Available online at www.sciencedirect.com
SCIENCE DIRECT®
Mutation Research 579 (2005) 200–213
Fundamental and Molecular Mechanisms of Mutagenesis
www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

# Phenolics as potential antioxidant therapeutic agents: Mechanism and actions

M.A. Soobrattee [a], V.S. Neergheen [a], A. Luximon-Ramma [a], O.I. Aruoma [b,**], T. Bahorun [a,*]

[a] *Department of Biosciences, Faculty of Science, University of Mauritius, Réduit, Mauritius*
[b] *Faculty of Health and Social Care, London South Bank University, 103 Borough Road, London SE1 0AA, UK*

Received 25 October 2004; received in revised form 7 March 2005; accepted 8 March 2005
Available online 26 August 2005

**Abstract**

Accumulating chemical, biochemical, clinical and epidemiological evidence supports the chemoprotective effects of phenolic antioxidants against oxidative stress-mediated disorders. The pharmacological actions of phenolic antioxidants stem mainly from their free radical scavenging and metal chelating properties as well as their effects on cell signaling pathways and on gene expression. The antioxidant capacities of phenolic compounds that are widely distributed in plant-based diets were assessed by the Trolox equivalent antioxidant capacity (TEAC), the ferric reducing antioxidant power (FRAP), the hypochlorite scavenging capacity, the deoxyribose method and the copper-phenanthroline-dependent DNA oxidation assays. Based on the TEAC, FRAP and hypochlorite scavenging data, the observed activity order was: procyanidin dimer > flavanol > flavonol > hydroxycinnamic acids > simple phenolic acids. Among the flavonol aglycones, the antioxidant propensities decrease in the order quercetin, myricetin and kaempferol. Gallic acid and rosmarinic acid were the most potent antioxidants among the simple phenolic and hydroxycinnamic acids, respectively. Ferulic acid displayed the highest inhibitory activity against deoxyribose degradation but no structure–activity relationship could be established for the activities of the phenolic compounds in the deoxyribose assay. The efficacies of the phenolic compounds differ depending on the mechanism of antioxidant action in the respective assay used, with procyanidin dimers and flavan-3-ols showing very potent activities in most of the systems tested. Compared to the physiologically active (glutathione, α-tocopherol, ergothioneine) and synthetic (Trolox, BHA, BHT) antioxidants, these compounds exhibited much higher efficacy. Plant-derived phenolics represents good sources of natural antioxidants, however, further investigation on the molecular mechanism of action of these phytochemicals is crucial to the evaluation of their potential as prophylactic agents.


*Keywords:* Phenolics; Flavonoid; Proanthocyanidin; Antioxidant; Structure–activity relationship; Therapeutic agents; Mechanism of action; Antioxidant medicine

## 1. Introduction

There is emerging interest in the use of naturally occurring antioxidants for the preservation of foods

* Corresponding author. Tel.: +230 454 1041; fax: +230 465 6928.
** Corresponding author.
*E-mail addresses:* aruomaoi@lsbu.ac.uk (O.I. Aruoma), tbahorun@uom.ac.mu (T. Bahorun).

0027-5107/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.mrfmmm.2005.03.023

and in the management of a number of pathophysiological conditions, most of which involve free radical damage. The implication of oxidative and nitrosative stress in the etiology and progression of several acute and chronic clinical disorders has led to the suggestion that antioxidants can have health benefits as prophylactic agents. Epidemiological studies have consistently shown an inverse association between consumption of vegetables and fruits and the risk of cardiovascular diseases and certain forms of cancer [1,2]. Although the protective effects have been primarily attributed to the well-known antioxidants, such as Vitamin C, Vitamin E and β-carotene, plant phenolics may also play a significant role. Moreover, restrictions over the use of synthetic antioxidants BHA and BHT in food further strengthen the concept of using naturally occurring compounds as antioxidants [3].

Phenolic compounds or polyphenols constitute one of the most numerous and ubiquitously distributed group of plant secondary metabolites, with more than 8000 phenolic structures currently known. Natural polyphenols can range from simple molecules (phenolic acids, phenylpropanoids, flavonoids) to highly polymerised compounds (lignins, melanins, tannins), with flavonoids representing the most common and widely distributed sub-group [4]. Phenolics are widely distributed in the plant kingdom and are therefore an integral part of the diet, with significant amounts being reported in vegetables, fruits and beverages [5–7]. Although the dietary intake of phenolics varies considerably among geographic regions, it is estimated that daily intake range from about 20 mg to 1 g, which is higher than that for Vitamin E [8]. Polyphenolics exhibit a wide range of biological effects including antibacterial, anti-inflammatory, antiallergic, hepatoprotective, antithrombotic, antiviral, anticarcinogenic and vasodilatory actions [9]; many of these biological functions have been attributed to their free radical scavenging and antioxidant activity.

Molecular studies have revealed that phenolics can exert modulatory actions in cell by interacting with a wide spectrum of molecular targets central to the cell signaling machinery. These include activation of mitogen-activated protein kinase (MAPK), protein kinase C (PKC), serine/threonine protein kinase Akt/PKB, phase II antioxidant detoxifying enzymes, downregulation of pro-inflammatory enzymes (COX-2 and iNOS) through the activation of peroxisome proliferator-activated receptor gamma (PPARγ), regulation of calcium homeostasis, inhibition of phosphoinositide 3-kinase (PI 3-kinase), tyrosine kinases, NF-κB, c-JUN, as well as modulation of several cell survival/cell-cycle genes [10]. The redox status of the cell has profound effect on the cell signaling pathways, in particular the MAP kinase cascade (Fig. 1). Oxidative insults can also perturb the cellular energy homeostasis by disrupting the mitochondrial integrity. ROS can induce permeabilization of the mitochondrial membrane resulting in the release of apoptosis initiating factors (AIF), such as cytochrome *c*, DIABLO/smac and dissipation of the mitochondrial membrane potential ($\Delta\psi_m$) [11]; these processes mark the point of no return in the cell death process. Although the exact mechanism involved is not fully elucidated, it seems to be mediated by translocation of Bad from the cytosol to the mitochondria where it dimerizes with Bcl-2 and Bcl-XL thereby neutralizing their mitochondrial stabilizing effect [12]. Phenolics may prevent oxidative stress induced mitochondrial transition pore complex opening by decreasing production of Bax and Bad protein, favouring an increase in Bcl2–BclXL/Bax–Bak ratio [12]. Thus, in addition to their antioxidant capacity, phenolics may exert protective effect by selectively inhibiting or stimulating key protein in the cell signaling cascades.

Phenolics are particularly attractive as prophylactic agents due to their high prevalence in the diet and also due to their pluripharmacological effects. The antioxidant activities of more than 30 commercially available phenolic compounds have been measured in the present study, physiologically active and synthetic standards have also been included for comparative purpose. The compounds were selected on the basis of their chemical structural characteristics, availability and prevalence in food plants. For the in vitro characterisation of antioxidant propensities use of single test system is widely discouraged as the mechanisms of reactions involving antioxidants are complex and depend on the physico-chemical parameters of the test reagents and substrates. There is an emerging view that a combination of rapid, sensitive and reproducible methods should be used whenever an antioxidant activity screening is designed and there should be great caution in extrapolating the in vitro data [13]. Consequently for the evaluation of the antioxidant capacities of the phenolic compounds five independent and highly