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Inhibition of plasma lipid oxidation induced by peroxyl radicals, peroxynitrite, hypochlorite, 15-lipoxygenase, and singlet oxygen by clinical drugs

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ABSTRACT

With increasing evidence showing the involvement of oxidative stress in the pathogenesis of various diseases, the effects of clinical drugs possessing antioxidant functions have received much attention. The unregulated oxidative modification of biological molecules leading to diseases is mediated by multiple oxidants including free radicals, peroxynitrite, hypochlorite, lipoxygenase, and singlet oxygen. The capacity of antioxidants to scavenge or quench oxidants depends on the nature of oxidants. In the present study, the antioxidant effects of several clinical drugs against plasma lipid oxidation induced by the aforementioned five kinds of oxidants were investigated from the production of lipid hydroperoxides, which have been implicated in the pathogenesis of various diseases. Troglitazone acted as a potent peroxyl radical scavenger, whereas probucol and edaravone showed only moderate reactivity and carvedilol, pentoxifylline, and ebselen did not act as radical scavenger. Probucol and edaravone suppressed plasma oxidation mediated by peroxynitrite and hypochlorite. Troglitazone and edaravone inhibited 15-lipoxygenase mediated plasma lipid oxidation, the IC_{50} being 20 and 34 μM respectively. None of the drugs used in this study suppressed plasma lipid oxidation by singlet oxygen. This study shows that the antioxidant effects of drugs depend on the nature of oxidants and that antioxidants against multiple oxidants are required to cope with oxidative stress in vivo.

The unregulated oxidative modification of biological molecules induced by reactive oxygen and related species (ROS) has been implicated in the pathogenesis of various diseases including cardiovascular diseases, neurodegenerative diseases, liver diseases, and cancer.[1] This attracted much attention to the role and effects of antioxidants in the maintenance of health and prevention and treatment of diseases. In fact, many pharmacological drugs possessing antioxidant functions have been developed and some are actually used clinically.

It is now widely accepted that the biological functions and effects of ROS and antioxidants are multifactorial. ROS may act as physiologically essential signaling molecules and also as self-defense agents, but on the other hand some ROS may react randomly with proteins, lipids, and nucleic acids giving rise to their irreversible modification and pathological effects. The capacity of pharmaceutical drugs as antioxidant has been the subject of extensive studies.[2] Multiple ROS with different reactivity and specificity may contribute to oxidative stress in vivo and importantly the effects of antioxidants depend on the nature of ROS.

Antioxidant action may be accomplished by several ways including scavenging or quenching of reactive oxidants, reduction of hydrogen peroxide and hydroperoxides, sequestration of metal ions, and induction of antioxidant compounds and enzymes. Vitamin E inhibits lipid peroxidation by scavenging lipid peroxyl radicals which act as chain carrying species.[3] Numerous large scale randomized clinical trials assessing the effect of vitamin E supplementation on cardiovascular protection have been carried out over the past 15 years but they failed to show consistent clinical data supporting beneficial role for vitamin E supplementation.[4,5] A number of possible reasons may be considered including choice of subjects, antioxidants, and dosage, timing and duration of supplementation. Furthermore, the importance of proper patient selection in gaining therapeutic benefit has been pointed out. However, it may be noted that relatively less attention has been paid to the antioxidant effects on different oxidants.

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It has been reported that many clinical drugs may function as antioxidant, including probucol (4,4′-[propane-2,2-diylbis(thio)]bis (2,6-di-*tert*-butylphenol)), carvedilol (3-(9-carbazol-4-yloxy)-2-hydroxypropyl)[2-(2-methoxyphenoxy)ethyl]amine), pentoxifylline (3,7-Dimethyl-1-(5-oxohexyl)-3,7-dihydro-1*H*-purine-2,6-dione, PTX), troglitazone (5-(4-[(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy]benzyl)thiazolidine-2,4-dione), ebselen (2-phenyl-1,2-benzoselenazol-3-one), and edaravone (5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one) (Scheme 1).

Probucol is a drug with lipid-lowering and antioxidant capacity that has been used for prevention and treatment of atherosclerotic cardiovascular diseases and xanthoma.[6] The antioxidant action of probucol, especially against LDL oxidation, has been studied extensively.[7] Probucol enhances plasma cholesteryl ester transfer protein activity and hepatic scavenger receptor class B type I, causing a decrease in HDL-C. It also accelerates the antioxidative function of HDL via increase in paraoxonase 1 activity.

Carvedilol is an adrenoreceptor blocker drug with antioxidant and antiproliferative effects.[8] The action of carvedilol as an antioxidant against lipid peroxidation in vitro has been reported in several reports, but it has been found that the capacity of carvedilol to scavenge oxygen radicals is low and that it acts as antioxidant primarily by chelating ferric ion.[9–11]

PTX, antitumor necrosis factor agent, is a drug used for treatment of several diseases including liver diseases and diabetic kidney diseases. Several papers reported antioxidant capacity of PTX.[12] Recent randomized controlled trial showed that the therapy with PTX improved histological features of non-alcoholic steatohepatitis (NASH) and overall nonalcoholic fatty liver disease (NALFD) activity score and that PTX therapy was associated with significant decreases in lipid peroxidation products.[13,14] It was also reported that PTX protected HDL from oxidative modification induced by polymorphonuclear neutrophils (PMNs) which impairs the ability of HDL to remove cholesterol from cells.[15]

Troglitazone, a member of thiazolidinedione family, was developed for the treatment of type 2 diabetes mellitus, but was subsequently withdrawn because of concerns about hepatotoxicity.[16] Troglitazone acts as PPARγ agonists and its derivatives having higher activity but less toxicity are still being investigated. It contains chromanol moiety like α-tocopherol and inhibits in vitro oxidation of LDL.[17]

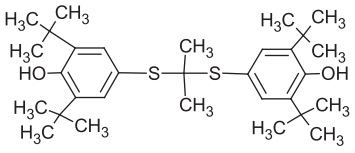
Ebselen is a selenium containing compound with anti-inflammatory, antioxidant and cytoprotective activity.[18] It acts as a mimic of glutathione peroxidase but it is not a potent scavenger of lipid peroxyl radical.[19]

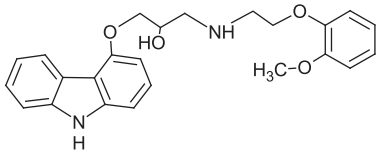
Edaravone is a drug approved for treatment of acute cerebral infarction and further for amyotrophic lateral sclerosis (ALS) in Japan.[20] It has been reported to act as a potent free radical scavenger,[21] although it has not been clearly shown quantitatively how potent to which free radicals.

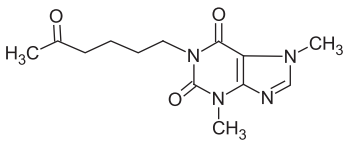
The oxidation of biological molecules in vivo is mediated by multiple oxidants with different reactivity and selectivity and proceeds by diverse mechanisms. In fact, higher levels of lipid oxidation products mediated by multiple oxidants have been found in human atherosclerotic tissues than in normal tissues.[22,23] Importantly, the effects of antioxidants depend on the nature of oxidants and furthermore the capacity to scavenge reactive oxidants does not always correlate linearly with that to inhibit oxidation of biological molecules.[23,24] It is imperative to assess the capacity of antioxidants to inhibit oxidation induced by multiple oxidants as well as the capacity to scavenge oxidants.

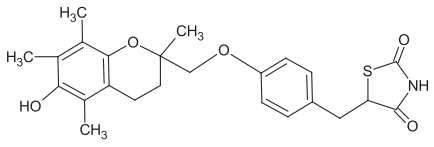
The objective of this study is to assess the capacity of the aforementioned six kinds of clinical drugs to inhibit plasma lipid oxidation induced by biologically relevant multiple oxidants including peroxyl radicals, peroxynitrite, hypochlorite, 15-LOX, and singlet oxygen, all of which produce lipid hydroperoxides as primary products.

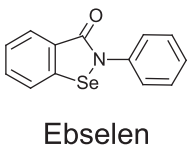
Peroxyl radicals are important chain-carrying species in lipid peroxidation.[25] Peroxynitrite is produced in vivo by a rapid combination of two free radicals, superoxide and nitric oxide, the rate constant being around $10^{10}\ M^{-1}\ s^{-1}$.[26] Hypochlorite is produced in vivo in response to xenobiotics at the site of inflammation and acts as one of the major oxidants in vivo.[27,28] 15-LOX plays an important role in several inflammatory diseases such as asthma, inflammation, and chronic bronchitis and LOX inhibitors are being exploited as a therapeutic target. Singlet oxygen is a non-radical oxidant which plays an important role especially in photooxidation of skin and eye.[29]

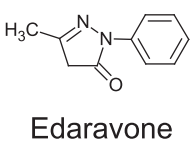












Scheme 1. Chemical structure of the drugs used in this study.