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COMMENTARY

Forging a modern generation of polyphenol-based therapeutics

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The long-standing debate that polyphenol secondary metabolites from dietary plants are important nutritional components continues due to compelling evidence for their abilities to ameliorate degenerative conditions including, cancer, neurological disorders and cardiovascular disease. The clinical use of polyphenols is not, however, mainstream as issues regarding poor selectivity, dosage, toxicity and delivery methods are unresolved. The paper by Rieder *et al.* suggests that the lack of selectivity, at least for the stilbene, resveratrol, may not be a major limiting factor. The present commentary is a critique of this significant finding that is focused on deciding how the use of resveratrol as clinical medicine could be advanced, and how this new information integrates with current knowledge of polyphenol physiological effects. This commentary suggests that the multi-target nature of polyphenols may be translated into reliable therapy using the current systems/network pharmacology approach concerned with developing viable therapeutic agents that achieve specific effects through interactions with a wide array of targets.

LINKED ARTICLE
This article is a commentary on Rieder *et al.*, pp. 1244–1258 of *BJP* 167:6. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2012.02063.x

Abbreviations
SEB, staphylococcal enterotoxin B; SIRT1, sirtuin (silent mating type information regulation 2 homologue) 1

Polyphenols are micronutrients produced as secondary metabolites by dietary plants (Scalbert, 1993). Although these compounds display poor bioavailability (only a proportion of ingested amounts are absorbed and excretion is rapid), and complex pharmacodynamics and metabolism (Manach *et al.*, 2005), they present therapeutic properties. A substantial body of evidence (epidemiological studies, animal studies and human clinical trials) indicate that polyphenols reduce a range of pathologies associated with cardiovascular disease including thrombosis (Navarro-Nuñez *et al.*, 2008), atherosclerosis (Chiva-Blanch *et al.*, 2012) and inflammation (Rieder *et al.*, 2012), as well as displaying anti-cancer (Gali *et al.*, 1991) and neuroprotective (Gatson *et al.*, 2013) properties. The activities of these compounds is achieved via a range of mechanisms including their well-characterized antioxidant effects (Pignatelli *et al.*, 2006), inhibition of intracellular kinase activity (Wright *et al.*, 2010), binding to cell surface receptors (Jacobson *et al.*, 2002) and disrupting the integrity of cell plasma membranes (Pawlikowska-Pawlega *et al.*, 2007).

Epidemiological and clinical studies demonstrating the therapeutic potential and benefits of polyphenols, do not definitively describe the true importance of these compounds. Dietary supplementation may elicit beneficial physiological effects, but these are often achieved at supra-physiological concentrations, which have been demonstrated to be toxic (Mennen *et al.*, 2005). Some studies take into account confounding effects of age, sex and lifestyle on polyphenol effects, but complete information on how these may disrupt the impact of these compounds on health is also lacking. Therefore, at present, methodology for therapeutic application of these compounds is not entirely clear, but what is clear, is that dietary supplementation is not enough. An understanding of the significance of individual functional groups on the inhibitory activity/potency of these compounds may allow more potent and selective analogues to be

made using polyphenols as a basis. Information from structure-activity studies has allowed the construction of more selective analogues, for example quercetin-3-*O*-amino acid esters were more selective for Src tyrosine kinase than EGF receptor kinase (Huang *et al.*, 2009). One strategy is to use these analogues together with dietary supplementation to reinforce and accelerate the actions of parent compound metabolites generated *in vivo*.

Rieder *et al.* (2012) suggested an alternative strategy involving an unmodified polyphenol (resveratrol) as viable treatment for lung injury. The authors demonstrated that the phyto-oestrogen/phytoallexin, resveratrol (trans-3,5,4′-trihydroxystilbene) was effective for the treatment of staphylococcal enterotoxin B (SEB)-induced lung injury. Resveratrol achieved this by decreasing SEB-induced pulmonary vascular permeability, inhibiting inflammation through blocking cytokine production and infiltration of monocytes, by increasing caspase 8-dependent apoptosis of T-cells and by up-regulating myeloid-derived suppressor cells that inhibit SEB-mediated T-cell activation. Mechanisms included up-regulation of sirtuin (silent mating type information regulation 2 homologue) 1 (SIRT1) and down-regulation of NF-κB activation in inflammatory cells. In addition, to affecting the expression and activity of these signalling proteins that regulate inflammation and apoptosis, resveratrol modulated the functions of a number of cells (endothelial cells, neutrophils, monocytes). Collectively, the activities of the stilbene were complementary and resulted in the single effect of reducing SEB-mediated injury. The dose (100 mg·kg^{-1}) of resveratrol administered was supraphysiological. The lack of toxicity was not surprising, however, as oral absorption of resveratrol is 75% of the ingested amount and considerably less than 1% of this is bioavailable (Walle, 2011). Major metabolites of resveratrol (glucuronides, sulphates and dihydroresveratrol conjugates) may have exerted the observed effects, or deconjugation by β-glucuronidase and sulphatase may have allowed specific tissue accumulation of resveratrol (Walle, 2011).

The anti-inflammatory properties of resveratrol present this small molecule as a potentially important therapeutic agent against a number of degenerative conditions (e.g. coronary artery disease, brain injury) that manifest acute inflammation as a major pathological factor. A key recent study described the preclinical application of a grape extract containing 8 mg total resveratrol to a group of coronary artery disease patients, and demonstrated an increase in anti-inflammatory factors (Tomé-Carneiro *et al.*, 2013). Importantly, this study did not report any adverse side effects due to high levels of resveratrol, indicating that the rapid clearance rates or poor absorbance of this polyphenol may be beneficial. This is in line with previous human studies that indicate that resveratrol is well-tolerated and does not induce marked toxicity (Cottart *et al.*, 2010).

Interestingly, Rieder *et al.* (2012) demonstrated that resveratrol was selective for apoptosis of cells as the stilbene induced apoptosis of SEB-activated T-cells, but protected endothelial cells from SEB-mediated apoptosis, indicating complex mechanistic actions for the stilbene. A number of supporting studies demonstrate that resveratrol selectively induces apoptosis of malignant cancer cells (Dhandayuthapani *et al.*, 2013; Quoc Trung *et al.*, 2013), and in healthy cells, apoptosis is attenuated by this compound (Liu *et al.*, 2013). Similar to the anti-inflammatory activities of resveratrol, the underlying mechanisms for pro- and anti-apoptotic activities of this compound involve down-regulation of the expression and attenuation of the function of a number of kinases and housekeeping proteins.

The structural features that influence mechanistic activities of resveratrol may allow important information to be gained to inform the synthesis of analogues selective for individual cellular process, regardless of multiple molecular targets. Novel analogues of resveratrol include HS-1793 (Kim *et al.*, 2012). At a pharmacological dose (1.3–20 μM), HS-1793 was demonstrated to exert a cytotoxic effect on murine breast cancer cells that resulted in apoptosis. Network/systems pharmacology may allow the development of methodology to direct the clinical use of resveratrol, through the use of enhanced pharmacodynamic models that analyse regulatory networks involved in drug action (Iyengar *et al.*, 2012). These can account for multiple targets of a drug as well as the effects of genomic, epigenomic and posttranslational changes on drug efficacy, and therefore, may allow the development of resveratrol or resveratrol analogues into precision therapy.

This approach will be possible with more complete clarification of the physiological effects and underlying mechanisms exerted by these compounds. The body of evidence for the application of resveratrol as drug therapy described by the Rieder *et al.* (2012) study left several questions unanswered. Resveratrol reduced capillary permeability after SEB infection by protecting lung endothelial cells – how was this achieved? Was this due to the anti-apoptotic properties of this compound and/or the reported ability of resveratrol to reinforce the integrity of tight junctions (Lin *et al.*, 2010)? The main transport system for polyphenols is blood, and blood vessel barrier function must be tightly regulated. How does resveratrol affect uninjured blood vessel walls – is resveratrol inactive in healthy, homeostatic cellular systems? Moreover, *in vivo*, would the functions of resveratrol be limited to anti-inflammatory and anti- or pro-apoptotic effects?

The anti-inflammatory properties of resveratrol may render this compound as an immunosuppressant. Resveratrol was previously reported to function as an immunosuppressant by decreasing the expression of CD28 and CD80, through augmentation of the production of IL-10 (Sharma *et al.*, 2007). This property may confound the beneficial effects exerted by this compound. The therapeutic effects of resveratrol may be directed through local delivery of the stilbene using biomaterial devices. This strategy has already been investigated using nanomaterial devices that allow controlled release of polyphenols (including resveratrol), concentrating the compound at predetermined amounts over specified time periods in the physiological region of interest. Hydrogel matrices with intrinsic porosity, particularly biocompatible alginate gels (Wright *et al.*, 2012), are suitable for the release of polyphenols to localized areas (Figure 1). A recent study described a method for coupling resveratrol through a hydrolysable covalent bond to the carboxylic acid groups in porous poly-ε-caprolactone surface grafted with acrylic acid, and used this construct for *in vivo* bone regeneration (Li *et al.*, 2011). Furthermore, sodium deoxycholate elastic liposomes loaded with resveratrol were shown to be

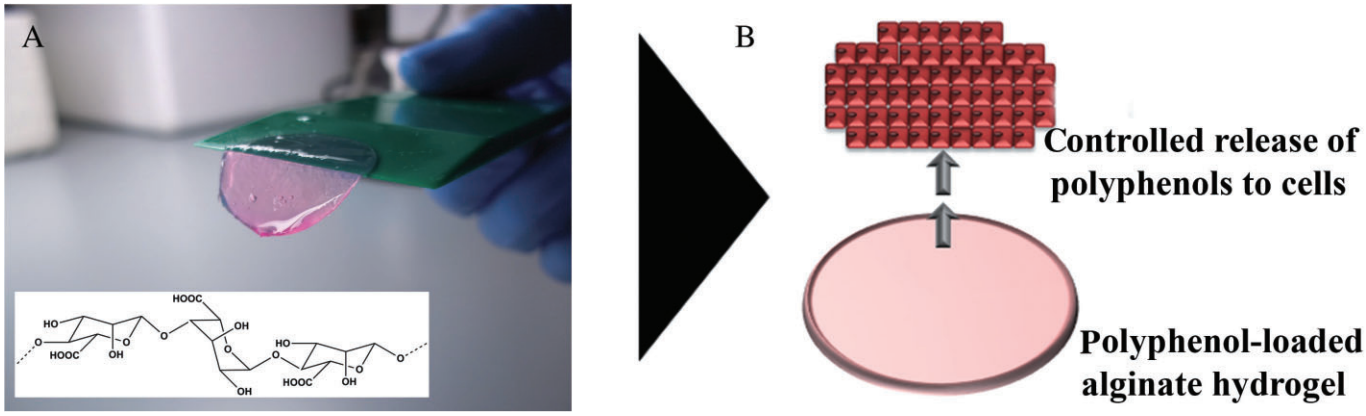

Figure 1

Biomaterial scaffolds for the delivery of polyphenols. Alginate hydrogels (A) are versatile, biocompatible matrices comprising cross-linked chains of mannuronic and guluronic acid (A: inset) that can be applied as medical devices for the controlled release (B) of polyphenols (including resveratrol) locally to sites of injury, to reduce adverse systemic effects.

stable when delivered subcutaneously (Cadena *et al.*, 2013). These novel delivery systems may allow greater understanding of the long-term effects of resveratrol.

Conclusions

Lessons concerning rational investigation of polyphenol mechanisms of action can be learnt from existing studies. Studies describing the physiological effects and therapeutic potential of these compounds appear, however, to be fragmentary and at times they are contradictory due to variations in conditions of administration and methods of assessment. We are at a stage where, although comprehensive maps of polyphenol *in vivo* activities are not available, the prediction of 'missing' information that would allow a complete picture of the modulatory effects of these compounds is possible. This is the foundation that is required for high throughput, holistic approaches, which involve standardized screening of the kinetics, activities, metabolism and bioavailability of these plant compounds. Polyphenols may be administered as a form of personalized medicine that involves tailoring polyphenol/analogue doses or dietary regimen dependent on the medical history, lifestyle and genetic make-up of the individual as well as the condition being treated. Routine medical use of polyphenols may be a goal for the distant future, but we now have the appropriate tools to solve the enigma surrounding their beneficial effects on health.

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