Institution: University of Reading

Unit of Assessment: 6 Agriculture, Veterinary & Food Science

Title of case study: Research informs development of flavanol-containing products, which benefit the food industry and provide health benefits for consumers

1. Summary of the impact

Novel research into the cardiovascular and other health benefits of consuming flavanol-containing foods at the University of Reading prompted a multi-national food and confectionary producer, Mars Incorporated, to invest over £1.1 million in research into the absorption, metabolism and health effects of cocoa-derived flavanols in humans. This research informed the development of a cocoa-extract supplement drink and supplement extract, both widely available in the US since 2010. This in turn sparked interest from other multinational corporations looking to market flavanol- and other flavonoid-containing health products, resulting in an additional £917K investment by industry. Mars' cocoa-extract supplements currently hold a 1% share of all food and drinks marketed on a cardiovascular health platform in the US; a market worth US$3.1 billion in 2012. Research by Reading and others has provided evidence that consumption of these products can improve memory and cognition, cardiovascular health and digestive health for consumers. These and other research findings have been widely disseminated to the general public by the Reading researchers.

2. Underpinning research

Background

Flavanols are a group of compounds found in cocoa beans, tea leaves and red grapes. Professor Jeremy Spencer, has pioneered research, first at King's College London (2002-2004) and more recently at the University of Reading (2004-2007, Lecturer, 2007-2010 Reader; 2010-current Professor), into how the human body absorbs and metabolises flavanols, and the impact they have on cardiovascular function. His research has added to a growing body of evidence suggesting that a diet rich in flavanols can have a positive impact on circulatory, cardiovascular and gastrointestinal (GI) tract health. Much of the early work on the role of flavanols in health focused on the antioxidant properties of these compounds and their potential role in attenuating pro-oxidant pathophysiological processes that underlie atherosclerosis and many cancers. Spencer's research at King's College London provided some of the first evidence that flavanols and other flavonoids exerted beneficial effects via non-antioxidant mechanisms [1]. This research indicated that the flavanol epicatechin, found in cocoa, berries, apple and wine, and its human metabolites (i.e. those forms of epicatechin found in the circulation after consumption) were effective at preventing oxidative-injury to cells, not via their role as classical antioxidants*, but rather by direct interaction with cellular signalling pathways.* Presentation of these results at international conferences prompted initial discussions with the American global food manufacturer Mars, Inc. regarding collaborative research potential.

Human absorption and metabolism of CocoaVia: identifying optimal delivery of flavanols

In 2004, when Spencer joined Reading as Lecturer in Nutritional Biochemistry, discussions with Mars, Inc. developed into a direct collaboration between the company and the university. Mars, Inc., which has conducted decades of research on cocoa flavanols and holds numerous patents for processing cocoa in a way that preserves flavanols, invested £400,000 over the period 2005-2013 to support a core research laboratory at Reading. Research on human absorption and metabolism of an early formulation of Mars' flavanol-containing product CocoaVia began in 2005, with the aim of understanding how flavanols are taken-up and utilised in different parts of the body, in particular the vascular system, gut and brain. Whilst CocoaVia had proved highly effective in improving health biomarkers such as vascular function, further promotion of the product on the basis of its health effects was limited by the fact that cocoa is a high fat, high sugar-containing product, which could counteract the beneficial effects of the flavanols. In 2009, Spencer and his colleagues began collaboration with Mars, Inc to specifically look at the impact of different types of sugars on flavanol absorption. This showed that although sucrose promoted flavanol absorption to a greater extent than did the calorie free maltitol, the differences in uptake were not large [2]. This research informed the development of a novel flavanol-containing drink that was both low in sucrose (sugar)

and fat, called *Cirku*.

First evidence that flavanols affect microbial community in the gut of humans
Further industry investment in 2007 supported investigations at Reading into the health effects of CocoaVia. As the majority of cocoa flavanols are passed through to the large intestine, it was hypothesised that they may be metabolised by resident microbiota, thereby encouraging the growth of some beneficial gut bacteria. In 2011, Spencer and Gibson (Professor Gut Microbiology, University of Reading, 1998- current), showed for the first time that consumption of cocoa flavanols could indeed significantly affect the growth of select gut microflora in humans, suggesting it did have potential prebiotic benefits [3].

Flavanol-rich foods improve human cognition, vascular system health and digestive health
Research carried out between 2007 and 2011, funded by Mars Inc. and by BBSRC [7,8], and using animal models of disease and human intervention studies, indicated that flavanol-rich foods, including Cirku and blueberry, were effective in improving cognitive and vascular function/health [3,4]. Spencer and his colleagues also provided concurrent supporting data that flavanols, present in blueberry were effective in acutely improving vascular function in healthy men in a time- and intake-dependent manner and that these benefits were mechanistically linked to the actions of circulating phenolic metabolites on neutrophil NADPH oxidase activity [5].

Linking flavanols to improvements in memory and cognition
While research from the University of Reading and elsewhere had provided evidence that flavonoid-rich foods were capable of improving memory and cognition in humans and other animals, it was still not clear whether flavonoids were the agents that caused the observed effects. In 2012/3, Spencer and his colleagues supplemented healthy rats with pure anthocyanins or pure flavanols (at levels found in both cocoa and blueberry) for six weeks. They found that spatial memory was enhanced in 18 month old rats, along with evidence of activation of signalling pathways linking to synaptic plasticity. These data supported the claim that it is these flavonoids that are the likely causal agents in mediating the cognitive effects of cocoa, blueberry and other flavonoid-rich foods [6].

Evidence that Cirku has cardiovascular benefits
In 2009, the European Commission funded research to provide proof-of-concept to the claim that Cirku helps support cardiovascular health by helping support healthy circulation and blood flow to the heart, brain, eye, muscle and skin health [9]. The collaborative project, named FLAVIOLA (www.flaviola.org), involved the Universities of Reading, Dusseldorf, Gent, Maastricht and Karolinska and INRA in France, with Spencer at Reading. Spencer's role in the studies was to develop an understanding of how flavanol absorption, distribution, metabolism and excretion (ADME) varies in different individuals within the general population and how these differences influence vascular health potential. Notably factors such as inter- and intra-individual difference in ADME, age, gender and background diet were investigated. The research consortium showed flavanols from Cirku were effectively absorbed, were delivered to the vascular system, and induced medically significant improvements in blood pressure and blood flow both acutely (1 day) and chronically (4 weeks) in different individuals (age, sex, background diet etc.). A number of manuscripts are currently submitted for publication and the data presented at conferences are available on the web site.

3. References to the research.
All references are in highly rated peer reviewed journals and have been internally and / or externally assessed as of at least 2*. Those marked * were submitted in the RAE 2008 exercise.

[1] * Spencer, J.P.E., Schroeter, H., Kuhnle, G., Srai, S.K.S, Debnam, Tyrrell, R.M., Hahn, U. and Rice-Evans, C. (2001). Epicatechin and its in vivo metabolite, 3′-O-methyl epicatechin, protect human fibroblasts from oxidative stress-induced apoptotic cell death involving caspase-3 activation. *Biochem. J.* **354**, 493-500*. (IF: 4.65)*

[2] Rodriguez-Mateos A, Oruna-Concha MJ, Kwik-Uribe C, Vidal A, Spencer JPE (2012). Influence

of sugar type on the bioavailability of cocoa flavanols. *British Journal of Nutrition,* 108(12): 2243-2250. DOI: 10.1017/S0007114512000475 (IF: 3.30)

[3] Tzounis X, Rodriguez-Mateos A, Vulevic J, Gibson GR, Kwik-Uribe C, Spencer JPE (2011). Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study. *American Journal of Clinical Nutrition*, 93 (1) :62-72. DOI: 10.3945/ajcn.110.000075 (IF: 6.50)

[4] *Williams CM, Abd El Mohsen M, Vauzour D, Butler LT, Ellis JA, Whiteman M, Spencer JPE (2008). Blueberry-induced changes in spatial working memory are associated with changes in hippocampal CREB phosphorylation and BDNF levels. *Free Radical Biology and Medicines,* 45 (3): 295-305. DOI: 10.1016/j.freeradbiomed.2008.04.008. (IF: 5.27)

[5] Rodriguez-Mateos A, Rendeiro C, Bergillos-Meca T, Tabatabaee S, George TW, Heiss C, Spencer JP. Intake and time dependence of blueberry flavonoid-induced improvements in vascular function: a randomized, controlled, double-blind, crossover intervention study with mechanistic insights into biological activity. Am J Clin Nutr. 2013 Nov;98(5):1179-91. doi: 10.3945/ajcn.113.066639. (IF: 6.50)

[6] Rendeiro C, Vauzour D, Rattray M, Waffo-Téguo P, Mérillon JM, Butler LT, Williams CM, Spencer JPE (2013). Dietary levels of pure flavonoids improve spatial memory performance and increase hippocampal brain-derived neurotrophic factor. *PLoS ONE*, 8 (5): Article numbere63535. DOI: 10.1371/journal.pone.0063535 (IF: 3.73)

Grants:

[1] Spencer (2008-2011) *Enhancement of learning and memory by* flavonoids, BBSRC Industrial Partnership Award (with Mars, Inc.) (BB/F008953/1), £485,357.

[2] Spencer (2008-2011) *The impact of cocoa processing on flavanol content, absorption and health* effects, BBSRC-DRINC grant (BB/G005702/1), £322,033.

[3] Spencer (PI) (2009-2012) *Targeted delivery of dietary flavanols for optimal human cell function: Effects on cardiovascular health (FLAVIOLA)*, European Union 7th Framework Grant (226588), £2,990,000 (£650,000 to Reading).

4. Details of the impact

Research leads to significant industry investment

Spencer's pioneering research on flavonoids and their benefits attracted significant investment by leading US food manufacturers. The initial grant of £400,000 from Mars, Inc in 2005 was based on research conducted at Kings College London, the two subsequent grants totalling £735,000 were based on the results of the research conducted at Reading.

Dissemination of the initial work with Mars, Inc gained the attention of other multinational food corporations including PepsiCo and Nestle. PepsiCo has its own portfolio of flavonoid-rich products, most notably the Tropicana range of citrus fruit juices, which are very high in a group of flavonoids called flavanones. Seeking scientific evidence of the health benefits of their products, PepsiCo invested £500,000 in research at Reading to look at the impacts of citrus juice consumption on neuro-cognitive performance and cardiovascular health. Florida State Citrus, USA also invested £187,000 in this research. In 2012, Nestle, agreed to invest £280,000 in research conducted at Reading to determine the impact of milk chocolate and coffee consumption on vascular health. This brings the total combined industry investment to £1,652,000, (~£1,200,000 since 2008) with several industry agreements with the University [these agreements are available upon request].

Research informs development of CocoaVia and Cirku products

The research conducted at Reading, which helped to understand the physiological and molecular actions of cocoa flavanols and evidence their effects in humans, informed the development of CocoaVia and Cirku. [section 3;2] These two products were launched in the US in 2010 by Mars

Botanical – the scientific business unit of Mars, Inc. Both products are lower in fat and sugar than other chocolate/cocoa products available on the market, such as chocolate, which is also high in saturated fat. The Global Director for Applied Health and Nutrition Research, Mars Inc. said: "*Professor Spencer's work provided fundamental insights into the effects of coca flavanol intake on the gut microbiome, cardiovascular functions, as well as cognitive performance, all of which were relevant to MARS in the context of cocoa flavanol development."* [a]

Mars Incorporated benefits from sale of new products

The sale of foods and beverages marketed in the US on a cardiovascular health platform was worth US $3.1 billion in 2012, growing 22% between 2007 and 2012 [a]. CocoaVia took a 1% share of this market in 2012 [b], which equates to US $31million. Within Europe the commercial potential for such products will be significantly benefitted if appropriate health claims are agreed by EFSA. In this context the Global Director for Applied Health and Nutrition Research, Mars Inc. said of the research findings: *"….they provided information important to product development as well as data with significant utility in the context of applying for an EFSA-approved health benefits claims."* [a]

Mars' CocoaVia product line and the associated research have received international recognition by industry through several awards. In 2013, Mars Incorporated was the winner of the 2013 Food Technology Industrial Achievement Award for its research program on cocoa flavanols [b], including the research conducted with Reading and the CocoaVia Cocoa extract supplement received honourable mention in the Delicious Living 2013 Supplement Awards [c].

Dissemination on the health benefits of plant flavanols through media

At the same time as this growing interest and investment from major companies in the food industry, the broad underpinning research into the health effects of Cirku and other flavanol-containing foods such as blueberries, has caught the attention of the public and the media. In October 2011 and November 2012, Spencer presented the Reading work on flavanols in relation to the importance of blueberries and cocoa on human cardiovascular and cognitive function, on Channel 4's 'The Food Hospital'. More recently, Spencer filmed with BBC One's 'Britain's Favourite Supermarket Foods' where the impact of cocoa and berries on human health were discussed; the episode aired July 2013. Spencer's research has also been widely covered in print and online media, including: *The Daily Mail ('*A bowl of blueberries keeps the brain active in the afternoon', 14 Sept 2009), with an average of nearly 8 million unique users online daily; and *Science Daily* ('Getting Forgetful? Then blueberries may hold the key', 12 Apr 2008), with an estimated 2.4 million unique monthly visitors.

5. Sources to corroborate the impact

[a] Global Director for Fundamental and Applied Health and Nutrition Research, MARS Symbioscience. Letter available from the University of Reading

[b] Watson, E. (26 Mar 2013) 'US sales of heart-friendly foods and beverages have grown 22% since 2007, says Euromonitor International', *Food Navigator-USA.com* <http://www.foodnavigator-usa.com/Markets/US-sales-of-heart-friendly-foods-and-beverages-have-grown-22-since-2007-says-Euromonitor-International> The article gives context for the value of heart-friendly foods in the US market and provides statistics for CocoaVia's market share.

[c] 'Mars, Incorporated awarded AOAC International's 2013 Multi-Laboratory Study of the Year Award for first-of-its-kind cocoa flavanol research', *CocoaVia* [Media Release, 27 Aug 2013] <http://www.cocoavia.com/press>

[d] 'CocoaVia Cocoa Extract Supplement featured at Expo West 2013 Recognized in the Delicious Living 2013 Supplement Awards', *CocoaVia* [Media Release, 8 Mar 2013] <http://www.cocoavia.com/media/Press_Kit/expo-west-press-release.pdf>