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REVIEWS

Main Methods and Approaches to the Determination of Markers of Oxidative Stress—Organic Peroxide Compounds and Hydrogen Peroxide

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Abstract—A review of publications, mainly for the last 15 years, characterizing the advantages, limitations, and prospects for the development of modern methods and approaches to the determination of organic hydroperoxides and hydrogen peroxide, which are the most important markers of the oxidative stress level in living organisms.

Keywords: oxidative stress, lipid peroxidation, hydroperoxides, determination, biological fluids

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Currently, both domestic and foreign scientists are paying attention to the diagnosis of oxidative stress (OS): in the past decade alone, about 40000 review articles have been published on oxidative stress. These publications can be divided into research articles; those devoted to the revelation and study of biochemical mechanisms of oxidative stress [1–4]; works on the effect of oxidative stress on the development of neurodegenerative, cardiovascular, and endocrine diseases [1, 2, 5, 6]; and analytical reviews representing the main methods for determining indicators and markers of oxidative stress, namely, methods for recording reactive oxygen species (ROS), oxidative damage of biomolecules, and the concentration and activity of antioxidants [7–10].

Oxidative stress is the imbalance between the formation of reactive oxygen species and the antioxidant defense of a body with the formation of free radicals [11]. The primary "tool" or driving force of oxidative stress is provided by reactive oxygen species. The most important of them are superoxide radical ($O_2^{\bullet-}$), singlet oxygen ($^1O_2$), hydroxyl ($^\bullet OH$) and peroxide ($^\bullet HO_2$) radicals, hydrogen peroxide (H_2O_2), peroxide ion (HO_2^-), and hypochlorite ion (OCl^-) [12]. Reactive oxygen species and other free radicals form in living organisms by means of a normal aerobic cellular metabolism and under the action of environmental factors, ultraviolet radiation, ionizing radiation, or cigarette smoke [13, 14]. Excessive formation of free radicals enhances lipid peroxidation (LPO), causing multicellular and multitissue damage due to the accumulation of oxidized products in the cells and tissues (Schiff bases, diene conjugates, malonic dialdehyde, etc.) [15]. The process of lipid peroxidation is deeply and comprehensively investigated in terms of the mechanisms, dynamics, determination of oxidation products, and their participation in diseases. Lipid peroxidation plays an essential role in the pathogenesis of many diseases, including cancer, Parkinson's and Alzheimer's diseases, atherosclerosis, hypertension, ischemia, diabetes mellitus, and idiopathic pulmonary fibrosis [16–18]. Therefore, it is vital to develop methods for determining oxidative stress at the early stages of its development, until it led to severe changes in the body. The diagnosis of oxidative stress in clinical performance in the analysis of biological fluids should be rapid (analysis duration should not exceed 15–30 min), accurate, and simple.

This review considers known methods for determining both the main primary products of peroxide oxidation (organic hydroperoxides) and hydrogen peroxide as a central redox signaling molecule in physiological oxidative stress [19] in living organisms. Their advantages and limitations are discussed, as well as prospects for the development of modern methods and approaches to the determination of organic hydroperoxides and hydrogen peroxide in matrices of complex composition, such as biological fluids, tissues, etc.

ROLE OF ORGANIC PEROXIDES AND HYDROGEN PEROXIDE IN LIVING ORGANISMS

Hydroperoxides are essential products of the oxidation of organic substances by molecular oxygen or hydrogen peroxide. They form in almost all foods and living organisms by a free radical chain reaction in the oxidation of organic substances with molecular oxygen. Metabolic products of lipid peroxidation can accumulate in tissues and body fluids if the antioxidant system does not have time to dispose of them at the necessary rate. This accumulation results in the disruption of the ion transport through the cell membrane, which can affect the ionic composition of the liquid part of blood and the rate of polarization and depolarization of the membranes of muscle cells. For example, this can disrupt the conductivity of nerve impulses and their contractility, increase the refractory period (the period of time after the appearance of the action potential on the excitable membrane, during which the excitability of the membrane decreases, and then gradually restored to the initial level), lead to the ingress of fluid into the extracellular space, causing swelling, thickening of the blood, and electrolyte imbalance in cells and tissues.

Changes in the structure of tissues as a result of lipid peroxidation can be observed on the skin: the number of age spots on the skin increases with age, especially on the dorsal surface of the palms. This pigment, called lipofuscin, is a mixture of lipids and proteins, interconnected by cross-covalent bonds and denatured as a result of interaction with chemically active groups of lipid peroxidation products. It is not hydrolyzed by lysosome enzymes and, therefore, accumulates in the cells, disrupting their functions [20].

It was previously noted that, in living organisms, lipid hydroperoxides play an important role in the development of various cardiovascular diseases and pathologies of the central nervous system (Alzheimer's and Parkinson's disease, stroke, etc.). A clear understanding of the mechanisms associated with the lipid metabolism and cell death/proliferation is essential for the pathogenesis and prevention of cancer. Brazilian scientists [21] showed that overeating meat and high-fat foods causes an increase in linoleic acid hydroperoxide and hemoglobin in the large intestine. In turn, the interaction of hemoglobin heme with lipid hydroperoxides contributes to genome instability and causes the development of a carcinogenic process that can lead to the development of colon cancer.

The oxidation of lipids in biological systems proceeds by a chain reaction, consisting of three stages: initiation of a chain reaction, its continuation, and termination (or completion). Organic hydroperoxides (primary LPO products) form at the stage of distribution (chain development) of lipid peroxidation. A hydroperoxide group may attach to various lipid structures, for example, fatty acids, triacylglycerols, phospholipids, or sterols. At the stage of initiation of the process of lipid peroxidation, the following transformations occur.

(1) A free oxygen radical (initiator, predominantly in the $^{\bullet}OH$ form) interacts with polyunsaturated fatty acids (LH) in the initiation stage.

(2) When the initiating radical attacks the diallyl carbon atom, on which the radical center formed, free radical oxidation is actively occurring. Acid (LH) is isomerized to form a more thermodynamically stable conjugated diene before reacting with molecular oxygen. Thus, an alkyl radical ($L^{\bullet}$) forms from the fatty acid.

At the stage of the continuation of the chain process, the following reactions take place.

(3) Oxygen molecule O_2 is attached to the alkyl radical ($L^{\bullet}$), resulting in the formation of a peroxide radical ($LOO^{\bullet}$).

(4) Peroxide radicals ($LOO^{\bullet}$) cleave a hydrogen atom from nearby molecules; it may be other polyunsaturated fatty acids, proteins, or nucleic acids, resulting in the formation of lipid hydroperoxides (LOOH) (Fig. 1).

Antioxidants, such as α-tocopherol and vitamin E, are donors of hydrogen atoms. Their interaction with peroxide radicals $LOO^{\bullet}$ also leads to the formation of lipid hydroperoxides (LOOH) and relatively inert α-tocopherol phenoxy radicals. In the absence of antioxidants, peroxide radicals $LOO^{\bullet}$ can cleave a hydrogen atom from another lipid molecule (LH), producing a highly active alkyl radical ($L^{\bullet}$), which then continues another chain reaction

(5) Lipid hydroperoxide (LOOH) is capable of intramolecular rearrangement and spontaneous decomposition into alkoxy ($LO^{\bullet}$) and hydroxyl ($^{\bullet}OH$) radicals. If lipid peroxidation is catalyzed by metals with variable valence (iron or copper), the decomposition of lipid hydroperoxides (LOOH) is accompanied by the formation of alkoxy ($LO^{\bullet}$) and peroxide ($LOO^{\bullet}$) radicals, as well as hydroxyl ions and hydrogen. All of these radicals, in interacting with other fatty acids (LH), can initiate new radical chain reactions. In addition, LOOH reacts again with O_2, which leads to the formation of numerous secondary derivatives, for example, cyclic peroxides, prostaglandin-like bicycloendoperoxides, multihydroxyl derivatives, etc.

(6) The alkoxy radical ($LO^{\bullet}$), under the continued free radical attack, can decay to form aldehydes and alkyl radicals. The process of lipid peroxidation is completed by the formation of oxygen bridges or C–C bonds between alkyl ($L^{\bullet}$), alkoxy ($LO^{\bullet}$), and peroxide ($LOO^{\bullet}$) radicals [1, 9, 23, 24].

The degree of oxidative stress can be assessed by the concentration of the participants or products of the reaction of lipid peroxidation, that is, oxidative stress

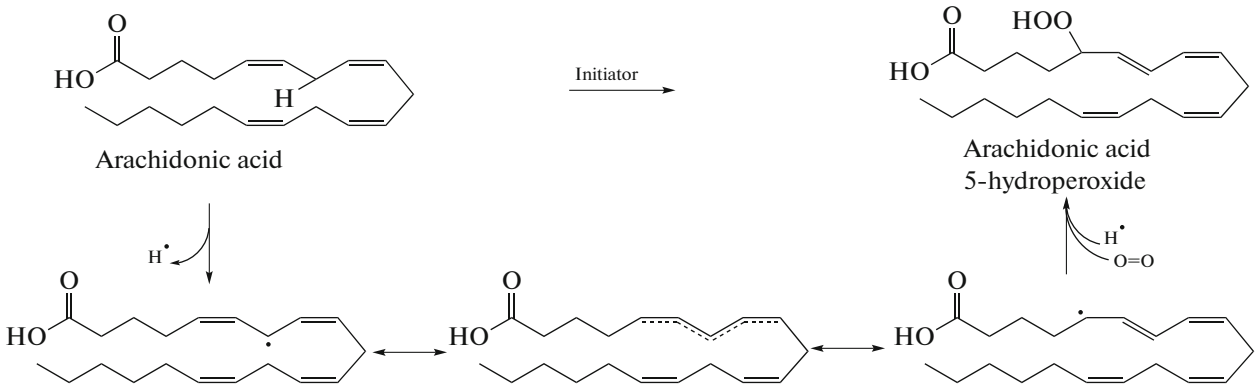


Fig. 1. General mechanism of peroxidation of unsaturated fatty acids by the example of arachidonic acid [22].

markers. Of all the oxidation products, lipid hydroperoxides are of the most significant interest because, on the one hand, they form as a result of lipid oxidation and can serve as markers of oxidative lipid stress and, on the other hand, they are actively involved in peroxide oxidation in the chain branching reaction [25].

Hydrogen peroxide belongs to active forms of oxygen, as well as chemically active molecules, which form during the incomplete reduction of molecular oxygen and are usually considered as undesirable byproducts of aerobic respiration, causing oxidative stress. Hydrogen peroxide is involved in the regulation of signaling enzymes and transcription factors. The totality of data accumulated to date indicates that hydrogen peroxide satisfies most of the criteria for secondary intermediaries. It plays an important role in cell proliferation, differentiation, migration, and apoptosis [26].

In contrast to free radicals (highly reactive and chemically unstable), lipid hydroperoxides and hydrogen peroxide are relatively stable under moderate reaction conditions, such as low temperature and the absence of metal ions and are informative markers. Using their concentration, one can assess the degree of oxidative stress [27], carry out the early diagnosis of various socially significant diseases to determine the severity of the pathological process, identify indirectly associated diseases, and monitor the effectiveness of the sophisticated medical, rehabilitative, preventive, and curative measures.

METHODS FOR DETERMINING ORGANIC HYDROPEROXIDES AND HYDROGEN PEROXIDE

Methods for the determination of organic peroxides were significantly less covered in publications [28, 29] than methods for the determination of hydrogen peroxide (Fig. 2), and the information on the concentration of organic hydroperoxides in the same biological samples is very different. For example, the concentrations of organic hydroperoxides in the plasma of a healthy person can vary from *n* pM to 4.5 μM. This difference can be explained by differences in the methods of sample preparation, or storage, or analysis techniques [30, 31]. Currently, there is no single universal quantitative characteristic of oxidative stress, and to estimate it, the total peroxide concentration is often converted into the concentration of cumene peroxide or *tert*-butyl hydroperoxide. A characteristic feature of methods for the determination of hydroperoxides is a poor solubility of many organic peroxides in water and, consequently, the need to determine them in organic or aqueous–organic media.

Estimation of peroxide value by iodometric titration is a conventional method for the determination of hydroperoxides [32, 33]. This method is insensitive and nonspecific. The main errors in iodometry result from the loss of iodine due to its volatility, oxidation of iodide ions by atmospheric oxygen, interfering effect of substances inducing the oxidation of iodide (Cu^{2+}, NO_3^-, NO, etc.) in an alkaline medium, adsorption of iodine molecules, the order of mixing solutions, and under the effect of other conditions of reactions. The main disadvantage of iodometric titration in the determination of lipid hydroperoxides in biological samples is the relatively high limit of detection and, as a result,

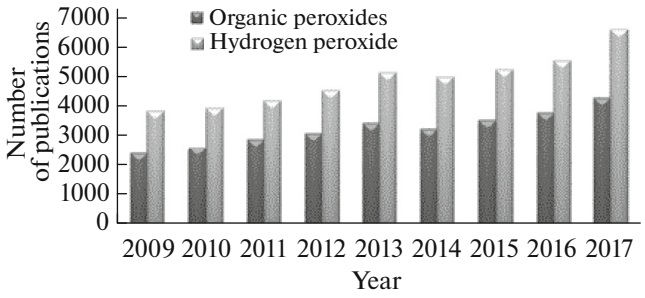


Fig. 2. Comparative chart of publications devoted to methods for the determination of organic peroxides and hydrogen peroxide.

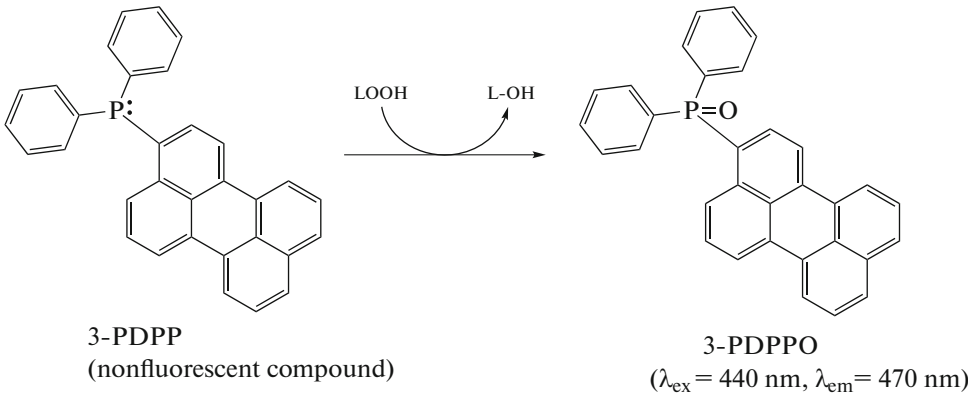


Fig. 3. Oxidation of 3-perylene diphenylphosphine by cumene peroxide [41].

a significant weight of the test sample. An advantage of titration is a possibility of using nonaqueous solvents.

Spectrophotometry with the formation of nonferrous metal complexes is used to determine protein hydroperoxides and lipid hydroperoxides [34–37]. Similar techniques are based on the oxidation of iron(II) ions by hydroperoxides in the presence of, for example, Xylenol Orange, with the formation of an iron(III)–chromophore complex, which strongly absorbs in the wavelength region 540–600 nm,

$$ROOH + Fe^{2+} = Fe^{3+} + RO^{\cdot} + OH^{-},$$

$$Fe^{3+} + XO = Fe - XO.$$

The total concentration of hydroperoxides in the blood plasma of healthy people and patients with type 2 diabetes, renal failure, and hypercholesterolemia was determined using this procedure [38].

Despite the simplicity and rapidness of this method, its disadvantage is the interfering effect of various compounds on the determination of hydroperoxides. For example, the addition of 0.3–5 mM ascorbic acid to the reaction mixture decreases the absorption of the resulting indicator complex compound. EDTA and other chelating agents used as anticoagulants in the preparation of blood samples also interfere with the determination of hydroperoxides [39]. In addition, the method is not specific to lipid peroxide compounds because many other compounds capable of oxidizing iron(II) ions also give a signal.

Fluorimetric determination of hydroperoxides. A more specific and sensitive method for determining lipid hydroperoxides in biological fluids is the fluorescence method. With the proper selection of the fluorophore, one can create analytical procedures with low limits of detection or conduct sufficiently comprehensive studies of biochemical interactions.

Fluorescence reagents, such as diphenyl-1-pyrenylphosphine (DPP) and 3-perylenediphenylphosphine (3-PDPP) [40, 41], are most often used to determine the total concentration of lipid hydroperoxides in model liposome or plasma systems. The method is based on a specific oxidation reaction with DPP and 3-PDPP hydroperoxides. The fluorescence intensity of the resulting oxides linearly increases with the concentration of hydroperoxides. The reaction of the oxidation of 3-PDPP is shown in Fig. 3. This approach enables determining lipid hydroperoxides at the level of nanomolar concentrations. For example, in using DPP, the limits of detection and the lower limit of the analytical range of cumene hydroperoxide were 0.08 and 0.25 nmol equivalents in 40 μL of plasma, respectively. EDTA and 2,6-di-*tert*-butyl-4-methylphenol were used to eliminate matrix effect in the analysis. Transition metals can decompose hydroperoxides in the plasma into radicals, while EDTA protects hydroperoxides from decomposition due to the binding of metals into a complex.

This approach is one of the most common; it is used not only for monitoring lipid peroxidation in cell membranes in the presence of DPP or 3-PDPP as fluorescent reagents [42–44], but also for postcolumn detection in HPLC [45–47]. A disadvantage of these indicator systems is that the excitation and emission wavelengths lie in the shortwave region (excitation wavelength λ_{ex} = 353 nm and emission wavelength λ_{em} = 380 nm in the case of DPP) or differ only slightly (λ_{ex} = 440, λ_{em} = 470 nm in the case of 3-PDPP); therefore, in determining hydroperoxides, the intrinsic fluorescence of biomatrix interferes.

A fluorescence method was proposed for determining not only organic peroxides (benzoyl peroxide and acetone peroxide) but also hydrogen peroxide [48]. The fluorophore was obtained by the reaction of oxidative deboronation: a solution of zinc acetate in methanol was added to the prochelator solution. The reaction is schematically shown in Fig. 4. When hydrogen peroxide is added to the mixture, fluorescence intensity at λ_{em} = 440 nm significantly increases. The limits of detection of hydrogen peroxide and organic peroxides are below 10 nM.

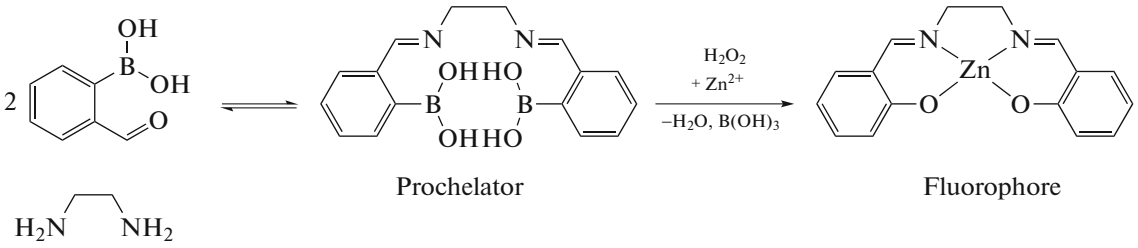


Fig. 4. Formation of a fluorophore with Zn(Salen) oxidative deboronation [48].

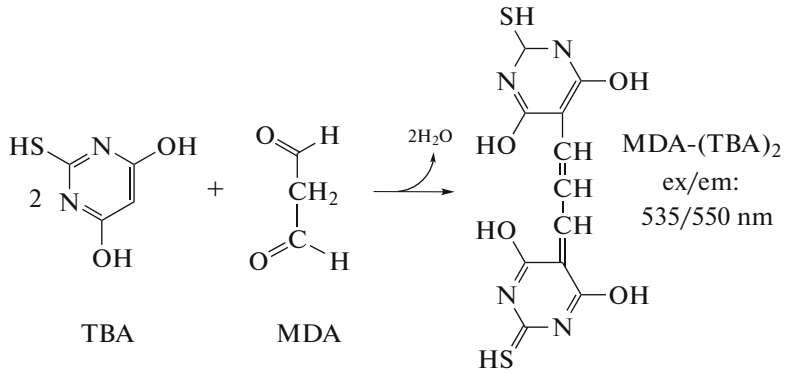


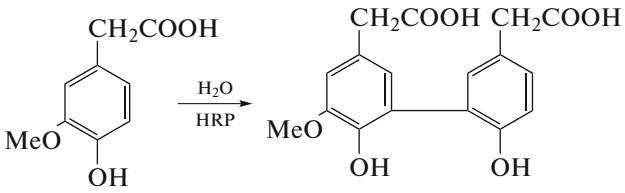
Fig. 5. Reaction for the determination of hydroperoxides with malonic dialdehyde [52].

In the determination of hydroperoxides in biological materials, the reaction with thiobarbituric acid (TBA) is widely used [49–51]. The TBA test is based on the capability of TBA of reacting with malonic dialdehyde (MDA), that is an intermediate product of the enzymatic oxidation of arachidonic acid and the final product of oxidative lipid degradation. In [52], MDA was determined in plasma by a fluorimetric reaction with a TBA, which at high temperature and low pH proceeds with the formation of a trimethine complex ($\lambda_{ex/em}$ = 535/550 nm) containing one molecule of MDA and two molecules of TBA (Fig. 5). The limit of detection of free and protein-bound malonic dialdehyde was 300 nM.

A disadvantage of this method consists in its nonspecificity. The results of the determination of the primary products of the LPO can contain errors, because the products of DNA decomposition during its oxidative damage and, possibly, other nonlipid molecules can be a source of MDA. TBA at high temperature and low pH can also react with some aldehydes, deoxy sugars, sialic acids, and glycosylated proteins. The TBA test gives information only about the presence of substances that react with TBA rather than about their composition and nature [53].

Fluorimetric determination of hydrogen peroxide. It is known that hydrogen peroxide plays a vital role in a human body. It participates in the metabolism of proteins, carbohydrates, fats, vitamins, and mineral salts, supports immune protection, and promotes the transport of sugar from blood plasma into the cells of the body. However, some questions about the participation of hydrogen peroxide in various processes have no answer, for example, why and at what point in the functioning of the cell does the transition from the normal synthesis of signal H_2O_2 to oxidative stress occur? What is the role of H_2O_2 in intracellular signaling? It is still unclear how much hydrogen peroxide accumulated in the cell causes adverse changes, and how much of it is necessary for the normal functioning of the body. Sensitive, selective, and rapid methods for determining hydrogen peroxide in biological fluids are needed to answer these questions. The data on the concentration of hydrogen peroxide in the blood plasma are ambiguous. For example, Forman et al. [54] consider 1–5 μM of H_2O_2 its normal concentrations. In other papers [55, 56], hydrogen peroxide levels in nanomole or micromole scale are reported.

A fluorometric procedure for the determination of hydrogen peroxide and other reactive oxygen species was proposed in [57]. It is based on the reaction between H_2O_2, cobalt(II), and fluorescein hydrazide in a micellar medium. The analytical range and the limit of detection for hydrogen peroxide were 2.1–460 and 0.7 ng/mL, respectively, at an emission wavelength of 527 nm (λ_{ex} = 460 nm). The reaction was carried out by heating for 10–60 min at 80°C. The procedure was successfully tested in the analysis of human



Homovanillic acid Homovanillic acid dimer

Fig. 6. Formation of a fluorescent dimer of homovanillic acid after the oxidation with H_2O_2, catalyzed by horseradish peroxidase [59].

urine. Nakahara et al. [58] used a similar fluorescent reaction between hydrogen peroxide and fluorescein in the presence of cobalt(II). Fluorescence was recorded at λ_{em} = 525 nm (λ_{ex} = 500 nm). Hydrogen peroxide was determined by the standard addition method in several biological and environmental samples, namely, in the blood serum of the calf, human saliva, and rainwater. An advantage of the method is the absence of interference with inorganic ions, such as Cu(II), Mg, Zn, Ca, Fe(II), Mo(VI), Na, K, chloride, fluoride, bromide, cyanide, phosphate, ammonium, nitrate, sulfate, and ammonia, present in large quantities in the test samples, for the determination of H_2O_2.

For the fluorimetric determination of H_2O_2 in the crab muscle tissues, the peroxidase oxidation reaction of homovanillic acid was used [59]. The dimer of homovanillic acid formed in the reaction fluoresces at 425 nm (λ_{ex} = 315 nm); the reaction product is stable for 12 h (Fig. 6). In the analysis of biological samples, glacial trichloroacetic acid was used to precipitate the protein fraction, followed by neutralization with an excess of a K_2HPO_4 solution. By this method, hydrogen peroxide can be adequately determined in tissues without using internal standards or expensive reagents.

Analysis in a neutral medium is of particular importance for samples containing proteins, enzymes, or other biological material. A fluorescence indicator system was proposed for the determination of hydrogen peroxide and the antibiotic tetracycline, based on the formation of the Eu(III)–tetracycline–hydrogen peroxide complex [60]. The use of this indicator system is most effective in the pH range 6.9–7.4 in a 13 mM MOPS buffer solution. The described method was used to determine hydrogen peroxide and urea peroxide in human blood [61]. The determination of hydrogen peroxide does not interfere with alkali and alkaline earth metal ions in concentrations lower than 100 mM; however, many transition metals (Co^{2+}, Fe^{3+}, Zn^{2+}) quench the luminescence at a concentration of 0.1–1 mM, and Cu^{2+} affects the signal even at a concentration of <0.1 μM. The presence of phosphate ions (>1 μM) increases the luminescence signal; therefore phosphate buffer solutions cannot be used for analysis, and samples containing unknown amounts of phosphate cannot be analyzed directly [62].

Chemiluminescence determination of hydroperoxides and hydrogen peroxide. Lipid peroxidation is accompanied by chemiluminescence. Chemiluminescence procedures for the determination of hydroperoxides, characterized by high sensitivity, are very promising [63–65]. For example, to evaluate oxidative stress under clinical conditions, a procedure for the chemiluminescence determination of the total concentration of lipid hydroperoxides was developed, based on their oxidation in the presence of microperoxidase and an isoluminol chemiluminescence activator in a borate buffer solution with pH 10.0. The limit of detection of linoleic acid hydroperoxide is 16 nM. The procedure was used to determine lipid hydroperoxides in the lipoproteins of follicular fluid and plasma of patients undergoing extracorporeal fertilization [66].

A chemiluminescence procedure for determining lipid hydroperoxides in the system lipid substrate–iron(II)–coumarin C-525 (chemiluminescence activator) was developed [67]. Lipid hydroperoxides were determined by the standard addition method using *tert*-butyl hydroperoxide as a standard compound. The limit of detection for *tert*-butyl hydroperoxide was 164 nM. Despite the high sensitivity and selectivity, the method cannot be applied to determine the total concentration of hydroperoxides because endogenous compounds, such as ubiquinol and tocopherols, affect the intensity of chemiluminescence [68].

A procedure was proposed for determining benzoyl peroxide and *tert*-butyl peroxide by the reaction of the catalytic oxidation of luminol in a carbonate buffer solution with pH 9.9 containing TRIS by a peroxidase mimetic, that is, iron(III)–TAML (iron(III) complex with a tetraamido macrocyclic ligand), in various organic media [29]. The effect of four solvent (acetonitrile, dimethyl sulfoxide, ethanol, and isopropanol) on the chemiluminescence intensity and the catalytic activity of the iron(III)–TAML complex was studied. The lowest limits of detection of benzoyl peroxide (70–100 nM) and *tert*-butyl peroxide (3–90 μM) are achieved in the presence of ethanol.

Chromatographic methods for the determination of peroxides with fluorescence detection. As noted above,

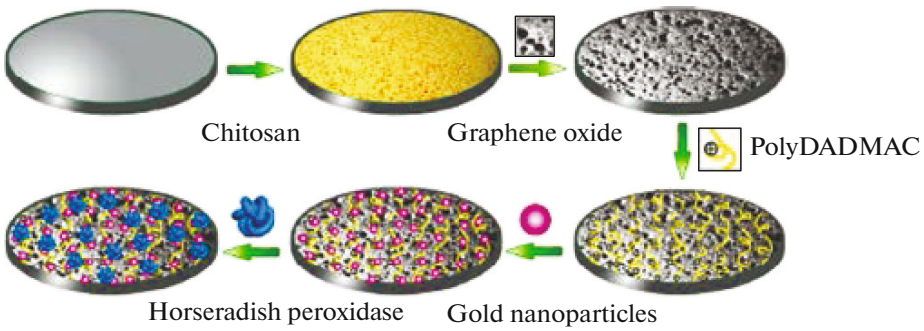


Fig. 7. Creation of an electrochemical biosensor [90].

an individual lipid hydroperoxide can be determined by chromatographic methods. Hui et al., in their work devoted to the determination of phosphatidylcholine hydroperoxide (the product of the primary oxidation of phospholipid contained in biomembranes) in plasma [69], used HPLC with chemiluminescence detection. Luminol was used as a chemiluminescent reagent for the postcolumn reaction, and a methanol–isopropanol mixture was used as a mobile phase. The linearity range for hydroperoxide was 10–100 pmol. In determining hydroperoxides in serum, Teselkin and Babenkova [70] used a method based on the recording of chemiluminescence that appeared in the interaction of hydroperoxides with a microperoxidase–isoluminol enzyme system. This indicator system in combination with HPLC enabled not only the separation of serum antioxidants (uric acid, ascorbic acid, albumin, bilirubin, etc.) from hydroperoxides and the elimination of their inhibitory effect on the isoluminol chemiluminescence but also the identification of the nature of lipid hydroperoxides. However, meeting the criteria of high sensitivity and specificity, this method is rather laborious, requires pre-extraction of lipids from serum, and suggests the use of sophisticated equipment. The serum apolipoproteins B of patients with type 2 diabetes were the object of the study. In the examined group of patients, the values of hydroperoxide levels were found to be in the range of 0.55–1.47 nmol/mg of protein.

A method was developed [71] for determining organic peroxides and hydrogen peroxide by HPLC with UV irradiation and subsequent peroxioxalate chemiluminescence detection. Organic peroxides (benzoyl peroxide, *tert*-butyl hydroperoxide, *tert*-butyl peroxybenzoate, cumene hydroperoxide) were subjected to UV irradiation (254 nm, 15 W) to obtain detectable hydrogen peroxide. Chromatographic separation of four organic peroxides and hydrogen peroxide was performed on a reversed-phase column under isocratic elution for 30 min. The limits of detection for hydrogen peroxide, benzoyl peroxide, *tert*-butyl hydroperoxide, *tert*-butyl peroxybenzoate, and cumene hydroperoxide were 1.1, 6.8, 31.3, 7.5, and 1.3 μM, respectively. This procedure was tested in the analysis of wheat flour. Individual cholesterol and triacylglycerol hydroperoxides in plasma were determined by HPLC followed by detection with diphenyl-1-pyrylphosphine; the limit of detection was 1 pmol [72]. To determine the amount of lipid hydroperoxides in the tissues of mice of different ages (20, 30, 40, 60, and 85 weeks), the fluorescence oxidation of 1-naphthyl diphenylphosphine to its oxide was carried out before chromatographic separation and determination [73, 74]. The level of lipid hydroperoxides in the organs and tissues of adult mice is almost twice the level of hydroperoxides in the organs of an immature mouse (at the age of 5 weeks). It is also found that ethanol enhances lipid peroxidation and increases the concentration of cholesterol hydroperoxides in the liver and muscles of rats [75].

HPLC methods with chemiluminescent and fluorescent detection [76–79] are used for the separation and individual determination of hydroperoxides in samples with a complex matrix. These methods have high sensitivity and selectivity, but they are not rapid enough, do not provide a complete picture of oxidative stress in vivo, and require qualified personnel and expensive equipment.

Electrochemical methods. All peroxides are electrochemically reducible and can be determined by electrochemical methods. Electrodes modified by Prussian Blue [80, 81], graphene oxide with Ag and Au nanoparticles, nanotubes, nanorods [82–84], and various polymers [85–87] and also electrodes with immobilized enzymes [88–90] are used for the electrochemical determination of lipid hydroperoxides and hydrogen peroxide. Most of the research articles and reviews are devoted to the electrochemical determination of hydrogen peroxide in various samples: food, cosmetic products, and disinfecting cleansers [91–94]. Some recent studies were devoted to the development of electrochemical sensors for determining hydrogen peroxide in biological fluids and cells [95–99]. For example, a biosensor modified by coenzyme A and gold(III) was developed [95] for the determination of H_2O_2 in human serum and urine and hydrogen peroxide released from human cervical cancer cells. Dutta et al. [98] determined hydrogen perox-

Table 1. Electrochemical sensors for the determination of hydrogen peroxide and organic peroxides (WE, a working electrode; mod., a modifier)

Analyte	Reaction conditions	Electrodes	Linear range, μM	c_{min}, μM	Reference
Hydrogen peroxide	0.1 M phosphate buffer solution, pH 7.0, $U = -0.4$ V, amperometric detection	WE: gold; mod.: peroxidase and silver nanotubes; stable for 1 month at 4°C	0.0048–0.31	0.0012	[104]
	0.1 M phosphate buffer solution, pH 7.4, cyclic voltammetry	WE: glassy carbon; mod.: graphene oxide and Prussian Blue	–	–	[105]
	0.1 M phosphate buffer solution, pH 7.4, cyclic voltammetry, or $U = -0.4$ V, amperometric detection	WE: glassy carbon, mod.: palladium nanoparticles or film, low stability (on the 10th day of storage, the signal drops by 71%)	10–1400, 1–1400	6.8, 0.3	[106]
	50 M phosphate buffer solution, pH 7.0, $U = -0.45$ V, amperometric detection	WE: glassy carbon; mod.: a film of Polymethylene Blue–flavin adenine dinucleotide copolymer, stable for 1 month in phosphate buffer solution	0.1–960	0.1	[107]
	$U = 0.05$ V, amperometric detection	WE: glassy carbon; mod.: Prussian Blue	0.01–10000	0.01	[108]
	0.1 M phosphate buffer solution, pH 6.0 (4.5), $U = -0.05$ V, amperometric detection	WE: graphite; mod.: peroxidase of horseradish/palm tree/sweet potato	1–700 (1–1000)/ 10–400 (10–200)/ 10–200 (10–200)	–	[109]
tert-Butyl hydroperoxide	0.1 M phosphate buffer solution, pH 8.0, $U = -0.4$ V, amperometric detection	WE: glassy carbon; mod.: cobalt phthalocyanine, stable for 1 month at 4°C	26–4800	5	[110]
Cumene peroxide, 2-butanone peroxide, *tert*-butyl hydroperoxide	0.05 M phosphate buffer solution, pH 8.5, $U = -0.70$ V, amperometric detection	WE: platinum; mod.: peroxidase and poly(vinylferrocene), stable for 5 days at 20°C	100–600, 25–400, 100–600		[111]

Table 1. (Contd.)

Analyte	Reaction conditions	Electrodes	Linear range, μM	c_{min}, μM	Reference
2-Butanone peroxide, *tert*-butyl hydroperoxide	Cyclic voltammetry or chronoamperometry at $U = -0.25$ V	WE: glassy carbon; mod.: Eastman-AQ 55D polymer-based film containing immobilized peroxidase and organic dyes: (1) Methylene Blue, (2) Methylene Green, (3) New Methylene Blue N, (4) Meldola's Blue, (5) *N*-Methylphenazonium methasulfate	(1) 2.5–520, 6.0–620, (2) 1.7–570, 4.7–560, (3) 3.0–467, 6.5–573, (4) 1.0–615, 4.0–675, (5) 0.4–584, 2.4–723	(1) 1.0 3.0 (2) 0.7, 2.5 (3) 1.5, 3.4, (4) 0.5, 2.0, (5) 0.2, 1.0	[112]
Hydrogen peroxide, cumene peroxide, *tert*-butyl hydroperoxide	0.1 M phosphate buffer solution, pH 4.0, $U = -0.05$ V, amperometric detection	WE: glassy carbon; mod.: peroxidase and poly(anilinomethylferrocene)	4–90, 10–80 (160–240), 40–240	–	[113]
2-Butanone peroxide, *tert*-butyl hydroperoxide	$U = -0.05$ V, amperometric detection in organic solvents	WE: graphite; mod.: peroxidase immobilized in organogel based on dimethylformamide and polyhydroxylcellulose	8–500, 50–100 (solvent chloroform)	5, 20	[114]
Lauryl peroxide, benzoyl peroxide	50 M phosphate buffer solution, cyclic voltammetry, $U = 0.1$ V, amperometric detection	WE: glassy carbon; mod.: peroxidase immobilized in osmium redox polymer based on polyallylamine	20–160, 0.3–4.1 (solvent ethanol (90%))	–	[115]
Benzoyl peroxide	0.1 M phosphate buffer solution, pH 5.2, $U = 0.0$ V, amperometric detection	WE: a biosensor consisting of a mixture of coal powder and coconut fibers containing peroxidase and phenolic compounds, stable for 3 months at room temperature	5–55	–	[116]
Cumene peroxide	$U = -0.4$ V, amperometric detection in acetonitrile	WE: graphite; mod.: horseradish peroxidase immobilized in Nafion, low stable	*n*–700	100	[117]
Linoleic peroxide	50 M phosphate buffer solution, pH 7.0, cyclic voltammetry	Disposable printing electrode; WE: carbon; mod.: peroxidase with covalently immobilized ferrocene groups, stable for 24 h	5–100	–	[118]

ide in human urine using a nonenzymatic amperometric sensor with immobilized CuS nanoparticles on the surface of a glassy carbon electrode.

Horseradish peroxidase and hemoglobin are the most widely used modifiers of the electrode surface for determining hydrogen peroxide [100–103]. For example, for the amperometric determination of H_2O_2. in human erythroleukemic cells (K526), a film was made on the surface of a graphene oxide electrode, coated with gold nanoparticles and immobilized horseradish peroxidase (HRP) (Fig. 7). The determination of cellular hydrogen peroxide is an essential aspect of the study of its functions in cell physiology [90]. The analytical range of hydrogen peroxide was from 0.02 to 1 μM, and its limit of detection was 7.5 nM. The developed sensor offers a selective determination of hydrogen peroxide in the presence of glucose, ascorbic acid, and dopamine. The biosensor is characterized by a high response rate (4 s) and stability (90% of the initial value of the analytical signal retained for at least 2 weeks). The enzyme electrode was stored at low temperatures (4°C) in a buffer solution before use.

The work on the electrochemical determination of organic peroxides is less numerous than those on the determination of hydrogen peroxide. Existing electrochemical sensors enable the determination of peroxides of various structures at the level of nanomolar or millimolar concentrations. In almost all cases, the analytical signal remains stable for a month (Table 1).

Most of the developed electrochemical sensors and biosensors were tested in the analysis of water-insoluble skin lotions and hair dye products [106, 110, 113, 115], pharmaceuticals [119], and foods [81]. In the last 15 years, works devoted to the electrochemical determination of hydroperoxides in biological fluids have not been published. The developed indicator systems and sensors were tested, probably, in model solutions. The current analytical task is to create such biosensors that could work stably and reproducibly in organic solvents capable of dissolving the liposomal biomatrix and that would have high sensitivity and selectivity with respect to the markers of oxidative stress.

CONCLUSIONS

Thus, the development of methods for the determination of peroxides of various structures is a dynamically developing field of chemical analysis and clinical diagnostics. Various methods and approaches are proposed for determining the total concentration of lipid hydroperoxides and hydrogen peroxide in various biological samples, because their role in the development of cell damage is determined by the activity of the peroxide group and does not depend much on the nature of the radical. However, most of the developed procedures are not free from shortcomings, which include the interfering effect of the matrix, insufficient sensitivity and reproducibility, a limited range of samples to be analyzed, or insufficient rapidity of analysis to obtain reliable results. The search for new indicator systems, enhancement of the possibilities of existing methods and techniques that could be successfully used in media of different polarities, with the minimal interfering effect of the components of the biological matrix, remains an urgent problem of analytical chemistry.

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