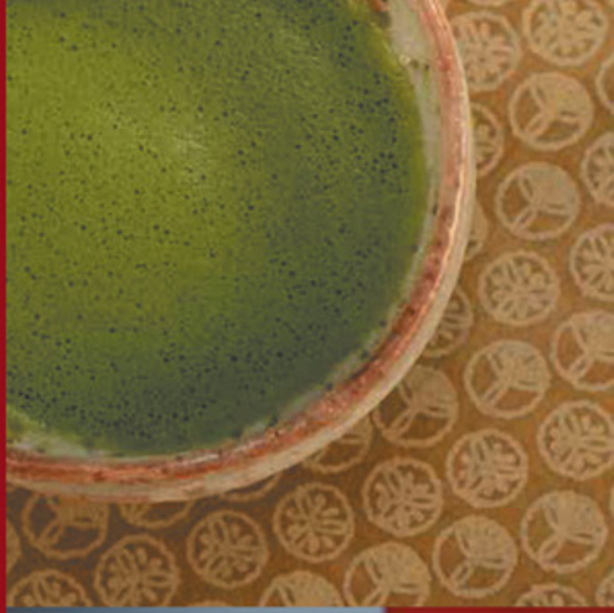
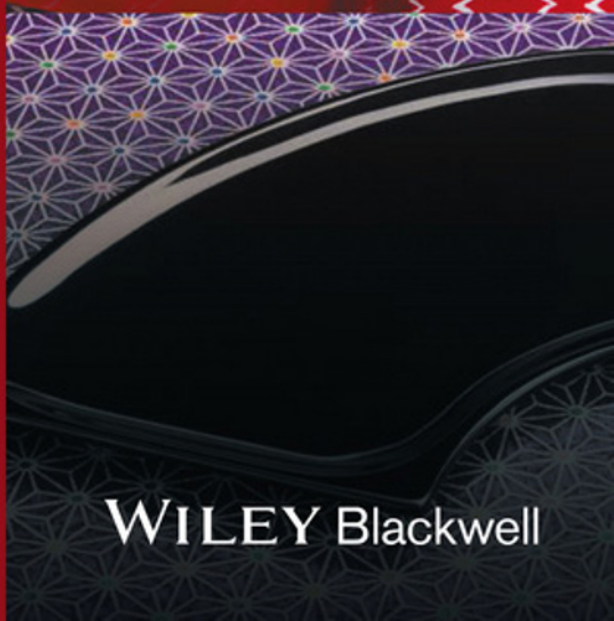
# Recent Advances in Polyphenol Research

## Volume 5

Edited by

Kumi Yoshida,
Véronique Cheynier
and Stéphane Quideau





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# Recent Advances in Polyphenol Research

**Recent Advances in Polyphenol Research**
A series for researchers and graduate students whose work is related to plant phenolics and polyphenols, as well as for individuals representing governments and industries with interest in this field. Each volume in this biennial series focuses on several important research topics in plant phenols and polyphenols, including chemistry, biosynthesis, metabolic engineering, ecology, physiology, food, nutrition, and health.

# Recent Advances in Polyphenol Research

Volume 5

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## Dedication

To **Michel Bourzeix**—one of the founders of Groupe Polyphénols and its secretary from 1972 to 1995—who devoted his career to promoting research on polyphenols and supported GP activities and conferences with dedication and enthusiasm

To **Dieter Treutter**—a faithful member of the Groupe Polyphénols board for many years and the organiser of ICP2000

*in memoriam*

The editors wish to thank all of the members of the "Groupe Polyphénols" Board Committee (2012–2014) for their guidance and assistance throughout this project.

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# Preface

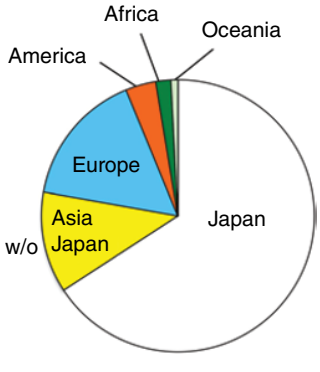
Polyphenols are secondary metabolites that are variously distributed in the plant kingdom and characterized by a wide diversity of chemical structures. On behalf of the international scholarly society "*Groupe Polyphénols*," which organizes the biennial conference, "*International Conference on Polyphenols*" (ICP), we define the term "polyphenol" as related to plant products exclusively derived from the shikimate/phenylpropanoid and/or the polyketide pathway, featuring more than one phenolic unit and deprived of nitrogen-based functions (http://www.groupepolyphenols.com/the-society/why-bother-with-polyphenols/). The number of known plant polyphenols is quite large, from structurally simple compounds such as the stilbenoid resveratrol or the flavonoid quercetin to complex macromolecules such as the proanthocyanidin oligomers or the lignin polymer. It is thus not surprising that their functions in plant and physicochemical properties are also quite varied. In the early 20th century, investigations on polyphenols were mainly dedicated to the determination of their structures and their roles in traditional medicines, as well as in vegetable tanning. Nowadays, research on plant polyphenols concerns a much wider area of science with novel and multidisciplinary efforts made toward the understanding of their properties and exploitation thereof in *inter alia* the development of new materials, the innovation in agriculture and food products, including the development of new crops and flowers, the higher fixation of carbon dioxide, and the formulation of functional foods with human health benefits, as well as the discovery of new pharmaceutical medicines.

This book series "*Recent Advances in Polyphenol Research*" began its publication in 2008 on the occasion of the 24th ICP in Salamanca, Spain. The content of this first volume was already mostly based on review articles written by plenary lecturers of the previous ICP, which had taken place in Winnipeg, Canada. Since then, this flagship publication of the *Groupe Polyphénols* has been released without any discontinuity every 2 years to provide the reader with authoritative updates on various topics of polyphenol research written by ICP plenary lecturers and by invited expert contributors.

This book, the fifth volume of the series, is concerned with the topics that were covered during the 27th ICP, which was organized jointly with the 8th edition of the *Tannin Conference* in September 2014 in Nagoya, Japan. In more than 40 years of the history of the *Groupe Polyphénols*, it was the first time that the *International Conference on*

*Polyphenols* took place in Asia. Six different main topics of the polyphenol science were selected for the scientific program of this memorable ICP2014 edition:

1) **Chemistry, Physicochemistry, and Materials Science**, covering structures, reactivity, organic synthesis, molecular modeling, fundamental aspects, chemical analysis, spectroscopy, molecular associations, and interactions of polyphenols.
2) **Biosynthesis, Genetics, and Metabolic Engineering**, covering molecular biology, genetics, enzymology, gene expression and regulation, trafficking, biotechnology, horticultural science, and molecular breeding related to polyphenols.
3) **Plants and Ecosystems, Lignocellulose Biomass**, covering plant growth and development, biotic and abiotic stress, resistance, ecophysiology, sustainable development, valorization, plant environmental system, forest chemistry, and lignin and lignan.
4) **Food, Nutrition, and Health**, covering food ingredients, nutrient components, functional food, mode of action, bioavailability and metabolism, food processing, influence on food and beverages properties, cosmetics, and antioxidant activity of polphenols.
5) **Natural Medicine and Kampo**, a special session for this first conference held in Asia covering oriental traditional medicine, herbal medicine, Chinese herbal medicine, folklore, mode of action, metabolism, natural products chemistry, and drug discovery.
6) **Tannins and Their Functions**, another special session on the occasion of this joint meeting with the *Tannin Conference* covering research topics related to condensed tannins, hydrolyzable tannins, tea, wine, persimmon, seed-coat color, mode of action, and enzymatic reactions.

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More than 500 scientists from 35 countries attended the conference, with 321 paper contributions that comprised 61 oral communications and 260 poster presentations. The fifth volume of "*Recent Advances in Polyphenol Research*" contains chapters from 14 guest speakers of the conference. The support and assistance of the *Groupe Polyphénols*, the *Tannin Conference* Group, several Japanese academic associations and foundations, notably the Nagoya University, the City of Nagoya and the Nagoya Convention & Visitors Bureau, and numerous private sponsors are gratefully acknowledged, as the great success of these joint editions of the *International Conference on Polyphenols* and the *Tannin*

*Conference* would not have been possible without their contributions. As a final note, we would also like to deeply thank all of the plenary, communication, and poster presenters for the quality of their contributions, from basic science to more applied fields, and all of the attendees, with a special thank to the numerous Asian researchers for their first participation in the ICP and for expressing their eagerness to attend the next ICP meetings.

Kumi Yoshida
Véronique Cheynier
Stéphane Quideau

Chapter 1

# The Physical Chemistry of Polyphenols: Insights into the Activity of Polyphenols in Humans at the Molecular Level

*Olivier Dangles, Claire Dufour, Claire Tonnelé and Patrick Trouillas*

**Abstract:** This chapter reviews the following versatile physicochemical properties of polyphenols in relation with their potential activity in humans:

1) Interactions with proteins and lipid–water interfaces. These interactions must be qualified with respect to the current knowledge on polyphenol bioavailability and metabolism. They are expected to mediate most of the cell signaling activity of polyphenols.
2) A general reducing capacity that may be expressed in the gastrointestinal tract submitted to postprandial oxidative stress and also in cells, for example, by direct scavenging of reactive oxygen species, especially if preliminary deconjugation of metabolites takes place
3) The complex relationships with transition metal ions involving binding and/or electron transfer in close connection with the antioxidant versus pro-oxidant activity of polyphenols

**Keywords:** polyphenol, flavonoid, Health effectsbiological activity, mechanism, antioxidant, protein, membrane, metal ion, gastrointestinal tract, DFT methods.

## 1.1 Introduction

The activity, functions, and structural diversity of polyphenols in plants, food, and humans reflect the remarkable diversity of their physicochemical properties: UV–visible absorption, electron donation, affinity for metal ions, propensity to develop molecular interactions (van der Waals, hydrogen bonding) with proteins and lipid–water interfaces, and

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nucleophilicity. This chapter aims to exemplify how polyphenols act to promote health in humans at the molecular level. It rests on two common assumptions based on epidemiological evidence and food analysis (Manach *et al*., 2005; Crozier *et al*., 2010; Del Rio *et al*., 2013):

- The consumption of fruit and vegetables helps prevent chronic diseases and, in particular, favors cardiovascular health.
- Phenolic compounds, from the simple hydroxybenzoic and hydroxycinnamic acids to the complex condensed and hydrolyzable tannins, constitute the most abundant class of plant secondary metabolites in our diet and take part in this protection.

By contributing to the sensorial properties of food, for example, color and astringency, native polyphenols and their derivatives obtained after technological and domestic processing can directly influence the consumer's choice. Moreover, polyphenols undergo only minimal enzymatic conversion in the oral cavity and in the gastric compartment although their release from the food matrix (bioaccessibility) is an important issue. Thus, intact food polyphenols may directly promote health benefits in the upper digestive tract, in particular by fighting postprandial oxidative stress resulting from an unbalanced diet (Sies *et al*., 2005; Kanner *et al*., 2012). Beyond the gastric compartment, polyphenol bioavailability[1] (Fig. 1.1) must be considered as a priority to tackle any biological effects (Manach *et al*., 2005; Crozier *et al*., 2010; Del Rio *et al*., 2013). Indeed, even for polyphenols that can be partially absorbed in the upper intestinal tract (aglycones, glucosides), most of the dietary intake reaches the colon where extensive catabolism by the microbiota takes place: hydrolysis of glycosidic and ester bonds, release of flavanol monomers from proanthocyanidins, hydrogenation of the C═C double bond of hydroxycinnamic acids, deoxygenation of aromatic rings, cleavage of the central heterocycle of flavonoids, and so on. Conjugation of polyphenols and their bacterial metabolites in intestinal and liver cells eventually results in a complex mixture of circulating polyphenol *O*-β-D-glucuronides and *O*-sulfo forms (less rigorously called sulfates). When present, catechol groups are also partially methylated.

The concentration of circulating polyphenols is usually evaluated after treatment by a mixture of glucuronidases and sulfatases that release the aglycones and their *O*-methyl ethers. This concentration is usually quite low (barely higher than 0.1 μM) and much lower than that of typical plasma antioxidants such as ascorbate (> 30 μM). At first sight, this does not argue in favor of nonspecific biological effects, such as the antioxidant activity by radical scavenging or chelation of transition metal ions to form inert complexes. This seems all the more true that the catechol group, displayed by many common dietary polyphenols and which is a critical determinant of the electron-donating and metal-binding capacities, is generally either absent in the circulating metabolites (bacterial deoxygenation) or at least

[1]Bioavailability: the fraction of ingested polyphenol (native form + metabolites) that enters the general blood circulation and is thus potentially available for health effects.

Bioaccessibility: the first step of bioavailability, the fraction of ingested polyphenol (native form + metabolites) that is released from the food matrix and is thus potentially available for intestinal absorption.

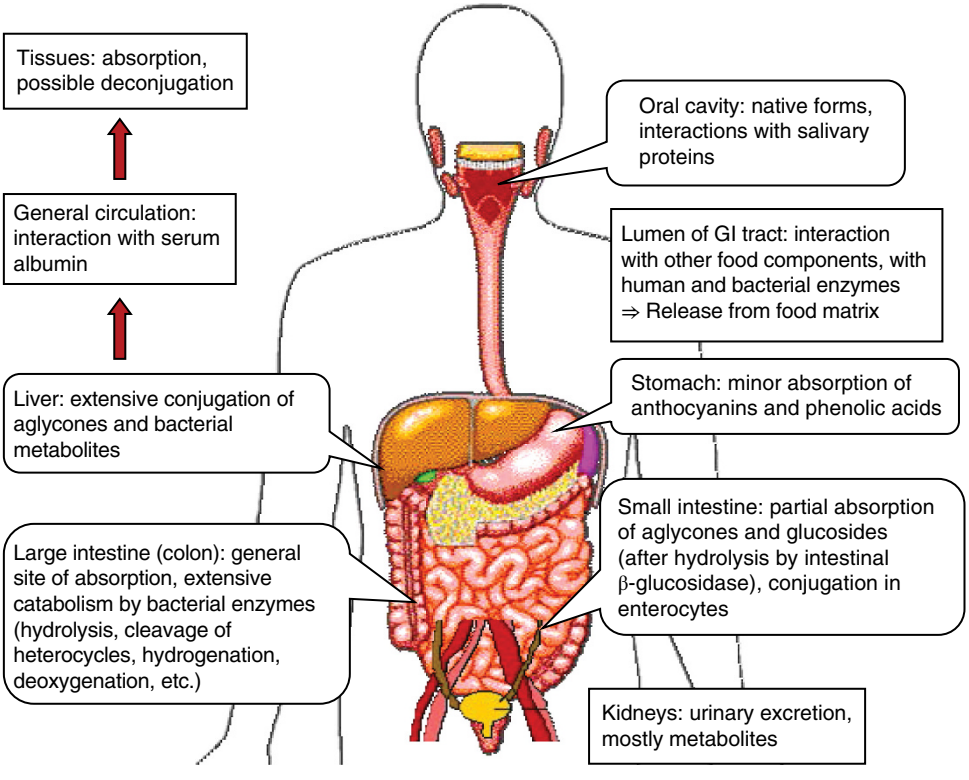


**Fig. 1.1** A simplified view of polyphenol bioavailability. (*See insert for color representation of the figure*)

partially conjugated. However, the claim that *in vivo* polyphenol concentrations are low should be nuanced for the following reasons:

1) The complete assessment of polyphenol bioavailability must include the bacterial catabolites and their conjugates, some being much more abundant in the circulation than the parent phenol. A spectacular example can be found in the case of anthocyanins. Indeed, after consumption of blood orange juice, the total amount of native cyanidin 3-*O*-β-D-glucoside (C3G) in plasma is 0.02% of the ingested dose versus 44% for (unconjugated) protocatechuic acid (PCA), its main catabolite (Vitaglione *et al.*, 2007). When the fecal content is also taken into account, PCA eventually represents ca. 73% of the metabolic fate of ingested C3G. Its absence in urine (unlike C3G) also suggests that it takes part in the antioxidant protection and is thus oxidized in tissues.
2) The circulating concentration and its time dependence say nothing concerning either the possibility of polyphenol metabolites accumulation at a much higher local concentration at specific sites of inflammation and oxidative stress or their deconjugation into more active forms.

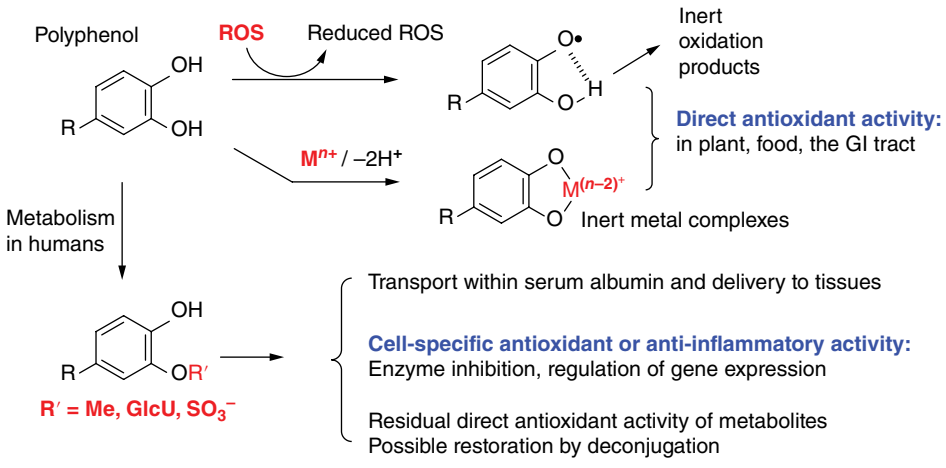


**Fig. 1.2** Health effects expressed by polyphenols.

For instance, when quercetin is continuously perfused through the vascular wall of arteries, it rapidly undergoes oxidative degradation into PCA, whereas the fraction retained in the wall is much more stable and partially methylated (Menendez *et al.*, 2011). By contrast, quercetin 3-*O*-β-D-glucuronide (Q3G), the main circulating metabolite, is not oxidized upon perfusion but slowly converted into quercetin. The kinetics of quercetin release parallels the inhibition in the contractile response of the artery. Thus, the biological effect can be ascribed to quercetin released from its glucuronide, which basically appears as a stable storage form. A schematic view for the bioactivity of polyphenols is summed up in Fig. 1.2.

## 1.2 Molecular complexation of polyphenols

The phenolic nucleus can be regarded as a benchmark chemical group for molecular interactions as it combines an acidic OH group liable to develop hydrogen bonds (both as a donor and as an acceptor) and an aromatic nucleus for dispersion interactions (the stabilizing component of van der Waals interactions).

### *1.2.1 Polyphenol–protein binding*

Polyphenol–protein binding of nutritional relevance can be classified as follows:

- Binding processes within the gastrointestinal (GI) tract, that is, with food proteins, mucins, and the digestive enzymes, with an impact on the bioaccessibility of polyphenols and the digestibility of macronutrients
  - Interactions with plasma proteins, with an impact on transport and the rate of clearance from the general circulation
  - Interactions with specific cell proteins (enzymes, receptors, transcription factors, etc.) that would mediate the nonredox health effects of polyphenols

As the last two situations lie downstream the intestinal absorption and passage through the liver, they concern the circulating polyphenol metabolites. However, some exceptions may be found. For instance, epigallocatechin 3-*O*-gallate (EGCG), the major green tea flavanol, is a rare example of a polyphenol entering the blood circulation mostly in its initial (nonconjugated) form (Manach *et al*., 2005). No less remarkable, EGCG is also one of the rare polyphenols for which a specific receptor has been identified, namely the 67-kDa laminin receptor (67LR) that is expressed on the surface of various tumor cells (Umeda *et al*., 2008). EGCG-67LR binding leads to myosin phosphatase activation and actin cytoskeleton rearrangement, thus inhibiting cell growth. It provides a strong basis for interpreting the *in vivo* anticancer activity of EGCG and its anti-inflammatory activity in endothelial cells (Byun *et al*., 2014).

It is not the authors' purpose to provide the reader with an exhaustive updated report on polyphenol–protein binding processes (see Dangles and Dufour (2008) for a specific review on this topic). Only a few recent important examples will be discussed with an emphasis on works dealing with polyphenol metabolites.

#### *1.2.1.1 Interactions in the digestive tract*

In the postprandial phase, black tea drinking leads to vasorelaxation as evidenced by flow-mediated dilation experiments in humans and a strong increase in the activity of endothelial nitric oxide synthase (eNOS) (Lorenz *et al*., 2007). However, these effects are completely abolished when 10% milk is added to black tea. Experiments with isolated fractions of milk proteins show that caseins are actually responsible for this inhibition. It can thus be proposed that caseins bind and probably precipitate black tea polyphenols in the GI tract, thereby preventing their intestinal absorption. This is a spectacular example of how food proteins may sequester oligomeric polyphenols and cancel their bioaccessibility and downstream biological effects.

The binding between dietary polyphenols and the digestive enzymes is best evidenced with large polyphenols such as oligomeric proanthocyanidins (OPAs). For instance, OPAs inhibit pancreatic elastase, a serine protease, proportionally to their mean degree of polymerization (Bras *et al*., 2010). A $K_i$ value of ca. 0.5 mM was estimated for a catechin tetramer. However, a mixture of *n*-mers ($n = 2$–6) rich in 3-*O*-galloyl flavanol units binds much more tightly ($K_i \approx 14\,\mu M$). Similar data were obtained with trypsin (Goncalves *et al*., 2007). By slowing down the digestion, such interactions could prolong the sensation of satiety and help fight weight gain and obesity. By contrast, simple phenols were shown to mildly enhance pepsin activity at pH 2 in the following order: resveratrol ≥ quercetin > EGCG > catechin (Tagliazucchi *et al*., 2005). Tannins are known to inhibit pancreatic lipase (McDougall *et al*., 2009), thereby possibly contributing to lowering fat intake. Polyphenol-rich berry extracts also inhibit pancreatic α-amylase (thus decreasing starch digestibility) and intestinal α-glucosidase, with tannins and anthocyanins being, respectively, the main contributors to the observed inhibition (McDougall *et al*., 2005). These mild inhibitory effects could help regulate the circulating D-glucose concentration.

### *1.2.1.2 Interactions beyond intestinal absorption*

In the circulating blood, polyphenol metabolites likely travel in association with serum albumin, the most abundant plasma protein, which displays several binding sites for the transport of drugs, free fatty acids, and other nutrients. Our recent work (Khan *et al*., 2011) has shown that flavanone glucuronides (conjugation at the A- or B-ring) are moderate serum albumin ligands ($K_b = 3–6 \times 10^4\,M^{-1}$) that bind site 2 (subdomain IIIA), in contrast to the more planar flavones and flavonols, which bind site 1 (subdomain IIA).

Once delivered to tissues, polyphenol metabolites are expected to bind specific cell proteins to express their biological effects, in particular their well-documented anti-inflammatory activity (Pan *et al*., 2010; Spencer *et al*., 2012; Wu & Schauss, 2012). Inflammation is an adaptive response to deleterious stimuli, activating the immune system. What is at stake with dietary polyphenols is the inhibition of chronic low-grade inflammation (in contrast to acute inflammation following microbial infection) associated with the development of degenerative diseases, such as type 2 diabetes and cardiovascular disease. Indeed, this pathological state is deeply influenced by lifestyle and environmental factors, especially dietary habits.

At the cell level, inflammation involves complex signaling pathways and cascades (Fig. 1.3). In particular, mitogen-activated protein kinases (MAPKs, e.g., ERK, JNK, and

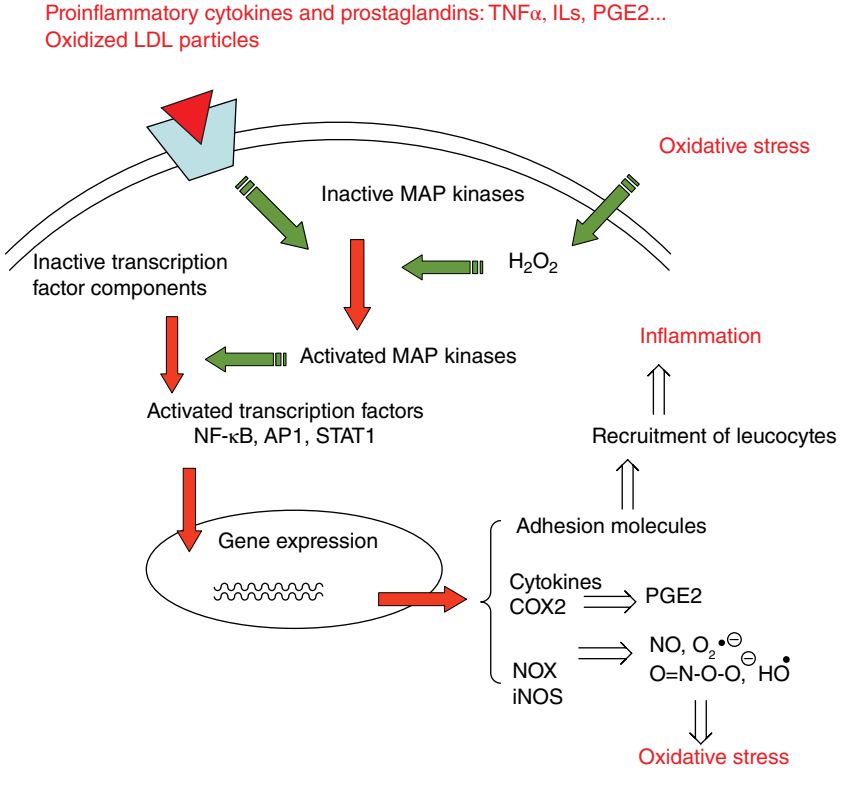


**Fig. 1.3** Pathways of inflammation and oxidative stress in cells. Kinases, proinflammatory transcription factors, and pro-oxidant enzymes are possible target proteins for polyphenols and their metabolites.