We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,600
Open access books available

177,000
International authors and editors

195M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter

Antioxidant Activity: The Presence and Impact of Hydroxyl Groups in Small Molecules of Natural and Synthetic Origin

Mohammed Ali Al-Mamary and Ziad Moussa

Abstract

Polyhydroxylated natural phenolic compounds, especially those with low molecular weights, are characterized by their ability to eliminate free radicals as they act as strong antioxidants. The various types of phenolic compounds represent the most important natural antioxidants in addition to some vitamins. The chemical structures of these compounds is discussed in details with their action mechanisms to remove free radicals and prevent many incurable and malignant diseases. In addition to these natural compounds, the last two decades have witnessed increased attempts by many scientific groups and research centers to synthesize chemical compounds in large quantities to mimic these natural compounds, but at a lower cost and greater biological effectiveness. Herein, we conduct a chemical survey of relevant synthetic compounds containing the hydroxyl groups prepared in chemical laboratories and studied for their biological efficacies, such as their effectiveness as antioxidants, as well as the mechanism of elimination of free radicals.

Keywords: antioxidants, hydroxyl Groups, natural antioxidants, synthetic antioxidants, small-molecules antioxidants

1. Introduction

1.1 Free radicals

Free radicals are chemical species such as atoms or group of atoms with an odd (unpaired) number of electrons. They are produced due to splitting weak bonds. The biological free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), are usually produced in our bodies. It is known that free radicals are very reactive and may quickly react with other chemical entities (atoms or molecules) by capturing the required electron to gain stability. There are two types of biologically important reactive species. The first type contains oxygen and is known as reactive oxygen species (ROS), while the second type contains nitrogen and is known as reactive nitrogen species (RNS). Both ROS and RNS can be classified into radicals and non-radical species.
1.1.1 Reactive oxygen species (ROS)

ROS can be classified into two types, radical species and non-radical species. The most important ROS radicals are: superoxide anion radical (O$_2$•$^-$), hydroxyl radical (OH), alkoxyl radical (RO$^.$), lipid peroxide radical (ROO$.$), and hydroperoxy radical (HOO$.$). While the non-radicals ROS are: hydrogen peroxide (H$_2$O$_2$), singlet oxygen ($^1$O$_2$), ozone (O$_3$), organic peroxide (ROOH), and hypochlorous acid (HOCl).

1.1.1.1 Superoxide anion radical

It is important to emphasize that the mitochondria is the main source of the most active biological ROS [1–5] such as superoxide anion radical (O$_2$•$^-$), hydrogen peroxide (H$_2$O$_2$) and hydroxyl radical (OH). Thus, the initial reactive oxygen species (O$_2$•$^-$) is produced due to the reduction of free oxygen by some electrons leaking out from the electron transport chain during the process of oxidative phosphorylation. This particle is relatively stable intermediate and considered as the precursor for most important ROS. The reduction of free oxygen by electrons in mitochondria can be illustrated as follows: O$_2$ + e$^-$ → O$_2$•$^-$.

The superoxide anion radical and hydrogen peroxide are formed in vivo, in the brain, and the central nervous system (CNS). It is known that several areas in the brain contain high amount of iron which stimulates free radical reactions.

1.1.1.2 Hydroxyl radical (OH)

The superoxide anion and hydrogen peroxide can be converted rapidly to hydroxyl radical (OH), which is known as the most reactive and destructive radical in biological system. This radical is quickly produced via Fenton [7] and Haber-Wiess reactions as follows [8, 9]:

\[
\begin{align*}
\text{Fenton reaction} & : H_2O_2 + Fe^{2+} → OH + OH^- + Fe^{3+} \\
\text{Haber-Weiss reaction} & : O_2^- + H_2O_2 → OH^- + OH + O_2
\end{align*}
\]

The reaction of H$_2$O$_2$ with Fe$^{2+}$ and Cu$^+$ metal ions which are typically complexed with certain intracellular proteins such as ferritin and ceruloplasmin, respectively [7], occurs due to stress conditions, which means an excess of superoxide anion radical (O$_2$•$^-$). This phenomenon releases free ions (Fe$^{2+}$) from ferritin which in turn reacts with H$_2$O$_2$ according to Fenton reaction to produce hydroxyl radical (OH). This free radical can strongly react with biomolecules such as DNA, proteins, lipids, and carbohydrates and cause severe damage to the cells than any other ROS [10]. The OH is the most destructive free radical and can more easily penetrate the phospholipid bilayer than O$_2$•$^-$, which is negatively charged. When OH is generated by Fenton reaction, the extent of its formation is largely determined by the availability and location of the metal ion catalyst. One feature of OH is that it leads to the generation of another radical, so when it reacts with...
a molecule, a new free radical is generated. However, the new free radical usually has lower reactivity than the hydroxyl radical (·OH). The ·OH attacks all proteins, DNA, polyunsaturated fatty acids (PUFA) in membranes, and almost any biological molecule it encounters [10]. The hydroxyl radical (·OH) can be obtained by another reaction in neutrophils, where HOCl reacts with superoxide anion radical [11, 12] as follows:

\[
\text{HOCl} + \text{O}_2^- \rightarrow \text{OH} + \text{O}_2 + \text{Cl}^-
\]  

(4)

The hydroxyl radical (·OH) is the strongest oxidant produced in biological systems. It reacts very rapidly and indiscriminately with most biological targets present at its site of formation.

1.1.1.3 Lipid peroxide radical (ROO·) and alkoxyl radical (RO·)

Peroxy radicals (ROO·) and alkoxy radicals (RO·) are moderately strong oxidants. Lipid peroxidation starts with abstraction of H-atom by ·OH, or by RO· to form alkyl radical (R·), then oxygen (O₂) is added to alkyl radical to generate peroxyl radical (ROO·). Lipid peroxidation or the oxidative destruction of PUFA containing methylene groups (–CH₂–) comprise the main targets [13]. This process can be illustrated in three steps as follows:

\[
\text{RH} + \cdot\text{OH} \rightarrow \text{R} + \text{H}_2\text{O} \quad \text{(Initiation step)}
\]  

(5)

\[
\text{R} + \text{O}_2 \rightarrow \text{ROO}
\]  

(6)

Then, peroxyl radical reacts with another polyunsaturated fatty acid (RH) to remove H-atom:

\[
\text{RH} + \text{ROO} \rightarrow \text{R} + \text{ROOH} \quad \text{(Propagation step)}
\]  

(7)

Finally, to terminate lipid peroxidation, the following reaction takes place:

\[
\text{ROO} + \text{ROO} \rightarrow \text{ROH} + \text{RO} + \cdot\text{O}_2 \quad \text{(Termination step)}
\]  

(8)

It is clear that lipid peroxidation leads to the formation of alkyl (R·), peroxyl (ROO·), and alkoxy (RO·) radicals. Generally, lipid hydroperoxide (ROOH) is relatively stable, but in the presence of Fe and Cu ions, it causes the formation of alkoxy and peroxyl radicals [14, 15].

\[
\text{ROOH} + \text{Fe}^{3+} \rightarrow \text{RO} + \text{Fe}^{2+}
\]  

(9)

\[
\text{ROOH} + \text{Fe}^{2+} \rightarrow \text{ROO} + \text{Fe}^{3+}
\]  

(10)

The reactivity of RO· and ROO· is related to the presence of substituents at the a-carbon. As a result, the presence of an electron-withdrawing group increases the reactivity, while the presence of an electron-donating group decreases it. Thus, aromatic ROO· and RO· must be less reactive because of single electron delocalization. These free radicals react with biomolecules by abstracting H-atom [16, 17].
1.1.1.4 Hydroperoxyl radical (HOO•)

Hydroperoxyl radical, also known as perhydroxyl radical (HOO•), is formed due to the reversible reaction occurring between superoxide anion radical and proton. This reaction takes place in cells as follows:

\[ \text{O}_2^- + \text{H}^+ \leftrightarrow \text{HOO}^- \]  

\[ (11) \]

The pKa of this radical is 4.88 [18]. At pH 7.2 in the cytoplasm, a small amount of this radical (1% of \( \text{O}_2^- \)) exists as \( \text{HOO}^- \) [19]. Perhaps for this reason, many researchers presumed that \( \text{HOO}^- \) has little or no role in initiation of lipid peroxidation [20]. In comparison with other oxidants, HOO• shows high specificity in reaction with PUFA, linoleic (C18:2), and linolenic (C18:3) acids [21].

1.1.2 Non-radicals of ROS

1.1.2.1 Singlet oxygen

The singlet oxygen (\( ^1\text{O}_2 \)) is a potent oxidizing agent, because it can react with different macromolecules such as DNA [22], and is responsible for lipid peroxidation of membrane and other tissues [23]. It is generated in cells, specifically in neutrophils and eosinophils [24, 23]. In addition, this particle can be formed by enzymatic reactions [25–27]. This reactive particle is produced due to the activation of molecular oxygen to two excited states. In the first excited state, oxygen has two electrons with opposite spins in the same \( \psi^* \) orbital, while in the second excited state oxygen has one electron in each of two degenerate \( \psi^* \) orbitals. However, singlet oxygen in the first excited state is extremely reactive in comparison with other excited states like the triplet state. Allen [28] suggested the mechanism for the production of singlet oxygen from \( \text{H}_2\text{O}_2 \) and \( \text{Cl}^- \) in the presence of the myeloperoxidase (MPO) enzyme as follows:

\[ \text{H}_2\text{O}_2 + \text{H}^+ + \text{Cl}^- + \text{MPO} \rightarrow \text{HOCl} + \text{H}_2\text{O} \]  

\[ (12) \]

\[ \text{H}_2\text{O}_2 + \text{HOCl} \rightarrow \text{H}_2\text{O} + \text{H}^+ + \text{Cl}^- + ^1\text{O}_2 \]  

\[ (13) \]

1.1.2.2 Hydrogen peroxide (\( \text{H}_2\text{O}_2 \))

Hydrogen peroxide is generated via an enzymatic reaction where the reactive superoxide anion radical is rapidly converted by an antioxidant enzyme called superoxide dismutase (SOD). The new formed oxygen species \( \text{H}_2\text{O}_2 \) is less reactive. Thus, hydrogen peroxide is formed as follows by SOD:

\[ 2\text{O}_2^- + 2\text{H}^+ + \text{SOD} \rightarrow \text{H}_2\text{O}_2 + \text{H}_2\text{O} \]  

\[ (14) \]

It is clear that, in the dismutation reaction (an oxidation–reduction process), two superoxide anion radicals are involved. In this reaction, one superoxide anion radical is oxidized to oxygen while the other is reduced to hydrogen peroxide [29]. The latter (\( \text{H}_2\text{O}_2 \)) is relatively stable and membrane permeable so this non-radical species can diffuse inside the cell and can be removed by mitochondrial antioxidant enzymatic systems such as catalase (CAT) and glutathione peroxidase (GPx) [30, 31].
Antioxidant Activity: The Presence and Impact of Hydroxyl Groups in Small Molecules...

DOI: http://dx.doi.org/10.5772/intechopen.95616

\[ 2\text{H}_2\text{O}_2 + \text{cat} \rightarrow \text{O}_2 + 2\text{H}_2\text{O} \]  
\[ 2\text{H}_2\text{O}_2 + 2\text{GSH} + \text{GP} \rightarrow \text{GSSG} + 2\text{H}_2\text{O} \]

(15)
(16)

As illustrated, glutathione peroxidase (GPx) removes hydrogen peroxide (H\(_2\)O\(_2\)) by oxidizing two glutathione molecules (GSH) to produce oxidized glutathione disulfide (GSSG). It is clear that the three SOD, CAT, and GPx enzymes show synergistic effect in the scavenging of superoxide anion radical (O\(_2^\cdot\)). The in vivo destruction effects of hydrogen peroxide (H\(_2\)O\(_2\)) result due to the presence of transition metals or enzymes, such as heme-peroxidase. The destruction of H\(_2\)O\(_2\) leads to the formation of other more reactive oxidants such as OH\(^-\), NO\(^-\), and HOCl. Thus, reaction of hydrogen peroxide with Cu\(^{2+}\) and Fe\(^{2+}\) leads to the production of OH. On the other hand, in phagocytic cells, myeloperoxidase uses its substrate H\(_2\)O to generate HOCl. The release of MPO during phagocytosis may play an important role in microbial elimination [32].

1.1.2.3 Ozone (O\(_3\))

Ozone gas (O\(_3\)) exists in polluted atmosphere and the inhalation of this gas by human may lead to lung injury and inflammation. In living organisms, ozone is thought to be formed due to oxidation of H\(_2\)O to H\(_2\)O\(_2\) in the presence of antibodies [33]. Thus, antibodies use H\(_2\)O as an electron source, facilitating its addition to O\(_2^\cdot\) to generate dihydrogen trioxide (H\(_2\)O\(_3\)), which is converted to ozone [34].

\[ \text{H}_2\text{O} + \text{O}_2^\cdot \rightarrow \text{HOO} \rightarrow \text{O}_3 + \text{H}_2\text{O}_2 \]  

(17)

Ozone reacts with fatty acids, cholesterol, amino acids and DNA. The lung is the most affected organ due to exposure to ozone. The effect of ozone on tissues occurs via free radical mechanisms [35–37]. The ozone radical anion then reacts with a proton to form the hydroxyl radical and oxygen as follows [36].

\[ \text{O}_3^- + \text{H}^+ \rightarrow \text{HO}^{-} + \text{O}_2 \]  

(18)

1.1.2.4 Hypochlorous acid (HOCl)

This species (HOCl) is generated in neutrophils by the reaction of Cl\(^-\) with H\(_2\)O\(_2\), which is catalyzed by the enzyme myeloperoxidase [38]. It is illustrated as follows:

\[ \text{H}_2\text{O}_2 + \text{Cl}^- + \text{MPO} \rightarrow \text{HOCl} + \text{OH} \]  

(19)

The hypochlorous acid is considered to be a very reactive oxidizing agent. So, it may affect different biomolecules and may destroy phagocytized pathogens by causing oxidative damage to their biomolecules which include proteins [39], DNA [40], and lipids [41]. On the other hand, the overproduction of HOCl can lead to many health problems such as atherosclerosis and cancer [42, 38].

1.1.3 Reactive nitrogen species (RNS)

Reactive nitrogen species (RNS) can be found in biological systems as free radical species and non-radical species. However, the most common RNS radical
is nitric oxide radical (NO) and nitrogen dioxide (NO₂). On the other side, the important non-radical RNS is peroxynitrite ion (ONOO⁻). Generations of these reactive species is discussed below.

1.1.3.1 Nitric oxide (NO⁻)

Nitric oxide free radical (NO) is an endogenous free radical synthesized in the presence of nitric oxide synthase (NOS) that oxidizes L-arginine to L-citrulline [43]. In this reaction, one of the guanidino nitrogen atoms is oxidized to form NO⁻. This process is shown below:

\[ \text{L - Arginine} + \text{O}_2 + \text{NADPH} + \text{NOS} \rightarrow \text{L - Citrullin} + \text{NO} + \text{NADP}^+ \] (20)

The NO⁻ radical can diffuse easily and has the ability to reach many intracellular targets and cause biological damage [44]. The enzyme nitric oxide synthase (NOS) is found in different cells such as vascular endothelial cells, smooth muscle cells, platelets, neuronal cells, macrophages, and neutrophils [45]. In addition, this radical plays an important role in biological tissues such as vasodilation, memory, neuronal response, among others [46–50].

1.1.3.2 Peroxynitrite (OONO⁻) and Other Reactive Nitrogen Species

This nitrogenous species is generated due to reaction of superoxide anion radical (O₂⁻) with nitrogen oxide radical (NO) radical as follows:

\[ \text{O}_2^- + \text{NO} \rightarrow \text{ONOO}^- \] (21)

It is noted that at physiological pH (7.4), peroxynitrite exists in equilibrium with peroxynitrous acid, ONOOH [51].

\[ \text{ONOO}^- + \text{H}^+ \leftrightarrow \text{ONOOH} \] (22)

Then, peroxynitrous acid (ONOOH) is subjected to homolysis to produce hydroxyl radical (OH⁺) and nitrogen dioxide radical (NO₂⁺), which may rearrange to form nitrate (NO₃⁻).

\[ \text{ONOO}^- + \text{H}^+ \leftrightarrow \text{ONOOH} \leftrightarrow [\text{HO}^- + \text{NO}_2^-] \rightarrow \text{NO}_3^- + \text{H}^+ \] (23)

The ONOO⁻ is a very reactive anion, even more so than the particle (NO and O₂⁻) from which it is formed [52–54]. The peroxynitrite anion can cross biological membranes and interact with most critical biomolecules [55]. Thus, it can cause oxidation of lipids, and proteins via oxidation of methionine and tyrosine residues and can oxidize DNA to generate nitroguanine [56]. Under most biological conditions, ONOO⁻ and ONOOH exist in equilibrium [57]:

\[ \text{ONOO}^- + \text{H}^+ \leftrightarrow \text{ONOOH} \] (24)

Indeed, protonation weakens the O–O bond in ONOOH and leads to homolytic cleavage to generate hydroxyl radicals (OH) and nitrogen dioxide (NO₂), two strongly oxidizing/hydroxylating and nitrating species, respectively.
As a nucleophile, a central reaction of peroxynitrite in biology is the addition of the anion to carbon dioxide (CO\(_2\)) to yield a nitrosoperoxocarboxylate adduct (ONOOCO\(_2\)) that undergoes fast homolysis to NO\(_2\) and [58–60].

\[
\text{ONOO}^- + \text{CO}_2 \rightarrow \text{ONOOCO}_2^- \rightarrow \text{NO}_2 + \text{CO}_3^-
\]

### 1.2 Antioxidants

An antioxidant is any substance that has the ability to prevent, inhibit, or delay the oxidation of other substances. In biological systems, antioxidants play a very important roles in removing free radicals such as ROS and RNS, and consequently reduce oxidative stress. Antioxidant molecules can be classified based on the type of mechanistic defense they offer:

#### 1.2.1 Antioxidants suppressing formation of free radicals

These are endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). These enzymes efficiently suppress or prevent the formation of free radicals and other ROS in tissues. Thus, SOD removes superoxide anion radical as follows:

\[
2\text{O}_2^- + 2\text{H}^+ + \text{SOD} \rightarrow \text{H}_2\text{O}_2 + \text{H}_2\text{O}
\]

On the other hand, CAT reduces formed H\(_2\)O\(_2\) to water and oxygen:

\[
2\text{H}_2\text{O}_2 + \text{cat} \rightarrow \text{O}_2 + 2\text{H}_2\text{O}
\]

The GPx enzyme system detoxifies H\(_2\)O\(_2\) by catalyzing its reduction using glutathione (GSH) as a sacrificial reductant to produce one molecule of oxidized glutathione (GSSG). Thus, the enzymes SOD, CAT, and GPx, work collectively to prevent the effect of O\(_2\)\(^{+}\).

\[
2\text{H}_2\text{O}_2 + 2\text{GSH} + \text{GPx} \rightarrow \text{GSSG} + 2\text{H}_2\text{O}
\]

In addition, Fe and Cu ions are included to this type of defense, since these ions bind proteins such as transferrin and caeruloplasmin and prevent them from free radical formation. Generally, any chemical compound having two or more of the following functional groups: –OH, –SH, –COOH, –PO\(_3\)H\(_2\), C=O, –NR\(_2\), –S– and –O– may have chelating activity [61]. The mechanism of metal ion chelation with some natural phenolics such as protocatechuic acid and anthocyanins is shown in Figure 1.

Transition metal ions (Fe\(^{2+}\) and Cu\(^{+}\)) make complex species with different types of phenolic compounds such as flavonoids containing multiple hydroxyl groups (polyhydroxylated). The involvement of these ions in the formation of complexes prevents the Fenton reaction which leads to the formation of hydroxyl radical (OH) which is considered as the most dangerous ROS.

\[
\text{H}_2\text{O}_2 + M^{m+} \rightarrow \text{HO}^- + \text{HO}^- + M^{(m+1)} (M = \text{Fe or Cu})
\]
1.2.2 Antioxidants that repair damage resulting from the action of free radicals

This type of antioxidants are enzymes which are involved in repairing damage due to the effects of free radicals on biomolecules (DNA, proteins, lipids and carbohydrates). These enzymes prevent the accumulation of toxic substances resulting from destruction of biomolecules in body tissues. Examples of this type of enzymatic antioxidants include the DNA repair enzyme systems (polymerases, glycosylases and nucleases), and proteolytic enzymes (proteinases, proteases and peptidases) located in both, cytosol and mitochondria of mammalian cells.

1.2.3 Antioxidants that utilize signals for the formation of free radicals

This type of antioxidants use the signals, which are required for the formation of free radicals. As a result, the signal generated from the formed free radical causes the formation and transport of the appropriate antioxidant to the appropriate and required site [62].

1.2.4 Antioxidants scavenging free radicals

This type of scavenging antioxidants can directly neutralize free radicals by two mechanisms, either by donating a hydrogen free radical (H\(^\cdot\)) or donating an electron (e\(^{-}\)). These mechanisms can be illustrated as follows:

\[
\text{Ar}-\text{OH} + \text{R} \rightarrow \text{Ar} - \text{O} + \text{RH} \quad (31)
\]

In the preceding mechanism, the antioxidant donates a hydrogen free radical (H\(^\cdot\)) to scavenge free radicals, and the antioxidant (Ar-OH) itself becomes a free radical, though not as biologically harmful.

\[
\text{Ar} - \text{OH} + \text{R} \rightarrow \text{Ar} - \text{OH}^\cdot + \text{R}^\cdot \rightarrow \text{Ar} - \text{O} + \text{H}^+ \quad (32)
\]

The second mechanism involves one-electron transfer where the antioxidant donates an electron to the free radical and becomes itself a radical cation. Generally, the new radicals are more stable and can be easily neutralized and made completely...
harmless and removed easily from biological systems. Many antioxidants such as ascorbic acid, uric acid, glutathione, vitamin E, and other natural compounds like polyhydroxyphenolic compounds belong to this class. This type of antioxidants are usually small molecules containing hydroxyl groups either of natural or synthetic origin. The importance of these compounds prompted us to review them in details.

2. Small antioxidant molecules containing hydroxyl groups

There are many studies that have shown the biological effectiveness of phenolic compounds as natural antioxidants. They play very important roles in the prevention of dangerous diseases such as cancers, heart diseases, diabetes and others. There is a need for simple molecules capable of neutralizing free radicals responsible for what is known as oxidative stress, the lead cause of dangerous diseases like cancers, heart disease, diabetes and others. Antioxidants play a critical role in biological systems in getting rid of free radicals and work to prevent the phenomenon of oxidative stress. The most available natural antioxidants exist in plants such as fruits, vegetables, and medicinal plants. Herein, we present an overview of the natural and synthetic phenolic compounds acting as antioxidants.

2.1 Natural antioxidants containing hydroxyl groups

2.1.1 Phenols

Simple phenols are known as compounds containing at least one hydroxyl group attached to an aromatic ring which comprises the basic skeleton. The most important compounds under this class are: phenol, catechol, resorcinol, and phloroglucinol. Generally, phenols are widely distributed in plants and play very important roles in human health because of their ability to neutralize free radicals due to their hydroxyl groups. It is considered that these simple phenols along with other phenolic compounds can inhibit and prevent cancer diseases in humans (Figure 2) [63].

The study by Spiegel et al. [64] has shown that the most active of simple natural phenols as antioxidants were those containing more than one hydroxyl group in the ortho position of the aromatic ring. This suggests that the most active antioxidant compound is catechol since it contains two hydroxyl groups in the ortho position. This could be attributed to the bond dissociation energy (BDE) of O-H which is typically used to evaluate the activity of an antioxidant to neutralize free radicals [65–67]. Thus, the weaker the O-H BDE, the faster the reaction of antioxidant with the free radical. In other words, the weaker the BDE of O-H in phenols, the easier it will be to transfer an H-radical to deactivate the free radical. The antioxidant activity of catechol and hydroquinone is illustrated as shown in Figure 3.

2.1.2 Phenolic acids: hydroxybenzoic and hydroxycinnamic acids

Phenolic acids are also known as phenol carboxylic acids (Figure 4). There are two important groups of natural phenolic acids which are hydroxybenzoic acids and hydroxycinnamic acids. These are derived from benzoic and cinnamic acid, respectively. The molecular structural features of phenolic acids, such as the numbers and positions of the hydroxyl groups in relation to the carboxyl functional group, esterification, and glycosylation great impacts their antioxidant properties. Many studies [68, 69] have shown that the antioxidant activity of phenolic acids and their esters was enhanced substantially when the number of hydroxyl (-OH) and methoxy (-OCH$_3$) groups increased. On the other hand, the carboxyl group has an electron
Antioxidants - Benefits, Sources, Mechanisms of Action

**Figure 2.**
Natural phenolic antioxidants containing hydroxyl groups.

**Figure 3.**
Mechanism of action of natural phenolic antioxidants by transfer of hydrogen free radical (H•).

**Figure 4.**
Benzoic acid and the related hydroxybenzoic acids.
Antioxidant Activity: The Presence and Impact of Hydroxyl Groups in Small Molecules...

withdrawing effect, making the H-atom less available to be donated. However, the antioxidant activity of hydroxylated cinnamates are greater than that of benzoates [70–72]. The antioxidant activities of different hydroxybenzoic acids such as 4-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid, and 3,4,5-trihydroxybenzoic acid were shown to be dependent on the number and position of attached hydroxyl groups to the aromatic ring [73]. Based on bond dissociation energy of O-H group, the dihydroxybenzoic acid has greater antioxidant activity than monohydroxybenzoic acid. It was observed that the BDE for -OH at 3-position is greater than the BDE of -OH at 4-position, as a result the abstraction of H-atom from the 4-position becomes easier than abstraction from the 3-position. Thus, it can be concluded that in 3,4-dihydroxybenzoic acid, the ability to abstract H-atom from the 4-position is easier than the 3-position. On the other hand, gallic acid (3,4,5-trihydroxybenzoic acid) showed lower antioxidant activity than that of 3,4-dihydroxybenzoic acid. This phenomenon could be attributed to the formation of a weak intramolecular H-bond between the -OH at 4-position and -OH at 5-position [74]. The obtained theoretical BDE of the -OH groups in gallic acid were in the order 4-OH ≤ 5-OH < 3-OH, which indicates that the removal of H-atom is easier from 4-OH and 5-OH. Both of these values in gallic acid become lower than that of 4-hydroxybenzoic acid. Thus, the introduction of two hydroxyl groups at 3-position and 5-position significantly increases the antioxidant activity [73].

Similarly, the antioxidant activities of hydroxycinnamic acids (Figure 5) are related to their hydroxyl groups. The study of relationship between antioxidant activities and structures of hydroxycinnamic acids was carried out by Chen and Ho [74]. The BDE value of O-H group is a good indicator to evaluate the antioxidant activity of an antioxidant. Thus, the weaker the O-H bond, the greater the ability of an antioxidant to neutralize free radicals. In addition, phenolic molecules bearing two hydroxyl groups in o-position relative to one another showed high antioxidant activities [75–77] as observed with caffeic acid. On the other hand, replacement of one hydroxyl group by methoxy group as in ferulic acid leads to lower antioxidant activity [65–67, 75–80]. Therefore, the BDE value of O-H would be expected to follow the following order: caffeic acid < ferulic acid < p-coumaric acid. As a result, the antioxidant activities of these acids will be in the order: caffeic acid < ferulic acid < p-coumaric acid. However, it is important to remember that the removal of H-atom from caffeic acid could arise from m-OH and p-OH to form free radicals. Consequently, the resulting free radical due to removal of the H-atom from p-OH would be more stable because of resonance where the electron is delocalized over the whole molecule, but in the case of removal of the H-atom from m-OH, the unpaired electron cannot be delocalized over the whole molecule since it cannot cross the propenoic tether [81].

2.1.3 Flavonoids

The flavonoids consist of a large group of low-molecular weight polyphenolic substances, benzo-γ-pyrene derivatives (Figure 5). The basic structural feature of all flavonoids is the flavane (2-phenyl-benzo-γ-pyran) nucleus, a system of two benzene rings (A and B) linked by an oxygen-containing pyran ring (C). According to the degree of oxidation of the C ring, the hydroxylation pattern of the nucleus, and the substituent at carbon 3, flavonoids can be categorized into the following subclasses: flavones, isoflavones, flavanols (catechins), flavonols, flavanones, anthocyanins, and proanthocyanidins. Flavonols differ from flavanones by a hydroxyl group at the C3 position and by a C2–C3 double bond. Anthocyanidins differ from the other flavonoids by possessing a charged oxygen atom in the C ring (Table 1).
Table 1. Types of flavonoids.

| Entry | Types of flavonoids | Examples |
|-------|---------------------|----------|
| 1     | Flavanone           | Flavanone, Naringtin, Hesperidin |
| 2     | Flavan-3-ol         | Flavan-3-ol, (+)-Catechin, (+)-Gallocatechin |
| 3     | Flavone             | Flavone, Apigenin, Luteolin |
| 4     | Flavonol            | Flavonol, Quercetin, Myricetin |
| 5     | Anthocyanidin       | Anthocyanidin, Delphinidin, Cyanidin |
| 6     | Isoflavones         | Isoflavones, Daidzein, Genistein |

Figure 5. Cinnamic acid and hydroxycinnamic acids.
Flavonoids are secondary metabolites and mainly distributed in the plant kingdom such as green and black tea, coffee, vegetables, fruits, olive oil, red wine, white wines, and chocolate [82–92]. They are consumed in milligrams per serving of these plant sources. Many researchers have shown that flavonoids possess different biological activities which include vasodilating, anti-allergenic, antiviral, and anti-inflammatory actions [93–95]. However, the antioxidant activity of these compounds attracted the most interest because, in addition to their ability to scavenge free radicals, they also reduce or prevent free radical formation.

The capability of antioxidant activities of flavonoids is mainly related to their chemical structures. Many previous investigations attributed the high antioxidant activities of these compounds to the presence and positions of hydroxyl groups attached to the A and B rings and/or to the C_2 = C_3 double bond in conjugation with the carbonyl group at 4-position, and the -OH group at 3-position [93, 94, 96]. On the other hand, the replacement of hydrogen atom by a saccharide at 3-position to form a glycosidic bond, the antioxidant activity decreases. The radical scavenging efficiency of flavonoids is related to their phenolic hydroxyl groups which follow the mechanism of H-atom transfer or the single electron transfer followed by sequential electron transfer-proton transfer (SETPT) [97–100]. As in the case of phenolic acids, the antioxidant activity of flavonoids, is based on the value of the dissociation energy of the O-H bond [67, 97, 101]. The study by Quan et al. [102] showed that the dissociation energy of C-H at 3-position in some flavonoids appeared to be lower than that of the dissociation energy of O-H. As a result, the antioxidant activity might be due the donation of H-atom from C-H at 3-position. However, the mechanism of antioxidant activity via H-atom transfer from the -OH group appeared to be the most significant [102]. Generally, flavonoids as antioxidants may act by different mechanisms such as hydrogen atom transfer, single electron transfer, and transition metal chelation. These mechanisms are shown below in Figures 6–9. Figure 6 shows the proposed mechanism of radical scavenging activity of cyanidin by Nimse and Palb [103] following HAT mechanism.

2.1.3.1 -Hydrogen atom transfer (HAT)

The flavonoid quercetin is found in many plants and foods and in notable quantities especially in onions, red wine, green tea, apples, berries, and others.

![Figure 6](image-url)  
Proposed mechanism of radical scavenging activity of cyanidin by Nimse and Palb [103].
The proposed mechanism of superoxide anion radical scavenging activity of quercetin by Nimse and Palb [103] is shown in Figure 7.

The proposed mechanism of single electron transfer by Leopoldini et al. [104] for single electron transfer (SET) and transition metal chelation (TMC) are shown in Figures 8 and 9.

2.1.3.2 Single electron transfer (SET)

2.1.3.3 Transition metal chelation (TMC)

Flavonoids with their multiple hydroxyl groups and the carbonyl group at the 4 position on ring C may offer several available sites for metal chelation. The ability of flavonoids to chelate Fe and Cu ions is related to their indirect antioxidant activities. This property of flavonoids is attributed to their multiple hydroxyl groups and the carbonyl group at 4-position [104].
2.1.4 Stilbenes

The Stilbene family includes several compounds [105] among which resveratrol, pterostilbene, and piceatannol are the main representatives, characterized by a trans double bond connecting the phenolic rings (Figure 10).

Stilbene compounds are part of a group of natural polyphenols occurring in plant kingdom such as grapes [106], peanuts [107], and berries [108]. Resveratrol (3, 5, 4′-trihydroxy-trans-stilbene), which is found in grapes, showed different biological activities including antidiabetic, antiobesity, and neuroprotective properties against Alzheimer’s disease (AD) [109]. In addition, other stilbenes have shown additional activities as antimicrobials and antioxidants [110]. Different studies have shown that piceatannol (4′, 5′, 3, 5-tetrahydroxystilbene) expresses a wide spectrum of biological activities: anti-inflammatory, anticarcinogenic, antiviral, antioxidative, neuroprotective and estrogenic properties, and antioxidant activities [111–117]. A study by Hussein [118] demonstrated the strong ability of resveratrol to scavenge free radicals using different tests. The mechanism of antioxidant activity of resveratrol was proposed to be as follows (Figure 11).

2.2 Synthetic antioxidants containing hydroxyl groups

Synthetic antioxidants are usually used as food preservatives to prevent lipid oxidation [119]. The well-known synthetic antioxidants are butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and t-butyl-hydroxyquinone

![Figure 10. Stilbene and its related polyphenolic derivatives.](image)

![Figure 11. Proposed mechanism of resveratrol antioxidant activity [118].](image)
Antioxidants - Benefits, Sources, Mechanisms of Action

These antioxidants stop the free radical chain of oxidative reactions via the donation of an H-atom radical from the phenolic -OH attached to the aromatic rings (Figure 12). The new formed radicals become stable and do not initiate or propagate further oxidation of lipids [120].

The progressively more sterically hindered BHT and the related BHA operated as radical terminators in a similar fashion to TBHQ (Figure 13).

Another type of radical quencher is shown in Figure 14 where the generated phenoxy radical is stabilized by intramolecular hydrogen bond.

The presence of a bulky group introduces steric hindrance in proximity to the radical center, decreasing the rate of further propagation reactions. Another example which illustrates the increase in antioxidant activity is the presence of an extra hydroxyl group at the ortho or para position of the hydroxyl group of phenol. The stability of the phenoxy radical in this case is enhanced by the formation of an intramolecular hydrogen bond. Other studies [121–123] described the synthesis of different compounds like aromatic Schiff bases and aromatic hydrazones containing hydroxyl groups attached to different positions in the aromatic rings. These compounds were designed to mimic as much as possible natural phenolic compounds such as stilbene and chalcones. The number of hydroxyl groups and their locations in the aromatic rings play an important role in the antioxidant activity. The mechanism of antioxidant activity can be illustrated as follows and involves the donation of hydrogen radical (Figure 15).

Figure 12. Antioxidant action of t-butyl-hydroxyquinone as a radical terminator via the donation of a hydrogen radical and subsequent radical delocalization by resonance.

Figure 13. Oxidation of BHT and BHA via donation of a hydrogen radical from a phenolic hydroxyl group.
3. Oxidative stress

Oxidative stress is a phenomenon occurring in living systems and is related to the presence of free radicals (oxidants) and antioxidants (reductants). When we talk about free radicals in biological systems, we mean two types: reactive oxygen species (ROS) and reactive nitrogen species (RNS). Imbalance between free radicals and antioxidants (endogenous and exogenous) in biological systems creates a state known as oxidative stress. In this case, the present antioxidants cannot remove the ROS and RNS from living species. As a result, excess free radicals can negatively impact different biological processes, leading to the destruction of cell membrane, blocking pathways of major enzymes, stopping cell division, destruction of DNA, and halting energy production [124–126]. On the other hand, free radicals appear to be necessary for some processes in living organisms since they destroy bacteria by phagocytes (granulocytes and macrophages). In addition, ROS can be beneficial for the maintenance of homeostasis as well as other cellular functions [125, 127]. Again, it is important to remember that the primary free radicals are superoxide anion radicals \( \text{O}_2^- \) and hydroxyl radical \( \text{OH} \) which are derived from molecular oxygen (O2). High levels of these radicals may cause different biological problems which may lead to cancer, stroke (Reuter et al., 2010) [126], myocardial infarction, diabetes, and other significant conditions [128].

It is not easy to avoid the exposure of free radicals and consequently oxidative stress. However, the increase of consumption of natural antioxidants through diet may help to decrease the production of free radicals. In other words, to prevent oxidative stress, it is highly recommended to consume enough amounts of vegetables, fruits, medicinal plants, and honey to ensure sufficient supplementation of natural antioxidants [129–133].

4. Conclusion

To maintain normal health and avoid incurable diseases such as cardiovascular disease, cancer diseases, diabetes, among others, it is necessary to protect the
existing balance between free radicals and antioxidants in biological systems. Naturally the human body has means of internal defense to neutralize free radicals. These means of defense are represented by a group of biological molecules known as antioxidant enzymes. In addition, there are a number of small molecules such as urea, bilirubin, vitamin E, vitamin A, and others. These simple molecules play a positive role in eliminating free radicals. However, when the internal system fails to get rid of free radicals, a supply of external antioxidants, especially those from natural sources, is needed to remove excess free radicals. There are many antioxidants in nature especially those that contain hydroxyl groups such as phenolic compounds, such as phenolic acids (derivatives of hydroxybenzoic and hydroxy cinnamic acids), flavonoids, stilbenes, chalcones and others. These compounds are found in fruits, vegetables and medicinal herbs. There are some chemically prepared antioxidants in laboratories which use is almost limited to the food and pharmaceutical industries. However, there are many attempts to manufacture antioxidants that mimic those found in nature, especially those containing hydroxyl groups, in the hope of obtaining compounds at the lowest cost, safe to use, and in large quantities.

Acknowledgements

Dr. Ziad Moussa is grateful to the United Arab Emirates University (UAEU) of Al-Ain and to the Research Office for supporting the research developed in his laboratory (Grant no. G00003291/Fund no.31S401/Project #852).
References

[1] Li X, Fang P, Mai J, Choi ET, Wang H, Yang XF. Targeting mitochondrial reactive oxygen species as novel therapy for inflammatory diseases and cancers. J Hematol Oncol. 2013; 6 (19): 19. DOI: 10.1186/1756-8722-6-19

[2] Reichart G, Mayer J, Zehm C, Kirschstein T, Tokay T, Lange F, Baltrusch S, Tiedge M, Fuellen G, Ibrahim S, Köhling R. Mitochondrial complex IV mutation increases ROS production and reduces lifespan in aged mice. Acta Physiologica. 2018; 225: e13214. DOI: 10.1111/apha.13214

[3] Maurel A., Hernandez C., Kunduzova O., Bompart G., Cambon C., Parini A., Francés F. Age-dependent increase in hydrogen peroxide production by cardiac monoamine oxidase A in rats. American Journal of Physiology; Heart and Circulatory Physiology. 2003; 84: 1460-1467. https://doi.org/10.1152/ajpheart.00700.2002

[4] Turrens JF: Mitochondrial formation of reactive oxygen species. J Physiol. 2003; 552: 335-344. https://doi.org/10.1111/j.1469-7793.2003.00335.x

[5] Cadenas E and Davies KJ: Mitochondrial free radical generation, oxidative stress, and aging. Free Radic Biol Med. 2000; 222-230. DOI: 10.1016/s0891-5849(00)00317-8

[6] Kuppusamy P, Zweier JL. Characterization of free radical generation by xanthine oxidase. Evidence for hydroxyl radical generation. J Biol Chem. 1989; 264(17):9880-4.

[7] Fenton HJH. Oxidation of tartaric acid in the presence of iron. J Chem Soc Trans. 1894; 65:899-910. https://doi.org/10.1039/CT8946500899

[8] Knight JA, in Free radicals, antioxidants, aging and disease, AACC Press, Washington, 1999.

[9] Haber F, Weiss J. The catalytic decomposition of hydrogen peroxide by iron salts. Proc R Soc London (A). 1934; 147:332-51. DOI: 10.1098/rspa.1934.0221

[10] Halliwell B. Oxidants and human disease: some new concepts. FASEB J. 1987;1(5):358-64. https://doi.org/10.1096/fasebj.1.5.2824268

[11] Cohen MS, Britigan BE, Hassett DJ, Rosen GM: Do human neutrophils form hydroxyl radical? Evaluation of an unresolved controversy. Free Radic Biol Med. 1988; 5:81. doi: 10.1016/0891-5849(88)90033-0

[12] Kettle AJ, Winterbourn CC: Superoxide-dependent hydroxylation by myeloperoxidase. J Biol Chem. 1994; 269:17146.

[13] Halliwell B, and Gutteridge JM. Oxygen toxicity, oxygen radicals, transition metals and disease. Biochem J. 1984; 219(1): 1-14. doi: 10.1042/bj2190001

[14] Repetto MG, Ferrarotti N, Boveris A. The involvement of transition metal ions on iron-dependent lipid peroxidation. Archives of Toxicology. 2010; 84(4):255-62. doi: 10.1007/s00204-009-0487-y

[15] Repetto MG, Semprine J, Boveris A. Lipid Peroxidation: Chemical Mechanism, Biological Implications and Analytical Determination. D.A. Catala (Ed.) Lipid Peroxidation (2012). InTechopen 2012: 1-30. DOI: 10.5772/45943

[16] Antunes F, Salvador A, Marinho HS, Alves R, Pinto RE. Lipid peroxidation in mitochondrial inner membranes.1.
An integrative kinetic model. *Free Radic Biol Med* 1996;21:917-43. doi: 10.1016/s0891-5849(96)00185-2

[17] Xu L, Davis TA, Porter NA. Rate constants for peroxidation of polyunsaturated fatty acids and sterols in solution and in liposomes. *J Am Chem Soc.* 2009;131:13037-44. https://doi.org/10.1021/ja9029076

[18] Bielski BHJ, Reevaluation of the spectral and kinetic properties of HO2 and O2-FREE radicals, Photochemistry and Photobiology. 1978; 28 (4-5): 645-649. DOI: 10.1111/j.1751-1097.1978.tb06986.x

[19] McCord JM, and Fridovich I. Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein), *The Journal of Biological Chemistry.* 1978; 244:6049-6055.

[20] Gutteridge JM, Lipid peroxidation and antioxidants as biomarkers of tissue damage, *Clinical Chemistry.* 1995; 41: 1819-28.

[21] Bielski BHJ, Arudi RL, Sutherland MW. A study of the reactivity of HO2/O2- with unsaturated fatty acids. *The Journal of Biological Chemistry.* 1983; 258 (8): 4759-4761.

[22] Sies H, Menck CF. Singlet oxygen induced DNA damage. *Mutat Res.* 1992;275:367-75. doi: 10.1016/0921-8734(92)90039-r

[23] Kanovasky JR. Singlet oxygen production by biological systems. *Chem Biol Interact.* 1989;70(1-2):1-28. doi: 10.1016/0009-2797(89)90059-8

[24] Hampton MB, Kettle AJ, Winterbourne CC. Inside the neutrophil phagosome: oxidants, myeloperoxidase, and bacterial killing. *Blood.* 1998;92(9):3007-17. https://doi.org/10.1182/blood.V92.9.3007

[25] Chan HWS. Singlet oxygen analogs in biological systems: coupled oxygenation of 1,3-dienes by soybean lipoxidase. *J Am Chem Soc.* 1971;93(9):2357-8. https://doi.org/10.1021/ja00738a064

[26] Hayashi O, Nozaki M. Nature and mechanisms of oxygenases. *Science.* 1969;164:389-96. doi: 10.1126/science.164.3878.389

[27] Kanofsky JR. Singlet oxygen production by lactoperoxidase. *J Biol Chem.* 1983;258(10):5991-3.

[28] Allen R C. Halide dependence of the myeloperoxidase-mediated antimicrobial system of the polymorphonuclear leukocyte in the phenomenon of electronic excitation. *Biochem. Biophys. Res. Commun.* 1975; 63: 675-683. https://doi.org/10.1016/S0006-291X(75)80437-2

[29] Bielski BHJ, Cabelli BH, Arudi RL, Ross AB. Reactivity of RO2/O2. Radicals in aqueous solution. *J Phys Chem Ref Data.* 1985;14:1041-100. https://doi.org/10.1063/1.555739

[30] Vitale M, Di Matola T, Đascoli F. Iodide excess induces apoptosis in thyroid cells trough a p53-independent mechanism involving oxidative stress. *Endocrinology Society.* 2000;141:598-605. doi: 10.1210/endo.141.2.7291

[31] Fernandez V, Barrientos X, Kipers K, Valenzuela A, Videla LA. Superoxide radical generation, NADPH oxidase activity and cytochrome P-450 content of rat liver microsomal fractions in an experimental hyperthyroid state: Relation to lipid peroxidation. *Endocrinology.* 1985;117:496-501. doi: 10.1210/endo.117-2-496.

[32] Klebanoff SJ. Oxygen metabolites from phagocytes. In: Gallin JI, Snyderman R, eds. *Inflammation: basic principles and clinical correlates.*
Antioxidant Activity: The Presence and Impact of Hydroxyl Groups in Small Molecules...

DOI: http://dx.doi.org/10.5772/intechopen.95616

Philadelphia: Lippincott Williams & Wilkins; 1999:721-68.

[33] Wentworth P Jr., McDunn JE, Wentworth AD, Takeuchi C, Nieva J, Teresa J. Evidence for Antibody-Catalyzed Ozone Formation in Bacterial Killing and Inflammation. Science. 2002; 298 (5601): 2195-2199. DOI: 10.1126/science.1077642

[34] Babior BM, Takeuchi C, Ruedi J, Gutierrez A, Wentworth PJr. (2003). Investigating antibody-catalyzed ozone generation by human neutrophils. Biochemistry. 2003; 100 (6): 3031-3034. doi: 10.1073/pnas.0530251100

[35] Mustafa, M.G., Biochemical Basis of Ozone Toxicity, Free Radical Biol. Med. 1990; 9:245-265. doi: 10.1016/0891-5849(90)90035-h

[36] Pryor WA. Mechanism of Radical Formation from Reactions of Ozone with Target Molecules in the Lung, Ibid. 1994; 17:451-465. DOI: 10.1016/0891-5849(94)90172-4

[37] Kanofsky, JR. and Sima P. Singlet Oxygen Production from the Reactions of Ozone with Biological Molecules, J. Biol. Chem. 1991; 266:9039-9042.

[38] Daugherty A., Dunn JL, Rateri, DL, Heinecke JW. Myeloperoxidase, a catalyst for lipoprotein oxidation, is expressed in human atherosclerotic lesions. J. Clin. Invest.1994; 94: 437-444. DOI: 10.1172/JCI17342

[39] Pullar JM, Vissers MC, Winterbourn CC. Living with a killer: the effects of hypochlorous acid on mammalian cells. IUBMB Life. 2000; 50: 259-266. doi: 10.1080/713803731

[40] Prütz WA. Hypochlorous acid interactions with thiols, nucleotides, DNA, and other biological substrates. Arch Biochem Biophys., 1996;332(1):110-20. doi: 10.1006/abbi.1996.0322

[41] David AF. Lipid oxidation by hypochlorous acid: chlorinated lipids in atherosclerosis and myocardial ischemia. Clin Lipidol. 2010; 5(6): 835-852. doi: 10.2217/clp.10.68

[42] Heinecke J W. Cellular mechanisms for the oxidative modification of lipoproteins: implications for atherogenesis. Coronary Artery Dis. 1994; 5: 205-210.

[43] Andrew PJ, Mayer B. Enzymatic function of nitric oxide synthases. Cardiovasc Res. 1999;43(3):521-31. doi: 10.1016/s0008-6363(99)00115-7

[44] Mayer B, Hemmens B. Biosynthesis and action of nitric oxide in mammalian cells. Trends Biochem Sci. 1997;22:477-481. doi:10.1016/s0968-0004(97)01147-x

[45] Moncada S, Higgs EA. Endogenous nitric oxide: physiology, pathology and clinical relevance. Eur J Clin Invest. 1991;21:361-374. doi: 10.1111/j.1365-2362.1991.tb01383.x

[46] Coleman W. Nitric oxide in immunity and inflammation, International Immunopharmacology. 2001; 1 (8): 1397-1406. doi: 10.1016/s1567-5769(01)00086-8

[47] Furchgott RF. Endothelium-derived relaxing factor: discovery, early studies, and identification as nitric oxide, Bioscience Reports. 1999; 19 (4): 235-251. doi: 10.1023/a:1020537506008

[48] Garthwaite J. Concepts of neural nitric oxide-mediated transmission. European Journal of Neuroscience. 2008; 27 (11): 2783-2802. doi: 10.1111/j.1460-9568.2008.06285.x

[49] Steinert JR, Chernova T, Forsythe ID. Nitric oxide signaling in brain function, dysfunction, and dementia. Neuroscientist. 2010; 16 (4): 435-452. doi: 10.1177/1073858410366481
[50] Thomas DD, Ridnour LA, J. S. Isenberg JS, Flores-Santana W., Switzer CH., Donzelli S., Hussain P., Vecoli C., Paolucci N., Ambs S., Colton CA., Harris CC., Roberts DD., Wink DA. The chemical biology of nitric oxide: implications in cellular signaling. Free Radical Biology & Medicine. 2008; 45 (1): 18-31. DOI: 10.1016/j.freeradbiomed.2008.03.020

[51] Liu X, Miller MJS, Joshi MS, Thomas DD, Lancaster JR. Accelerated reaction of nitric oxide with O2 within the hydrophobic interior of biological membranes. Proc Natl Acad Sci U S A. 1998;95:2175-2179. doi: 10.1073/pnas.95.5.2175

[52] Beckman JS. Ischaemic injury mediator. Nature. 1990; 345:27-28. doi: 10.1038/345027b0

[53] Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci USA 1990;87:1620-1624. doi: 10.1073/pnas.87.4.1620

[54] Beckman JS, Koppenol WH. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. Am J Physiol Cell Physiol 1996;271:C1424–C1437. Beckman JS, Koppenol WH. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. Am J Physiol Cell Physiol 1996;271:C1424–C1437

[55] Pryor WA, Squadrito GL. The chemistry of peroxynitrite: a product from the reaction of nitric oxide with superoxide. Am J Physiol Lung Cell Mol Physiol 1995;268:L699–L722. doi: 10.1152/ajplung.1995.268.5.L699

[56] Douki H, Cadet J. Peroxynitrite mediated oxidation of purine bases of nucleosides and isolated DNA. Free Rad Res. 1996;24(5):369-80. doi: 10.3109/10715769609088035

[57] Ferrer-Sueta G., and Radi, R. Chemical biology of peroxynitrite: kinetics, diffusion, and radicals. ACS Chem. Biol. 2009; 4: 161-177. https://doi.org/10.1021/cb800279q

[58] Goldstein S., and Mere’nyi G. The chemistry of peroxynitrite: implications for biological activity. Methods Enzymol. 2008; 436: 49-61. doi: 10.1016/S0076-6879(08)36004-2

[59] Lyman, SV, and Hurst JK. Rapid reaction between peroxynitrite ion and carbon dioxide: implications for biological activity. J. Am. Chem. Soc. 1995; 117: 8867-8868. https://doi.org/10.1021/ja00139a027

[60] Denicola A., Freeman BA., Trujillo M, Radi R. Peroxynitrite reaction with carbon dioxide/bicarbonate: kinetics and influence on peroxynitrite-mediated oxidations. Arch. Biochem. Biophys. 1996; 333: 49-58. doi: 10.1006/abbi.1996.0363.

[61] Lindsay RC. Food additives. In O. R. Fennema (Ed.), Food chemistry, Marcel Dekker Inc. New York, USA, 1996; 778-780.

[62] Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev. 2010; 4(8): 118-126. doi: 10.4103/0973-7847.70902

[63] Preethi G. Anantharaju, Prathima C. Gowda, Manjunatha G. Vimalambike & SubbaRao V. Madhunapantula. An overview on the role of dietary phenolics for the treatment of cancers. Nutrition Journal. 2016; 15:99. https://doi.org/10.1186/s12937-016-0217-2

[64] Spiegel M, Kapusta K, Kołodziejczyk W, Saloni J, Zbikowska B, Hill GA, Sroka Z. Antioxidant Activity of Selected Phenolic Acids–Ferric

22
Reducing Antioxidant Power Assay and QSAR Analysis of the Structural Features. Molecules. 2020; 25: 3088. https://doi.org/10.3390/molecules25133088

[65] Galato D, Ckless K, Susin MF, Giacomelli C, Ribeiro-do-Valle RM, Spinelli A. Antioxidant capacity of phenolic and related compounds: correlation among electrochemical, visible spectroscopy methods and structure–antioxidant activity. Communications in Free Radical Research. 2001; 6 (4): 243-250. https://doi.org/10.1179/135100001101536391

[66] Ohkatsua Y, Ishikawab SI, Tobitab E. Consideration on the effect of ortho-substituents of phenols by semiempirical molecular orbital method MOPAC. Polym Degrad Stab. 2000; 67: 541-545.

[67] Wright JS., Johnson ER., DiLabio GA. Predicting the activity of phenolic antioxidants: Theoretical method, analysis of substituent effects, and application to major families of antioxidants. Journal of the American Chemical Society. 2001; 123(6): 1173-1183. https://doi.org/10.1021/ja002455u

[68] Dziedzic SZ, B. Hudson BJF. Food Chem. 1984; 12: 205. https://doi.org/10.1016/0308-8146(84)90152-3

[69] Nardini M, D’Aquino M, Tmassi G, Gentili V, Di Felice M, Scaccini C. Inhibition of human low-density lipoprotein oxidation by caffeic acid and other hydroxycinnamic acid derivatives. Free Radic Biol Med 1995; 19:541-52. doi: 10.1016/0891-5849(95)00052-y

[70] Bors W, Heller W, Michel C, Saran M. Met. Flavonoids as antioxidants: determination of radical-scavenging efficiencies Enzymol. 1990; 186: 343. doi: 10.1016/0076-6879(90)86128-i

[71] Mansouri A, Makris DP, Kefalas P. Determination of hydrogen peroxide scavenging activity of cinnamic and benzoic acids employing a highly sensitive peroxyoxalate chemiluminescence-based assay: structure–activity relationships. J. Pharm. Biomed. Anal. 2005; 39: 22-6. doi: 10.1016/j.jpba.2005.03.044

[72] Andreasen MF, Landbo AK, Christensen LP, Hansen A, A. S. Meyer AS. Antioxidant Effects of Phenolic Rye (Secale cereale L.) Extracts, Monomeric Hydroxycinnamates, and Ferulic Acid Dehydrodimers on Human Low-Density Lipoproteins. J. Agric. Food Chem. 2001; 49: 4090-4096. doi: 10.1021/jf0101758

[73] Nsangou M, Dhaouadi Z, Jaidane N, Lakhdar ZB. J. Mol. Struc: THEOCHEM. DFT study of the structure of hydroxybenzoic acids and their reactions with OH and O2-radicals. 2008; 850: 135-143. https://doi.org/10.1016/j.theochem.2007.10.032

[74] Chen JH, and Ho CT. Antioxidant Activities of Caffeic Acid and Its Related Hydroxycinnamic Acid Compounds. J. Agric. Food Chem. 1997; 45 (7): 2374-2378. https://doi.org/10.1021/jf970055t

[75] Omar, HS, El-Beshbishy HA, Moussa Z, Taha K F, Singab ANB. Antioxidant Activity of Artocarpus heterophyllus Lam. (Jack Fruit) Leaf Extracts: Remarkable Attenuations of Hyperglycemia and Hyperlipidemia in Streptozotocin-Diabetic Rats. The Scientific World JOURNAL 2011; 11: 788-800. DOI: 10.1100/tsw.2011.71

[76] Back TG, Moussa Z. Remarkable activity of a novel cyclic seleninate ester as a glutathione peroxidase mimetic and its facile in situ generation from allyl 3-hydroxypropyl selenide. J Am Chem Soc 2002; 124: 12104-12105. https://doi.org/10.1021/ja028030k
Antioxidants - Benefits, Sources, Mechanisms of Action

[77] Back TG, Moussa Z. Diselenides and allyl selenides as glutathione peroxidase mimetics. remarkable activity of cyclic seleninates produced in situ by the oxidation of allyl ω-hydroxyalkyl selenides. J Am Chem Soc 2003; 125: 13455-13460. https://doi.org/10.1021/ja0357588

[78] Lien EJ, Ren S, Bui H, Wang R. Quantitative structure–activity relationship analysis of phenolic antioxidants. Free Radic Biol Med 1999; 26: 285-294. doi: 10.1016/s0891-5849(98)00190-7

[79] Zhang H, Ge N, Zhang Z. Theoretical elucidation of activity differences of five phenolic antioxidants. Acta Pharmacol Sin 1999; 20: 363-366.

[80] Castelluccio C, Paganga G, Melikian N, Bolwell GP, Pridham J., Sampson J., Rice-Evans C. Antioxidant potential of intermediates in phenylpropanoid metabolism in higher plants. FEBS Lett 1995; 368: 188-192. DOI: 10.1016/0014-5793(95)00639-q

[81] Leopoldini M, Marino T, Russo N, Toscano M. Antioxidant properties of phenolic compounds: H-atom versus electron transfer mechanism. J Phys Chem A 2004; 108: 4916-4922. https://doi.org/10.1021/jp037247d

[82] Gardner EJ, Ruxton CHS, Leeds AR. Black tea—Helpful or harmful? A review of the evidence. European Journal of Clinical Nutrition. 2007; 61: 3-18.

[83] Vinson JA. Flavonoids in foods as in vitro and in vivo antioxidants. Advances in Experimental Medicine and Biology. 1998; 439: 151-164. https://doi.org/10.1007/978-1-4615-5335-9_11

[84] Nardini M, Cirillo E, Natella F, Scaccini C. Absorption of phenolic acids in humans after coffee consumption. Journal of Agricultural and Food Chemistry. 2002; 50: 5735-5741. doi: 10.1021/jf0257547

[85] Vinson JA., Su X, Zubik L, Bose P. Phenol antioxidant quantity and quality in foods: Fruits. Journal of Agricultural and Food Chemistry. 2001; 49: 5315-5321. doi: 10.1021/jf0009293

[86] Mertens-Talcott SU, Jilma-Stohlawetz P, Rios J, Hingorani L, & Derendorf H. Absorption, metabolism, and antioxidant effects of pomegranate (Punica granatum L.) polyphenols after ingestion of a standardized extract in healthy human volunteers. Journal of Agricultural and Food Chemistry. 2006; 54: 8956-8961. DOI: 10.1021/jf061674h

[87] Seeram NP, Aviram M, Zhang Y, Henning SM, Feng L, Dreher M, Heber D. Comparison of antioxidant potency of commonly consumed polyphenol-rich beverages in the United States. Journal of Agricultural and Food Chemistry. 2008; 56: 1415-1422. DOI: 10.1021/jf073035s

[88] Gil MI, Tomás-Barberán FA., Hess-Pierce B, Holcroft DM, Kader AA. Antioxidant activity of pomegranate juice and its relationship with phenolic composition and processing. Journal of Agricultural and Food Chemistry. 2000; 48: 4581-4589. doi: 10.1021/jf000404a

[89] Oboh G., and Rocha JBT. Polyphenols in red pepper [Capsicum annuum var. aciculare (Tepin)] and their protective effect on some pro-oxidants induced lipid peroxidation in brain and liver. European Food Research and Technology. 2007; 225: 239-247. DOI: 10.1007/s00217-006-0410-1

[90] Visioli F., Bellomo G., Galli C. Free radical-scavenging properties of olive oil polyphenols. Biochemical and Biophysical Research Communications. 1998; 247: 60-64. doi: 10.1006/bbrc.1998.7875
Antioxidant Activity: The Presence and Impact of Hydroxyl Groups in Small Molecules...
DOI: http://dx.doi.org/10.5772/intechopen.95616

[91] Lodovici M, Guglielmi F, Casalini C, Meoni M, Cheynier V, Dolara P. Antioxidant and radical scavenging properties in vitro of polyphenolic extracts from red wine. European Journal of Nutrition. 2001; 40: 74-77. https://doi.org/10.1007/PL00007386

[92] Vinson JA., Proch J, Zubik L. Phenol antioxidant quantity and quality in foods: Cocoa, dark chocolate, and milk chocolate. Journal of Agricultural and Food Chemistry. 1999; 47: 4821-4824. doi: 10.1021/jf990312p

[93] Wang TY, Li Q, Bi KS. Bioactive flavonoids in medicinal plants: Structure, activity and biological fate. Asian J. Pharm. Sci. 2018; 13: 12-23. doi: 10.1016/j.aiprs.2017.08.004

[94] Heim KE, Tagliaferro AR, Bobilya DJ. Flavonoid antioxidants: chemistry, metabolism and structure-activity relationships. J. Nutr. Biochem. 2002; 13:572-584. doi: 10.1016/s0955-2863(02)00208-5

[95] Harborne JB, and Williams CA. Advances in flavonoid quantity and quality since. Phytochemistry. 2000; 55: 481-504. doi: 10.1016/s0031-9422(00)00235-1

[96] Cai YZ, Sun M, Xing J, Luo Q, Corke H. Structure-radical scavenging activity relationships of phenolic compounds from traditional Chinese medicinal plants. Life Sci. 2006; 78:2872-2888. DOI: 10.1016/j.lfs.2005.11.004

[97] Back TG, Moussa Z, Parvez M. The exceptional glutathione peroxidase-like activity of di (3-hydroxypropyl) selenide and the unexpected role of a novel spiroidioxaselenonanone intermediate in the catalytic cycle. Angew. Chem. Int. Ed. Engl 2004; 43: 1268-1270. https://doi.org/10.1002/ange.200353128

[98] Janeiro P, Brett AMO. Catechin electrochemical oxidation mechanisms.

[99] Nakanishi I, Miyazaki K, Shimada T, Ohkubo K, Urano S, Ikota N, Ozawa T, Fukuzumi S, Fukuhara K. Effects of metal ions distinguishing between one-step hydrogen-and electron-transfer mechanisms for the radical-scavenging reaction of (+)-catechin. J. Phys. Chem. 2002; 106: 11123-11126. https://doi.org/10.1021/jp026190c

[100] Mahmoud MAA, Chedea VS, Detsi A, Kefalas P. Ascorbic acid modifies the free radical scavenging behaviour of catechin: An insight into the mechanism. Food Res. Inter. 2013; 51: 907-913. https://doi.org/10.1016/j.foodres.2013.02.023

[101] Rimarcík J, Lukes V, Klein E, Ilcin M. Study of the solvent effect on the enthalpies of homolytic and heterolytic N–H bond cleavage in p-phenylenediamine and tetracyano-p-phenylenediamine. J. Mol. Struct.: THEOCHEM. 2010; 952: 25-30. DOI:10.1016/j.theochem.2010.04.002

[102] Quan VVo, Nam PC, Thong NM, Trung NT, Cam-Tu DP, Mechler A. Antioxidant Motifs in Flavonoids: O–H versus C–H Bond. ACS Omega. 2019; 4: 8935-8942. https://doi.org/10.1021/acsomega.9b00677

[103] Nimse SB and Palb D. Free radicals, natural antioxidants, and their reaction mechanisms. RSC Adv. 2015; 5: 27986-28006. https://doi.org/10.1039/C4RA13315C

[104] Leopoldini M, Russo N, Toscano M. The molecular basis of working mechanism of natural polyphenolic antioxidants. Food Chemistry. 2011; 288-306. DOI: 10.1016/j.foodchem.2010.08.012

[105] Soleas GJ, Diamandis EP, Goldberg DM. Resveratrol: a molecule
whose time has come? And gone.
Clin Biochem. 1997; 30(2):91-113. doi: 10.1016/s0009-9120(96)00155-5

[106] Bavaresco L, Fregoni M, Trevisan M, Mattivi F, Vrhovsek U, Falchetti R. The occurrence of the stilbene piceatannol in grapes. Vitis. 2002; 41: 133-136.

[107] Ku KL, Chang PS, Cheng YC, Lien CY. Production of stilbenoids from the callus of *Arachis hypogaea*: A novel source of the anticancer compound piceatannol. Journal of Agricultural and Food Chemistry. 2005; 5: 33877-3881. https://doi.org/10.1021/jf050242o

[108] Rimando AM, Kalt W, Magee JB, Dewey J, Ballington JR (2004) Resveratrol, pterostilbene, and piceatannol in vaccinium berries. Journal of Agricultural and Food Chemistry. 2004; 52: 4713-4719. doi: 10.1021/jf040095e

[109] Chang J, Rimando A, M. Pallas M, Camins A, Porquet D, Reeves J, Shukitt-Hale B, Smith MA, Joseph JA, Gemma Casadesus G. Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer’s disease, Neurobiology of Aging. 2012; 33 (9): 2062-2071. DOI: 10.1016/j.neurobiolaging.2011.08.015

[110] Chong J, Poutaraud A, Hugueney P. Metabolism and roles of stilbenes in plants. Plant Science. 2009; 177 (3): 143-155, 2009. https://doi.org/10.1016/j.plantsci.2009.05.012

[111] Jang M, Cai L, Udéani GO, Slowing KV, Thomas CF, Beecher CWW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM. (1997) Cancer chemo-preventive activity of resveratrol, a natural product derived from grapes. Science. 1997; 275: 218-220. DOI: 10.1126/science.275.5297.218

[112] Stivala LA, Savio M, Carafoli F, Perucca P, Bianchi L, Maga G, Forti L, Pagnoni UM, Albini A, Prosperi E, Vannini V. (2001) Specific structural determinants are responsible for the antioxidant activity and the cell cycle effects of resveratrol. Journal of Biological Chemistry. 2001; 276: 22586-22594. DOI: 10.1074/jbc.M101846200

[113] Djoko B, Chiou RYY, Shee JJ, Liu YW. Characterization of immunological activities of peanut stilbenoids, arachidin-1, piceatannol, and resveratrol on lipopolysaccharide-induced inflammation of RAW264.7 macrophages. Journal of Agricultural and Food Chemistry. 2007; 55: 2376-2383. https://doi.org/10.1021/jf900612n

[114] Bastianetto S, Dumont Y, Han Y, Quirion R. Comparative neuroprotective properties of stilbene and catechin analogs: action via a plasma membrane receptor site? CNS Neuroscience & Therapeutics. 2009; 15: 76-83. DOI: 10.1111/j.1755-5949.2008.00074.x

[115] Murias M, Jager W, Handler N, Legrand A, Jore D, Gardès-Albert M, Bonnefont-Rousselot D. (2005) Antioxidant, prooxidant and cytotoxic activity of hydroxylated resveratrol analogues: structure-activity relationship. Biochemical Pharmacology. 2005; 69: 903-912. DOI: 10.1016/j.bcp.2004.12.001

[116] Rhayem Y, Therond P, Camont L, Couturier M, Beaudeux JL, Legrand A, Jore D, Gardès-Albert M, Bonnefont-Rousselot D. Chain-breaking activity of resveratrol and piceatannol in a linoleate micellar model. Chemistry and Physics of Lipids. 2008; 155: 48-56. DOI: 10.1016/j.chemphyslip.2008.06.001

[117] Yang Lu, AiHua Wang, Peng Shi, Hui Zhang. A Theoretical Study on the Antioxidant Activity of Piceatannol and Isorhapontigenin Scavenging Nitric Oxide and Nitrogen Dioxide Radicals. PLOS ONE. 2017; 12(1):e0169773.
Antioxidant Activity: The Presence and Impact of Hydroxyl Groups in Small Molecules...

DOI: http://dx.doi.org/10.5772/intechopen.95616

https://doi.org/10.1371/journal.pone.0169773

[118] Hussein MA. A Convenient Mechanism for the Free Radical Scavenging Activity of Resveratrol. International Journal of Phytomedicine. 2011; 3 (4): 459-469.

[119] Shahidi, F, Janitha, P.K, Wanasundara, P.D. (1992). Phenolic antioxidants. Critical Reviews in Food Science and Nutrition. 1992; 32: 67—103. https://doi.org/10.1080/10408399209527581

[120] Anderson K, Domingos I, Emir B, Saad I, Wellington W, D. Vechiato D, Helena M. Wilhelm HM, Luiz P. Ramos LP. The influence of BHA, BHT and TBHQ on the oxidation stability of soybean oil ethyl esters (biodiesel). J. Braz. Chem. Soc. 2007; 18 (2): 416-423. https://doi.org/10.1590/S0103-50532007002000026

[121] Al-Mamary MA, Abdelwahab SI, Ali HM, Salma Ismail, Abdulla MA, Darvish P. Synthesis of Some Schiff Bases Containing Hydroxyl and Methoxy Groups: their Antioxidant and Antibacterial Activities. Asian Journal of Chemistry. 2012; 24(10):4335-4339.

[122] Said MA, Hughes DL, Al-Mamary MA, Al-Kaff NS, Al-Harbi WS. Different Chemical Behaviors and Antioxidant Activity of Three Novel Schiff bases Containing Hydroxyl Groups. X-ray structure of CH2(cyclo-C6H10-NH=CH-(2-O-naphth))2H2O. Journal of Molecular Structure. 2018; 1165: 305-311. DOI: 10.1016/j.molstruc.2018.03.089

[123] Moussa Z, Al-Mamary MA, Al-Juhani S, Ahmed SA. Preparation and biological assessment of some aromatic hydrazones derived from hydrazides of phenolic acids and aromatic aldehydes. Heliyon. 2020; 6 (9): e05019. https://doi.org/10.1016/j.heliyon.2020.e05019

[124] Kurutas EB. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. Nutrition Journal. 2016; 15:71. https://doi.org/10.1186/s12937-016-0186-5

[125] Finkel T and N J Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000; 408(6809):239-47. doi: 10.1038/35041687

[126] Reuter S, Gupta SC, Chatturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: are they linked?. Free Radic Biol Med. 2010; 49(11):1603-16. doi: 10.1016/j.freeradbiomed.2010.09.006

[127] Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiol Rev. 2014; 94(2):329-54. doi: 10.1152/physrev.00040.2012

[128] Padureanu R, Albu CV, Mititelu RR, Bacanoiu MV, Docea AO, Calina D, Padureanu V, Olaru G, Sandu RE, Malin RD, Buga AM. Oxidative Stress and Inflammation Interdependence in Multiple Sclerosis. J Clin Med. 2019; 8(11):1815. doi: 10.3390/jcm8111815

[129] Stanner SA, Hughes J, Kelly CNM, Buttriss J. A review of the epidemiological evidence for the 'antioxidant hypothesis'. Public Health Nutrition. 2004; 7 (3): 407-422. doi: 10.1079/phn2003543

[130] Cherubini A, Vigna GB, Zuliani G, Ruggiero C, Senin U, Fellin R. Role of antioxidants in atherosclerosis: epidemiological and clinical update, Current Pharmaceutical Design. 2005; 11 (16): 2017-2032, 2005. doi: 10.2174/1381612054065783

[131] Lotito SB and Frei B. Consumption of flavonoid-rich foods and increased
plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? Free Radical Biology and Medicine. 2006; 41 (12): 1727-1746, 2006. doi: 10.2174/1381612054065783

[132] Boeing H, Bechthold A, Bub A, Ellinger S, Haller D, Kroke A, Leschik-Bonnet E, Müller MJ, Oberritter H, Schulze M, Stehle P, Watzl B. Critical review: vegetables and fruit in the prevention of chronic diseases, European Journal of Nutrition. 2012; 51 (6): 637-663. doi: 10.1007/s00394-012-0380-y

[133] Crowe FL, Roddam AW, T. J. Key TJ et al. Fruit and vegetable intake and mortality from ischaemic heart disease: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Heart study. European Heart Journal. 2011; 32 (10):1235-1243. doi: 10.1093/eurheartj/ehq465