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**Functional Food Synergies: improving the effect of the omega-3 fatty acid docosahexaenoic acid on cardiovascular disease risk factors through concurrent dietary consumption of canola or soy isoflavones**

Leisa Ridges

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Functional Food Synergies: Improving the effect of the omega-3 fatty  
acid docosahexaenoic acid on cardiovascular disease risk factors  
through concurrent dietary consumption of canola or soy isoflavones.

A thesis submitted in (partial) fulfilment of the  
requirements for the award of the degree

DOCTOR OF PHILOSOPHY (PhD)

From

UNIVERSITY OF WOLLONGONG

By

Leisa Ridges (BSc Hons)

School of Health Sciences  
2007

## **Certification**

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I, Leisa Anne Ridges, declare that this thesis, submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Health Sciences, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

Leisa Anne Ridges

14 September 2007

## Table of contents

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<b>1</b>	<b>Literature review .....</b>	<b>1</b>
1.1	Cardiovascular disease prevalence .....	2
1.2	Cardiovascular disease risk factors.....	2
1.2.1	Total and LDL cholesterol.....	3
1.2.2	HDL cholesterol .....	4
1.2.3	Triglycerides.....	5
1.2.4	Blood pressure .....	6
1.3	Guidelines for reducing CVD risk.....	7
1.4	Functional foods for CVD risk reduction .....	10
1.4.1	The shift to polyunsaturated fats .....	11
1.5	The Cardiovascular Benefits of Omega-3 Fatty Acids.....	14
1.6	Mechanisms of omega-3 fatty acid CVD protection .....	21
1.6.1	Blood lipid effects .....	21
1.6.2	Blood pressure and vascular function.....	25
1.7	Summary of cardiovascular risk factor effects of EPA and DHA.....	27
1.8	Omega-6 versus omega-3 fatty acids.....	28
1.9	Soy Isoflavones as a means for reducing LDL cholesterol .....	32
1.9.1	Introduction to soy protein and isoflavones.....	33
1.9.2	The cardiovascular protection offered by isoflavones.....	34
1.10	Complementary effects of soy isoflavones and DHA .....	39
1.11	Thesis Aims .....	42
<b>2</b>	<b>Monounsaturated oils and fish oil (MOFO) study.....</b>	<b>43</b>
2.1	Introduction .....	44
2.2	Study hypothesis.....	47
2.3	Methods .....	48
2.3.1	Subjects.....	48
2.3.2	Study design and protocol .....	48
2.3.3	Food and supplements .....	49
2.3.4	Arterial compliance instrumentation .....	52
2.3.5	Methodology for the assessment of arterial compliance .....	53
2.3.6	Laboratory analysis .....	54
2.3.7	Plasma and erythrocyte membrane analysis .....	55
2.3.7.1	Plasma fatty acid extraction procedure .....	56
2.3.7.2	Red blood cell membrane fatty acid extraction procedure.....	56
2.3.7.3	Flame-ionization capillary gas chromatography.....	56
2.4	Statistical analysis .....	57
2.5	Results .....	58
2.5.1	Plasma fatty acids.....	59
2.5.2	Erythrocyte membrane fatty acids.....	64

2.5.3	Plasma lipids.....	69
2.5.4	Arterial compliance and blood pressure .....	74
2.6	Discussion.....	76
2.6.1	Fatty acids.....	76
2.6.2	Lipids.....	83
2.6.3	Blood pressure, arterial compliance and heart rate.....	91
2.7	Conclusion .....	92
<b>3</b>	<b>Omega-Soy study .....</b>	<b>94</b>
3.1	Introduction .....	95
3.2	Study hypothesis.....	98
3.3	Methods .....	99
3.3.1	Subjects.....	99
3.3.2	Study design .....	100
3.3.3	Food and supplements .....	102
3.3.4	Clinical assessment protocol .....	104
3.3.5	Dietary compliance assessment .....	105
3.3.6	Clinical measurements.....	106
3.3.7	Twenty-four hour blood pressure assessment.....	106
3.3.8	Non-invasive arterial compliance assessment .....	107
3.3.9	Sample collection and analyses .....	107
3.3.10	Lipoprotein composition.....	108
3.3.11	Isoflavone analysis .....	109
3.3.11.1	Extraction and hydrolysis.....	109
3.3.11.2	Analysis of isoflavones .....	110
3.3.12	Statistical analysis .....	110
3.4	Results .....	113
3.4.1	Anthropometric results .....	113
3.4.2	Dietary intake .....	114
3.4.3	Initial plasma and urinary isoflavones.....	117
3.4.4	Isoflavones following soy cereal consumption.....	118
3.4.5	Erythrocyte membrane fatty acids.....	123
3.4.6	Total omega-3 fatty acids .....	127
3.4.6.1	Omega-3 Index.....	127
3.4.6.2	Omega-6 fatty acids .....	128
3.4.6.3	Omega-6:omega-3 fatty acid ratio .....	131
3.4.6.4	Oleic acid (OA).....	131
3.4.6.5	Saturated Fatty acids .....	132
3.4.7	Plasma lipids.....	134
3.4.8	Lipid correlations with isoflavones and fatty acids .....	139
3.4.9	Plasma lipoprotein composition .....	140
3.4.9.1	Very low density lipoprotein (VLDL) .....	140
3.4.9.2	Intermediate density lipoprotein (IDL) .....	146
3.4.9.3	Low density lipoproteins (LDL) .....	147
3.4.10	Arterial compliance .....	149
3.4.11	Additional cardiovascular measures .....	150
3.4.12	Blood pressure – clinic and ambulatory .....	152

3.5	Discussion.....	154
3.5.1	DHA supplementation .....	155
3.5.2	Soy isoflavone consumption.....	160
3.5.3	Combined effect of isoflavones and DHA on lipid metabolism.....	164
3.5.4	Arterial compliance, blood pressure, heart rate and other cardiovascular measures ..	165
3.6	Conclusion .....	170
<b>4</b>	<b>Discussion.....</b>	<b>171</b>
4.1	Food synergies and functional food combinations .....	172
4.2	How could EPA and DHA decrease fasting triglyceride concentrations?.....	173
4.3	How could EPA and DHA cause an increase in LDL cholesterol?.....	179
4.4	Theoretical framework for combined effect of canola and DHA on LDL cholesterol metabolism .....	182
4.4.1	Evidence to support a cholesterol lowering effect of canola or its components.....	183
4.4.2	Canola phytosterols and their potential for cholesterol reduction .....	185
4.5	Theoretical framework for combined effect of DHA and isoflavones on cholesterol metabolism .....	190
4.5.1	Effect of isoflavones and DHA on LDL receptor activity.....	191
4.5.2	Potential explanations for a combined effect of soy isoflavones and DHA on LDL cholesterol.....	192
4.5.3	Proposed mechanism #1 – An isoflavone enabling effect of DHA similar to soy protein. ....	195
4.5.4	Proposed mechanism #2: Formation of isoflavone-omega-3 fatty acid esters .....	197
4.5.5	Mechanism #3: Modification of hepatic redox state via antioxidant effect of isoflavones promoting hepatic LDL uptake by DHA .....	198
4.5.6	Summary of proposed mechanisms .....	199
4.6	Summary.....	201
4.7	Implications of this research.....	203
4.8	Conclusion .....	206
	References.....	208

## List of Tables

---

<b>Table 1.1</b> Review of outcomes from systematic reviews of the scientific literature on fish, fish oil and omega-3 fatty acids and the risk of CVD mortality and events. ....	18
<b>Table 1.2</b> Number of studies based on data contained in the systematic review by Wang et al. (2006) that reported significant reductions, trend toward a reduction, no effect or potential negative effect of dietary omega-3 fatty acid intake, fish oil or fish consumption on CVD outcomes in the general population.....	20
<b>Table 2.1</b> Blocking characteristics of the four intervention groups .....	49
<b>Table 2.2</b> Fatty acid profile of Hi-DHA Tuna Oil.....	51
<b>Table 2.3</b> Fatty acid content of dietary oils and margarines.....	51
<b>Table 2.4</b> Body weight at baseline and after six week with the four interventions.....	58
<b>Table 2.5</b> Plasma omega-3 fatty acids at baseline and after six weeks of the four interventions .....	60
<b>Table 2.6</b> Plasma omega-6 fatty acids at baseline and after six weeks of each intervention .....	62
<b>Table 2.7</b> Plasma monounsaturated and saturated fatty acids at baseline and after six weeks of intervention .....	63
<b>Table 2.8</b> Erythrocyte membrane omega-3 fatty acid content at baseline and after six weeks with the four interventions .....	66
<b>Table 2.9</b> Erythrocyte membrane omega-6 fatty acids, omega-6: omega-3 ratio and Omega-3 Index at baseline and after six weeks of the interventions.....	68
<b>Table 2.10</b> Erythrocyte membrane monounsaturated and saturated fatty acid content at baseline and after six weeks of the interventions.....	69
<b>Table 2.11</b> Fasting plasma lipid concentrations at baseline and after six weeks of dietary supplementation .....	73
<b>Table 2.12</b> Arterial compliance, blood pressure and heart rate at baseline and after six weeks with each intervention.....	75
<b>Table 2.13</b> Changes in blood lipids in human clinical trials using DHA supplementation.....	86
<b>Table 3.1</b> Blocking characteristics for the four intervention groups .....	100
<b>Table 3.2</b> Fatty acid profile of DHA Gold .....	103
<b>Table 3.3</b> Ingredient profile of the soy and control breakfast cereals .....	103
<b>Table 3.4</b> Body weight at zero, six and twelve weeks of the intervention period and changes in body weight after six and twelve weeks, in the four intervention groups.....	114
<b>Table 3.5</b> Dietary intake data obtained from diet histories for the two olive oil groups at zero, six and twelve weeks of the intervention period .....	115
<b>Table 3.6</b> Dietary intake data obtained from diet histories in the two DHA groups at zero, six and twelve weeks of the intervention period .....	116
<b>Table 3.7</b> Concentration of daidzein, genistein and equol in plasma and urine for each group and all groups combined at the commencement of the intervention period .....	117
<b>Table 3.8</b> Plasma isoflavone concentrations in the four groups before and after six weeks of soy cereal consumption .....	119



<b>Table 3.9</b> Concentrations of isoflavones in 24hr urine samples in the four groups before and after six weeks of soy cereal consumption.....	121
<b>Table 3.10</b> Estimated percent of total isoflavones consumed that were recovered in urine.....	122
<b>Table 3.11</b> Results from a 3 Factor ANOVA for plasma and urine concentrations of daidzein, genistein and equol using type of oil supplementation and order of soy cereal consumption as between group factors and time as the within group factor .....	122
<b>Table 3.12</b> Erythrocyte membrane omega-3 fatty acid content in the four groups before and after six and twelve weeks of either olive oil or DHA-rich oil supplementation.....	124
<b>Table 3.13</b> Erythrocyte membrane omega-6 fatty acid content in the four groups before and after six and twelve weeks of either olive oil or DHA-rich oil supplementation.....	129
<b>Table 3.14</b> Erythrocyte membrane saturated and monounsaturated fatty acid content in the four groups before and after six and twelve weeks of either olive oil or DHA-rich oil supplementation .....	133
<b>Table 3.15</b> Fasting plasma lipids in the two olive oil groups at baseline and after six and twelve weeks .....	135
<b>Table 3.16</b> Fasting plasma lipids in the DHA groups at zero, six and twelve weeks of the intervention period .....	137
<b>Table 3.17</b> Components in VLDL in which a significant difference was found between the groups taking olive oil and the groups taking DHA-rich oil at the end of the control cereal period.....	141
<b>Table 3.18</b> Change from baseline (t=0) in VLDL total cholesterol, cholesterol ester, triglyceride and apolipoprotein B as determined by repeated measures, 2 factor ANCOVA with age and BMI as covariates .....	142
<b>Table 3.19</b> LDL composition in DHAc-s compared with the two olive oil groups after six weeks of oil supplementation and control cereal consumption.....	148
<b>Table 3.20</b> Mean change in LDL total cholesterol, free cholesterol and phospholipid following six weeks of olive oil and DHA oil supplementation as determined by repeated measures ANCOVA with age and BMI as covariates .....	149
<b>Table 3.21</b> Large artery compliance in the two olive oil groups compared with the two DHA-rich oil groups before and after six weeks of oil supplementation and control cereal consumption.....	150
<b>Table 3.22</b> Heart rate in the olive oil and DHA oil groups at baseline and after six and twelve weeks .....	151
<b>Table 3.23</b> Cardiovascular parameters which were significantly different after six or twelve weeks of DHA supplementation compared with olive oil supplementation.....	151
<b>Table 3.24</b> Clinic blood pressure in the four intervention groups at baseline and after six and twelve weeks .....	152
<b>Table 3.25</b> Ambulatory systolic and diastolic blood pressure in the four intervention groups at baseline and after six and twelve weeks .....	153
<b>Table 3.26</b> Summary of the effects of DHA supplementation alone and the combination of DHA and soy isoflavones on plasma lipids between baseline and six weeks (0-6wks) and between six and twelve weeks of the study (6 – 12 wks).....	155

**Table 3.27** Comparison of lipid outcomes from clinical trials testing the effect of soy isoflavone supplementation (in the absence of soy protein) on plasma lipids, with the findings from the current study .....162

**Table 4.1** Similarities between soy protein and EPA and DHA effects on lipid metabolism enzymes .....196

## List of Figures

---

<b>Figure 2.1</b> Change in plasma EPA and DHA (% of total fatty acids) after 6 weeks of dietary intervention .....	60
<b>Figure 2.2</b> Change in the plasma and erythrocyte membrane omega-6: omega-3 fatty acid ratio after six weeks with the four interventions .....	62
<b>Figure 2.3</b> Changes in erythrocyte membrane omega-3 fatty acids with the four interventions.....	65
<b>Figure 2.4</b> Percent change in fasting plasma triglycerides based on tertiles of baseline triglyceride concentrations .....	70
<b>Figure 2.5</b> Change in LDL cholesterol after six weeks with the four interventions .....	71
<b>Figure 2.6</b> Change in total cholesterol after six weeks with the four interventions .....	72
<b>Figure 2.7</b> Comparison of percent change in fasting plasma triglycerides and dose of DHA supplementation from eleven human clinical trials .....	85
<b>Figure 3.1</b> Diagrammatical representation of the four dietary interventions .....	100
<b>Figure 3.2</b> A diagrammatical representation of study timeline showing clinic visit measurements and dietary monitoring tools. Each arrow represents one clinic visit. ....	105
<b>Figure 3.3</b> Plasma daidzein concentrations in the four groups before and after soy cereal consumption.....	119
<b>Figure 3.4</b> Plasma genistein concentrations in the four groups before and after soy cereal consumption.....	120
<b>Figure 3.5</b> Plasma equol concentrations in the four groups before and after soy cereal consumption .....	120
<b>Figure 3.6</b> Erythrocyte membrane DHA in the four groups before, and after six and twelve weeks of the intervention period.....	123
<b>Figure 3.7</b> Erythrocyte membrane EPA in the four groups before, and after six and twelve weeks of oil supplementation.....	125
<b>Figure 3.8</b> Erythrocyte membrane DPA in the four groups before, and after six and twelve weeks of oil supplementation .....	126
<b>Figure 3.9</b> Total omega-3 fatty acids in the four groups before, and after six and twelve weeks of oil supplementation .....	127
<b>Figure 3.10</b> Erythrocyte membrane LA in the four groups before and after six and twelve weeks of oil supplementation .....	128
<b>Figure 3.11</b> Erythrocyte membrane AA in the four groups before and after six and twelve weeks of oil supplementation.....	130
<b>Figure 3.12</b> Total erythrocyte membrane omega-6 fatty acids in the four groups before and after six and twelve weeks of oil supplementation .....	131
<b>Figure 3.13</b> Total cholesterol concentrations in the two DHA groups at baseline and at six and twelve weeks of the intervention period .....	136
<b>Figure 3.14</b> LDL cholesterol concentrations in the two DHA groups at baseline and at six and twelve weeks of the intervention period .....	136

<b>Figure 3.15</b> Change from baseline (t=0) in VLDL total cholesterol in the olive oil and DHA oil groups during the 6 weeks of control cereal and soy cereal .....	143
<b>Figure 3.16</b> Change from baseline (t=0) in VLDL cholesterol ester in the olive oil and DHA oil groups during the 6 weeks of control cereal and soy cereal .....	143
<b>Figure 3.17</b> Change from baseline (t=0) in VLDL triglyceride in the olive oil and DHA oil groups during the 6 weeks of control cereal and soy cereal .....	144
<b>Figure 3.18</b> Change from baseline (t=0) in VLDL apolipoprotein B in the olive oil and DHA oil groups during the 6 weeks of control cereal and soy cereal .....	144
<b>Figure 3.19</b> Percentage composition of VLDL in the two olive oil groups and two DHA groups at baseline and after six and twelve weeks of oil supplementation .....	145

## List of Abbreviations

AA	Arachidonic acid
ALA	Alpha linolenic acid
CAD	Coronary artery disease
CHD	Coronary heart disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
DHAc-s	Daily DHA-rich oil supplementation for twelve weeks with concurrent consumption of control cereal for the first six weeks followed by consumption of soy cereal between six and twelve weeks of the intervention period.
DHAs-c	Daily DHA-rich oil supplementation for twelve weeks with concurrent consumption of soy cereal for the first six weeks followed by consumption of control cereal between six and twelve weeks of the intervention period.
DPA	Docosapentaenoic acid
FXR	Farnesol X receptor
HDL	High density lipoprotein
HNF-4 $\alpha$	Hepatocyte nuclear factor 4 $\alpha$
IDL	Intermediate density lipoprotein
LCAT	Lecithin-cholesterol acyltransferase
LDL	Low density lipoprotein
LXR	Liver X receptor
OOc-s	Daily olive oil supplementation for twelve weeks with concurrent consumption of

	control cereal for the first six weeks followed by consumption of soy cereal between six and twelve weeks of the intervention period.
OOs-c	Daily olive oil supplementation for twelve weeks with concurrent consumption of soy cereal for the first six weeks followed by consumption of control cereal between six and twelve weeks of the intervention period.
PPAR	Peroxisome proliferator - activated receptor
SBP	Systolic blood pressure
SR-B1	Scavenger receptor B class-1
SREBP	Sterol regulatory element binding protein

## **Abstract**

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Ischaemic heart disease and cerebrovascular disease are among the leading causes of death in Australian men and women with heart diseases being the third highest cause of death in Australian women and fourth highest cause of death in Australian men (AIHW, 2006). In Australia more than 50% of all adults have two or three (out of a possible nine) risk factors for cardiovascular disease and 15% having four or more risk factors.

It has long been recognised that diet modification can reduce these risks. Recently dietary advice has moved from an “exclusionary” to an “inclusionary” paradigm. That is, rather than identify dietary items to avoid, current guidelines recommend incorporating advice to increase the consumption of a range of functional foods including marine sourced omega-3 fatty acids EPA and DHA and vegetable oils.

EPA and DHA are effective functional foods in reducing CVD mortality, cardiac death, sudden death and myocardial infarction. EPA and DHA provide this cardiovascular benefit by improving several risk factors including: fasting plasma triglycerides, blood pressure and arterial compliance. However, a safety concern of dietary EPA and DHA supplementation is their capacity to cause a significant increase in LDL cholesterol concentrations.

Dietary intake levels of EPA and DHA in the Australian diet are well below those associated with reductions in CVD risk. In 50% of the population a potential 20 – fold increase in EPA and DHA would be required to increase intake levels to those commensurate with reduced CVD risk.

While dietary supplementation with EPA and DHA is one means of increasing dietary intake levels, strategies to increase the efficacy of EPA and DHA would also be advantageous and could reduce supplement doses. Dietary strategies that could simultaneously counteract the rise in LDL cholesterol caused by DHA would also be beneficial.

The research described in this thesis aimed to modify the bioavailability and cardiovascular effects of DHA by modifying other dietary factors and combining DHA with other active ingredients. To address these aims two human clinical trials were conducted. The first examined the effect of altering the types of oil and margarine consumed in the diet with view to reducing the dietary intake of omega-6 fatty acids while supplementing the diet with DHA-rich fish oil (MOFO study). This study showed that replacing usual dietary oil and margarine with canola products while supplementing the diet with 1.1g/d of DHA favourably improved total omega-3 fatty acid incorporation and reduced the omega-6: omega-3 fatty acid ratio in plasma and erythrocyte membrane phospholipids as effectively as double the supplement dose of DHA. Additionally, there was a similar rise in erythrocyte membrane and plasma DHA when either safflower or sunola oil, which contain very different amounts of linoleic acid, were consumed concurrently with a daily dietary supplementation of 1.1g/d of DHA. A distinguishing feature of canola is its relatively high omega-3 ALA content. Thus, these findings add to the body of scientific evidence supporting the view that the total amount of dietary omega-3 consumed has greater impact on the bioavailability of supplemented DHA than the ratio of dietary omega-6: omega-3 fatty acids.

The MOFO study also showed that the combination of canola plus 1.1g/d of DHA is equally as effective as daily supplementation with 2.2g/d of DHA at reducing fasting plasma triglyceride concentrations with the added benefit of preventing the significant rise in both LDL and total cholesterol caused by both doses of DHA alone. While further research is warranted based on the findings from animal studies, it can reasonably be proposed that the findings from the MOFO study may be an example of a synergistic effect of canola phytosterols and DHA, rather than ALA and DHA, working together to significantly reduce fasting plasma triglyceride concentrations while preventing detrimental effects on LDL cholesterol in people with mild hypertriglyceridemia.

The second human clinical trial conducted as part of this thesis examined the effect of combining omega-3 fatty acids with soy isoflavones on fasting blood lipids, blood pressure and arterial compliance (Omega-Soy study). The Omega-Soy study showed that the



combined consumption of DHA with soy isoflavones resulted in an 8-10% improvement in HDL cholesterol, an 18-20% reduction in plasma triglyceride concentrations and the absence of a 10.8% rise in LDL cholesterol observed with DHA supplementation alone. Furthermore, the increases in LDL and total cholesterol observed with DHA supplementation in the first six weeks were reversed and significantly reduced when soy cereal was concurrently consumed. The results showed that the dietary combination of soy isoflavones and DHA improve the lipid profile of moderately hyperlipidemic individuals more favourably than either constituent alone.

While further research is warranted based on evidence from *in vitro* cell culture and *in vivo* animal models demonstrating functional effects of soy isoflavones and DHA on lipid metabolism pathways, it can reasonably be proposed that the findings from the Omega-Soy study demonstrate a synergistic effect of soy isoflavones and DHA, working together to significantly reduce fasting plasma triglyceride concentrations without detrimental effects on LDL cholesterol in people with mild hyperlipidemia.

The findings from this thesis support two functional food synergies for effective improvement of blood lipid concentrations when consumed as part of the usual diet of men and postmenopausal women with moderately elevated blood lipids. These functional food combinations are DHA with canola and DHA with soy isoflavones. The findings of this thesis sheds some light on how isoflavones may be actively involved in reducing plasma cholesterol concentrations when consumed with soy protein or in soy containing foods, furthermore the findings of this thesis provide strategies for ultimately reducing the negative side effects of dietary DHA supplementation and for achieving a better outcome in overall lipid profile improvements than could be achieved with DHA supplementation alone. Future research into these synergistic combinations of functional food ingredients with DHA may lead to new directions in functional food development by food manufacturers to enable more consumers to manage their blood lipid concentrations with minimal or without drug therapy requirements.

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