Chemico-Biological Interactions 275 (2017) 13–21

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

Protective role of benzoselenophene derivatives of resveratrol on the induced oxidative stress in intestinal myofibroblasts and osteocytes

Vladana Domazetovic [a], Filippo Fontani [a], Damiano Tanini [b], Veronica D'Esopo [b], Caterina Viglianisi [b], Gemma Marcucci [c], Lucia Panzella [d], Alessandra Napolitano [d], Maria Luisa Brandi [c], Antonella Capperucci [b], Stefano Menichetti [b], Maria Teresa Vincenzini [a], Teresa Iantomasi [a, *]

[a] Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", University of Florence, Viale Morgagni 50, I-50134 Florence, Italy
[b] Department of Chemistry "Ugo Schiff", University of Florence, Via della Lastruccia3-13, I-50019 Sesto Fiorentino, Italy
[c] Department of Surgery and Translational Medicine, Bone Metabolic Diseases Unit, University of Florence, Viale Pieraccini 6, I-50139 Florence, Italy
[d] Department of Chemical Sciences, University of Naples "Federico II", Via Cintia 4, I-80126 Naples, Italy

ARTICLE INFO

Article history:
Received 24 February 2017
Received in revised form
18 July 2017
Accepted 20 July 2017
Available online 21 July 2017

Keywords:
Resveratrol
Benzoselenophene derivatives
Antioxidants
Myofibroblasts
Osteocytes

ABSTRACT

Resveratrol (RE), a polyphenolic compound present in some food and plants, is characterized by anti-inflammatory and antioxidant properties. However, it is quickly metabolized with consequent loss of its efficacy. In this study, the antioxidant effect of 2-phenyl-benzoselenophene derivatives (VD0, VD1 and VD2) was detected in intestinal myofibroblast and osteocyte cell lines in which the oxidative stress was induced by GSH depletion or starvation, respectively. In fact, the oxidative stress is involved in pathogenesis of inflammatory bowel diseases (IBD) and in increased osteoclastogenesis in osteoporosis. Our results show that these derivatives have major antioxidant power in reducing and/or restoring radical oxygen species to control values than RE itself in both cell types. Moreover, derivatives have different antioxidant capacity in myofibroblasts and in osteocytes and this can be due to different degree of oxidative stress and structural characteristics of these compounds. Some of the synthesized RE analogs have shown anti-bacterial role in IBD and anti-resorptive activity in bone pathologies related to inflammatory and osteoporotic processes. Thus, we suggest benzoselenophene derivatives as good candidates for alternative therapy and/or therapeutic support in these pathologies.

1. Introduction

Resveratrol (RE)[1] (3,5,4′-trihydroxy-*trans*-stilbene) belongs to the family of polyphenolic compounds and is present in the grapes and grape-derived foodstuffs, such as red wine, in some berries and oilseeds (peanut) and in particular plants. In traditional Asian medicine the plant Polygonum cuspidatum, particularly rich in RE, is used to treat disorders of the heart and liver [1–3]. RE has attracted much interest considering its protective effects against metabolic and immune-mediated pathologies, as well as its many beneficial properties in treating cancer, cardiovascular diseases, bacterial infections, inflammation and aging [4,5]. RE exerts its anti-inflammatory and anti-autoimmune properties by interacting with signaling molecules, transcriptional factors and various immune cell types [6–11]. In fact, RE ameliorates experimentally induced inflammatory arthritis, ulcerative colitis, autoimmune myocarditis and encephalomyelitis in animal models [12–15]. The beneficial effects of RE are also ascribed to its antioxidant properties. RE induces various intracellular antioxidant enzymes [16], prevents the LDL oxidation [17] and scavenges reactive oxygen species (ROS) protecting biological macromolecules from oxidative damage [18]. ROS are involved in inflammatory processes and in various diseases such as inflammatory bowel disease (IBD), cardiovascular disease and cancer [18,19]. In particular, in IBD a crucial role is attributed to antioxidants and it has been demonstrated that

* Corresponding author. University of Florence, Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Viale Morgagni, 5, 50134 Firenze, Italy.
E-mail address: tiantomasi@unifi.it (T. Iantomasi).

[1] *Abbreviations:* RE, Resveratrol; ROS, reactive oxygen species; IBD, inflammatory bowel disease; GPx, glutathione peroxidase; GSH, glutathione; BSO, buthionine sulfoximine; H_2DCF-DA, 2′-7′-dichlorodihydrofluorescein diacetate; CD, Crohn's disease; Ph_2Se_2, diphenyl diselenide.

http://dx.doi.org/10.1016/j.cbi.2017.07.015
0009-2797/

RE, by reducing the oxidative stress, can be considered an important compound to use in the IBD therapies [20,21]. Oxidative stress, due to estrogen deficiency condition or inflammatory bone disorders [22], is involved in bone loss by contributing to osteoporosis and bone resorption [23]. Antioxidants protect against these events and RE affects bone cell activity by inducing osteoblastogenesis and by inhibiting osteoclast activation [23,24]. The antioxidant activity of RE is due to the presence of phenolic hydroxyl groups and their H^*-transfer ability [25]; however, this effect is not comparable to that of other natural phenols. Moreover, considering that RE is rapidly metabolized with consequent loss of its efficacy, RE derivatives with more powerful antioxidant and anti-inflammatory properties have been synthesized [18,26,27].

It is well known that selenium plays a crucial role in antioxidant system and selenium-containing compounds are essential for biological activities. In this context, organoselenium compounds have continued to attract considerable attention for their essential role in many biological processes, showing for instance antioxidant, anti-inflammatory, and neuroprotective properties [28–30]. Moreover, for their redox chemistry, selenium-containing organic molecules have been widely applied as synthetic mimics of glutathione peroxidase (GPx) [31,32]. GPx is, together with iodothyronine deiodinase and thioredoxin reductase, one of the most important and most studied mammalian selenoenzymes. GPx plays a key role in the cellular defence against oxidative stress, catalyzing the reduction of hydroperoxides at the expense of two molecules of glutathione (GSH). In this regard, selenium-based functionalization of phenolic compounds has been applied to improve the antioxidant potency of such molecules by decreasing the bond dissociation enthalpy of phenolic groups [33], with the aim to conjugate the GPx-like activity with the chain-breaking properties. In particular, Tanini et al. [34] have synthesized three selenated RE derivatives with an increased rigidity, obtained by the construction of a benzoselenophene ring, see Fig. 1 compounds VD0, VD1 and VD2. These RE derivatives were more efficient than RE in ferric reducing/antioxidant power assay and in chain breaking ability evaluation using 'in vitro' styrene autoxidation experiments. Preliminary results showed that these novel selenium-containing RE derivatives proved to behave as GPx-mimics, being able to efficiently oxidize GSH in the presence of H_2O_2. In particular, 150 μM RE benzoselenophene derivatives in the presence of 5 mM GSH reduced 2 mM H_2O_2 in phosphate buffer (pH 7.4) and the highest catalytic activity was found for VD0. This compound indeed showed a T_{50} value (8 min) shorter than diphenyl diselenide (Ph_2Se_2) (16 min) used as reference GPx-mimic, and an activity value of 3.3 as compared to the activity of control with no additive (value = 1) and to that of Ph_2Se_2-treatment (value = 1.6) [unpublished observations].

In this study, we compared RE effects to that of 2-phenyl-benzoselenophene derivatives, VD0, VD1 and VD2, in countering the oxidative stress, induced in myofibroblast cell line derived from human colonic mucosa (18Co), and in murine osteocyte-like cell line, MLO-Y4. In particular, the antioxidant ability of RE derivatives in restoring the physiological redox state of these cells was studied.

2. Materials and Methods

2.1. Reagents

All common reagents were purchased from Sigma-Aldrich (Saint Louis, Missouri, USA), GE Healthcare (Little Chalfont, Great Britain) and Thermo Scientific (Waltham, Massachusetts, USA), unless specified in the text.

Sigma-Aldrich: Minimum Essential Medium Eagle, L-glutamine, sodium bicarbonate, non-essential amino acids, sodium pyruvate, dimethyl sulfoxide (DMSO), buthionine sulfoximine (BSO), trypsin, bovine serum albumin, Tris/HCl, Triton X100, NaCl, NaF, Ethylenebis(oxyethylenenitrilo)tetraacetic acid (EGTA).

GE Healthcare: fetal bovine serum, calf serum, penicillin/streptomycin 100X solution, phosphate buffered saline (PBS), alpha-MEM medium.

Thermo Scientific: Pierce BCA protein assay kit, trypan blue.

2.2. Cell culture and treatment

CCD-18Co (18Co) cells, obtained from American Type Culture

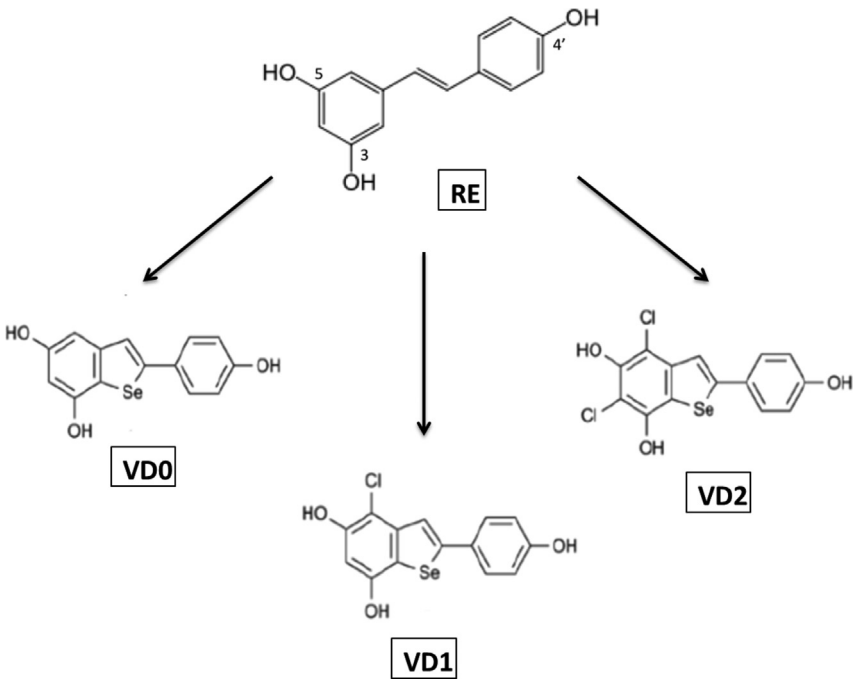

Fig. 1. Chemical structure of RE and benzoselenophene derivatives (VD0, VD1, VD2).