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Vascular Mechanisms in Osteoarthritis

Rationale for treatment with a marine-based complementary medicine

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Aim

To undertake *in vitro* biological studies in Biolane™ to determine the levels of selected biological activities. These activities are indicated as potentially useful in modifying disease progression in a vascular concept of osteoarthritis (OA) causation (Figure 1).

Methods

The assay tested cholesterol synthesis inhibition, anti-oxidant capacity and inhibition of the following components of the inflammatory pathways – tissue necrosis factor alpha (TNF-α), nuclear factor κB (NFκB), cyclo-oxygenase-2 (Cox-2) expression, prostaglandin E_2 (PGE_2) and phospholipase A_2 (PLA_2). Platelet aggregation inhibitory activity was assessed with the agonists collagen and ADP and fibrinolytic activity was also assessed with the euglobulin clot lysis time (ECLT).

Prior to testing in the bioassays the Biolane™ was digested with gastric and duodenal enzymes to simulate *in vivo* digestive processes. Biolane™ was digested with the gastric enzyme pepsin followed by pancreatic enzymes to produce a complete digest sample for testing.

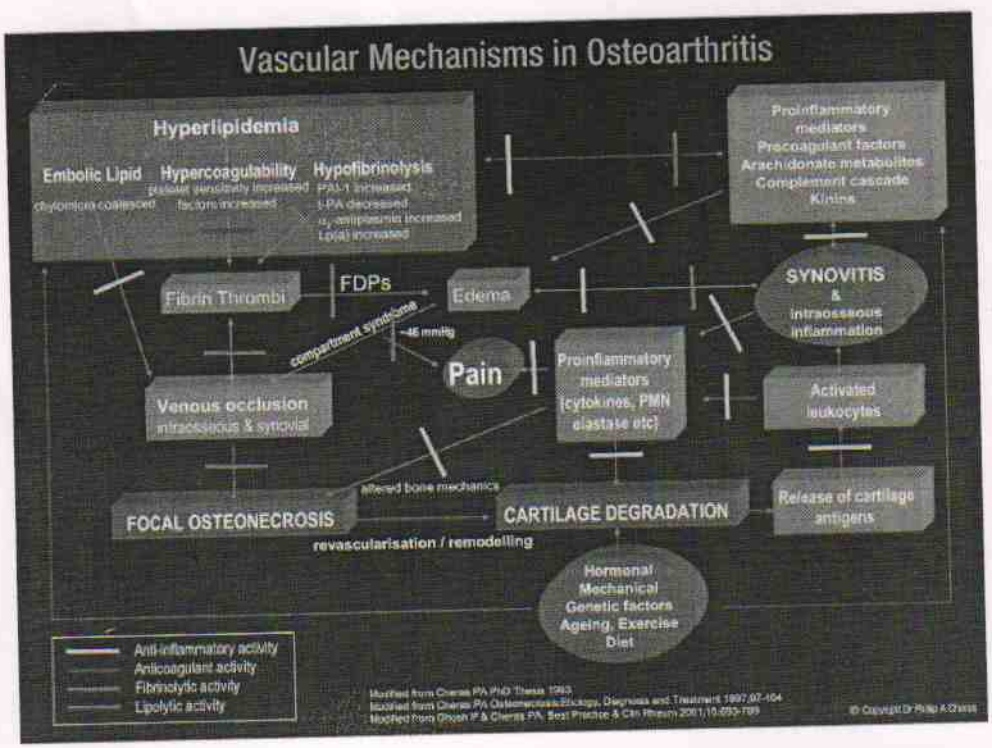

Figure 1
Vascular mechanisms in osteoarthritis - showing the web of pathological interactions between coagulation and inflammation that drive the disease and the effect of anti-inflammatory, anticoagulant, fibrinolytic and lipolytic activity on disrupting the vicious cycle of disease drivers.

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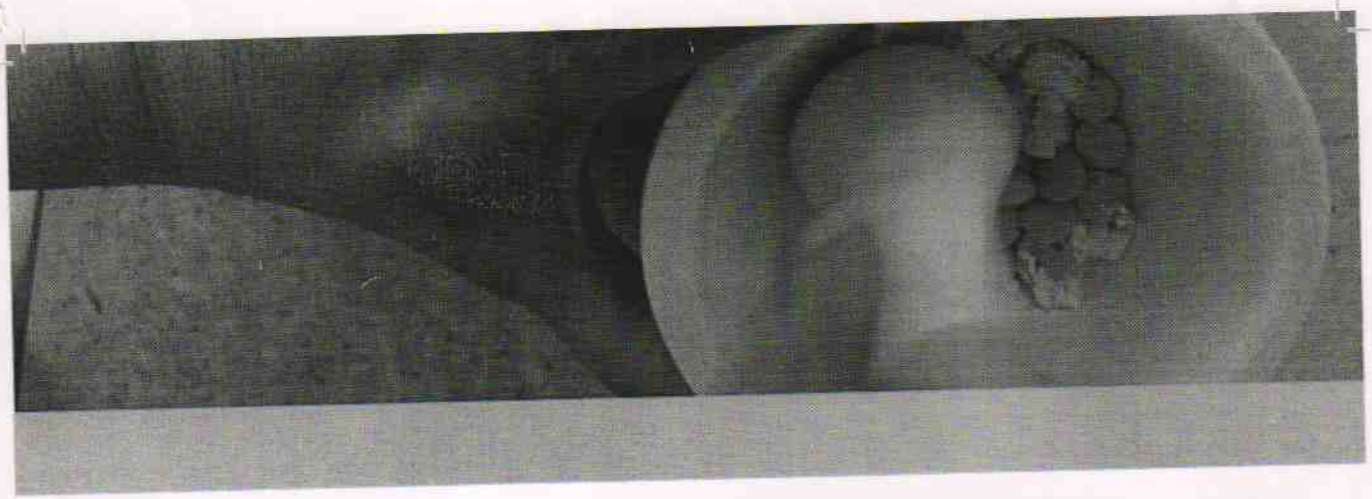


Results

Table 1 shows reduced anti-inflammatory activity associated with the Biolane™ complete digest across a range of inflammatory mediators. The low inhibitory Cox-2 expression observed in this study following Biolane™ dosing suggests that Biolane™ is not influencing gene expression here. Mild anti-oxidant activity is shown together with inhibition of platelet aggregation. Fibrinolytic activity is enhanced as shown by the reduced clot lysis time while the level of cholesterol synthesis inhibition would be clinically beneficial if it was translated to a clinical outcome.

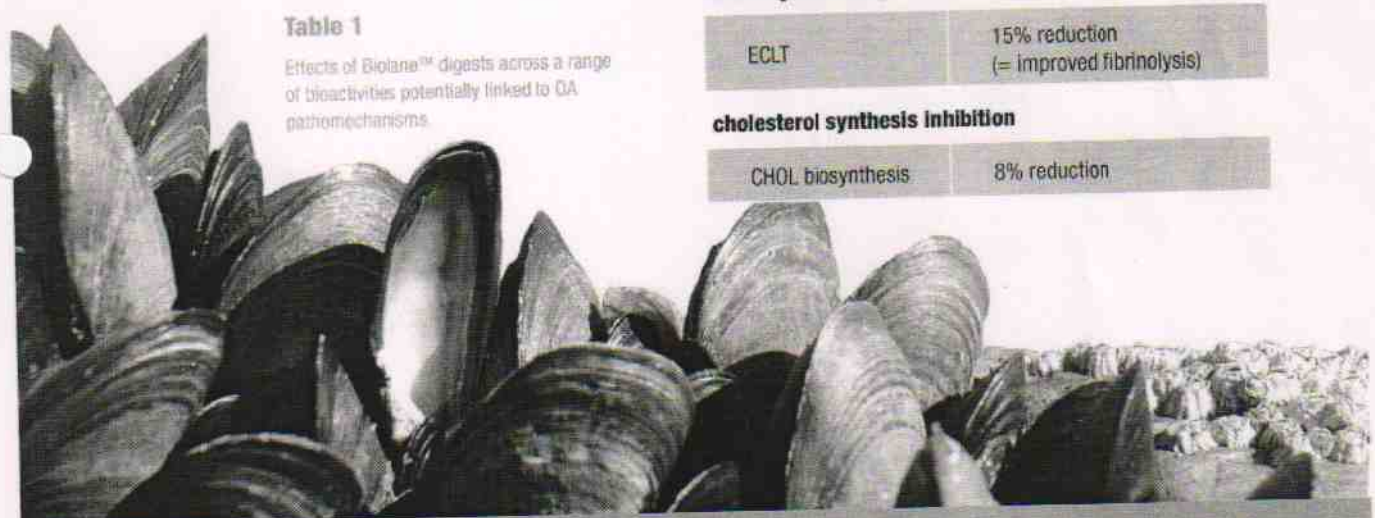
Conclusions

A vascular concept of OA causation predicts that a range of biological activities including anti-inflammatory, anticoagulant, lipolytic and fibrinolytic activity are potentially necessary in order to effectively break the web of pathology linking increased coagulation risk factors, decreased fibrinolytic activity and inflammation that drives the pathomechanisms associated with OA. Biolane™ shows these *in vitro* biological activities in a laboratory system designed to mimic gastric and duodenal secretions. These findings are consistent with anecdotal claims of symptomatic OA benefit in patients treated with Biolane™.

Test	Result
anti-inflammatory activity	
TNF-α	25% reduction
Cox-2	0.4% reduction
PGE_2	45% reduction
PLA_2	27% reduction
anti-oxidant activity	
ORAC	=285µmol Vit E analogue/g sample
platelet aggregability	
collagen	24% reduction
ADP	18% reduction
fibrinolytic activity	
ECLT	15% reduction (= improved fibrinolysis)
cholesterol synthesis inhibition	
CHOL biosynthesis	8% reduction

Table 1

Effects of Biolane™ digests across a range of bioactivities potentially linked to OA pathomechanisms



REPORT

Australian Centre for Complementary Medicine

EDUCATION & RESEARCH

14 September 2005

In-vitro Biological Activities of Healtheries' Biolane™ – a Comparative Study

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In-vitro Biological Activities of Healtheries' Biolane™: A Comparative Study of Biolane™ versus Glucosamine Sulphate vs Chondroitin Sulphate vs combined Glucosamine Sulphate/Chondroitin Sulphate vs Lyprinol™

STUDY AIM

In vitro laboratory studies were undertaken by the Australian Centre for Complementary Medicine Education and Research (ACCMER), a joint venture of the University of Queensland and Southern Cross University. The aim of the studies was to compare selected biological activities of Healtheries' Biolane™ Green Lipped Mussel Extract versus the biological activities in a range of well known complementary anti-arthritic agents.

SAMPLE PREPARATION

All samples were subjected to two enzyme digestions to simulate *in vivo* digestive processes.

Various components of gastrointestinal secretions may have an impact on potential actives within a product. In this study we used a two stage *in vitro* model based on gastric and duodenal secretions. The digests prepared from the samples were a pepsin digest containing the prominent gastric enzyme pepsin and a complete digest where the sample was exposed to pepsin followed by pancreatic enzymes.

ASSAYS

Assays assessed:

- cholesterol synthesis inhibition
- anti oxidant capacity

Inhibition of the following components of inflammatory pathways

- tissue necrosis factor alpha (TNF-α)
- Cox-2 expression
- prostaglandin E_2 (PGE_2)
- phospholipase A_2 (PLA_2) – also associated with platelet aggregabillity

- platelet aggregation inhibitory activity
- fibrinolytic activity

SYNOPSIS OF RESULTS

Comparison of aggregate *in vitro* data – Chondroitin Sulphate (CS) vs Glucosamine Sulphate (GS) vs Glucosamine sulphate:Chondroitin sulphate (GS/CS) vs Lyprinol™ vs Healtheries Biolane™ Green Lipped Mussell Extract (GLME)

Test	Anti-arthritic agent				
	CS	GS	GS/CS	LYP	GLME
Cholesterol biosynthesis inhibition	●	●	●	●	●
TNFα inhibition	●	●	●	○	●
Cox-2 inhibition	○	●	●	ND	●
PGE_2 inhibition	○	○	●	●	●
PLA_2 inhibition	●	●	○*	●	●
Oxygen radical absorbance capacity - antioxidant (ORAC)	○	○	○	○	●
Fibrinolytic activity	○	●	●	○	●
Anti-platelet aggregation activity	○	●	○	●	●

Note ● denotes activity present ○ denotes activity not found
○* denotes activity not found at low concentration but present at higher concentration
ND = not done (test unable to be performed due to assay artefact)

The results show that Healtheries Biolane™ Green Lipped Mussel Extract (GLME) demonstrates the most comprehensive range of activities across the suite of *in vitro* tests performed when compared with the other agents that were tested.

Relevance of the in vitro Biolane™ green lipped mussel extract (GLME) findings to putative Osteoarthritis pathomechanisms

The vascular theory of osteoarthritis causation is based on epidemiological, laboratory, experimental and clinical findings that support the concept that compromised microcirculation in affected joints initiated through a combination of inflammation and imbalance between coagulation and fibrinolysis can initiate and perpetuate the disease. One implication of this theory is that in order to treat more than just painful symptoms ie to slow or halt the disease process will require a range of biochemical activities to effectively break the web of pathology. It has been proposed that these should include a number of key activities such as anti-inflammatory, anticoagulant, fibrinolytic and lipolytic activities. If these are realised then chondroprotection is likely to ensue.

The use of highly potent anti-inflammatory agents, particularly the Cox-2 inhibitors would appear to be at odds with the known data showing that patients with osteoarthritis are at greater risk of thrombotic episodes than those without the disease. Cox-2 inhibitors pose a theoretical risk of increased thrombotic complications in many patients with osteoarthritis who already have cardiovascular risk factors. The recent removal of Vioxx from the market and restrictions governing the use of Celebrex – the Cox-2 market leaders, based on these concerns would appear to support this proposition.

A successful anti-arthritic agent should have multiple low level activities that address a range of disease drivers while avoiding the serious side effects that frequently accompany massive disruption of major biochemical pathways such as total Cox-2 inhibition.

The current *in vitro* study has shown that GLME has a range of activities that the vascular theory of osteoarthritis causation predicts as desirable for disease treatment. These include anti-inflammatory activity through its inhibition of TNFα, PGE_2, Cox-2 and PLA_2 in addition to its anti-oxidant activity. It is not critical for these activities to be at extremely high levels. In fact it is advantageous from the perspective of a low side effect profile that they should not be so. It is the multiplicity of activities that is of greater importance. In addition to anti-inflammatory activity, GLME also has *in vitro* activities that can reduce thrombotic risk (decreased PLA_2 and cholesterol biosynthesis inhibition activity in addition to decreased platelet aggregability – that is also assisted through cholesterol biosynthesis inhibition) and enhance the removal of blood clots (mild fibrinolytic activity).

The results obtained in this study indicate that GLME has *in vitro* activities in key areas associated with arthritis pathophysiology. In addition, across the range of *in vitro* tests performed in this comparative study, Healtheries Biolane™ green lipped mussel extract demonstrated a more extensive range of potential anti-arthritic activities in comparison to the other agents tested.

It is important to note that these results apply specifically to Biolane™ Green Lipped Mussel Extract and can not be extrapolated to include other green lipped mussel extracts.

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