include high content of n-3 PUFA, that in some studies has been shown to increase A1C, fasting and postprandial glycemia in type 2 diabetes (12).

Dietary n-3 PUFA have been associated with reduction of serum triglycerides but at the expense of increasing LDL cholesterol levels. In the Lyon Diet Heart Study, the addition of n-3 PUFA to a high-carbohydrate, low-fat Mediterranean diet did not affect either TG, LDL, HDL or TC, yet still produced a 65% reduction in coronary heart disease (CHD) mortality, indicating that changes in traditional risk factors such as blood lipids are not the sole cause of CHD (13). Our study provides evidence that 37 g of Salba (7 g ALA) has no detrimental effect on blood lipid profile in a group of individuals with type 2 diabetes that are typically 2-4 times more susceptible to heart disease than the non-diabetic population.

Diet has long been implicated in reducing blood pressure. In addition to sodium, the micronutrients potassium (K), calcium (Ca) and magnesium (Mg) have also demonstrated blood pressure lowering effects both individually and in combination (14). With the exception of higher quantity of n-3 PUFA and magnesium on Salba, the treatments were not significantly different in known factors affecting blood pressure such as protein, fiber, sodium, potassium and calcium. Although nine subjects were receiving anti-hypertensive medications, both SBP and DBP dropped on the Salba treatment although the DBP did not achieve statistical significance, indicating that the drug therapy did not obscure response of blood pressure to n-3 treatment (15). It can be speculated that the mechanism of the reduction seen in SBP and possibly DBP, could be due a conversion of Salba’s ALA
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to EPA leading to the production of less vasoconstrictive prostaglandins through modification of the eicosanoid pathway. Most intervention studies show benefits of fish oil and EPA on blood pressure (16).

**Emerging cardiovascular RF**

Inflammation plays a major role in cardiovascular disease, and measurement of inflammatory markers such as hs-CRP may be beneficial for risk stratification (17). Many of the previous prospective studies evaluating the effect of either fish oil or ALA on hs-CRP did not find significant changes in hs-CRP levels with n-3 PUFA consumption (18). However, in several recent randomized controlled trials conducted in hypercholesterolemic subjects (19,20) consumption of ALA diets significantly decreased serum levels of C-reactive protein. Consistent with these findings, our results demonstrate that consumption of Salba, a grain naturally high in ALA, resulted in a significant decrease of hs-CRP, and the changes in serum ALA and EPA were inversely associated with changes in CRP. More recently, it has been suggested that increased levels of EPA alone may be cardioprotective. This is supported by the results of our study and a recent study which demonstrated that supplementation of purified EPA over 3 months to individuals with the metabolic syndrome resulted in reductions in small dense LDL particles and CRP levels (21).

Fibrinogen is negatively associated with the relative risk for cardiovascular disease and cardiovascular risk factors (22). Although fibrinogen level was not different from control, it significantly decreased from baseline on the Salba by 0.15 g/L. A systematic review by Wendland et al (23) indicated that ALA significantly affects fibrinogen concentrations, decreasing it by 0.17 mmol/L. This reduction would be expected to lead to a 6% decrease in CHD.

Although vWF is only weakly associated with the risk of CVD in the general population, it is more significant in high-risk populations such as people with diabetes (24). Salba treatment decreased the plasma level of this risk factor by 21% but whether it could be attributed to n-3 fatty acids or other components of the grain is unclear.

There was a trend towards reduction of Factor VIII (by 23%) in our study. Similarly, previous studies demonstrated either no change (25) or decrease (26) in activity of this factor with ALA or fish oil supplementation.

**Implications of preliminary results**

A simple whole-grain dietary intervention with Salba may potentially play an important role in the primary prevention of type 2 diabetes, by increasing adherence to the recommended three servings per day, as well as a therapeutic option which could be effective beyond currently recommended conventional therapies in improving major and emerging cardiovascular risk factors in type 2 diabetes. The amount of Salba consumed daily on this study was equivalent to the two portions of whole-grain as recommended by the FDA.

**Limitations**

The study was designed to determine the safety and efficacy of consuming the novel whole-grain Salba when added to the diet of individuals with type 2 diabetes while on conventional diabetes therapies. In such a design, no specific functional component from Salba treatment can clearly be implicated in any effect seen, but is comparable to the cardioprotective effect seen of other whole-grains. In addition to the numerous functional components in Salba, the supplementation of the Salba produced changes in the dietary macronutrient profile between the two treatments. Therefore, the changes in RF observed could possibly be explained by the
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change in carbohydrate and fat composition of the different diets (27) and future studies should compare Salba with control supplements that are matched for macronutrient composition. Furthermore, although subjects were instructed not to change their level of physical activity, the physical activity level during the study was not quantified which might bias the results. Finally, our main objective was to assess the effect of Salba on A1C in subjects with type 2 diabetes and the power of the study, limited to 20 participants, may not be sufficient for other than A1C parameters. Although the participants who completed the study were stable and well-controlled, they may not represent typical candidates for adjunctive therapy. Both of these cavities render the conclusion that larger studies need to be conducted with the need for intent-to-treat analysis instead of per-protocol analysis.

In conclusion, the novel whole-grain Salba which can be simply added to conventional treatment for type 2 diabetes improves major and emerging CVD RF while maintaining good glycemic and lipid control in well-controlled type 2 diabetes. The systolic blood pressure was reduced by 6.3±4 mmHg, despite the fact that nine out of 20 participants were taking anti-hypertensive medications which were not changed throughout the course of the study.

As Salba contains a high amount of n-3 PUFA, high dietary fiber, vegetable protein and magnesium, the combination may have resulted in the pronounced BP lowering effects seen on the Salba treatment. Emerging CVD risk factors (hs-CRP and vWF) were attenuated beyond usual therapy (three subjects taking low-dose aspirin) on the Salba. This effect could be attributed to a high content of ALA in the Salba and possibly the subsequent increase in EPA blood levels. No adverse effects of the conventional diet supplemented with the addition of Salba were documented, and liver function, kidney function, coagulation and bleeding time were normal. In addition, there were no adverse effects on either FPG, A1C or LDL cholesterol unlike previous studies with high doses of n-3 PUFA acids in individuals with diabetes.

ACKNOWLEDGMENTS
We wish to thank Salba Nutritional Solutions Inc, Toronto, Canada for providing Salba grain and to Lawrence Brown for invaluable logistic assistance in relation to study planning and ensuring the quality control of the test products. We also thank Trudy Brown for assistance in planning the study, and whose diligence in supplement preparation made this study possible.
REFERENCES


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### Table 1 – Changes in major and emerging CVD risk factors during and between the Salba and control study periods (n=20) *

<table>
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<th>Major CVD RF:</th>
<th>Salba</th>
<th>Control</th>
<th>Between treatment</th>
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<td>A1C (%)</td>
<td>Week 0</td>
<td>Week 12</td>
<td>Change %</td>
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<tr>
<td></td>
<td>6.9±0.8</td>
<td>6.7±0.9</td>
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<td>FBG (mmol/L)</td>
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<td>FBI (pmol/L)</td>
<td>74.4±28.8</td>
<td>86.1±39.1</td>
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<td>TC (mmol/L)</td>
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<td>4.9±1.2</td>
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<td>LDL (mmol/L)</td>
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<td>-1.2±1.0</td>
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<th></th>
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<td>-7.0±2.3</td>
<td>2.6±2.1</td>
<td>3.4±2.3</td>
<td>32.9±2.2†</td>
<td>-39.9±1.6</td>
<td>0.04</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.52±0.76</td>
<td>3.37±0.61</td>
<td>-5.32±</td>
<td>3.24±0.69</td>
<td>3.35±0.713</td>
<td>3.57±0.69</td>
<td>-8.89±</td>
<td>0.1</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>vWF</td>
<td>1.14±0.38</td>
<td>1.038±0.45</td>
<td>-9.12±</td>
<td>1.158±0.66</td>
<td>1.299±0.61</td>
<td>12.13±0.63</td>
<td>-21.25±</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Factor VIII</td>
<td>1.04±0.36</td>
<td>0.95±0.36</td>
<td>-8.68±0.36</td>
<td>0.85±0.39</td>
<td>0.97±0.47</td>
<td>14.3±0.43</td>
<td>-22.98±0.36</td>
<td>0.06±0.29</td>
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</tr>
</tbody>
</table>

*Data are mean ± SD and represent measures of efficacy. The safety and compliance data are described in the text. P values refer to between treatment differences using repeated measures GLM ANOVA adjusted for age, sex, weight, anti-hyperglycemic agents (A1C, FBG, FBI); adjusted for age, sex, weight, BMI, lipid lowering medications (TC, LDL, HDL, TG, hs-CRP); adjusted for age, sex, weight and aspirin use (fibrinogen, vWF, Factor VIII); adjusted for age, sex, weight, and BP medications (SBP, DBP). Percent changes for each variable are based on the calculation for each individual subject’s percent change.

† p<0.05.