

THE FUNCTION OF DIETARY PHENOLIC
ACIDS IN CARDIOVASCULAR HEALTH

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The Function of Dietary Phenolic Acids in Cardiovascular Health

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- (i) Aidilla Mubarak, Ewald E. Swinny, Simon Y.L. Ching, Steele R. Jacob, Kevin Lacey, Jonathan M. Hodgson, Kevin D. Croft, and Michael J. Considine. Polyphenol composition of plum selections in relation to total antioxidant capacity. *Journal of Agricultural and Food Chemistry*. 2012; 60: 10256-10262.

Contribution of Aidilla Mubarak : 80%

- (ii) Aidilla Mubarak, Catherine P. Bondonno, Alex H. Liu, Michael J. Considine, Lisa Rich, Emilie Mas, Kevin D. Croft, and Jonathan M. Hodgson. Acute effects of chlorogenic acid on nitric oxide status, endothelial function, and blood pressure in healthy volunteers; a randomized trial. *Journal of Agricultural and Food Chemistry*. 2012; 60: 9130- 9136.

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- (iii) Aidilla Mubarak, Jonathan M. Hodgson, Michael J. Considine, Kevin D. Croft, Vance B. Matthews. Supplementation of a high fat diet with chlorogenic acid is associated with insulin resistance and hepatic lipid accumulation in mice. 2012. *J. Agric. Food Chem.* 2013, 61, 4371–4378.

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For any work in this thesis that has been co-published with other authors, I have the permission of all co-authors to include this work in my thesis.

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(Dr Michael Considine)

(Prof Kevin Croft)

Acknowledgements

“By prevailing over all obstacles and distractions, one may unfailingly arrive at his chosen goal or destination”

(Christopher Columbus)

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PUSAT PEMBELAJARAN DIGITAL SULTANAH NUR ZAHIRAH

List of Publications, Presentations and Awards

Publications arising from works in this thesis:

1. Aidilla Mubarak, Ewald E. Swinny, Simon Y. L. Ching, Steele R. Jacob, Kevin Lacey, Jonathan M. Hodgson, Kevin D. Croft, and Michael J. Considine. Polyphenol composition of plum selections in relation to total antioxidant capacity. *Journal of Agricultural and Food Chemistry*. 2012; 60, 10256–10262.
 2. *Aidilla Mubarak, *Catherine P. Bondonno, Alex H. Liu, Michael J. Considine, Lisa Rich, Emilie Mas, Kevin D. Croft, and Jonathan M. Hodgson. Acute effects of chlorogenic acid on nitric oxide status, endothelial function, and blood pressure in healthy volunteers: A randomized trial. *Journal of Agricultural and Food Chemistry*. 2012; 60: 9130–9136.
- * Joint first authors.
3. Aidilla Mubarak, Jonathan M. Hodgson, Michael J. Considine, Kevin D. Croft, and Vance B. Matthews. Supplementation of a high fat diet with chlorogenic acid is associated with insulin resistance and hepatic lipid accumulation in mice. *The Journal of Agricultural and Food Chemistry*. 2013; 61: 4371-4378.

Presentations arising from works in this thesis:

1. UWA Institute of Agriculture 2012 Postgraduate Showcase, 'Frontiers in Agriculture'. 2012. Perth. (Oral presentation).

2. Western Australia Australian Society for Medical Research Symposium 2012. Perth. (Oral presentation)
3. International Life Science Institute Symposium on Health Benefits for Polyphenol-rich Foods and Beverages: Latest Science 2012. Adelaide. (Poster)
4. Annual Scientific Meeting of High Blood Pressure Research Council of Australia. 2011. Perth (Oral presentation)
5. International Conference of Polyphenols and Health 2011. Barcelona. (Poster)
6. Annual Scientific Meeting of Nutrition Society of Australia 2010. Perth. (Poster)

Awards received:

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- Ad Hoc Top-up Scholarship 2012
- SLAB/SLAI Scholarship from Ministry of Higher Education, Malaysia (2009-2013)

Publications arising from work unrelated to this thesis:

Catherine P. Bondonno, Xingbin Yang, Kevin D. Croft, Michael J. Considine, Natalie C. Ward, Lisa Rich, Ian B. Puddey, Ewald Swinny, Aidilla Mubarak, Jonathan M. Hodgson. Flavonoid-rich apples and nitrate-rich spinach augment nitric oxide status and improve endothelial function in healthy men and women: a randomized controlled trial. *Free Radical Biology and Medicine*. 2012; 52: 95–102.

Thesis Abstract

Dietary phenolics have been associated with protection against the various forms of cardiovascular disease (CVD). This thesis outlines three independent studies, from analytical to intervention, which increase our knowledge on the role of phenolic compounds in preventative health. Particular attention was paid to phenolics found in fruit, as they are a rich source and widely available and consumed, and hence make a large contribution to dietary phenolics intake.

While many fruits are rich in phenolic compounds, it is known that specific cultivars vary greatly in phenolic composition. In this thesis, the composition of major phenolics in 29 pre-varietal selections of Western Australian plums was investigated. This knowledge was essential as the first step in a pathway to develop breeding tools to aid identification of fruit that may have enhanced health-promoting capacities. Total phenolics, selected individual phenolic compounds and total antioxidant capacity (TAC) were quantified. Total phenolic concentration was significantly correlated with TAC. Neo-chlorogenic acid and quercetin glycosides were found to be the predominant phenolics. Composition of these predominant phenolic compounds in plums was not significantly correlated with the TAC. In this study, it is argued that the value of *in vitro* TAC assays to breeding programs may be limited. Further, increasing the focus on individual bioactive phenolic compound was also argued to be more productive to breeding than TAC assays, as patterns of inheritance of TAC are likely to be very complex.

Further understanding on the mechanisms of phenolics in preventative health was sought. There is increasing evidence that specific dietary phenolics can enhance production of nitric oxide (NO) a mediator in vascular health. A randomized, double-blind, placebo-controlled, cross-over trial in healthy men and women ($n = 23$) was conducted to investigate the acute effects of chlorogenic acid on blood pressure, NO status and endothelial function. A dose of 400 mg chlorogenic acid (equivalent to 2 cups of coffee) was chosen as an amount achievable in a usual diet. Relative to control, systolic blood pressure and diastolic blood pressure were significantly lower after 400 mg chlorogenic acid treatment. This result was observed without concomitant enhancement in biomarkers of NO status and endothelial function assessed by flow mediated dilatation. In this study, it was concluded that chlorogenic acid can lower blood pressure acutely; an effect which if sustained would benefit cardiovascular health.

To further understand the potential benefits of chlorogenic acid on CVD, it is also important to recognize its effect on metabolic abnormalities which are known to be a significant risk factor of developing CVD. Benefits of chlorogenic acid on several features of the metabolic syndrome through coffee consumption were proposed. In this thesis, an 11-week dietary intervention study was performed to assess whether chlorogenic acid (1 g.kg^{-1} diet) had a protective effect on high fat diet induced obesity, glucose tolerance, insulin sensitivity, fatty acid oxidation and insulin signaling in C57BL/6J mice. In the study, it was found that supplementation of chlorogenic acid in the high fat diet did not reduce body weight compared to mice fed the high fat diet alone. In contrast, chlorogenic acid was found to increase insulin resistance compared to mice fed a high fat diet only. Furthermore, chlorogenic acid resulted in decreased phosphorylation of AMPK and ACC β , a downstream target of AMPK in liver. These observations were supported by evidence of higher lipid content and more steatosis in

the liver of mice fed a high fat diet supplemented with chlorogenic acid, relative to mice fed a high fat diet only. Therefore, this study demonstrated that chlorogenic acid supplementation in a high fat diet did not protect against features of the metabolic syndrome in diet-induced obese mice. It remains to be determined if chlorogenic acid will have benefits in metabolic disorders in human intervention trials.

The studies in this thesis provide additional knowledge to the available evidence in the literature on the potential preventative health benefits of chlorogenic acid. Targeting increased and more consistent consumption of chlorogenic acid-rich food such as fruits could assist prevention of CVD in the community. In future work, investigation of a time course effect of chlorogenic acid is crucial to understand the mechanism of cardiovascular protective effect in more depth. A dose response effect of chlorogenic acid is also warranted to further understand the protective health benefits.

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