Future opportunities for the production and marketing of Blackcurrant standardised active compounds

Anthony Jacobs
Marketing and Sales Director

BerryPharma – A division of Iprona AG/SPA
BerryPharma

- Extract Division of Iprona AG
- Production in Graz, Austria and Lana, Italy
- Producing Blackcurrant Extracts since 1998
- Specialist in Membrane Filtration extracts
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What are Blackcurrant „Standardised Active Compounds“
What are Blackcurrant „Standardised Active Compounds“

Liquids or Powders

Standardised on Polyphenols or Anthocyanins

Produced by either?
Alcohol Extraction

- Used to maximise Anthocyanin Concentration

Pharmaceutical

- Approx 120 kg of blackcurrants = 1 kg of extract
Membrane Ultra Filtration Extract

- Broader spectrum of concentrated active compounds

60 kg of blackcurrants = 1 kg of extract
How Did we decide?

Alcohol Extraction

Or

Membrane Ultra Filtration
Nutrigenomic Microarray Analysis

BC 10% Membrane Concentrate

BC 25% Ethanol Extract

Old Rat

Young Rat

Old Rat

Young Rat
Number of Differential Expression Genes by Feeding Rats with Blackcurrants

- Membrane concentrate:
  - Young Rat: 164
  - Old Rat: 234

- Ethanol Extract:
  - Young Rat: 119
  - Old Rat: 208
Differentially expressed genes in rat liver responsive to black currant feeding of different manufacturing process.

<table>
<thead>
<tr>
<th>GO biological process</th>
<th>Description</th>
<th>Gene symbol</th>
<th>Membrane filtrate</th>
<th>Ethanol extract</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>old</td>
<td>young</td>
<td>old</td>
</tr>
<tr>
<td>Stress response</td>
<td></td>
<td></td>
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<tr>
<td>Metallothionein 1a</td>
<td>Mt1a</td>
<td>0.33</td>
<td>0.38</td>
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<td>Metallothionein-2</td>
<td>ENSRNOT00000047663</td>
<td>0.48</td>
<td>0.37</td>
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<td>mRNA for hydroxysteroid sulfotransferase subunit</td>
<td>Sult2a1</td>
<td>0.48</td>
<td>0.55</td>
<td>1.32</td>
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<tr>
<td>Alpha-1-B glycoprotein</td>
<td>A1bg</td>
<td>1.20</td>
<td>0.27</td>
<td>1.74</td>
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<tr>
<td>Metabolic process</td>
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<tr>
<td>Fatty acid synthase</td>
<td>Fasn</td>
<td>2.82</td>
<td>2.40</td>
<td>0.97</td>
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<tr>
<td>Solute carrier family 1 (glial high affinity glutamate transporter), member 3</td>
<td>Slc1a3</td>
<td>5.38</td>
<td>4.04</td>
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<tr>
<td>Aldo-keto reductase family 1, member B8</td>
<td>Akr1b8</td>
<td>0.56</td>
<td>0.22</td>
<td>0.90</td>
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<td>VI ADH=class VI alcohol dehydrogenase</td>
<td>S79716</td>
<td>0.42</td>
<td>0.39</td>
<td>0.84</td>
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<td>Differentiation</td>
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<tr>
<td>Uroplakin 1B</td>
<td>Upk1b</td>
<td>1.19</td>
<td>1.13</td>
<td>0.29</td>
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<td>Plasticity-related protein 3</td>
<td>LOC298062</td>
<td>0.41</td>
<td>0.41</td>
<td>1.13</td>
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<td>Signal transduction</td>
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<tr>
<td>Olfactory receptor 1057</td>
<td>Olr1057_predicted</td>
<td>0.74</td>
<td>0.34</td>
<td>1.23</td>
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<td>Phospholipase C, delta 4</td>
<td>Plcd4</td>
<td>0.64</td>
<td>0.63</td>
<td>1.65</td>
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### Differentially expressed genes in rat liver responsive to blackcurrant feeding

<table>
<thead>
<tr>
<th>Biological process</th>
<th>Description</th>
<th>Gene symbol</th>
<th>Average ratio</th>
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<td><strong>Immune response</strong></td>
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<td>Chemokine (C-C motif) ligand 11</td>
<td>Ccl11</td>
<td>4.56</td>
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<td></td>
<td>Secretory leukocyte peptidase inhibitor</td>
<td>Slpi</td>
<td>4.31</td>
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<tr>
<td><strong>Metabolic process</strong></td>
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<tr>
<td></td>
<td>ATP citrate lyase</td>
<td>Acly</td>
<td>2.73</td>
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<td></td>
<td>Carnitine acetyltransferase</td>
<td>Crat</td>
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<td>UDP glycosyltransferase 2 family, polypeptide B</td>
<td>Ugt2b</td>
<td>7.63</td>
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<tr>
<td><strong>Oxidoreduction</strong></td>
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<td></td>
<td>Cytochrome P450, family 4, subfamily a, polypeptide 14</td>
<td>Cyp4a14</td>
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<tr>
<td></td>
<td>Cytochrome P450, subfamily 4A, polypeptide 11</td>
<td>Cyp4a11</td>
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<td><strong>Peroxisome biogenesis</strong></td>
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<td>Peroxisomal biogenesis factor 11A</td>
<td>Pex11a</td>
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<tr>
<td><strong>Signal transduction</strong></td>
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<td></td>
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<tr>
<td></td>
<td>Protein phosphatase 1, regulatory subunit 14c</td>
<td>Ppp1r14c</td>
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<td>Olfactory receptor 1337</td>
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<tr>
<td><strong>Cell cycle</strong></td>
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<tr>
<td></td>
<td>Pleiomorphic adenoma gene-like 1</td>
<td>Plagl1</td>
<td>4.39</td>
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<td><strong>Cell differentiation</strong></td>
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<tr>
<td></td>
<td>Delta-like 1 homolog</td>
<td>Dlk1</td>
<td>4.88</td>
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</tbody>
</table>
BC-MFE anthocyanins cause a flow-dependent increase in blood perfusion in isolated human intracerebral arteries, reducing endothelial dysfunction.

G. Siegel\textsuperscript{1,2}, A. Becker\textsuperscript{1}, E. Ermilov\textsuperscript{1}, S. Hammersen\textsuperscript{3}

\textsuperscript{1}Charité - University Clinic Berlin, Institute of Physiology, Berlin, Germany
\textsuperscript{2}University of Uppsala Biomedical Center, Uppsala, Sweden
\textsuperscript{3}Charité - University Clinic Berlin, Dept of Neurosurgery, Berlin, Germany
We adopted the Flow Measurement Model which is also used by the pharmaceutical industry to test the efficacy of fluvastatins. This provided a benchmark for evaluation of BC-MFE.
Human Brain Tissue Results

BC- MF Liquid produced:

• 40.4% reduction in tension,
• 45.2% increase in flow-dependent relaxation,
• 50.7% rise in blood perfusion

Results comparable to Fluvastatins!
Conclusion from First Study Phase:

These experiments impressively show that BC-MF extract liquid clearly improves endothelial and cardiovascular micro circulation.

The Study Team concluded that BC-MFE should have a beneficial effect on the cognitive functions in dementia of the Alzheimer type and in the prevention of stroke.

We also commissioned further ellipsometry work, just printed in „Circulation“, the American Heart Association Journal which further confirms earlier findings including VLDL resistance and plaque reduction.
Why is Blackcurrant Extract so Active?
It has a Unique „delphinidin“ Composition

BC contains four main dominant anthocyanins:
- delphinidin-3-glucoside,
- cyanidin-3-glucoside,
- delphinidin-3-rutinoside,
- cyanidin-3-rutinoside

Matsumoto 2004, Relaxes smooth muscle...

Reverse-phase HPLC chromatogram of anthocyanins detected at 520 nm from blackcurrant (cv. Ben Alder). Elution gradient 1 was used to separate anthocyanins (Wu et al., 2004)
Why support the Marketing of BC Std Active Compounds?

• Health Benefits already accepted by consumers
• Health Claims already exist for marketing
• Built on 1000 years of recorded traditional use
• Stable with up to 3 years shelf life.

• Profitable - value adding
  • 1 Kg of fresh Blackcurrants 80 pence per Kg
  • 1 Kg of Blackcurrant 25% Extract, 350 EUR p/Kg

• Global Nutraceutical Market shows continuous Growth
Global Nutraceutical Market

• Global nutraceutical market:
  - 2011: estimated at about $151 billion
  - 2016: estimated at about $207 billion
  → projected compound annual growth rate (CAGR) of 6.5% between 2011 and 2016

• Functional beverages market:
  - 2011: expected to be worth $57 billion
  - 2016: expected to be worth $87 billion
  → expected CAGR of 8.8%

• Nutraceutical food market: second largest market
  - 2011: estimated $49 billion
  - 2016: estimated $67 billion
  → estimated CAGR of 6.4%

Application Opportunities

Established
- Powerful Antioxidant
- Eye Health
- Coughs Colds and Flu treatment

New Opportunities
- Micro circulation and Brain Health
- Migraine
- Anti-inflammatory
- Cardiovascular Health
- Metabolic Syndrome
Opportunities are built from Clinical Studies confirming Benefits and Claims

Research Driven

Eye Stress Relief - Meiji and Cerebos
Eye Ring Shadow - beauty (microcirculation)
Migraine Relief - Complen Germany
Microcirculation - improved endothelial function Meiji & BerryPharma
Oxidative Stress - Science in Sport UK
Metabolic Syndrome - New EU Sponsored Initiative
1. Consumer demand for Nutraceuticals has a projected 6.5% compound annual growth rate.

2. We are still to realise the marketing potential of the unique delphinidin compounds.

3. Scientists are building even stronger cases for further health claims including brain health.

4. Quality of the extracts can only continue to improve with new Blackcurrant Fruit Cultivars and improved extraction technology.
 Berrypharma is a division of Iprona AG/SPA with manufacturing in Graz and R&D in Lana, Italy. Iprona is owned by the Philipp family who have always supported scientific endeavours to promote Blackcurrant extracts.

Special thanks to Dr Pircher and colleagues at Iprona and to Dr Derek Stewart for his help and encouragement to pursue clinical studies.
Thank you for your attention!
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