CLINICAL HAEMOPOIETIC IMPLICATIONS OF FUCOIDAN TREATMENT

BY

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SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN MEDICINE
UNIVERSITY OF TASMANIA

MARCH, 2008
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DECLARATION

This is to certify that this thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information with due acknowledgment in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis.

……………………..
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"This is the creation of Allah.
Now show me that which those (ye worship)
beside Him have created.
Nay, but the wrong doers are in error manifest"

[The Holy Quran 31:11]
This dissertation is the culmination of an expedition that began in 1997 when I decided to start my Masters degree in the field of Haematology in Jordan. During that period I worked on the haemorheology of red blood cells. I used different natural preparations to protect the cell proteins and lipids from the oxidation processes caused by the free radical generating systems that I used. This work inspired me and gave me ideas towards the current work. Through my doctoral journey that started in September 2003, several people supported my efforts and championed my endeavour to investigate this new field.

My foremost thanks and sincere gratitude go to my supervisor, Prof. Ray Lowenthal for providing the opportunity to undertake these studies with him at the Clinical School, University of Tasmania, and the Clinical Haematology and Medical Oncology Unit at the Royal Hobart Hospital. I am thankful to his tremendous support and encouragement throughout my research period. I am most appreciative of his guidance, reviewing of manuscripts and thesis, and variable support through out this work.

I am indebted for my PhD consultant Dr Helen Fitton (Marinova Pty. Ltd.) for her many contributions to this work. Her guidance, practical advice, assistance with information about Undaria fucoidan, reviewing of manuscripts and thesis, her dedication and enthusiasm are especially appreciated.

I am very thankful for Dr Prachya Kongtawelert from Chiang Mai University in Thailand for allowing me to do part of the 1B1 antibody work in his lab. I am thankful to all of his students at the department of biochemistry for their help.

Special thanks to Dr Robert Nordon for his guidance and support during the research project that was conducted with him as part of this work at the Graduate School of Biomedical Engineering, University of New South Wales (UNSW) in Sydney. My thanks also extend to everybody in his lab especially Kaphoun Ko, who I wish a
successful PhD journey. I want to thank Dr David Haylock at Peter MacCallum Cancer Institute in Melbourne for providing the mobilised PB CD34 cells as a gift.

My sincere thanks are extended also to everyone, staff and postgraduate students, at the Discipline of Medicine (UTAS), Discipline of Pathology (UTAS) especially A/Prof Greg Woods. Thank you to all staff at the Clinical Haematology and Medical Oncology Unit, and Pathology Services Department at Royal Hobart Hospital, in particular Dr Katherine Marsden, Dr Scott Ragg, Beth Rees and Belinda Snooks for all the technical and not so technical discussions. Thanks to Dr Margaret Nelson for proof-reading the thesis.

I have greatly profited from hints, generously lavished in the course of correspondence, from Dr Jane Teas at the University of South Carolina, USA in the collaboration work.

Thanks to the Hashemite University in Jordan for their scholarship award supporting me to start this journey. Special thanks for University of Tasmania for providing me with the International Postgraduate Research Scholarship. Thanks also to my industrial partner, Marinova Pty. Ltd., Hobart TAS, for conceptual and financial support. They have provided me with the fucoidan extracts and supported parts of the research financially. They have supported the research project that I have conducted at UNSW. I am also thankful for the School of Medicine, UTAS for their School Award.

Last but not least, special thanks are conveyed to my family especially my parents for their continuing love, support and encouragement throughout my PhD journey and for instilling in me a desire to realize my full potential.

This page seems to be incomplete without thanking The One Almighty for all these blessings and others for it is to Him that I am indebted.
Abnormalities is a term that describes the formation of mature cellular blood components from haemopoietic progenitor stem cells (HPC). The majority of HPC reside in the bone marrow (BM) with a small number continually escaping into the circulation then re-homing back into the BM in a process called trafficking. Stromal cells in the BM constitutively express and secrete stromal cell derived factor (SDF-1). This highly conserved chemokine binds to heparin and to CXCR4 receptor acting as a chemo-attractant for CXCR4+ cells; the system plays a role in regulating stem cell trafficking.

This study examined the clinical effects of ingesting fucoidan extracted from brown macro-algae (*Undaria pinnatifida*) *in vitro* and *in vivo* in a series of single blinded placebo-controlled clinical trials. Fucoidans comprise sulphated long branched chains of sugar, containing large amounts of fucose and galactose. Fucoidan is biologically active and is known to modulate coagulation, inflammation, cell proliferation and adhesion, tumorigenesis and resistance to viral infection. To study its clinical value an ELISA assay based on a novel antibody was established to quantify the level of the bio-available fucoidan in human plasma after oral doses. The consequences of ingesting fucoidan on healthy volunteers were investigated in detail by studying different biological and pathological parameters including liver and kidney functions.

This study established that daily ingestion of 3 g of different fucoidan extracts for 2 weeks is safe. To study the anticoagulant activity of fucoidan, haemostasis was examined closely *in vitro* and *in vivo*. Although, fucoidan is a highly potent anticoagulant *in vitro* there was limited activity when used orally. Fucoidan was found also to positively regulate the lipid profile by reducing cholesterol and triglyceride plasma levels. The effect of fucoidan on HSPC trafficking was tested. Ingestion of fucoidan increased the expression of CXCR4 on CD34+ cells and increased the plasma level of SDF-1 and IFN-γ. A decrease in CD4+ and CD8+ cells was also observed in volunteers who ingested fucoidan. When either peripheral blood or cord blood CD34+ cells were cultured *in vitro* in a cytokine expansion system CXCR4 on CD34+ cells
was down-regulated. This study also showed that fucoidan slows down the CD34\(^+\) cell cycle and interacts and binds with different cytokines (SCF, TPO, Flt-3 and SDF-1) and presents them to cells. In conclusion, this study showed that fucoidan has several clinical effects including effects on lipids regulation, haemostasis, immune system, haematopoiesis, trafficking of HSPC and related cytokines.
AWARDS:

- Postgraduate Scholarship Award, Hashemite University, Jordan, (Sep 2003-Sep 2006).
- Clinical School Award, University of Tasmania, (Mar 2004-Dec 2004 and from Apr 2005-Dec 2005).
- International Postgraduate Research Scholarship (IPRS), University of Tasmania, 2005-2007.
- Australian Postgraduate Award (APA), Industrial grant from Marinova, Jan 2006 to Mar 2007.
- Travel award from Discipline of Medicine, University of Tasmania to conduct experimental work and develop the 1B1 MoAb at University of Chang Mai, Thailand, 2004.
- Travel Award from Marinova Pty. Ltd., Australia to present at the Australasian Association of Clinical Biochemists 43rd Annual Scientific Conference, Sydney, NSW Australia, 2005.
- Travel awards from Clinical Haematology and Medical Oncology Unit, Royal Hobart Hospital, UTAS to present my research at the ASH-meetings in USA, 2005 and 2006.

RESEARCH GRANTS:


- Marinova and University of New South Wales Research Agreement to conduct a project entitled “Investigation of the in vitro effects of fucoidan on haemopoietic cell expansion” AU$9,899.

- Seed fund to start a project on the effect of human ingestion of fucoidan on plasma SDF-1 level. AU$3,500 from Marinova Pty. Ltd., Australia.
PUBLISHED RESEARCH PAPERS IN PEER-REVIEWED JOURNALS:


BOOK CHAPTERS


PEER-REVIEWED PUBLISHED ABSTRACTS:


**MEDIA RELEASES:**

- Spaceship Earth, Marine pests; warning from the invaded port town. 12th June 2005. TV-Asahi, Japan.
- Sunday Morning program. November 2004. WIN TV, Australia.
CONTENTS

Table of Contents

Contents

Declaration................................................................. ii
Right copy statement......................................................... iii
Acknowledgments............................................................. v
Abstract................................................................. vii
Awards and grants............................................................ ix
Publications..................................................................... x
Table of contents................................................................ xii
List of Tables...................................................................... xix
List of Figures..................................................................... xx
Abbreviations..................................................................... xxi

Chapter One - [Literature Review]........................................... 7

1.1 Haemopoietic stem and progenitor cells (HSPC).................. 8
  1.1.1 Historical background............................................... 8
  1.1.2 Definition of HSC and HSPC........................................... 9
  1.1.3 Characterisation of HSC in BM and microenvironment........ 12
  1.1.4 The bone marrow microenvironment.............................. 14
    1.1.4.1 Stromal cells...................................................... 15
    1.1.4.2 The extracellular matrix........................................... 15
  1.1.5 Mobilisation of HSPC.................................................. 15
    1.1.5.1 Different mobilisation mechanisms......................... 17
      1.1.5.1.1 Chemotherapy............................................... 17
      1.1.5.1.2 Cytokines such as G-CSF................................... 18
      1.1.5.1.3 Chemotherapy plus cytokines............................ 22
      1.1.5.1.4 AMD-3100.................................................... 22
      1.1.5.1.5 CTCE-0021 (SDF-1 peptide agonist)........................ 24
      1.1.5.1.6 Stem cell factor (SCF)........................................ 24
      1.1.5.1.7 CXCL2 (Gro-β)................................................. 25
      1.1.5.1.8 Interleukin-8 (IL-8)......................................... 25
      1.1.5.1.9 Recombinant human growth hormone (rhGH)........ 26
      1.1.5.1.10 Human recombinant parathyroid hormone (hrPTH).... 26
      1.1.5.1.11 Pegfilgrastim (pegylated G-CSF)...................... 27
      1.1.5.1.12 Thrombopoietin (TPO/MGDF)............................. 27
      1.1.5.2 The role of neutrophils and proteases in mobilisation... 28
  1.1.6 Homing of HSPC...................................................... 31
    1.1.6.1 Extravasation of HSPC through BM sinuses................ 34
    1.1.6.2 Migration of HSPC through the BM stroma................ 35
    1.1.6.3 Lodgement of HSPC into specific HSC niches.............. 37
  1.1.7 In vitro expansion of HSPC......................................... 39
  1.1.8 Engraftment and repopulation.................................... 41

1.2 Haemopoietic cytokines and their receptors....................... 42
  1.2.1 SDF-1 (CXCL12).................................................. 42
  1.2.2 CXCR4.......................................................... 43
  1.2.3 SDF-1 and CXCR4 interaction and disruption.................. 44
1.2.4 CXCR4 and tumour ........................................ 46
1.2.5 Interleukin-12 (IL-12) ........................................ 46
1.2.6 Interferon-gamma (IFN-γ) .................................. 48
1.2.7 Nitric oxide (NO) ............................................ 51
1.3 Seaweed (Algae) ............................................. 52
1.3.1 Undaria pinnatifida ........................................ 52
1.3.2 Undaria fucoidan .......................................... 55
1.3.3 Structural comparison of different sulphated polysaccharides 57
   1.3.3.1 Fucoidan structure ..................................... 57
   1.3.3.2 Heparan sulphate ..................................... 57
   1.3.3.3 Heparin .................................................. 58
   1.3.3.4 Hyaluronic acid ........................................ 59
1.3.4 Physiological properties of fucoidan ............................ 60
1.3.5 Urinary sulphated glycosaminoglycan ......................... 63
1.3.6 Fucoidan antiviral activity ................................ 64
1.3.7 Fucoidan anti-tumour activity ................................ 65
1.3.8 Fucoidan anticoagulation effect ............................. 65
1.4 Factorial experimental design and analysis ...................... 68
   1.4.1 Factorial analysis of cytokine interactions ............... 69

CHAPTER TWO - [Human subjects, general materials and methods] .... 72
2.1 Ethics approvals ........................................... 73
2.2 Human subjects ............................................ 73
2.3 Study design .................................................. 74
   2.3.1 Population and setting .................................. 74
      2.3.1.1 Target population and eligibility criteria .......... 74
      2.3.1.2 Exclusion criteria ................................... 74
      2.3.1.3 Number of volunteers ................................ 75
   2.3.2 Study scheme ............................................ 75
   2.3.3 Drug administration and compliance ..................... 76
   2.3.4 Outcomes and measures ................................ 77
   2.3.5 Study procedures ......................................... 77
   2.3.6 Statistical considerations ................................ 79
   2.3.7 Accrual rate and feasibility ............................. 79
2.4 Blood samples collection .................................... 80
2.5 Preparation of study capsules ................................ 80
2.6 Harvest of Undaria pinnatifida and the extraction procedure of fucoidan 83
2.7 Assay data for different seaweed extracts ....................... 85
   2.7.1 Assay data for 10% GFSTM fucoidan .................... 85
   2.7.2 Assay data for 75% GFSTM fucoidan .................... 88
      2.7.2.1 Determination of the degree of acetylation of fucoidan 89
      2.7.2.2 Analysis of sulphur in fucoidan using Magnetic Sector ICP-MS 90
2.8 Human cells .................................................. 92
   2.8.1 KG1a cells ................................................. 92
   2.8.2 Human peripheral blood CD34+ cells ..................... 92
   2.8.3 Cord blood CD34+ cells .................................. 92
      2.8.3.1 Human umbilical cord blood (HUCB) collection .... 92
      2.8.3.2 Cord blood CD34+ cells isolation .................... 93
      2.8.3.3 MACS of HUCB ....................................... 94
   2.8.4 Mononuclear cells preparation ............................. 94
   2.8.5 Staining CD34+ cells with CFSE .......................... 94
   2.8.6 Immunophenotyping ....................................... 95
   2.8.7 Cell count using beads ................................... 95
2.8.8 Cryopreservation of mammalian cells ............................................... 95
2.8.9 Thawing of cells ............................................................................ 96
2.9 Factorial experimental design ............................................................. 96

CHAPTER THREE - [Clinical pathology tests] .......................................... 98

3.1 Summary .................................................................................... 99
3.2 Introduction ................................................................................ 100
3.3 Materials and methods ................................................................. 102
3.3.1 Chemistry tests ........................................................................ 102
3.3.1.1 Total protein (TP) ................................................................. 102
3.3.1.2 Albumin (Alb) .................................................................... 103
3.3.1.3 Alkaline phosphatase (ALP) ............................................... 103
3.3.1.4 Alanine transaminase (ALT) ............................................... 103
3.3.1.5 Gamma-glutamyl transferase (GGT) .................................. 104
3.3.1.6 Total bilirubin (TBIL) ........................................................ 104
3.3.1.7 Glucose .............................................................................. 104
3.3.1.8 Sodium (Na+) .................................................................... 104
3.3.1.9 Potassium (K+) .................................................................. 105
3.3.1.10 Chloride (Cl-) ................................................................... 105
3.3.1.11 Bicarbonate (HCO₃⁻) ........................................................ 105
3.3.1.12 Blood urea nitrogen (BUN/Urea) ....................................... 105
3.3.1.13 Creatinine (Creat) ............................................................. 106
3.3.1.14 Cholesterol (Chol) ............................................................. 106
3.3.1.15 Triglyceride (Trig) .............................................................. 106
3.3.1.16 High density lipoprotein cholesterol (HDL). ...................... 107
3.3.1.17 Low density lipoprotein ..................................................... 107
3.3.1.18 Osmolality ........................................................................ 107
3.3.1.19 Anion gap ......................................................................... 107
3.3.1.20 Nitric oxide (NO) ............................................................... 108
3.3.1.21 Insulin .............................................................................. 109
3.3.2 Haematology tests ................................................................... 110
3.3.2.1 Full blood count ................................................................. 110
3.3.2.2 Erythrocyte sedimentation rate (ESR) ............................... 111
3.4 Results ........................................................................................ 112
3.4.1 Chemistry tests ....................................................................... 112
3.4.1.1 Total protein ....................................................................... 112
3.4.1.2 Albumin ............................................................................. 112
3.4.1.3 Alkaline phosphatase .......................................................... 112
3.4.1.4 Alanine transaminase .......................................................... 112
3.4.1.5 Gamma-glutamyl transferase ............................................. 112
3.4.1.6 Total bilirubin ................................................................. 113
3.4.1.7 Glucose .............................................................................. 113
3.4.1.8 Sodium ............................................................................. 113
3.4.1.9 Potassium .......................................................................... 113
3.4.1.10 Chloride .......................................................................... 113
3.4.1.11 Bicarbonate ................................................................. 113
3.4.1.12 Blood urea nitrogen ......................................................... 114
3.4.1.13 Creatinine ................................................................. 114
3.4.1.14 Cholesterol ................................................................. 114
3.4.1.15 Triglyceride ................................................................. 114
3.4.1.16 High density lipoprotein cholesterol .............................. 116
3.4.1.17 Low density lipoprotein .................................................... 117
3.4.1.18 Osmolality ................................................................. 117
3.4.1.19 Anion gap………………………………………………... 118
3.4.1.20 Nitric oxide…………………………………………… 118
3.4.1.21 Insulin………………………………………………... 119
3.4.2 Haematology tests…………………………………………… 119
3.4.2.1 Full blood count…………………………………………… 119
3.4.2.2 Erythrocyte sedimentation rate………………………... 123
3.5 Discussion………………………………………………... 124
3.6 Conclusions………………………………………………... 126

CHAPTER FOUR - [Detection of fucoidan in plasma and urine]…….. 127
4.1 Summary……………………………………………………... 128
4.2 Introduction………………………………………………… 129
4.3 Materials and methods………………………………………… 131
4.3.1 Volunteers………………………………………………... 131
4.3.2 Blood samples collection………………………………... 131
4.3.3 Pronase treated plasma samples…………………………... 131
4.3.4 Urine sample collection………………………………….. 131
4.3.5 Urine glucose measurement…………………………….. 133
4.3.6 Urine pH and specific gravity measurement……………... 133
4.3.7 Affinity chromatography………………………………….. 133
4.3.8 Preparation of 1B1 antibody…………………………….. 134
4.3.9 Microtitre plate preparation……………………………….. 134
4.3.10 Construction of standard curves using 1B1……………… 134
4.3.11 Construction of standard curves using DMB…………….. 135
4.3.12 ELISA detection of fucoidan in plasma and urine……… 136
4.3.13 Spectrophotometric detection of fucoidan in urine……… 137
4.3.14 Statistical analysis……………………………………….. 137
4.4 Results……………………………………………………... 138
4.4.1 1B1 affinity for heparin and fucoidan……………………… 138
4.4.2 Plasma fucoidan level……………………………………... 139
4.4.3 Fucoidan level in protein-purified plasma samples……….. 141
4.4.4 Urine fucoidan level……………………………………... 142
4.4.5 Urine glucose level……………………………………….. 143
4.4.6 Urine specific gravity……………………………………... 143
4.4.7 Urine pH………………………………………………... 143
4.5 Discussion………………………………………………….. 143
4.6 Conclusion………………………………………………... 146

CHAPTER FIVE - [Anticoagulant activity of fucoidan]………………… 147
5.1 Summary……………………………………………………... 148
5.2 Introduction………………………………………………….. 149
5.3 Materials and methods………………………………………… 151
5.3.1 Volunteers………………………………………………... 151
5.3.2 Blood sample collection and plasma preparation…………... 151
5.3.3 Plasma level of fucoidan………………………………….. 151
5.3.4 Full blood count…………………………………………... 151
5.3.5 Preparation of fucoidan serial dilutions for in vitro experiments…... 152
5.3.6 Coagulation study………………………………………… 152
5.3.6.1 Activated partial thromboplastin time (aPTT)……………... 152
5.3.6.2 Antithrombin –III (AT-III)…………………………….. 152
5.3.6.3 Thrombin time (TT)………………………………….. 152
7.3.9 Effect of cytokines and N3 on PB or CB CD34^+ cultures................. 208
7.3.10 Immunophenotyping................................................................. 209
7.3.11 Growth factors (cytokines).......................................................... 210
7.3.12 Experimental design ................................................................. 212
7.3.13 Staining CD34^+ cells with CFSE............................................... 214
7.3.14 Viability staining................................................................. 214
7.3.15 Statistical analysis................................................................. 215
7.4 Results.............................................................................. 217
7.4.1 Studying the growth of KG1a cells in the presence of beads........ 217
7.4.2 Cytotoxicity of fucoidan against KG1a cells............................ 219
7.4.3 Factorial design experiment examining the interaction of growth factors and fucoidan on the expansion of mobilised CD34^- cells........... 226
7.4.4 Effect of fucoidan on PB expansion................................................. 230
7.4.5 Effect of fucoidan on CB expansion................................................. 233
7.4.6 Effect of fucoidan on the appearance of cultures.......................... 241
7.4.7 Effect of fucoidan on cell proliferation............................................ 242
7.5 Discussion................................................................... 243
7.6 Conclusion.................................................................. 247

CHAPTER EIGHT – [General discussion and conclusions] ................. 248

REFERENCES........................................................................... 257

APPENDICES.......................................................................... 297
Appendix-1 Volunteer information sheet (Sample) .............................. 297
Appendix-2 Informed consent form (Sample) ....................................... 300
Appendix-3 Information sheet and consent form used at UNSW to donate cord blood.................................................. 301
Appendix-4 Material safety data sheet for 75% fucoidan....................... 304
Appendix-5 Midstream urine collection instructions ............................... 306
Appendix-6 Fractional factorial design 2^{5-1} to analyse the interaction of fucoidan (0 versus 10 µg/mL, 100 versus 500 µg/mL) and growth factors (0 versus 100 ng/mL)......................................................... 307
Appendix-7 Full factorial design to analyse the interaction of fucoidan (0 versus 10 µg/mL, 100 versus 500 µg/mL) and growth factors (100 versus 1000 ng/mL)......................................................... 308
<table>
<thead>
<tr>
<th>TABLE</th>
<th>DESCRIPTION</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>The major common cellular antigens for both human and mice HSPC.</td>
<td>12</td>
</tr>
<tr>
<td>1.2</td>
<td>The major characteristic differences between heparan sulphate and heparin.</td>
<td>59</td>
</tr>
<tr>
<td>2.1</td>
<td>The evacuated blood collection tubes and anticoagulants used for different pathology tests.</td>
<td>80</td>
</tr>
<tr>
<td>2.2</td>
<td>General characteristics of the polysaccharides administered orally to volunteers in the clinical trials.</td>
<td>82</td>
</tr>
<tr>
<td>2.3</td>
<td>Properties of fucoidan fractions used in the study.</td>
<td>82</td>
</tr>
<tr>
<td>2.4</td>
<td>Sugar analysis of a typical whole seaweed sample (10% GFS™ fucoidan) collected and analysed in November 2003.</td>
<td>85</td>
</tr>
<tr>
<td>2.5</td>
<td>Microbiological data on historical stock illustrates stability of 10% GFS™ over three years.</td>
<td>85</td>
</tr>
<tr>
<td>2.6</td>
<td>Pesticides assay conducted to detect the pesticide residues in randomly chosen seaweed samples.</td>
<td>86</td>
</tr>
<tr>
<td>2.7</td>
<td>Metals assay and other different properties for randomly chosen samples of 10% GFS™ fucoidan have been tested at AGAL.</td>
<td>87</td>
</tr>
<tr>
<td>2.8</td>
<td>Sugar, protein, and sulphate assay data for a purified 75% GFS™ fucoidan extract sample chosen randomly from November 2003 batch.</td>
<td>88</td>
</tr>
<tr>
<td>2.9</td>
<td>Microbiology assay data for a purified 75% GFS™ fucoidan extract sample chosen randomly from November 2003 batch.</td>
<td>88</td>
</tr>
<tr>
<td>2.10</td>
<td>Metal assay data for a purified 75% GFS™ fucoidan extract sample chosen randomly from November 2003 batch tested at AGAL.</td>
<td>89</td>
</tr>
<tr>
<td>2.11</td>
<td>Physical assay data for a purified 75% GFS™ fucoidan extract sample chosen randomly from November 2003 batch tested at AGAL.</td>
<td>89</td>
</tr>
<tr>
<td>3.1</td>
<td>Tests included in the CBC performed on all volunteers.</td>
<td>92</td>
</tr>
<tr>
<td>3.2</td>
<td>Haematology tests for the male placebo-control group.</td>
<td>102</td>
</tr>
<tr>
<td>3.3</td>
<td>Haematology tests for the female placebo-control group.</td>
<td>102</td>
</tr>
<tr>
<td>3.4</td>
<td>Haematology tests for the male 10% fucoidan group.</td>
<td>103</td>
</tr>
<tr>
<td>3.5</td>
<td>Haematology tests for the female 10% fucoidan group.</td>
<td>103</td>
</tr>
<tr>
<td>3.6</td>
<td>Haematology tests for the male 75% fucoidan group.</td>
<td>104</td>
</tr>
<tr>
<td>3.7</td>
<td>Haematology tests for the female 75% fucoidan group.</td>
<td>104</td>
</tr>
<tr>
<td>3.8</td>
<td>The average ESR readings for volunteers treated with 75% fucoidan.</td>
<td>105</td>
</tr>
<tr>
<td>4.1</td>
<td>Average inhibition concentration 50% (IC_{50}) for heparin and fucoidan standard curves using 1B1 Ab and the competitive ELISA.</td>
<td>139</td>
</tr>
<tr>
<td>4.2</td>
<td>Concentration of fucoidan (median) in human plasma samples of the three groups of volunteers, measured by the 1B1 competitive ELISA.</td>
<td>139</td>
</tr>
<tr>
<td>5.1</td>
<td>The in vitro effect of the 75% fucoidan on the different coagulation assays.</td>
<td>155</td>
</tr>
<tr>
<td>5.2</td>
<td>aPTT readings for both placebo control and 75% fucoidan groups.</td>
<td>156</td>
</tr>
<tr>
<td>5.3</td>
<td>Average readings and reference range for the coagulation tests for the healthy volunteers who ingested 3 g tid of 75% fucoidan.</td>
<td>156</td>
</tr>
</tbody>
</table>
5.4 Placebo control group average readings for platelet count, mean platelet volume (MPV) and platelet distribution width (PDW). Volunteers (n = 6) ingested 3 g tid of guar gum placebo capsules for 12 days.

5.5 Active treatment group average readings for platelet count, mean platelet volume (MPV) and platelet distribution width (PDW). Volunteers (n = 25) ingested 3 g tid of 75% fucoidan capsules for 12 days.

6.1 Monoclonal antibody panels.

6.2 The average-readings of all of the tests at 4 time points; baseline and on the 4th, 8th and 12th day after ingesting 3 g tid of guar gum as a placebo-control.

6.3 The average-readings of all of the tests at 4 time points; baseline and on the 4th, 8th and 12th day after ingesting 3 g tid of 10% fucoidan.

6.4 The average-readings of all of the tests at 4 time points; baseline and on the 4th, 8th and 12th day after ingesting 3 g tid of 75% fucoidan.

6.5 The average-percentage of cells that are CXCR4+ out of the total CD34+ cells at 4 time points; baseline and on the 4th, 8th and 12th day after ingesting 3 g tid of each treatment.

7.1 Properties of fucoidan fractions used in the study.

7.2 Monoclonal antibody panels.

7.3 Fractional factorial growth factors combinations.

7.4 Full factorial design growth factors combinations.

7.5 Example for one 2^5−1 fractional factorial design experiment in two blocks.

7.6 PB HSC and CB HSC phenotypes analysed.

7.7 Effect of fucoidan fractions on the growth of cord blood CD34+ cells.