ANTIOXIDANTS IN FOOD AND PHARMACEUTICAL RESEARCH.

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Abstract. In this work we provide a general overview about the natural and synthetic antioxidants and studies carried out to improve their potential. These compounds are able to scavenge free radicals that cause deterioration of food and pharmaceutical products during processing and storage. Today there are several known natural compounds with antioxidant properties that are extracted from plants, which are mainly phenols and polyphenols. The limit for the use of these compounds in the food and pharmaceutical industry as antioxidants concerns their poor solubility in hydrophobic environment. This limitation was overcome in the past years by the introduction of synthetic antioxidants, such as BHA (butylated hydroxyl anisole), BHT (butylated hydroxyl toluene), TBHQ (tert butyl hydroquinone) and PG (propyl gallate). Unfortunately several authors showed that BHA, BHT, TBHQ and PG may present adverse effects on the health of living organisms. In recent years novel antioxidants have been synthesized from natural polyphenols in order to modify the hydrophobicity/lipophilicity balance and increase their biological functionalities arising from insertion of new functional groups or molecule moieties in pre-existing natural polyphenols. The aim of these modifications was to avoid the major adverse effects associated with the use of BHT, BHA, TBHQ and PG.

Key words. Natural antioxidants, oxidation, BHT, BHA, TBHQ, radicals, lipids, novel antioxidants.

Introduction. In the food industry an antioxidant is a substance having the technical function of delaying the oxidation of nutrients, such as lipids, sugars and proteins, whose oxidation leads to an inevitable deterioration of the organoleptic qualities of a food. Detrimental effects include undesirable formation of chemical compounds like aldehydes, ketones and organic acids that yield off-flavours [1,2]. Antioxidants must be inexpensive, nontoxic, effective at low concentrations (0.001–0.02%), capable of surviving processing (carry-through), stable in the finished products, and devoid of undesirable colour, flavour and odour effects [3]. Today in the food and pharmaceutical industry there is an extensive use of natural and synthetic antioxidants. Natural antioxidants such as polyphenols are primarily derived from plants, while the synthetic antioxidants are chemically produced. Common synthetic antioxidants used in the food industry are BHA, BHT, PG and TBHQ, that have been under scrutiny because of the potential injurious effects in the health field, (i.e. carcinogenic effects, DNA damage properties, allergic contact dermatitis and others adverse effects) [4-15]. Antioxidants can be classified as primary or long-term antioxidants and secondary or processing antioxidants. Primary antioxidants include hindered phenols and secondary aryl amines, while secondary antioxidants include organophosphates and thioesters. The first ones are active radical scavengers or hydrogen donors or chain reaction breakers while the secondary ones are peroxide scavengers [16]. Consequently, it is clear the importance of antioxidants in food conservation. Lipids and nutrients, contained in many kinds of foods such as chiken meat, red meat, diary food, seafood, can undergoe deterioration in foods such as chiken meat, red meat, diary food, seafood, can undergoe in food conservation. Lipids and nutrients, contained in many kinds of foods such as chiken meat, red meat, diary food, seafood, can undergoe deterioration in foods such as chiken meat, red meat, diary food, seafood, can undergoe

Initiation reaction

\[ R^* + \text{H} \rightarrow RH + L^* \]  

L* = Lipid radicals

Propagation reactions

\[ L^* + O_2 \rightarrow LOO^* \]  
\[ \text{LOO}^* + \text{H} \rightarrow \text{LOOH} + L^* \]  
\[ \text{LOOH} \rightarrow \text{LOO}^*, \text{LO}^*, \text{aldehydes} \]  

Breakdown of lipid hydroperoxide

Termination reactions

\[ 2L^* \rightarrow \text{L-} \]  
\[ 2\text{LOO} \rightarrow \text{LOOL} \]  
\[ 2\text{LOO}^* \rightarrow \text{LOOL} + \text{O}_2 \]  

Table 1. Lipid peroxidation and radical / non-radical intermediates formation.
The radical form of kaempferol is able to donate another hydrogen atom to DPPH, forming the kaempferol quinone. In the second case polyphenolic compounds are also able to form chelation complexes with metal ions involved in the production of free radicals, inhibiting this process [27]. For example, iron is implicated in many oxidative-stress-related pathways and conditions, and is the primary generator of \( \text{H}_2\text{O}_2 \) and hydroxyl radical (•OH), the most reactive ROS known, that abstracts a hydrogen atom from biological substrates damaging biomolecules as lipids, proteins, DNA and other [20]. Iron, in nature, can be found as either ferrous or ferric ion with the latter form of ferric ion predominating in foods. Ferrous chelation may provide important antioxidative effects by retarding metal-catalyzed oxidation [30, 31]. Acid phenolic hydrogens of polyphenols show pKa values in the range of 7–9 [32], but in the presence of iron polyphenols are easily deprotonated at or below physiological pH and form very stable complexes. Precisely catechol and gallate moieties of polyphenols, when deprotonated, are able to chelate Fe(II) and Fe(III) ions to form complex with octahedral geometry [20]. However, since polyphenol compounds are so structurally varied and the complexes are pH dependent, they often exhibit variable coordination modes. At pH values previously reported polyphenols stabilize the Fe(III) relative to the Fe(II), moreover catecholate and gallate complexes of Fe(II) rapidly oxidize in the presence of \( \text{O}_2 \) to give Fe(III)-polyphenol complexes that cannot participate in the Fenton reaction [20, 33].

The Fenton reaction: \( \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot \text{OH} + \text{OH}^- \)

In the third case polyphenols may function as protein inhibitors. Precisely their structures formed by hydrophobic benzene rings and phenolic hydroxy groups are capable to form hydrogen-bonds and have the potential to interact with proteins and inhibit enzymes involved in radical generation processes, such as various cytochrome P450 isozymes, lipox-
Table 3. General information about synthetic antioxidants.

<table>
<thead>
<tr>
<th>OTHER NAMES</th>
<th>BHT</th>
<th>BHA</th>
<th>PG</th>
<th>TBHQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,6-bis(1,1-dimethylethyl)-4-methylphenol / 2,6-di-tert-butyl-p-cresol / 2,6-di-tert-butyl-4-methylphenol / Antraceine 8 / Lonol CP / Dalpac / Impruvol / Violan / Tenox / Tenox 8 / Sustane BHT.</td>
<td>Mixture of two iso-mers: 3-tertiary butyl-4-hydroxyanisole and 2-tertiary butyl-4-hydroxyanisole / (1,1-dimethylethyl)-4-methoxyphenol / Antraceine 12 / Embanox / Nipantiox / Sustane BHA / Sustane 1-F / Tenox 4B / Tenox 5B.</td>
<td>n-propyl-3, 4, 5-trihydroxybenzoic acid / Gallic acid, propyl ester / Nipa 49 / Nipagallin P / Tenox PG / Sustane PG.</td>
<td>2-(1,1-dimethylethyl)-1,4-benzenediol / mono-t-butyl hydroquinone / Sustane TBHQ / Tenox TBHQ.</td>
<td></td>
</tr>
</tbody>
</table>

**FOOD USE**
- Breakfast cereals, Baked goods, potato chips, vegetable oils, snack foods, margarine, frozen seafoods, chewing gum base
- Bakery products, meat products, spices, cereals, dehydrated mashed potatoes, beverage mixes, dessert mixes, nuts, vitamins, yeast, vegetable oils, animal fats, processed cheeses, margarine, essential oils, chewing gum base.
- Chewing gum base, non alcoholic beverages, margarine, mixed nuts, fresh or dry sughes, pre-grilled beef patties, rendered animal fat, pizza toppings and meatball.
- Dry cereals, edible fats, margarine, pizza toppings, potato chips, poultry, dried meats, sausages, beef patties, vegetable oils.

**“E” NUMBER**
- E321
- E320
- E310
- E319

**SYNERGISTS**
- BHA
- BHT, propyl gallate, methionine, lecithin, thiodiropionic acid, citric acid, phosphoric acid.
- BHA, BHT.
- BHA, citric acid.

**SOLUBILITY %**

<table>
<thead>
<tr>
<th>SOLUBILITY %</th>
<th>In water at 20°C</th>
<th>Insoluble</th>
<th>Insoluble</th>
<th>&lt;1%</th>
<th>&lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vegetable oils at 25°C</td>
<td>30% cottonseed, coconut, corn, peanut and soybean oils.</td>
<td>30% in cottonseed oil - 40% in coconut, corn, peanut oils -50% in soybean oils.</td>
<td>1% in cottonseed oil – 2% in soybean oils – Insoluble in con oil.</td>
<td>10% in corn, cottonseed and soybean oils...</td>
<td></td>
</tr>
<tr>
<td>In ethanol solution 100% at 25°C</td>
<td>25%</td>
<td>&gt;25%</td>
<td>&gt;60%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>In propylene glycol at 20°C</td>
<td>Insoluble</td>
<td>70%</td>
<td>-</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3.** General information about synthetic antioxidants.

genases, cyclooxygenase and Xanthine oxidase. [27,34] Synthetic antioxidant. Today among all synthetic compounds that have been evaluated for their efficacy as radical scavenger or for their other inhibitory effect, only four are widely used in foods, namely butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate (PG), and tert butyl hydro quinone (TBHQ) [35]. Introduction of alkyl groups into an aromatic ring is a useful and general approach to produce these antioxidants, in general alkylation involves attack of electrophilic carbon species on the ring. One of the well known reaction is the Friedel-Crafts alkylation, that uses an alkyl chloride as reagent and anhydrous aluminum chloride as catalyst [36]. The choice of reagents and conditions depends upon the alkyl group and the reactivity of the ring. Industrially BHT is prepared by the reaction of p-cresol (4-methylphenol) with isobutylene (2-methylpropene) catalyzed by sulfuric acid while BHA is prepared from 4-methoxyphenol and isobutylene in a similar reaction [37]. BHT is a white crystalline solid with a faint characteristic odor. It is insoluble in water and in propylene glycol, but is freely soluble in alcohol. It is used as a chemical antioxidant for food, cosmetics, and pharmaceuticals much like butylated hydroxyanisole (BHA). On the other hand BHA is a mixture of 3-tert-butyl-4-hydroxyanisole (typically 90% w/w) and 2-tert-butyl-4-hydroxyanisole. BHA is insoluble in water, but is freely soluble in alcohol and in propylene glycol. These phenol derivatives react with the free radicals slowing the rate of lipids autoxidation that can lead to changes in the food’s color and taste. BHT and BHA are also used as antioxidants in plastics, elastomers and petroleum (lubes, greases and waxes), practically bigger market size than food field. TBHQ (2-tert-butylhydroquinone) is a white, crystalline solid insoluble in water but soluble in alcohol and in ether. It can be synthesized selectively from hydroquinone (HQ) and isobutylen by alkylation in the presence of H3PO4 or H2SO4/H3PO4 catalyst [38] or by alkylation with tert-butanol. In foods, it is used as a preservative for unsaturated vegetable oils and many edible animal fats [39]. It’s also used in formulating vernish, lacquer, resins and oil field additives. It is used as a fixative in perfumery to reduce the evaporation rate and improve stability and as a stabilizer to inhibit the autopolymerization of organic peroxides. PG (propy gallate or propyl-3,4,5-trihydroxy benzoate ) is a white, odorless powder having a slightly bitter taste. It is slightly soluble in water and freely soluble in alcohol and in ether. This compound is an ester formed by the condensation of gallic acid and propanol. Since 1948 it is used in food industry as antioxidant to prevent oxidation of foods containing oils and fats [40]. In addition to the food industry, the
PG is used as an anti-fade reagent in fluorescence microscopy to reduce photo-bleaching of fluorescences such as rhodamine and fluorescein [41] and is also used as antioxidant in cosmetics, hair products, adhesives, and lubricants. Tab. 3 shows all the most important information about the antioxidants mentioned above, along with their respective E numbers, that identify substances which can be used as food additives within the European Union and Switzerland (the “E” stands for “Europe”). They are commonly found on food labels throughout the European Union. The additives for food use undergo a process of safety assessment before being approved by European and international countries. In Europe, the evaluation is carried out by the Food Safety Authority (EFSA), and at international level by the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization (FAO) and the World Health Organization (WHO). As previously mentioned, these compounds in food have the technical function of antioxidant preservatives. So they prevent oxidative rancidity development in oil-containing foods by terminating free radicals formed during autoxidation of unsaturated lipids. Moreover they possess antimicrobial activity as a phenolic compound [35].

**Novel antioxidant.** Common synthetic antioxidants used in the food industry, namely BHA, BHT, PG and TBHQ offer good protection during storage, but have been under scrutiny owing to the growing concern over their potential carcinogenic effects [4-15]. Moreover natural polyphenolic compounds are water-soluble due to the hydrophilicity arising from their hydroxyl groups. This may compromise their effective application as antioxidants in lipophilic systems, such as fats, oils, lipid-based food or cosmetic formulas and emulsions, as well as biological environments [21]. As a consequence, the development of compounds with better antioxidant capacity and less toxicity is desirable in health (es. prevention of diseases), in food, in pharmaceutical and cosmetic field to improve shelf life of respective consumer products [42]. A possible way to prepare novel anti-
oxidant from natural phenols and polyphenols is to manipulate lipophilicity/hydrophilicity balance (HLB) through chemical structure modification of these compounds [21]. The change in the solubility characteristics of natural antioxidants, without changing the molecular moieties responsible for antioxidant activity, can enhance antioxidant application in food, pharmaceutical and cosmetic fields [42]. In general the synthesis of esters or amides of polyphenols with fatty acids or fatty alcohols represent a general way to make novel antioxidants. Moreover the conjugation between polyphenols with fatty acids may provide additional advantages by introducing new bioactive functional groups to the antioxidant molecules[21]. The chemical literature is full of examples of esterification of phenolic acids with aliphatic alcohols or polyphenols with fatty acids. Specifically these last were used to synthesize ester derivatives of ascorbic acid, tyrosol, rutin, protocatechual alcohol, vanillyl alcohol, esculine, naringin, genistein and daidzein[43-48], while aliphatic alcohols have been used to esterify ferulic, chlorogenic, cinnamic, sinapic, p-coumaric and caffeic acids [49-53]. In the following paragraphs some examples will be reported. **Fatty acids-Epigallocatechin gallate (EGCG) conjugation.** Green tea is an important source of epigallocatechin gallate (EGCG), a natural powerful antioxidant that is effective in radical scavenging and metal chelation [54-55]. EGCG is the predominant one among the catechins in tea, a group of flavonoids that are also responsible for the characteristic colour, flavor and aroma of this famous drink. Like many other polyphenols, EGCG is poor soluble in lipophilic systems and this fact can greatly restrict its use as antioxidant in fats, oils, lipid-based food or cosmetic formulas and emulsions, as well as biological environments [56]. In recent works [57-58] epigallocatechin gallate was esterified by acylation with acyl chlorides of selected long-chain saturated or polyunsaturated fatty acids such as SA (stearic acid), EPA (Eicosapentaenoic acid) and DHA (docosaa- eicosanoic acid) to produce three esters (Fig. 4) with enhanced lipophilicity [56]. These products showed higher radical scavenging activity against peroxyl radicals than the parent EGCG molecule in acetone/water solvent medium [for more information see [57]] and better or comparable antioxidant activities to that of the parent EGCG in biological model systems including LDL-cholesterol, DNA and liposome[56]. Moreover EGCG derivatives have demonstrated the ability to chelate proxidant metal ions Fe2+ and showed excellent antiviral activities in inhibiting HCV protease and α-glucosidase, which were not significant for EGCG [57]. In conclusion these lipophilic derivatives of EGCG could be considered for use in food preservation and health promotion. **Ricinoleate-phenolic acids conjugation.** K.K. Reddy et al. published a very interesting work in 2012 [42] focused on the synthesis, characterization and evaluation of four novel antioxidants, synthesized by conjugation between the phenolic acids as ferulic and vanillic acids with methyl ricinoleate and methyl-12-hydroxy stearate (see Fig.5), the first is the principal unsaturated fatty acid present in castor oil, the last one is its saturated analogue. Precisely about 90% of the fatty acid content in castor oil is the triglyceride formed from ricinoleic acid, that is known to exert laxative, analgesic and anti-inflammatory effects in human health [59]. The choice of such compounds has allowed the authors to assess the influence of unsaturation in the alkyl chain and in the side chain of phenolic acid on the antioxidant activity. The reactions to prepare four novel antioxidants were performed according to the chemoselective Mitsunobu esterification method [60]. Moreover antioxidant, antibacterial and antifungal activity of these novel molecules were evaluated. The radical-scavenging activity of the synthesized compounds was determined through the use of DPPH radical scavenging assay in a polar homogeneous medium. In this polar conditions the four novel molecules, after lipophilisation, showed decreased radical-scavenging activity respect to the starting free phenolic acids. The authors explained this fact considering the increased hydrophobicity of the synthesized phenolipids. It is also to be noted that the ferulic acid derivatives showed better radical-scavenging activity than the vanillic acid derivatives. This fact proves the importance of the allylic double bond of ferulic acid in stabilising the phenoxy radical. Moreover the phenolipid products have demonstrated to inhibit the autoxidation of linoleic acid in Tween 20 micellar system (Tween represent a common commercial brand for nonionic surfactants polysorbates) significantly more than ferulic and vanillic acids and similar to DGG (dodecyl gallate), the well known grade antioxidant. This fact is particularly important because antioxidants are widely used in cosmetic and food products to inhibit lipid peroxidation and most of these products exist in a formulated complex emulsion system[42]. Moreover the prepared compounds showed interesting antifungal properties but none of the synthesized phenolic lipoconjugates showed any activity against the studied bacteria (for more information see [42] and references there cited). In conclusion these novel compounds have shown to be potential and interesting antioxidant additives for the storage of lipids against oxidative stresses. **Dihydro-**
CAFFEIC ACID AMIDE DERIVATIVES AS NOVEL ANTIOXIDANTS. In 2012 was published a work [61] based on the synthesis of a variety of new N-alkyl-N-aryl-3-(3,4-dihydroxyphenyl) propane--amides (Fig.6) as novel caffeic acid amide antioxidants. These compounds contain the aromatic structure of the dihydro-cafeic acid, that results to have higher radical scavenging and antioxidant activity compared to caffeic acid [61]. The choice to synthesize amide derivatives of caffeic acid is based on the fact that many reports have demonstrated the potential of these derivatives in the food and health fields. For example in 2001 Rajan P. et al. reported a new caffeic acid amides with good antioxidant activity and enhanced metabolic stability [62]. Furthermore in 2002 was published a work in which the authors described the synthesis of 4-hydroxyphenylacetic acid amide, which possess potent analgesic activity [63]. Moreover the synthesis of caffeic acid amides, possessing antimicrobial activities, was reported in 2010 [64]. As is shown schematically in Fig.6 a variety of new N-alkyl-N-aryl-3-(3,4-dihydroxy phenyl) propane-amides were prepared in two steps synthesis. In the first step amines A,Bx were obtained by reductive amination between four different aldehydes that are Benzaldehyde(A1), 4-hydroxybenzaldehyde(A2), vanillin(A4), syring aldehyde(A3) and three different amines (propylamine, hexylamine decylamine) for which the imines produced were subsequently reduced with sodium borohydride. In the second step antioxidants dihydro-cafeic acid amide derivatives were prepared through coupling reaction between dihydro-cafeic acid (DCA) and the corresponding amines Ax-Bx, using BPO as a coupling reagent. DPPH assays demonstrated a significantly higher radical scavenging activities of novel antioxidants N-alkyl-N-aryl-3-(3,4-dihydroxy phenyl) propane-amides than α-tocopherol, BHT and DCA. Furthermore, when compared to α-tocopherol and BHT, the new compounds offered better protection to polysaturated oils both under storage and frying conditions [61].

Novel 5H-dibenzo[b,f]azeepine derivatives. Comparing to the importance of the O-H groups in phenols, that give good antioxidant capacity against radicals as idrogen donors, also the aryl secondary amines are able to act as chain transfer and chain terminators against free reactive radicals [64,65]. Recently H. Vijay Kumar and Nagaraja Naik published the synthesis (RSA) was derived between dihydro-cafeic acid and the corresponding amines Ax-Bx, using BPO as a coupling reagent. DPPH assays demonstrated a significantly higher radical scavenging activities of novel antioxidants N-alkyl-N-aryl-3-(3,4-dihydroxy phenyl) propane-amides than α-tocopherol, BHT and DCA. Furthermore, when compared to α-tocopherol and BHT, the new compounds offered better protection to polysaturated oils both under storage and frying conditions [61].

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