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REVIEWS: CURRENT TOPICS

Role of polyphenols and polyphenol-rich foods in the modulation of PON1 activity and expression

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Abstract

Paraoxonase 1 (PON1) is a high-density lipoprotein (HDL)-associated enzyme involved in the protection of low-density lipoprotein and HDLs against lipid peroxidation. Several studies documented the capacity of polyphenols to stimulate PON1 transcription activation.

The objective of the present review is to provide the main evidence about the role and the potential mechanism of action of polyphenols and polyphenol-rich foods in the modulation of PON1 gene expression and activity.

A total of 76 *in vitro* and *in vivo* studies were included in the review. Overall, while evidence obtained *in vitro* is limited to quercetin and resveratrol, those deriving from animal models seem more convincing for a wide range of polyphenols but only at pharmacological doses. Evidence from human studies is promising but deserves more substantiation about the role of polyphenol-rich foods in the regulation of PON1 activity and expression.

Research focused on the understanding of the structure–activity relationship of polyphenols with PON1 and on the mechanisms at the base of PON1 modulation is warranted. Well-designed human intervention studies are encouraged to corroborate the findings of polyphenols also at physiological doses.

Keywords: Polyphenols; Polyphenol-rich foods; Paraoxonase-1; *In vitro* studies; *In vivo* studies

Contents

1. Introduction

Paraoxonases (PONs) are a family of three enzymes named PON1, PON2 and PON3. PON1 and PON3 are predominantly synthesized in the liver and secreted into the plasma where they are associated with high-density lipoprotein (HDL). PON2 is not generally present in plasma but widely distributed also in cells and tissues such as liver and kidneys. Both PON2 and PON3 have antioxidant properties but lack PON or arylesterase activities compared to PON1. Although all the three enzymes have shown antiatherogenic activity, PON1 is considered the major protective factor against low-density lipoprotein (LDL) and HDL oxidation [1]. Studies investigating the role of PON1 in cardiovascular disease have provided evidence that PON1 status is a better predictor of disease than PON2 and PON3. The mechanism by which PON1 protects LDL from oxidation seems to be related to its capacity to hydrolyze oxidized fatty acids derived from phospholipids, cholesterylester and triglycerides hydroperoxides that are potentially

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atherogenic compounds [2]. In this regard, data from several animal models of atherosclerosis demonstrated the ability of PON1 to retard and reverse atherosclerosis through a reduction of oxidized LDL, a reduction of macrophages oxidative stress and foam cell formation, an increase in reverse cholesterol transport and an improvement of arterial function. In addition, PON1 is involved in the detoxification of homocysteine (Hcy)-thiolactone, a reactive metabolite that, through a process of *N*-homocysteinylation, affects the structure and function of proteins and lipoproteins including HDL [3].

Several studies support the hypothesis that a low PON and lactonase activity of PON1 has been associated with an increased oxidative stress and vulnerability to plaque formation, atherosclerosis and cardiovascular diseases [1,4–9]. Moreover, alterations in circulating PON1 levels have been found in a variety of diseases including diabetes mellitus, hepatic and renal diseases, psoriasis and rheumatoid arthritis [10]. It is well known that PON1 activity can be influenced by several factors such as lifestyle and diet.

Very recently, Lou-Bonafonte and colleagues [11] critically revised the role of Mediterranean diet, and its components, in the modulation of PON1 activity. The authors suggested that the Mediterranean diet, through the intake of nuts, fruit and vegetable, may affect PON1 activity by protecting the enzyme from oxidative stress-induced inactivation and/or by improving its activity.

Regarding the effects of dietary constituents, several *in vivo* studies showed an increase in PON1 activity/expression following vitamin C [12,13], vitamin E [14–16], folate [13], carotenoids [17], mono- and poly-unsaturated fatty acids [18–22], selenium [21,22], and polyphenol supplementation [23–25]. Polyphenols are a heterogeneous family of bioactive compounds widely distributed in the plant kingdom. Chemically, they are characterized by the common presence of at least one aromatic ring in their structure, linked with other phenolic-, hydroxyl-, carbon- or other chemical groups [26]. Polyphenols can be classified into *flavonoids* (*i.e.*, flavonols, flavanones, flavones, isoflavones, anthocyanidins and flavan-3-ols) and *nonflavonoids* (*i.e.*, condensed and hydrolysable tannins, stilbenes, phenolic acids, hydroxibenzoic and hydroxycinnamic acids and lignans) depending of their chemical structure [26,27]. They can be in the form of oligomers and polymers, or esterified with other chemical compounds (mainly sugars or organic acids), while rarely are present as aglycones (without sugar). Minor *nonflavonoids* include also derivatives of colonic microbiota metabolites such as phenylvaleric, phenyl-lactic, phenylpropionic, phenylmandelic and phenylhydracrylic acid [28]. In the last years, several studies focused on the bioactivity of polyphenols and polyphenol-rich foods. Most of the studies have been performed *in vitro* and in animal models, while limited are those in humans. In particular, observational and intervention studies documented an effect of polyphenols in the prevention/modulation of metabolic syndrome [28], endothelial dysfunction [29], hypertension [30–32] and cardiovascular and coronary diseases [33,34]. The effects seem related to the antioxidant and anti-inflammatory activity [35,36], to vascular function modulation [33,37] and to lipid/cholesterol regulation [38]. In addition, it has been hypothesized that polyphenols effects may be mediated also by the regulation of PON1 activity and gene expression. In the present review, we attempt to summarize the main evidence on the potential effects of polyphenols and polyphenol-rich foods on PON1 expression and activity also considering, when available, the contribution of genetic factors and the mechanisms of action. The review will focus on both *in vitro* and *in vivo* studies.

2. Overview of *in vitro* and *in vivo* studies on polyphenols as modulators of PON1 expression and activity

A systematic search for literature focused on the effect of polyphenols and polyphenol-rich foods in the modulation of PON1 was carried out. The search of the studies was performed based on the preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram (Fig. 1). PUBMED, ScienceDirect and Scopus databases were searched to identify pertinent articles. The systematic computerized literature search was performed from January 2000 up to November 2016. The exploration used the combination of the following terms: “polyphenols,” “polyphenol-rich foods,” “flavonoids,” “anthocyanins” and “paraoxonase 1”. Reference lists of the obtained papers were also searched for additional articles. The selection of the *in vitro* and *in vivo* studies was performed according to the following inclusion and exclusion criteria. *Inclusion criteria*: (a) be performed in cells and/or in animal models and/or in humans, (b) be a study evaluating PON1 activity and/or expression and (c) be a study evaluating polyphenols and/or polyphenol-rich foods. *Exclusion criteria*: (a) evaluating foods not having polyphenols as major bioactive compounds, (b) be performed *in vitro* but not using cells, (c) be written not in English and (d) be performed without a statistical analysis. A total of 406 records were screened and 323 out of them were excluded based on title or abstract or because duplicate papers. Eighty-three full-text articles were obtained from the databases and from the reference lists of the obtained papers. Based on the full-text, inclusion and exclusion criteria, 7 articles were excluded while 76 papers were analyzed. Five of them combined two or three experimental models [39–43] for a total of 81 studies. Among them, 11 were *in vitro* studies, 44 were performed on animal models and 26 were intervention studies in humans. The studies included in the review are described in Tables 1–3 (provided as supplemental material) and the following details were included: polyphenol/s or polyphenol rich-food (composition was reported when available) tested, cell model, animal model or subjects selected and their characteristics, study design, type of intervention and main findings.

2.1. In vitro studies

Eleven *in vitro* studies evaluated the role of polyphenols and polyphenol-rich extracts on PON1 expression and activity (*see* Supplementary Table 1 under “Supplemental data” in the online issue) [39,42–51].

The main polyphenols considered were resveratrol [47–51], used in two studies also as positive control [42,43], and quercetin [39,43,45]. The human hepatoma cell line Huh7 was the main cell line tested, being utilized in 9 out of the 11 *in vitro* studies considered [39,42–45,49,50]. The duration of treatments generally ranged from 24 to 48 h, while the doses of resveratrol ranged from 2 to 25 μM, with the exception of one study that used also concentrations of 200 μM [48]. Gouédard et al. [44] and Guyot et al. [50] reported an increased PON1 gene expression in human hepatocyte primary cultures and in HuH7 hepatoma cell line following a 48-h supplementation with 10 μM of resveratrol. Similar results were also observed by Gupta and colleagues [51] following an incubation of HepG2 cells for 48 h with 15 μM of resveratrol. Curtin et al. [48] found the optimal induction of intracellular and extracellular PON1 activity within 2–20 μM of resveratrol, while no effect was observed at doses higher than 20 μM, which in turn resulted cytotoxic leading to a decrease of cell metabolic activity.

Three studies found a dose-dependent in increase of PON1 activity [42,45,46]. Schrader and colleagues [42] documented that Huh7 liver hepatoma cells supplemented with curcumin (1–20 μM for 48 h) increased PON1 activation in a dose-dependent manner for concentrations higher than 10 μM. Khateeb et al. [46] reported that supplementation with pomegranate juice (PJ) polyphenols such as punicalagin and gallic acid (from 17.5 to 70 μg gallic acid equivalent/ml for 24 h) increased HuH7 hepatocyte-secreted PON1 arylesterase activity and the effect was dose-dependent. Garige and coworkers [45] showed a progressive up-regulation of PON1 expression and activity