



## A synthetic model gut system to study macronutrient digestion *in vitro*

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The digestion and absorption of macronutrients (fat, protein and carbohydrate) is a major factor in health and metabolic disease. By 2015 it is projected that 2.3 billion people will be overweight and 700 million obese<sup>(1)</sup>. Obesity alone affects more than 25% of the adult population costing the NHS over £5 billion per year<sup>(2)</sup>. Modulating macronutrient digestion with food additives and pharmaceuticals has been shown to be a fruitful approach to the treatment of obesity (Orlistat)<sup>(3)</sup> and diabetes (Acarbose)<sup>(4)</sup>. Previous work has shown that bioactive agents have novel modulatory effects on the major enzymes of digestion<sup>(5)</sup>. Work in this lab has shown that specific alginates can inhibit pancreatic lipase up to 70%, this is now being investigated as a potential anti-obesity agent<sup>(6)</sup>.

A model gut system which provides a physiologically relevant *in vitro* simulation of the digestive tract was developed to simulate the gastrointestinal tract from mouth to terminal small intestine capable of providing a continuous profile of digestion of whole foods, substrates, therapeutics, delivery systems and their effects on digestion. The model gut system (MGS) consists of a temperature and pH controlled system with compartments that accurately model physiological amounts and concentrations of enzymes, digestive secretions and cofactors.

The model gut system was validated using known enzyme inhibitors. At T<sub>[60]</sub> by the end of the gastric phase, pentosan polysulphate significantly inhibited the digestion of protein by 87.6%. At T<sub>[180]</sub> by the end of the small-intestinal phase protein digestion was completely inhibited by Soybean Trypsin Inhibitor. With Orlistat (10 mg/ml), fat digestion was reduced by 99.1%. With 100 mg Acarbose, by T<sub>[180]</sub> carbohydrate digestion was inhibited by 98.55%. Full time-course data is available for all inhibitors.

A number of novel regulatory effects have been demonstrated with seaweed biopolymers being studied in this lab. Alginate showed dose dependent inhibition of fat digestion, with a maximum inhibition of  $58.3 \pm 22.2\%$  ( $p = 0.018$ ) at 3 mg/ml at the end of the small intestinal phase. Alginate reduced protein digestion by 50.5% ( $P = 0.001$ ) at the end of the gastric phase T<sub>[60]</sub>. Alginate reduced carbohydrate digestion in the first 15 minutes of the small intestinal phase by 89.3% ( $P = 0.025$ ), after which digestion recovered to control levels. Fucoïdan reduced protein digestion at T<sub>[60]</sub>, by 59.1% ( $P = 0.0274$ ) at 6 mg/ml. In the first 15 minutes of the small intestinal phase, carbohydrate was reduced by 81.87% by fucoïdan. Further regulatory effects of seaweeds and seaweed extracts have been demonstrated in microplate assays, ethanol extracts of both fresh and dried Malaysian Red Seaweed showed potent inhibition of lipase activity, up to 92% and significant inhibition of  $\alpha$ -amylase by 88%.

Conclusions: The model provides a robust, cost effective and ethical alternative to animal models or human studies and provides a tool for the investigation of novel therapeutics and food additives for treatment of metabolic diseases such as obesity, diabetes and pancreatic insufficiency.

1. World Health Organization. Obesity and Overweight Statistics (2006). Geneva:WHO.
2. Department of Health. Programme Budgeting Guidance 2006–07. (2008) London: Department of Health.
3. Lucas KH, *et al.* (2001). *Ann. Pharmacother.* 35, 314–328.
4. Martin A.E. and Montgomery P.A (1996). *Am. J. Health Syst. Pharm.* 53, 2277–90.
5. Balasubramaniam V *et al.* (2013) *J. Appl Phycol.*
6. Wilcox *et al.* (2014) *Food Chemistry*, 146, 479–484