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Stobadine – An Indole Type Alternative to the Phenolic Antioxidant Reference Trolox

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1. Introduction

Treatment of free radical pathologies by antioxidants has been substantiated by studies in animal models of diseases. However, so far the therapy of oxidative stress-related diseases has not found satisfactory application in clinical practice. This may be due to an insufficient efficacy of the antioxidants available, their unsuitable pharmacokinetics, lack of selectivity, presence of adverse side effects, their toxicity, etc. Thus, new antioxidants have to be identified. In numerous studies searching for novel antioxidant compounds, trolox, a water soluble analogue of alpha-tocopherol, is commonly utilized as a reference antioxidant. Chemically, trolox represents a carboxylic acid chromane (Fig. 1A). Due to its good water solubility, this antioxidant has been broadly used as a standard when screening antioxidant efficacy of other prospectively active compounds in studies involving chemical, subcellular, cellular and tissue models of oxidative stress mediated injury (Aruoma, 2003; Huang et al., 2005; Prior et al., 2005). On the other hand, a fairly large and specific group of substances with beneficial antioxidant effects is derived from indole structure (Suzen, 2007). This puts a demand on the reassessment of the suitability of a phenol-type reference trolox, particularly in studies on screening of nitrogen heterocyclic antioxidants.

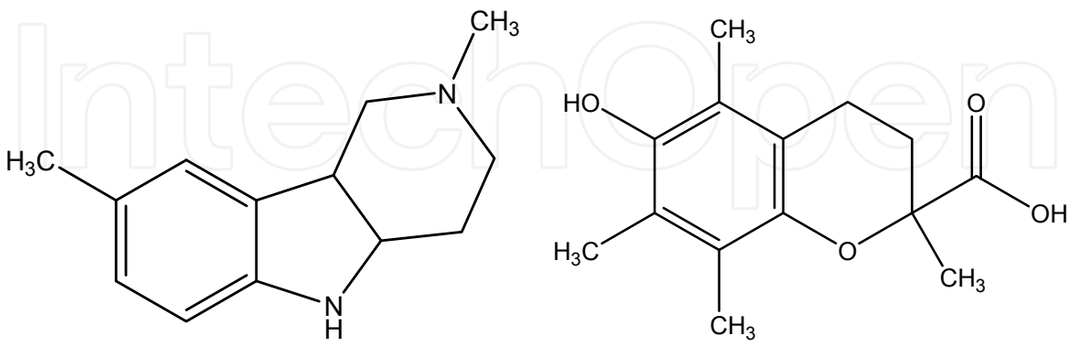
The pyridoindole stobadine (Fig. 1A) has been found out to be an effective chain-breaking antioxidant scavenging a variety of reactive oxygen species (Kagan et al., 1993; Steenken et al., 1992; Stefek & Benes, 1991). The input of stobadine into the literary data on indole-type antioxidants comprises more than two hundred PubMed references. Several comprehensive reviews cover stobadine action as determined in a variety of models including simple chemical systems, biological models at subcellular, cellular or organ level, followed by extensive studies in vivo in a number of free-radical disease models, and that also in comparison with other drugs (Horakova et al., 1994; Horakova & Stolc, 1998; Juranek et al., 2010; Stolc et al., 1997; Stefek et al., 2010). The main goal of the present paper is to provide an overview on the current data of the indole-type antioxidant stobadine and to compare them with those of the phenol-type antioxidant trolox.

2. Comparison of stobadine with trolox

Structural features, physicochemical properties, mechanism of action and efficiency of stobadine in various models of free radical damage are summarized and compared with those of trolox. Consequently, stobadine may be highlighted as a promising reference

antioxidant, which may readily be utilized as a standard in studies testing antioxidative efficacy of other indole-type substances.

A)



Stobadine **Trolox**

B)

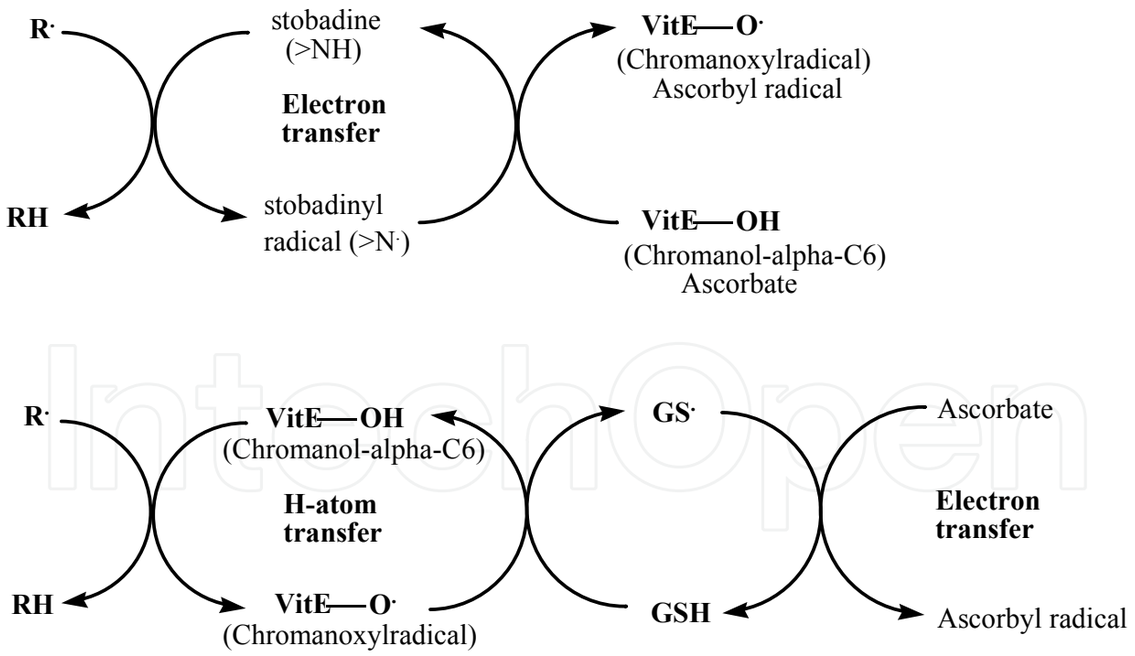


Fig. 1. Structures of stobadine and trolox (A) and possible mechanisms of free radical scavenging by stobadine and vitamin E/trolox (B).
Biologically relevant coupled reactions that might recycle stobadine (Kagan et al., 1993) and vitamin E/trolox (Davies et al., 1988) are depicted.

2.1 Physico-chemical properties

Trolox, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, has the character of organic acid (Nonell et al., 1995), while stobadine, (-)-cis-2,8-dimethyl-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3b]indole, is an organic base. Despite the fact that trolox is more lipophilic than stobadine (log P values 2.83 and 1.95, respectively), at the physiological pH 7 stobadine preferentially distributes into lipid compartment, while trolox preferentially resides in the water phase. The acidobasic behaviour accounts for this apparent discrepancy. With the pKa value of the carboxyl group 3.89 (Barclay & Vinqvist, 1994), trolox undergoes virtually complete dissociation at physiological pH (99.92% of COO^- form of trolox). On the other hand, stobadine with the pKa value of the tertiary nitrogen 8.5 (Stefek et al., 1989) has around 92% of the basic nitrogen in protonated form at pH 7. As a result of the acidobasic equilibrium, the corresponding distribution ratios at pH 7 of trolox and stobadine, D = 0.33 (Barclay et al., 1995) and 3.72 (Kagan et al., 1993), respectively, clearly favour partitioning of stobadine into the lipid phase, yet not that of trolox. This may explain the profound drop of the apparent antioxidant efficiency of trolox in experimental models involving membranous systems (Horakova et al., 2003; Juskova et al., 2010; Rackova et al., 2002; Rackova et al., 2004; Stefek et al., 2008).

2.2 Redox properties

Early pulse radiolysis studies indicated differences with regard both to the centre of antioxidant activity, residing in the indolic nitrogen or phenolic moiety of stobadine or trolox, respectively, and to deprotonation mechanism following the oxidation of the parent molecules (Fig. 1B). It was demonstrated that one-electron oxidation of stobadine leads to the formation of its radical cation (Steenken et al., 1992). That deprotonates from the indolic nitrogen and gives a resonance stabilised nitrogen-centred radical. With regard to the pKa value of approx. -5 of trolox-derived phenoxyl radical cation (Davies et al., 1988) and its expected extremely rapid deprotonation, no spectral evidence for generation of the trolox radical cation was obtained. However, depending on the reaction conditions, electron transfer followed by proton shift or even sequential proton loss and electron transfer (SPLET) has been suggested as a radical scavenging mechanism of phenolic antioxidants involving trolox and alpha-tocopherol (Musialik, 2005; Svanholm et al., 1974).

As shown in Table 1, stobadine and trolox are characterised by comparable rate constants of their interactions with the majority of individual reactive oxygen species tested. The major differences concern the second order rate constants of their reactions with superoxide and hydroxyl radicals. A considerably higher $k_{superoxide}$ value was found for trolox (Nishikimi & Machlim, 1975) than that of stobadine (Kagan et al., 1993) (Table 1). On the other hand, the study by Bielski (1982) showed a notably low second order rate constant of trolox for its reaction with superoxide ($k_{superoxide}$ <0.1 $M^{-1}.s^{-1}$), while Davies et al. (1988) reported an apparent absence of trolox reaction with superoxide.

Regarding the hydroxyl radical scavenging, Davies et al. (1988) reported the value $k_{.OH}$ for trolox to be comparable with that of stobadine (Table 1). Nonetheless, according to the study of Aruoma et al. (1990), the second order rate constant of trolox for scavenging HO· radicals is about one order higher than that of stobadine. These findings are in a good agreement with our data obtained in a study where the efficacy of stobadine and trolox in inhibition of hydroxyl-radical-induced cross-linking of bovine serum albumin were assessed (Kyselova et al., 2003).

Reactive oxygen species	Rate constant ($M^{-1}.s^{-1}$)	
	Stobadine	**Trolox**
$HO^{\cdot}$	7×10^9 15.9×10^9 (Steenken et al., 1992; Stefek & Benes, 1991)	8.5×10^{10} (Aruoma et al., 1990)
$CH_3COO^{\cdot}$ $Cl_3COO^{\cdot}$	$< 5 \times 10^6$ 6.6×10^8 (Steenken et al., 1992)	2.5×10^6 3.7×10^8 (Simic, 1980; Davies et al., 1988)
$DPPH^{\cdot}$	4.9×10^2 (Rackova et al., 2004)	1.6×10^3 (Rackova et al., 2004)
$C_6H_6O^{\cdot}$	5.1×10^8 (Steenken et al., 1992)	4.1×10^8 (Davies et al., 1988)
$O_2^{\cdot -}$	7.5×10^2 (Kagan et al., 1993)	1.7×10^4 <0.1 (Nishikimi & Machlin, 1975; Bielski, 1982)
$^1O_2$	1.3×10^8 (Steenken et al., 1992)	pH6 3.5×10^8 (Nonell et al., 1995)

Table 1. Second-order rate constants of stobadine and trolox interaction with reactive oxygen species and 1,1`-diphenyl-2-picrylhydrazyl (DPPH) stable free radical.

Redox potential of stobadine (E = 0.58 V) (Steenken et al., 1992) is more positive than that of vitamin E (E = 0.48 V) (Neta & Steenken, 1982). Hence, at pH 7, the stobadine radical, formed as a consequence of stobadine free-radical-scavenging activity, may subtract proton from the trolox molecule resulting in regeneration of the parent stobadine molecule. Indeed, Steenken et al. (1992) in their pulse radiolytic study demonstrated the ability of trolox to recycle stobadine from its one-electron oxidation product, to give a corresponding trolox phenoxyl radical. When stobadine and trolox were present simultaneously in oxidatively stressed liposomes, trolox spared stobadine in the system in a dose-dependent manner (Rackova et al., 2002). Direct interaction of trolox with the stobadinyl radical resulting in the recovery of parent stobadine molecule appears to be a plausible mechanism. Thus, under physiological conditions, the antioxidant activity of stobadine may be potentiated by vitamin E. In a good agreement with this idea, Horakova et al. (1992) showed that the antioxidant action of stobadine was profoundly diminished in tocopherol-deficient rat liver microsomes.

Analogically, in biological systems, vitamin E (E = 0.48 V) can be regenerated from its phenoxyl radical via the interaction with ascorbate (Davies et al., 1988), which possesses a more negative redox potential (E = 0.30 V) (Neta & Steenken, 1982); depicted in Figure 1B. In a similar way, the stobadinyl radical was shown to be quenched by ascorbate, as demonstrated by the increased magnitude of the ascorbyl radical ESR signal generated in the presence of stobadine in the system of lipoxygenase + arachidonate (Kagan et al., 1993). Hence, one may expect that in biological systems, the antioxidant potency of both

trolox and stobadine may be modulated by their mutual interactions with other lipid- or water-soluble antioxidants.

2.3 Antioxidant efficacies in various assay systems

In a homogeneous system, antioxidant activity stems from an intrinsic chemical reactivity towards radicals. In membranes, however, the reactivity may differ as there are additional factors involved, such as a relative location of the antioxidant and radicals, ruled predominantly by their distribution ratios between water and lipid compartments. As already mentioned, a notably lower distribution ratio of trolox compared to that of stobadine may account for their different efficacies in systems involving lipid interface (membranes) in comparison to homogenous units (true solutions).

In the ethanolic solution, trolox scavenged 1,1`-diphenyl-2-picrylhydrazyl (DPPH) radical more efficiently than did stobadine, based on the initial velocity measurements (Rackova et al., 2002). The finding was corroborated by the respective rate constants (Rackova et al., 2004) as shown in Table 2.

In the models of oxidative damage comprising soluble proteins in buffer solutions, the water-soluble antioxidants stobadine and trolox have free access both to free radical initiator and to protein-derived radicals. Stobadine inhibited the process of albumin cross-linking due to the oxidative modifications induced by the Fenton reaction system of Fe^{2+}/EDTA/H_2O_2/ascorbate less effectively than did trolox (Kyselova et al., 2003). The experimental IC_{50} values correlated well with the reciprocal values of the corresponding second order rate constants for scavenging OH radicals.

Trolox, in comparison with stobadine, was found to be a more potent inhibitor of 2,2'-azobis-2-amidinopropane (AAPH)-induced precipitation of the soluble eye lens proteins (Stefek et al., 2005). In contrary, production of free carbonyls due to protein oxidation was more efficiently inhibited by stobadine. Both stobadine and trolox showed comparable efficacies in an experimental glycation model in preventing glycation-related fluorescence changes of bovine serum albumin as well as in lowering the yield of 2,4-dinitrophenylhydrazine-reactive carbonyls as markers of glyco-oxidation (Table 2) (Stefek et al., 1999).

On the other hand, trolox was found to be much less effective in inhibiting AAPH-induced peroxidation of di-oleoyl-phosphatidylcholine (DOPC) liposomes with respect to stobadine (Rackova et al., 2004; Rackova et al., 2006; Stefek et al., 2008), as exemplified by the respective IC_{50} values 25.3 and 93.5 μM, shown in Table 2. Stobadine, in comparison with trolox, more effectively prolonged the lag phase of Cu^{2+}-induced low-density lipoprotein (LDL) oxidation measured by diene formation (Horakova et al., 1996). The same pattern of efficacy in prevention of the lipid oxidation boost was shown in the system of tissue homogenate. Stobadine showed a more potent inhibitory effect than trolox on lipid peroxidation in rat brain homogenates exposed to Fe^{2+}/ascorbate as documented by thiobarbituric acid reactive substances (TBARS) levels (Table 2; Horakova et al., 2000). Interestingly, in the case of alloxan-induced lipid peroxidation of heat denaturized rat liver microsomes, the inhibitory efficacy of stobadine and trolox was comparable (Stefek & Trnkova, 1996). This finding may indicate that the critical competition of the scavengers with the alloxan-derived initiating reactive oxygen species takes place outside the membrane in the bulk solution.

Assay system		Parameter measured	Stobadine	Trolox
AAPH induced LPO in DOPC liposomes (Rackova et al., 2002)		IC_{50} (μmol/L)	25.3 ± 14.6	93.5 ± 8.5
BSA cross-linking induced Fe^{2+}/EDTA/H_2O_2/ascorbate (Kyselova et al., 2003)		IC_{50} (μmol/L)	0.65 ± 0.08	0.13 ± 0.02
AAPH-induced oxidative modification of soluble eye lens proteins (Stefek et al., 2005)	Inhibition of protein precipitation	IC_{50} (μmol/L)	121 ± 15	79 ± 8
	Inhibition of protein oxidation		44 ± 8	131 ± 20
Oxidative modification of BSA in an experimental glycation model (Stefek et al., 1999)	Glucose attachment into the molecule of BSA	Amadori product (with respect to 8.2 ± 0.4 nmol/mg BSA for control without inhibitor)	8.1 ± 0.5 (0.25 mmol/L)	7.4 ± 0.7 (0.25 mmol/L)
	Glycation-induced fluorescence changes of BSA	Relative fluorescence (with respect to 11.2 ± 0.7 nmol/mg BSA for control without inhibitor)	7.9 ± 0.7 (0.25 mmol/L)	6.5 ± 0.4 (0.25 mmol/L)
	Formation of DNPH-reactive carbonyl groups in BSA	Carbonyl groups (with respect to 5.6 ± 0.4 nmol/mg BSA for control without inhibitor)	3.4 ± 0.5 (0.25 mmol/L)	3.3 ± 0.2 (0.25 mmol/L)
Cu^{2+}-mediated oxidation of LDL (Horakova et al., 1996)		Δt_{lag} (min) (The increase in lag time given by one stobadine molecule per single LDL particle)	1.5	0.38
Fe^{2+}/ascorbate induced oxidative damage of rat brain homogenate (Horakova et al., 2000)	Inhibition of TBARS production	IC_{50} (μmol/L)	35	98

Assay system	Parameter measured	Stobadine	Trolox
AAPH-induced haemolysis of rat erythrocytes (Juskova et al., 2010)	t_{lag} (min) (88.6 ± 2.2 for control erythrocytes)	> 300 (100 μmol/L)	144 (100 μmol/L)

LPO, lipid peroxidation; DOPC, dioleoyl phosphatidylcholine; BSA, bovine serum albumin; AAPH, 2,2`-azobis (2-amidinopropane)hydrochloride; DNPH, dinitrophenylhydrazine; TBARS, thiobarbituric acid reactive substances.

Table 2. Summary of antioxidant and protective efficacies of stobadine and trolox in experimental models of oxidative damage.

In the cellular system of intact erythrocytes exposed to peroxyl radicals generated by thermal degradation of the azoinitiator AAPH in vitro, stobadine, in comparison to trolox, protected more powerfully erythrocytes from haemolysis, as shown (Table 2) by the respective lag phase prolongations (Juskova et al., 2010). In another cellular model, stobadine increased the viability of hydrogen-peroxide treated PC12 cells more effectively than did trolox, while both compounds reduced the content of malondialdehyde with a comparable efficiency (Horakova et al., 2003).

3. Conclusion

On balance then, the present paper, by summarizing the current data on both trolox and stobadine, underscores the structural and physicochemical differences between the two compounds as respective representatives of phenolic- and indole-type antioxidants. The structural variance explains their different mechanisms of antioxidant action and variable efficacies in the range of assay systems studied. Considering a plethora of studies reported on stobadine antioxidant action, physicochemical properties, and on a variety of its other biological activities, stobadine may represent a pertinent indole-type reference antioxidant. Hence, in studies of indole compounds, stobadine antioxidant standard may be utilized as a more relevant alternative to structurally diverse trolox.

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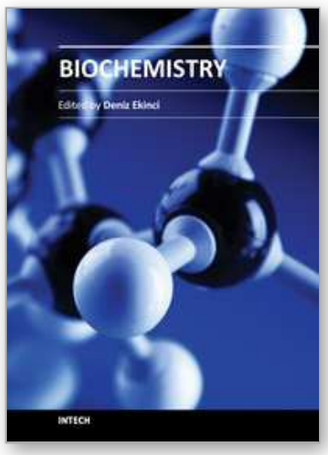

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