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Polyphenols and cholesterol efflux: is coffee the next red wine?

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Despite strong evidence for an inverse association between high-density lipoprotein cholesterol (HDL-C) levels and cardiovascular risk¹, successful therapeutic strategies to target HDL have remained elusive. A recent Phase III clinical trial failed to show clinical benefit with the cholesteryl ester transfer protein (CETP) inhibitor torcetrapib despite markedly increased HDL-C levels.^{2,3} This outcome reinforced a growing consensus that measurement of HDL-C alone may be an incomplete surrogate for the *in vivo* functionality of HDL and the clinical efficacy of targeting HDL. The careful mechanistic assessment of HDL function has thus emerged as a potential way forward.⁴

Macrophage reverse cholesterol transport (RCT), the process by which cholesterol is transported from macrophage “foam” cells to the liver for ultimate fecal excretion, has been postulated to play a major role in HDL-mediated atheroprotection.⁵ Indeed, quantitative measures of macrophage RCT are more strongly associated with atherosclerosis than plasma HDL-C concentrations in mice.⁶ The first critical step of macrophage RCT involves efflux of cellular cholesterol to circulating HDL particles. Research in recent years has documented a specific role for the macrophage transporters ATP-binding cassette subfamilies A1 and G1 (ABCA1 and ABCG1) in cholesterol efflux (See Figure 1). These findings have stimulated efforts to target the macrophage at the cellular level as a means of enhancing overall RCT. For example, pharmacologic agonism of the liver X receptor (LXR) upregulates both ABCA1 and ABCG1 expression,^{7,8} promotes macrophage cholesterol efflux *ex vivo* and RCT *in vivo*,⁹ and recently entered early phases of clinical testing.¹⁰

Coffee is one of the most widely consumed beverages in the world.¹¹ Chronic coffee consumption has been extensively studied in relation to cardiovascular disease, although the results of these studies have been inconclusive.^{12–15} Many of these inconsistencies likely reflect inherent limitations of observational epidemiology; residual confounding from other lifestyle variables that vary according to coffee intake, including cigarette smoking, almost assuredly complicates these analyses. Furthermore, the physiologic effects of coffee likely vary according to precise formulation and across individuals. An interesting case-control analysis reinforced this point—caffeinated coffee consumption was associated with an

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increased risk of myocardial infarction only in those with slow caffeine metabolism.¹⁶ Limited data is available with regard to the impact of coffee on lipid metabolism, although one randomized controlled trial noted modest increases in both HDL-C and LDL-C levels after daily consumption of filtered coffee for eight weeks.¹⁷

While the relationship between coffee and coronary disease has not been conclusively determined, it remains plausible that some individual components may be atheroprotective and worthy of further study. Specifically, coffee is a major source of polyphenols,¹⁸ a group of compounds that has received substantial interest in recent years. The term polyphenol represents a wide variety of compounds derived from plants, and polyphenols are present in many components of the human diet.¹⁹ It is widely believed that polyphenols have protective properties, and there is increasing evidence to support their beneficial relationship to various diseases. Although there is limited data on specific polyphenols, polyphenol-rich foods have previously been associated with decreased risk of cardiovascular disease in multiple studies.²⁰ Interestingly, certain polyphenols, such as resveratrol and anthocyanins (both found in red wine among other sources), have been shown to increase macrophage cholesterol efflux *ex vivo* (Table 1).^{21–23}

In the current issue of *Circulation Research*, Uto-Kondo et al., describe a careful series of experiments that tested the hypothesis that polyphenols found in coffee may promote macrophage cholesterol efflux.²⁴ The authors focused their study on caffeic and ferulic acids, phenolic acids (a subclass of polyphenols) known to be present in coffee and increased in plasma by coffee consumption.²⁵ Importantly, both compounds increased HDL-mediated cholesterol efflux *in vitro* in a dose-dependent fashion via enhanced expression of the ABCG1 (and SR-BI) transporters. Ferulic acid, but not coffee itself, was additionally shown to modestly enhance macrophage reverse cholesterol transport *in vivo* in mice. Finally, the authors elegantly extended these findings to humans using a placebo-controlled crossover study design. As expected, plasma isolated 30 minutes after consumption of one cup of caffeinated coffee was substantially enriched in phenolic acids. Intriguingly, “post-coffee serum” displayed a forty percent increase in its ability to promote cholesterol efflux from human monocyte-derived macrophages, together with upregulation of ABCG1 and SR-BI. This study thus provides compelling evidence that phenolic acids, with coffee as a delivery mechanism, can increase macrophage specific cholesterol efflux via upregulation of known cholesterol transporters.

The authors are to be commended for their creative combination of *in vitro*, mouse *in vivo*, and human *ex vivo* approaches in answering questions regarding the complex RCT pathway. However, several limitations should be noted. Although intuitive, an association between enhanced macrophage cholesterol efflux capacity of serum and cardiovascular disease in humans has not been definitively demonstrated. Secondly, the quantitative importance of ABCG1- and SR-BI- mediated cholesterol efflux in the overall human macrophage RCT pathway remains unclear. The authors did not prove that consumption of phenolic acids in isolation, rather than via coffee, is linked to similar results. Finally, because plasma phenolic acid levels decline rapidly after a bolus of coffee, the authors’ findings may not be generalizable to a longer and more relevant time frame of coffee consumption.

Despite these limitations, this study lays the foundation for multiple avenues of additional research. Ongoing optimization of assays to assess macrophage RCT in humans may permit definitive studies to show that coffee (or polyphenols in general) promote RCT *in vivo*.²⁶ Future efforts may systematically characterize the many polyphenols, particularly with regard to their impact on cholesterol efflux and RCT. If indeed the constituent phenolic acids, rather than coffee as a whole, enhance HDL metabolism and RCT, it may ultimately be possible to deliver them more reliably and efficiently in pill form. This approach would

not be without precedent in the field of lipid biology; the beneficial effects of omega-3 fatty acids, traditionally delivered via a high-fish diet, have been recapitulated for the treatment of dyslipidemia as the prescription drug Lovaza® (GlaxoSmithKline; Philadelphia, PA).

In summary, Dr. Uto-Kondo and colleagues provide a useful methodologic framework for studies that explore the association between various compounds and cholesterol efflux. Their work adds to a growing body of evidence that suggests a role for polyphenols in cellular cholesterol efflux. If confirmed, this conceptual approach to enhancement of macrophage RCT flux could prove valuable in the prevention and treatment of cardiovascular disease in humans.

Non-Standard Abbreviations and Acronyms

HDL-C	high-density lipoprotein cholesterol
LDL-C	low-density lipoprotein cholesterol
Apo-A1	apolipoprotein A1
CETP	cholesterol ester transfer protein
RCT	reverse cholesterol transport
ABCA1	ATP-binding cassette subfamily A1
ABCG1	ATP-binding cassette subfamily G1
SR-BI	scavenger receptor class B type I
LXR	liver X receptor

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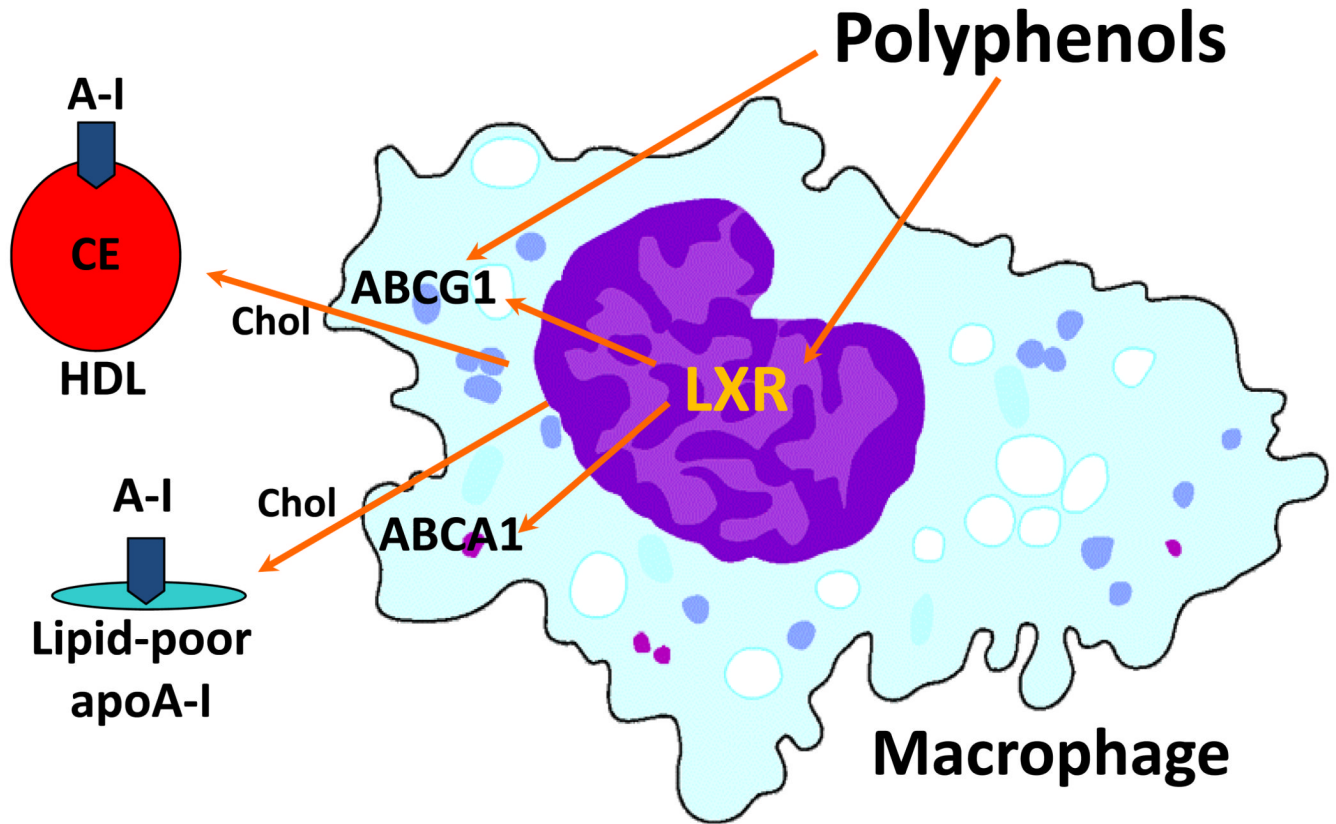


Figure 1.

Postulated Mechanisms for effects of polyphenols on macrophage cholesterol efflux. Cholesterol is effluxed out of macrophage foam cells in the first step of reverse cholesterol transport (RCT). Efflux to lipid-free or lipid-poor Apo-A1 particles (which then become mature HDL) occurs via the ATP-binding cassette subfamily A1 (ABCA1) transporter, while efflux directly to mature HDL particles occurs via the ATP-binding cassette subfamily G1 (ABCG1) transporter.²⁷ Resveratrol and anthocyanins promote the efflux pathway via upregulation of liver X receptor (LXR).^{21,22} Uto-Kondo et al demonstrated that two phenolic acids, as well as whole coffee, increased both mRNA and protein levels of ABCG1 and scavenger receptor class B type I (SR-BI), but not ABCA1, by enhancing mRNA stability.²⁶

Table 1

Selected polyphenols and their dietary sources

Polyphenol	Dietary Source	Effect on Chol Efflux	Mechanism	Reference
Resveratrol	Red wine, berries, Peanuts	Positive	Increased expression of LXR	21, 22
Anthocyanins	Red wine, berries	Positive	Increased expression of ABCA1	23
Phenolic acids (caffeic and ferulic)	Coffee, wheat	Positive	Increased expression of ABCG1 and SR-BI	24
Isoflavones	Soy	Unknown	NA	NA
Quercetin	Onions, apples	Unknown	NA	NA
Catechins	Tea, red wine Chocolate	Unknown	NA	NA