International Journal of Sciences
(ISSN 2305-3925)
http://www.ijSciences.com

Research Article
Volume 1, Issue Oct 2012

Pharmacophore Superfamily to Operate the Cell Proliferation and Apoptosis Processes

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Abstract: Fullerene derivatives superfamily attracts a serious attention of pharmacologists since some of these variable agents were proven to be not only drug delivery carriers but anti - cancer and immunomodulators as well. Most specifically, photodynamic therapy of malignant tumors is known for the fullerenes engagement. However, there is an obvious deficit of information on the cellular and molecular mechanisms of the fullerenes pharmacological effects which is a true obstacle on the way leading to practical medicinal use of the latters. Particularly, the mode of both direct (immediate) and distant side effects origin along with a fullerenes impact on necrosis, apoptosis and cell proliferation processes are no doubt needed to get far more clearified. It is hardly possible to exaggerate a significance of the fullerene nanoparticles functionalization type, their sizes and surface nanotopology for further promoting of either cytoprotective or cytotoxic effects. Noteworthy, the antioxidant properties of some water soluble fullerene derivatives were revealed while the fullerenes induced ROS formation might be also occurred. One of the most intriguing peculiarity of the fullerenes as pharmacophores consists in capabilities of some of them to intervene into the structure domains of functional proteins including enzymes and organelles linked receptors as well as to play a role of intercalators interacting with DNA double helix which, in turn, leads to a number of crucial consequences such as the biopolymer conformational flexibility shifts, catalytic activity changes, ligand docking affinity impacts in cell signaling pathways. Last not least, the fullerens are about to compete with several natural metabolites and effectots which is itself a valid platform for pharmacological outreach. This Review deals with an Authors's original attempt to analyse the above mentioned points with an aim to elucidate those properties, methodological and structural, of numerous fullerene adducts that determine their apoptosis- and cell proliferation – modulating effects with a special respect to a target cell / tumor type.

Keywords: fullerenes, signaling pathways, oxidative stress, cancer treatment, apoptosis control, targeted drug delivery

Introduction

Nanotechnologies, that study particles of about 1-100 nm in size, open new possibilities for different fields of research and industry [1] with involvement of fields of pharmacy and medicine. Fullerenes as a structurally distinguished class of chemical compounds were discovered relatively recently (1985) and are of a particular interest among nanomaterials. Nanoparticles of 1-100 nm in size have various physical and chemical parameters, mechanisms and biomedical application. This is due to location of majority of their atoms at interphase of outer surface of the particles that, in turn, provides physicians and biologists with new quantum and mechanical mechanisms of their action. To imagine the size of nanoparticles let's take a height of a child of 4 years old to be equal to 1, than a diameter of the red blood cell will be in the range of 10^{-5}-10^{-6}, diameter of hepatitic C virus is ~10^{-7}, carbon nanotube - ~10^{-8}-10^{-9}, and water molecule – 10^{-10} [2].

Fullerenes possess properties that make them attractive for various applied investigations. In particular, they may enter reactions of addition at double bonds (exoderivatives), introduction of atoms and clusters into the carbon backbone (endoderivatives) and are able to form

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heterofullerenes (metallofullerenes) and supramolecules. Due to this, they possess a whole spectrum of various effector properties useful for the human organism.

Buckminster fullerene (C_{60}) and its water-soluble derivatives, prepared by addition of various functional groups to the fullerene core, are suitable under different conditions for cytoprotection as well as antitumor therapy [3]. For example, some hydroxylated C_{60} and C_{60}-malonates behave as absorbers (acceptors, sponges) of radicals and protect cells from damages, caused by the oxidative stress [3-8]. However, they are also capable under higher concentrations and also, due to impact of UV-light, to cause a cell death through ROS (reactive oxygen species)-dependent and ROS-independent mechanisms [8-11]. In the case of some fullerene derivatives a cytotoxic effect regarding certain (in particular, cancer) cells has been described [12]. This may be purposefully used for tumor therapy without significant damage of a healthy tissue [13,14]. All fullerene derivatives bearing S-triazine fragment demonstrated a moderate to good level of inhibition of bacteria [15]. It is interesting, that the stable colloid solution of hydrated fullerenes forms a structured water layer around its carbone backbone that represents a special spheric cluster. Finally, a broad set of spheric clusters $(C_{60}@\{H_2O\}_n)_m$ [16] may be formed that leads to occurrence of particular properties mediated by water structure (Fig.1b).

Colloid solutions of C_{60} during interaction with water are able to form aggregates of different size and, respectively, of different toxicity. So, a like increasing of attractability of fullerenes for their usage in medical purposes, there is an uncertainty due to their toxicity and remote consequences of their application. Especially, it is pricked up when nanoparticles are used everywhere, for example, in cosmetics and other social branches. Derivatization of C_{60} decreasing of apparent toxicity may significantly influence on the mode of interaction of fullerenes with biological systems [17]. This increases the uncertainty in relation to the consequences for health and sometimes establishes an effect of "Trojan horse". So, it is of great importance to assess correctly risks and consequences of the fullerene-based nanotechnologies development. Debates regarding toxicity of nanoC_{60} and hydroxylated fullerenes are described in detail in a review [18].

Over past several years the field of functional drug component delivery to definite organs and tissues in the organism (drug delivery) has acquired a special interest in the medical research. The fullerene derivatives, especially, porphyrin and supramolecular ones, are capable to act as a transporter as well as a drug. The latter is provided by the fact that fullerenes possess their own influence on the oxidative stress, proliferation, apoptosis, gene expression and other important functions of the organism.

A number of books that comprehensively describe an organic chemistry of fullerenes [19,20] and their application in biochemistry and medicine [21] were issued in 2005. Many reviews were also published [22-27] on the investigation of synthesis of new compounds, belonging to this class, and their possible medical usage [28-34]. Antimicrobial action of fullerenes and their derivatives was considered in the review [35]. Water-soluble fullerenes are of particular significance for medicine and their porphyrin derivatives [36,37] and fullerols (hydroxyfullerenes, fullerenols) [38] attract great attention.

Since main research fields on fullerenes are devoted to synthesis of new constructions, biochemical results have, in many cases, some stochastic character. In the present work we tried to concentrate our attention on the important aspects of fullerenes impact on the organism, including those linked with apoptosis and proliferation. These phenomena are especially important for cancer and neurodegenerative diseases prevention and therapeutics. We have also considered trends in intensively developing field of usage of fullerene nanoparticles on drug delivery and targeting. The question if fullerenes are useful for medical purposes or they are one more risk factor is a subject for debates in the scientific literature [39], and there is no certain answer for it. Also, the risks and success of nanomaterials application, as a whole, are discussed in detail [40].

It is necessary to take into account ecological and technogenic components of fullerenes impact, because fullerenes emerge in the environment from natural and anthropogenic sources such as volcano eruptions, forest fires and burning of carbon materials **[**41**]**. Moreover, in the last time production and usage of industrial fullerenes in different branches of industry are greatly increased. All these facts increase importance of comprehensive assessment of their toxicity for the environment and human health. Recent data [42] on risk assessment demonstrate a possible non-toxic concentration of fullerenes with average pore size of 96 nm that equal to 0.39 mg/m^3. Calculations were made on the basis of trials results on rat lungs. However, this is not the last result in this research field.

I. FULLERENES AND OXIDATIVE STRESS

One of the main factors of the impact of environment and effectors on apoptosis is an oxidative stress that is expressed in emergence of ROS. The latter includes singlet oxygen, superoxide radical, hydrogen peroxide and hydroxyl radicals, which arise in catalyzed by metal ions Fenton and Haber-

Weiss reactions. ROS participate in initiation of receptor as well as non-receptor mechanisms of apoptosis, autophagy, lipid peroxidation and indirectly influence on many signaling pathways [43,44].

It is known, that the main impact of nanoparticles, as a whole, and fullerenes, in particular, is concluded in the oxidative stress that emerges in the organism due to their appearance in it **[**45**].** However, definite consequences greatly depend on physicochemical properties of nanoparticles: size, shape, degree of dispersion in the solution, solubility in water, side chain composition etc. Their action is in the range from toxic to protective one. Concentration dependence is one of the most important indicators that determine consequences of the fullerene introduction. Thus, the most obvious effector impacts of fullerenes on proliferative processes are linked with their "relationships" with ROS, and the results of which may be directly opposite ones.

Due to its unique spheric structure, C_{60} has a possibility to accept up to 6 electrons [46]. These electrons move quickly around the structure (fullerene grid) due to dipole moments. When C_{60} is subjected to action of light, then an electron moves to more high energetic level, thereby producing an excited singlet C_{60} that reacts with O_2 to form a singlet oxygen ($^1O_2$) [20**]**.

Fullerenes are exclusively effective generators of the singlet oxygen with quantum yield of $^SO_2$ close to one. They absorb greatly in UV- and slightly – in visible spectrum **[**24**]** that allows their usage in photodynamic therapy (PDT, chapter VIII). Originally formed the singlet excited state ($^SC_{60}$*) undergoes intercombination transition into a triplet state ($^TC_{60}$*). The triplet excited state is an excellent acceptor of electrons and potential producer of the superoxide anion radical $O_2^{-\cdot}$ (Fig.2). This pathway, in contrast to singlet oxygen generation, usually is observed in organic solvents, predominantly, in polar ones, especially, in the presence of reducers such as NADH [47].

Increasing number of functional groups, added to fullerene, leads to decreasing of quantum yield of the singlet oxygen. Toxicity is significantly decreased or even is fully absent in hydrophilic fullerenes [48**]**. Fullerene derivatives are able to control exogenic as well as endogenic ROS [49].

It is necessary to distinguish a pure fullerene C_{60} and so-called nanoC_{60} or n-C_{60} that is an aggregate with indefinite (but, sometimes, stable) composition and poorly predicted size due to aggregation. Size of aggregates depends on preparation conditions. Nano-C_{60} is formed often in the presence of a solubilizing agent, and a part of the latter, as suggested, is introduced into such nanoparticles **[**50,51**].** However, in some cases, a spontaneous transition of C_{60} into в n-C_{60} was described **[**7,52**]**. It is considered that "pure" C_{60} does not exhibit visible toxicity that, however, depends on its concentration. In the same time, n-C_{60} is, as a rule, a cytotoxic agent **[**24**]**, which power depends on the size of aggregates and type of solution.

It is known **[**53**]** that the ROS-produced cytotoxicity is decreased under increasing of fullerene framework functionalization. However, there are suggestions that cytotoxicity of n-C_{60} is not an internal property of C_{60}, but a property of a residual solvent, for example, tetrahydrofuran (THF) **[**7**]**, intercalating into the grid. Suspensions, prepared during long stirring in water only, in some cases, did not demonstrate acute toxicity **[**54**].** Suggested cytotoxic action of the residual THF **[**55,56**]** have not been confirmed yet. Authors **[**57**]** consider that water suspensions, prepared in the absence of organic solvents, not only have no acute or slightly acute toxicity, but must be protectors. Thus, the discussion about the reasons for the aggregates toxicity: contribution of solubilizators remainders or newly acquired properties of C_{60} due to changes of the size and morphology because of the aggregation (in particular, due to a possibility or impossibility of a direct interaction with proteins), is still actual. Most likely, both variants are probable however, the second one is more sufficient under correct execution of an experiment.

C_{60} toxicity was evaluated on different cells [5,58**].** No cytotoxicity was observed in alveolar macrophages at 1.41-226 μg/cm^2 of C_{60} **[**59**]**. In rat lungs there was no effect under inhalation of C_{60} in concentration up to 3 μg/kg. [60] and particles of nC_{60} of 55 nm in size at concentration 2.22 mg/m^3 induced minimum alterations [61]. All this evidence that C_{60}-cytotoxicity depends, in addition to other factors (procedures for preparation and concentration), on the cell type. For example, thin layers of pure C_{60} may even act as a suitable substrate for formation of cell colonies that was demonstrated [25] on human osteoblast-like MG-63 cells.

Stable and homogeneous C_{60}-dispersion medium did not influence on survival and did not cause apoptosis nor necrosis in human keratinocytes (HaCaT). The same picture was observed for A549 human lung cancer cells [62]. However, in both cases the cell proliferation was hampered.

Antioxidant properties of fullerene derivatives are determined by affinity of C_{60} to electrons capture. This indicator is high for tris-malonyl-C_{60} (C3) that removes superoxide radical in various cell lines at the level of active metal-containing mimetic of superoxide dismutase (SOD). DFT (density functional theory)-calculations showed [63] that, after superoxide radical contacting with C3 surface, its unpaired electron moves onto fullerene. In the

result the aggressive $O_2^{-\cdot}$ is transformed into neutral O_2. After that another superoxide radical reacts with C3-radical to form hydrogen peroxide, involving the electron transferred at the first stage. This process is an exothermic one with low energy of activation.

To modulate nC_{60} toxicity, mainly, caused by ROS-production, and improve possibilities for its medical usage, fullerenes undergo different treatments to become soluble or pseudo-soluble in water. This process, besides other properties, influences on the ability to aggregation and depends on the type of side radicals. There are different structures for derivatives of fullerene: rods, bubbles, balls, membranes and linear constructions [64,65]. Morphology of C_{60} derivatives aggregation, mainly, linked with hydrophobic interactions and hydrogen bonds. Few hydrophilic components are sufficient to prevent strong hydrophobic three-dimensional interactions between fullerene fragments and decrease their tendency for formation of aggregates. Differences in the affinity to electron and physical properties (degree of aggregation) influence greatly on biological and biomedical activity of derivatizied fullerenes [66]. Supramolecular properties may promote affinity to radicals.

To prepare soluble samples of $C_{60,}$ methods that lead to different results in geno- a cyto-toxicity are used. At present time, 4 approaches are offered to provide fullerenes with functions of solubility: hydro- and amphi-phility **[**24**]**:

1 – Chemical modification of fullerene framework by addition of different hydrophilic functional groups (derivatization or functionalization of fullerene) **[**12,67,68**]**.

2 – Introduction of fullerene into water-soluble supramolecular structures with help of SAS (for example, polyvinylpyrrolidone - PVP [69]), calixarenes or cyclodextrins (CD) **[**70-72**],** when the fullerene nucleus is fully coated by modificator and has no contact with water. It is necessary to consider that cyclodextrins themselves tend to form aggregates in solution, linked with each other by hydrogen bonds network. CD-fullerene-conjugates demonstrated independent assembling of amphiphilic conjugates into spheric micelles in water [73] that, however, does not interfered capture of OH-radical by C_{60}-fragments.

3. – Method of exchange of solvents (MES) [74,75] uses volatile mixing with water solvents that dissolves fullerene. After water addition the solvent is evaporated and nC_{60} suspension is formed **[**76**]**. The suspension is also prepared with use of ultrasound to promote fullerene transfer from non-polar solvents into water **[**77**]**, by dispergating in water with Tween-80 [57,78], sugar syrup polyoxiethylene-hydrogenized castor bean oil **[**79**].** Initial concentrations of $C_{60,}$ in these cases, were less than 100 μg/ml **[**74,75**]**. Suspensions of nanosize dimension with large concentrations were prepared [78] by combination of SAS and disruption by ball grinder.

4. – Long (more than 2 weeks) stirring of pure C_{60} with water. However, large aggregates may be formed and concentration of fullerene may be low **[**54,77**]**.
Effector action of C_{60}, suspended in the solution, was determined on E.coli. [80] in dependence on degree of dispergation. It was considered that solubilizing solvents promote more high toxicity. 1% concentrations of solvents and 0.04% Tween-80 were used. According to these data, the most safe solvent in necessity of biocompatibility is N,N-dimethylformamide, but the solubility is not directly linked with cytotoxicity. Moreover, ozonation of nC_{60} obviously and greatly increases degree of E.coli inactivation [81].

Modification of C_{60} by hydrophilic component produces amphyphilic molecules that dissolve C_{60} in H_2O. In that, a question is under discussion, is it possible to consider the amphyphilic molecules, prepared during modification of C_{60}, as really water-soluble ones? High level of solubility in water – 34 mg/ml at pH 7.4 – was obtained [82,83] with dendrite derivatives of fullerene with 18 carboxyl groups.

ROS-mediated cytotoxicity of different nC_{60} suspensions (prepared by MES) was studied [84] with use of THF (THF/nC_{60}), ethanol ($EtOH/nC_{60}$) and stirring in water (aqu/nC_{60}). According to the ability to generate ROS, they were arranged in the next sequence: $THF/nC_{60} > EtOH/nC_{60} > aqu/nC_{60}$. Mathematical modeling of the singlet oxygen generation showed that the power of its quenching ($THF/nC_{60} < EtOH/nC_{60} < aqu/nC_{60}$) by solvents, intercalated into fullerene crystals, influences on their ability to produce ROS and causes damage of cells.

The oxidative stress induction, leading to mediated by extracellular signal-regulated kinase (ERK) cells death from necrosis, accompanying by damages of cell membranes without degradation of DNA [85], was observed at high concentration of nC_{60} (1 μr/ml), while studying the anti-glioma action of nC_{60} (MES in DMSO) on human cell line U251 and rat C6 [3]. A similar picture was observed in murine sarcoma cells. Autophagy and proliferation blocking in G2/M phase took place at low concentration (0.25 μg/ml nC_{60}). C_{60} in concentration-dependent manner influences on differentiation of murine embryonic stem cells [86].

In case of endotracheal instillation and inhalation, C_{60} fine dispersed in water with 0.1% Tween-80 (33 nm, agglomerates up to 96 nm), in a dose of 0.1-1 mg and at different exposing duration [87] do not

cause inflammation reaction (there was no significant elevation of neutrophils number). Clearance-kinetics of C_{60} after intratracheal instillation and inhalation showed that concentration of C_{60} in the liver and brain was lower than 8,9 ng/g tissue and in lungs the loading was reduced with time and depended on the initial concentration of C_{60}[88].

Nano-C_{60}(THF) are able to cause a lysis of human erythrocytes in a dose- and time-dependent manner [89]. nC_{60}(THF)-mediated hemolysis preceded the shrinkage of erythrocytes and increasing of cellular surface roughness. The hemolytic activity may be restored by use of N-acetyl-L-cysteine (NAC) that indicates the role of ROS in this process. In the meantime, C_{60}(CD-complex) and nC_{60}(so-polymer of ethylene vinylacetate - ethylene vinylversalate) were unable to perform the process.

Administration of C_{60} may alter the toxic action of other micro-impurities. Cells, co-exposed with C_{60} and As(III), had higher accumulation of As(III), thereby demonstrating the effect of "Trojan horse", because, due to fullerene, there was no elevation of cellular toxicity [90].

An opinion is often presented in the literature [91] that the observed difference of cytotoxicity of modified fullerenes is directly proportional to the ability of a fullerene derivative to induce ROS. However, the data analysis evidences that this dependence, probably, is more complex and multifunctional.

Nitrogen-containing fullerene compounds may possess greatly varied properties in dependence on the structure up to the significant toxicity. Addition of pyridines and pyrimidines to C_{60} fullerenes significantly increased their selective neurotropic activity, but increased 3-5 times the general toxicity in comparison to fullerenyls, $C_{60}F_{36}(NH_2)_{12}$. Fullerenyls were relatively low toxic ones and had no visible toxicological effects in doses not exceeding 800 mg/kg [85], and a tertiary water-soluble ammonia salt, fluor-fullerene-pyridinium fluoride $C_{60}[FNC_5H_5]$+F- already in a dose of 300 mg/kg demonstrated features of acute toxicity in relation to the brain and some parenchymatous organs. In the same time, the antioxidant action $C_{60}(ONO_2)_{7\pm2}$ decreases consequences of ischemia, induced by damages of lungs [92]. Next derivatives of C_{60} such as N-methyl (2-quinolyl) fulleropyrrolidine and N - methyl (2-indolyl) fulleropyrrolidine have also demonstrated high antioxidant properties [93].

Hexa-sulfobutyl-derivatives of fullerene were used as radical sponges [94,95]. They inhibited lipid peroxidation and acted as anti-proliferative agents in atherosclerosis.

The next derivatives of fullerene such as fullerenes modified by different amino acids and also carboxy-fullerenes are under active investigation. Cystine-C_{60} derivative **[**96**]** showed a high activity of antioxidant action against superoxide and hydroxyl radicals (IC_{50}=0.167 and 0.008 mg/ml, correspondingly) and prevented H_2O_2-induced apoptosis **[**97**].** It is known [98] that 5 μg/ml of cystine-C_{60}-derivative decreases apoptosis of PC12 cells.

Due to hydrophobic interactions, many amino acid-C_{60} derivatives are assembled independently to form spherical aggregates. Cystine-C_{60} and arginine-C_{60} (in difference from alanine-C_{60}) may form further multilayer bubbles due to hydrogen bonds. Experiments demonstrate that the bubbles morphology significantly influences cytotoxic as well as protective effect of these compounds against H_2O_2-induced apoptosis [99].

Amphiphilic derivatives, folic acid-C_{60} (FDD, Fig.1c) [100] and oxidized glutathione-C_{60} (OGED) [101], are also able to self-assembling into spherical aggregates. They penetrate cell membrane and, due to the antioxidant action, protect cells of rat pheochrome cells (PC12), treated by H_2O_2 [100], from cytotoxicity without demonstration of visible toxicity. In that, the size of FDD-aggregates was lower than those for cystine-C_{60} and arginine-C_{60} derivatives that caused a greater amount of FDD in cells [96,99] and significantly increased the anti-apoptosis activity. Moreover, OGFD is able to overcome blood brain barrier (BBB) [101].

C3 is able to remove superoxide radical with rate constant of 2 10^6 $mole^{-1}s^{-1}$ that is approximately 100 times lower than action of SOD. Such a value is in the range, described for manganese-containing SOD mimetic [102]. It was shown that a reaction between C3 and superoxide radical has a catalytic mechanism. Taking into account that C3 localizes in mitochondria, it is possible to consider that C3 functionally substitutes Mn-SOD, acting as biologically active SOD-mimetic.

Significant differences between lipophilic and hydrophilic particles of (C_3/D_3-C_{60}) are observed under consideration of different variants of C_{60} modification by residues of hexacarboxylic acid (C_3 or D_3 conformations) [103]. Antioxidant action of fullerenes against lipid peroxidation and membrane disruption caused by radicals that are produced in xanthine/xanthine oxidase and Fenton reactions was used as a model system. Lypophilic derivatives of C_{60} demonstrated protective effect that was greater than those of natural antioxidant–vitamin E. Anti-apoptotic functions of such fullerene derivatives may be also independent from their anti-ROS-acceptor role [17**]**. So, tris-carboxy-C_{60} is a strong inhibitor of apoptosis in human skin epithelial cells (HEK), blocking G_0/G_1 of the cell cycle and causing the cell senescence. In that, there is decreasing of the

expression level of ubiquitin ligase HERC5, participating in the innate immune response to virus and bacterial infections. In these conditions, no changes in proliferation were observed in cells, treated by hexa-carboxy-C_{60} and γ-CD-C_{60} .

It is known that 10 μmole/l of carboxyfullerenes decreases apoptosis of PBMC cells **[**5**]** and 1.2 mmole/l of a derivative, protocatechic acid-C_{60} [104], decreases apoptosis of PC12 cells. It is obvious that the level of concentration depends on the chemical structure of a derivative that determines its further behavior in the field of aggregation and binding with various sites of biological components (and then toxicity) and on specificity of a cell line. Obviously, the conformational component plays an important (probably, major) role in these processes.

Comparison of antioxidant properties of PEG (polyethyleneglycol)-C_{60}, PVP (polyvinylpyrrolidone) – C_{60}, CD-C_{60}, C_{60}, containing OH-groups (Fig.1a) and C_{60}-isostearic acid [105] in relation to human skin keratinocytes (HaCaT) was conducted. All these fullerenes exhibit a powerful antiradical acceptor potential. However, the influence of side radicals (of the modificator) was expressed in necessary concentration of preparations: PEG-C_{60} – 200-2700 μmole/l, PVP-C_{60} – 400-2700 μmole/l, OH-containing fullerenes – 9 μmole/l, C_{60}-isostearic acid – 18 μmole/l.

PVP-C_{60} and poly(2-alkyl-2-oxazolin)-C_{60} (POX-C_{60}) form a homopolymer and casual co-polymer forming nanocomplexes with the same antioxidant activity [106]. However, only POX-C_{60}-complex was effectively captured by catecholaminergic neurons and attenuated elevation of intraneuron superoxide, induced by stimulation of angiotensin II.

Fullerols inspire a particular interest due to the absence of visible toxicity that are declared by many authors and due to unique physico-chemical properties. Hydroxylated, water-soluble C_{60} due to its antioxidant properties inhibits catabolic stress-induced production of matrix metalloproteinases MMP-1, MMP-3 and MMP-13, and also apoptosis and preliminary aging in human chondrocytes. This makes it possible to use it as a protective agent against osteoarthritis [107].

Hydroxylated fullerene (C_{60}HyFn) in a dose of 4 μg/kg decreasing oxidative stress in rats that suffer from STZ (streptosotocin)-produced diabetes, prevented complications such as testicular dysfunction and disruption of spermatogenesis [108**]**. Usage of C_{60}HyFn did not cause toxicity and leaded to elevation of some important polyunsaturated fatty acids. Hydrated fullerenes in concentration of 30 nmole/L protected nervous system tissues, preventing loss of astrocytes [93], and $C_{60}(OH)_{16-18}$ in concentration up to 50 mg/L did not influence on Danio rerio [109]. The ability of $C_{60}(OH)_{36}$ $8H_2O$ to hamper the oxidative stress in adipocytes leads to inhibition of lipogenesis-linked activation of macrophages in the adipose tissue [110]. Under certain conditions such highly hydroxylated fullerenes may sufficiently decrease the fat accumulation, ROS generation and infiltration of macrophages.

Fullerol $C_{60}(OH)_{24}$ demonstrated an acceptor activity in relation to superoxide radical in xanthine/xanthine oxidase system [111]. It did not cause genotoxic effects and demonstrated cytoprotective properties in a wide range of concentrations. However, other data [93] demonstrated that this fullerol of 7 nm in size and concentration of 1-100 μmole/mL causes morphological alterations in cells of endothelium vessels, damages of cytosole (changing the level of lactate dehydrogenase) and inhibition of cell growth. This is accompanied by accumulation of polyubiqutinated proteins that activates autophagy. $C_{60}(OH)_{24}$ showed in vivo and in vitro a cytotoxic effect in relation to HepG2 cell line under doxorubicin (DOX)-induced hepatotoxicity. However, under even very strong oxidative stress cytotoxic effects of the fullerol were overcame by its protective role as a strong antioxidant [112].

Another fullerol $C_{60}(OH)_{22}$, in the range of nanomolar concentrations caused inhibition of a cell growth. The effect depended on the definite cell line, dose and time. In the same time $C_{60}(OH)_{22}$ as well as $C_{60}(OH)_{24}$ significantly suppressed the DOX-induced cytotoxicity at any concentrations independently from the time of fullerol addition. It is considered that these properties of $C_{60}(OH)_{22}$ are provided by its high acceptor activity in relation, namely, to OH-radicals [113**]**. Fullerols are cytotoxic for pigment epithelial cells of human retina in concentrations of more 10 μmole/L [114].

A gel, containing 75 μmole/L of C_{60}, was utilized for treatment of acne as a receptor of radicals, which formation is a key moment in the disease development. As an antioxidant, fullerenes inhibited development of acne [115], seemingly, due to decreasing of neutrophilic infiltration.

Interestingly, fullerenes, dissolved with help of 1% Tween-80 (0.1 mL/10g of weight), were an effective preparation against action of polynarcotics. A lethal effect was observed under simultaneous action of methamphetamine and morphine due to increase of poly(ADP-ribose) polymerase (PARP) immunoreactivity of cells that both narcotics induce. These events are sufficiently linked with growth of hydroxyl radical number and they are sufficiently decreased by preliminary treatment by fullerene [116]. Moreover, this effect was stronger than those in the case of mepacrine (inhibitor of phospholipase A2) usage.

II. FULLERENES AND BRAIN CELLS

Fullerene and its derivatives, for example, FDD, OGFD [101] and some other water-soluble fullerenes [117] are able to penetrate through the BBB and influence on the brain cells proliferation, in particular, through the oxidative stress [118].

As an example, in vitro modeling of interaction with BBB cells under oxidative stress, induced by H_2O_2, was demonstrated for nanoparticles of water-soluble carboxyfullerene $C_{60}(C(COOH)_2)_2$ [119]. As a model, brain cells of the endothelium microvessels (CMECs) were used because apoptosis of CMECs under action of ROS plays a key role in BBB dysfunction. It was revealed [120] that particles of $C_{60}(C(COOH)_2)_2$ selectively and predominantly penetrate into oxidized (not normal) CMECs, keeping their integrity at the expense of H_2O_2-induced F-actin depolymerization suppression.

Intraperitoneal and intravenous introduction of the suspension (0.3 mg C_{60}/kg) of C_{60}-PVP [23], less than 10 nm in size, inhibited differentiation of embryonic stem cells and brain cells that caused morphological alterations in murine embryos and correlated with increasing of cytotoxicity. In that, disruption of yolk sac function and embryonic morphogenesis were observed. Because proliferation was restored in addition of antioxidant enzymes, then the relationship between functional changes and effects of ROS is obvious.

After injection into hippocampus C_{60}-PVP [121] prevents disorders in the development of long-term memory, caused by a protein biosynthesis inhibitor-glutaramide antibiotics cycloheximide. The mechanism of inhibition is concluded in neurons apoptosis due to infringement of the protein synthesis chain that disrupts storage of information. Action of the fullerene complex is based on the antioxidant property, however, it is suggested [122] that absorption features of C_{60} may play a significant role in the prevention of neuronal apoptosis.

A derivative, malonic acid-C_{60}, promotes protection of dopamine in neurons of mesencephalon from toxin-induced degeneration **[**123**]**. Carboxyfullerenes demonstrated in vivo their efficiency in the prevention of neurodegeneration in the case of amyotrophic lateral sclerosis [82]. They also decrease the oxidative stress caused by iron in dopaminergic nigrostrial way [124].

C_{60}-methionine derivative [125] (FMD) protected human neuroblastoma cells (SH-SY5Y) against neurotoxicity of a lead (in pretreatment with the 500 μmole/L lead for 72 h.), which is realized through the oxidative stress. The protective effect was expressed in increasing of cells survival, anti-apoptotic action, elevation of a reduced glutathione (GSH) level and decreasing of a malonyl dialdehyde (MDA) level. The effect was higher for FMD in comparison with other amino acid-C_{60} derivatives, in particular, for β-alanine-C_{60} and cystine-C_{60} that, seemingly, is linked with specific properties of an amino acid. A hexacarboxylic acid- C_{60} derivative inhibits excitotoxic death of brain cortex neurons [4].

Water-soluble fullerols are considered to be a main achievement of nanotechnologies for neuromedicine [126]. They inhibit activity of glutamate receptors (GluR) from 10 to 80% under concentrations from 10 to 100 μmole/L. The most sensitive one was AMPA (2-amino-3(3 - hydroxy- 5 -methyloxazole-4-yl) methylisopropionic acid) -receptor (up to 90% inhibition in concentration of fullerol of 100 μmole/L), then KA (kainate) and NMDA (N-methyl-D-aspartate)-receptors are followed, where 73% and 54% of activity, correspondingly, are inhibited [127].

Treatment of SK-N-MC cells by a single non-toxic concentration of water-soluble C_{60}-bis-adduct (Fig.3) caused modulation of adenosine receptors expression. Elevation of expression of A2A and A2B receptors mRNA and elevation of A1 and A2A protein level was observed [88], but no influence on the cells viability was revealed.

Fullerene derivatives have been studied regarding their possible usage in therapy of Alzheimer`s disease (AD). To compare antioxidant activity in relation to β-amyloid (Aβ)-induced cytotoxicity, the effect of PEG-C_{60} nanoparticles and its pentoxyfillin carrying hybrid (PTX-C_{60}) on neuro-2A cells was studied [128]. Aβ-generated free radicals may alter a structure of the lipid membrane in order to modulate neuronal systems of signal transduction. It is known that autophagy is induced by ER (endoplasmatic reticulum)-stress that is stimulated by ROS, level of cytosole Ca^{2+}, hypoxia etc. [129] and is linked with activity of AMP-activated cellular protein kinase (AMPK) [130]. All these processes are included into Aβ-induced reactions in neuro-2A-cells [131]. C_{60} in a dose of 7.2 nmole inhibits process of fibril formation interfering formation of amyloid fibrils by $A\beta_{25-35}$ peptide [132]. Simultaneously, a cognitive process in rats is improved. Action of PTX in this case is included in activation of AMP-pathway that leads to decreasing of ID4 (inhibitor of differentiation 4) genes expression in cell lines, derived from astrocytes, and is expressed in decrease of cellular apoptosis. Cytoprotective effect of fullerene derivatives is linked with inhibition of autophagy [128], caused by activation of AMPK. Namely, hybrid molecule was more effective. Detailed evaluation of therapeutics possibilities of fullerene derivatives for the treatment of AD was performed in [133].

It is not possible to forget that a like neuroprotective functions, neurotoxic activities of fullerenes are possible and their manifestations have not been fully studied yet. Systematic introduction of

carboxyfullerenes (10 mg/kg) did not prevent neurotoxicity, caused by known neurotoxin – 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [134]. Moreover, even a dose-dependent increasing of striaric dopamine exhaustion was observed. In a dose of 30 mg/kg carboxyfullerene promoted death of MPTP-treated mice. However, during local application the same carboxyfullerene may act as neuroprotector agent [134].

Toxicity of fullerenes for brain cells is linked with oxidative stress, lipid peroxidation and glutathione depletion **[**53**]**. These processes participate in dopamine-mediated cell death in case of Parkinson disease (PD). Moreover, it is necessary to consider that transfer of β-amyloid-binding compounds through BBB is elevated due to of drugs encapsulation in polymer nanoparticles **[**135,136**]**.

III. INFLUENCE OF FULLERENES ON SIGNALING PATHWAYS INVOLVED IN APOPTOSIS

Research in the field of fullerene derivatives is mostly directed to expand classes of their derivatives, while the mechanism and depth of impact on proliferation processes as well as relationship with action of other pro- and anti-apoptotic factors have not been revealed. As a result, there is no certain prognostic model to predict which derivatives of fullerene and under which conditions will exhibit anti-apoptotic properties and which derivatives may be considered as probable antitumor agents. Moreover, pro- or anti-apoptotic effects of fullerenes and their derivatives are mediated through different signaling pathways that may intersect. So, the grouping given below is conditional, but it helps to stress some relationships.

It is known [137] that dendrite single-substituted fullerenes with great number of OH-groups in the substitute and also C3-carboxyfullerenes with mirror reflection, pentaC3-exo and pentaC3-endo position are inhibitors of cell death. However, there is a question is this justified for all cell types and to what degree is it universal?

Ionic homeostasis

It was shown that water-soluble fullerenes influence ionic homeostasis [138]. Some derivatives of C_{60} demonstrated properties of blockators of ionic channels in biomembranes with exclusion of CIC3 channels [139]. Inhibition is reversible and, as suggested, interaction proceeds in extracellular domains of a channel. To assess a possibility of nanoparticles penetration through a membrane, Gibbs energy of C_{60} transfer along axis perpendicular to the membrane bilayer surface was calculated [140] that demonstrated the possibility of C_{60} penetration in principle. It is considered [141] that C_{60} possesses by affinity to transmembrane domain of K^+-ionic channels and K^+-ionic flow may be inhibited by addition hydrophobic medicinal preparations, causing a cell death.

Porphyrinfullerenes [142] are able to penetrate through lymphocytes cell membrane and BBB. As whole, water-soluble derivatives fullerenes readily penetrate through biological membranes of different types of cells [143].

Bcl-2 family

Expression of proteins of Bcl-2 family (Bcl-2 and Bcl-xl) was increased after pretreatment of cells by C_{60}-$(glucosamine)_6$. As a result, decreasing of oxidative stress and apoptosis, caused by kidney ischemia/perfusion and also decreasing of superoxide radical generation and improvement of kidney hemodynamics took place [144].

It is necessary to note that ced-3, ced-4, ced-9 genes, responsible in Caenorhabditis elegans for analogs of Bcl family proteins, are subjected to modulation in consumption, as a food, of $C_{60}(OH)_{19\text{-}24}$ with average size of nanoparticles equal to 4.7 and 40.1 nm [145]. Activation of apoptosis is observed in the result that cause decreasing of animal lifetime. At high doses of nanoparticles (100 μg/mL) a prompt reduction of viability takes place.

Mitogen-activated protein kinases (MAPK)

MAPKinases perform a control of cell division and are critical regulators of transcription [146], interacting with some signaling pathways in apoptosis [43].

There are indications in some works that the toxic action of nC_{60} is similar to effect of single wall carbon nanotubes [147] and may be linked with activation of MAPKinases that, in turn, interrelated with activation of the transcription factor NF-κB. The process was studied on keratinocytes and it depends on a dose of a preparation [148].

Water-soluble fullerenes, on the contrary, were studied in vitro and in vivo [149] as protective agents against induction of osteoclasts genesis through RANK (receptor activator NF-κB)-signaling pathway and destruction of bone osteoclasts under arthritis. Fullerenes are able to down-regulate the RANK-induced differentiation of osteoclasts and suppress degradation of rat bone osteoclasts under intra-articular introduction of 20 μL of water-soluble C_{60} (C=1 μmole/L).

$C_{60}(C(COOH)_2)_2$ nanoparticles inhibit apoptosis linked with JNK (c-Jun amino-terminal kinases)-signaling pathways [119], because they decrease JNK-phosphorylation, AP-1 (activator protein 1) and caspase-3 activation (Fig..4). In that, no influence on ERK activation was observed. There are data that the

protective role of nC_{60} may be mediated through activation of p38 [150,151], however, no contribution of nC_{60}-activation of JNK or p38 MAPK into cell necrosis was observed [3].

Anoikis

C_3-fullero-tris-methanedicarboxylic acids (C_3-tris-MDC) are able to cause resistance to such a form of apoptosis as anoikis ("homeless state") in epithelial cells through mechanism of "trophic" effect with participation of actin of microfilaments [152].

Cytoskeleton damage

$C_{60}(OH)_x$ was cytotoxic in millimolar concentrations in relation to renal proximal channel cells (LLC-PK1) [153], but there was no links with oxidative stress. Cells death, induced by fullerol, was caused by cytoskeleton damage and accumulation of autophagy vacuoles. Moreover, a loss of mitochondrial membrane potential and depletion of ATP was observed. Authors consider the cytoskeleton damage to be a primary cause.

Caspases and ionic composition changes

Caspase pathway of apoptosis is the most prevalent one, and modulations of multiple components of a biosystem may lead to activation of the caspase cascade [44]. However, these pathways were discussed in a very few works on fullerenes. More often separate factors able to cause activation of caspases are considered or activation of caspase-3 is established.

Effect of a substitution was considered in the case of apoptosis of human THP1 monocytes under action of free different fullerene derivatives: CD-C_{60}, hexa-adduct of carboxyfullerene $C_{60}[C(CO_2H)_2]_6$ (hexaC_{60}, T_h-symmetry) and tris-adduct of carboxyfullerene $C_{60}[C(CO_2H)_2]_3$ (trisC_{60}, C_3-symmetry) [154]. It was revealed that a substitute is especially important in characterization of compounds regarding apoptotic function. In the same time, dispersion characteristics are more important for redox-function. Preliminary treatment of cells by hexa-C_{60} and tris-C_{60} prevented valinomycin-induced apoptosis in difference from CD-C_{60}. In that, there was no dependence of apoptotic influence of preparations through cell ROS responses, caused by them. Nevertheless, it is necessary to consider the cell redox status, because some fullerenes are able, partly, by increasing expression of antioxidant proteins, protect cells from apoptosis, caused by oxidative stress.Thus, carboxylated fullerenes and encapsulated C_{60} demonstrate opposite effects on pro-apoptotic caspase pathway [154].

Oxidative stress, mitochondrial depolarization and, as a result, activation of the caspase cascade were observed in vitro under action of nanoC_{60}, prepared by MES (THF), on the growth of B16 murine melanoma tumor cells [155].

On the contrary, nanoparticles of $C_{60}(C(COOH)_2)_2$ expressed an ability to inhibit cleavage of PARP and release of mitochondrial cytochrome C (Cyt C) that led to effective inhibition of the caspase-dependent apoptosis, caused by oxidative stress **[**119**]**.

Transforming growth factor (TGF-β)

Derivatives of C_{60}-hexacarboxylic acid were described [156], as blocking agents of apoptosis TGF-β signaling in human hepatoma cells and there are differences in actions of regio-isomers on the same or the different cell types [156,157].

Lysosomal-mitochodrial pathway

Bis-adduct of fullerene with malonic acid, $C_{60}(C(COOH)_2)_2$, may inhibit apoptosis, initiated by TNF-α in HeLa cells by stabilization of lysosomes [158]. During internalization of $C_{60}(C(COOH)_2)_2$, expression of molecular chaperone Hsp70 is up-regulated and this promotes cells viability by inhibition of lysosomal membranes permeability (Fig.5). Acidic medium inside lysosomes is an important factor that makes significant, but temporal, influence on the aggregation state of nanoparticles. Size distribution varies, in average, from 100 to 10 nm and even to single molecules. Disaggregated particles may incorporate into lysosomal membranes, forming fullerene-containing mixed bilayer membranes. This stabilizes lysosomes and decrease permeability of lysosomal membranes, in particular, for destructing factors. Decrease of cathepsin release from lysosomes and inhibition of apoptosis, induced by TNF-α., takes place.

Mitochondrial deficiency

Cytotoxic effect of fullerols attracts a special attention. Studies [159], executed on rat hepatocytes, demonstrated that $C_{60}(OH)_{24}$ exhibits cytotoxicity, depending on drug concentration (0-0.25 mmole) and duration of exposition (0-3 hours), that is accompanied by formation of bubbles, loss of cellular ATP and GSH, elevation of MDA and oxidized glutathione (GSSG) levels. All this indicate the lipid peroxidation process. However, $C_{60}(OH)_{12}$ in concentration of 0.125 mmole demonstrated significantly lesser cytotoxicity at all parameters. It is considered that mitochondria represent the main target for fullerenes, so a mitochondrial deficiency, depolarization and inhibition of ATP synthesis are observed at an early stage. Lipid peroxidation in the result of oxidative stress is observed at more late stage. It is obvious that the toxic effect of fullerols depends on the hydroxyl group amount.

Pro-inflammatory cytokine

Derivatives of amino acid-C_{60} composition showed interesting concentration dependence in their effects on human epidermis keratinocytes. They in concentrations of 0.4 and 0.04 mg/mL caused decreasing of cells viability and initiated the pro-inflammatory reaction, but in concentrations less than 0.04 mg/mL, initiated loss of activity of

cytokines and supported survival of cells [160].

Strong anti-inflammatory properties were demonstrated by fulleropyrrolidone-thalidomide-C_{60} and C_{60}-fulleropyrrolidine-xanthine dyads [161]. In the same time, fullerol $C_{60}(OH)_{24}$ influences negatively on endothelial cells, because it has pro-inflammatory and pro-apoptotic effect on HUVECs culture [162], and $C_{60}(OH)_x$ activated macrophages and promoted releasing of TNF-α [163].

A mixture of nanocrystal suspension of C_{60}/C_{70}, prepared by MES (THF), demonstrated an ability to modulate a TNF-induced oxidative stress and subsequent apoptosis [164].
Attempts to utilize fullerenes as modulator of action of known drugs are prospective. For example, a hybrid C_{60}-dexamethasone preserves an anti-inflammatory activity of dexamethasone, but has a sufficiently more lower immunosuppressive effect [165].

Dendrite cells play a key role in immune defense of the organism, in particular, in inhibition of tumor growth. $[Gd@C_{82}(OH)_{22}]_n$ may cause phenotypic maturation of dendrite cells. These nanoparticles are the powerful activator for dendrite cells as well as for Th1 immune response. The mechanism proceeds through stimulation of cytokines, including IL-12, p70; predominant increasing of IFN-γ, IL-1β, and IL-2 production and up-regulation of co-stimulators CD80, CD83, CD86 [166].

NO-generation

Mechanochemically solubilized C_{60} is able to act as a cytoprotector against NO-induced cytotoxicity, but indirectly [167]. It seems that there is neutralization of superoxide radicals, produced by mitochondria, which interrupt a chain of peroxynitrite formation and caspases activation. However, it was shown [168] that, namely, the induction of peroxynitrite may be a critical event for genotoxicity of nanoC_{60}. Immune system of mollusks in a great degree serves as a target for nC_{60}, dissolved in artificial seawater [169]. The process is mediated by NO release simultaneously with activation of p38.

A pristine fullerene, in difference from carbon nanotubes, does not stimulate release of NO [170] in murine macrophages that show very low consumption of nanoparticles.

Under action of nC_{60} on tumor cells in murine melanoma in vivo, the tumor growth was increased, despite accumulation of nanoparticles in cells and their cytotoxic effect [155]. The process was accompanied by elevation of production of immunoregulatory free NO radicals in splenocytes and reduction of splenocyte-mediated proliferative responses on T- and B-cell mitogens: concanavalin A and bacterial lipopolysaccharide.

To study protective activities of fullerene against NO-induced cytotoxicity (NO was released into solution by sodium nitroprusside, SNP), soluble fullerenes were used and they were modified by β-alanine, valine and folic acid, which possess a direct acceptor activity in relation to NO-radicals [171]. A contact of rat pheochromocytoma with 1 mmole/L SNP caused a notable decrease of the mitochondrial membrane potential, activity of SOD, catalase (CAT) and glutathione peroxidase (Gpx), decreased viability of cells and increased the level of intracellular accumulation of NO and MDA. Increasing of caspase-3 activity was also observed. Nevertheless, pretreatment of cells by amino acid-C_{60}-derivatives before their contact with SNP sufficiently inhibited all these NO-induced events. The degree of inhibition depended on the morphology of aggregation of fullerene nanoparticles (a visible toxicity was absent). Morphology of aggregates also influenced their protective effect against H_2O_2-induced apoptosis [99].

Sulfonate derivatives of C_{60} increased NO content in the blood plasma after their intravenous administration [172]. In the same time, fullerols $C_{60}(OH)_{24}$ and $C_{60}(OH)_x$ demonstrated a direct NO quenching [111,163]. In the result, there was reducing of NO-induced decrease of CAT, glutathione-S-transferase (GST) and Gpx activities in the denucleated fraction of interstitial testicular cells of adult rats after SNP injection. It is suggested [**160-224**] that in vivo a competition between arginase and inducible NO-synthase (iNOS) for arginine as a substrate may take place. In the case of $C_{60}(OH)_x$ the elevation of arginase and suppression of NO was really observed.

It is interesting that a pure graphene is able to cause apoptosis through depletion of mitochondrial potential and elevation of intracellular ROS, activation of MAPKinases (JNK, ERK, p38) and TGF-β-signaling pathway, activating pro-apoptotic proteins of Bcl-2 family and also PARP and caspase-3 [173].

IV. EFFECTS OF FULLERENES ON PROTEINS AND DNA

Nanoparticles of modified fullerenes may potentially influence on proteins and biosystems, because their effects on cellular ionic homeostasis [174] and replication of viruses [138] are described. It is known a possibility of polyhydroxylated C_{60} [6,175], C_{60}-(glucosamine)$_6$ [176], carboxyfullerenes [4,5,152,156,177] and C_{60}-(cystine)$_5$ [98] derivatives to be involved in the relationships and reactions with proteins and biostructures that leads to modulation of apoptosis in different types of cells, including neurons.

Interacting with proteins, fullerene and its derivatives are able to alter their activity and properties [178,179]. An attempt was made to model interactions of C_{60} and a set of proteins that represent targets for drugs [180], in order of future developing of bioconjugate materials. Moreover, such modeling provides a possibility to obtain information about potential toxicity of conjugates as well as C_{60}-compounds. In modeling the data on antibacterial [181], neuroprotector [4,182] activity of fullerenes, their participation in DNA cleavage [183] and apoptosis [156], and also inhibition of amyloid structures [184] and ionic channels [139] were utilized.

Using docking [180], structures of C_{60} complexes with NOS, GST, and also with some proteins, in particular, β-secretase-1 and hypoxanthine phosphoribosyl transferase [185] were obtained. There are experimental data that fullerene derivatives participate in the inhibition of NOS [186], and glutathione reductase (Gsr) [187], and also of cysteine and serine proteases [67]. Anti-HIV (inhibitory) activity of fullerene derivatives [138,188,189], and also formation of fullerene-specific antibodies [190] are known.

It becomes evident on this basis that C_{60}-derivatives possess a possibility to readily interfere biochemical processes in the organism due to their binding with proteins and enzymes. From one side, it is important to learn how to use these possibilities in therapeutics purposes, predicting by docking the most favorable targets with help of fullerene derivatives. However, these processes may be dangerous for the organism, when unpredictably disrupting proliferation and interfering signaling pathways of apoptosis, which are not completely studied.

Interactions of fullerenes with BSA (bovine serum albumin) [191,192], HSA (human serum albumin, $K_{bind.}=1.2\ 10^7\ mole^{-1}$, Fig.6) [193] and lysozyme [194] are of particular importance. BSA and HSA execute a function of universal transporter of proteins and biologically active microelements (metals) in the organism [43].

A high affinity to HSA was demonstrated by organic phosphate-containing fullerols $C_{60}O_m(OH)_n(C(PO_3Et_2)_2)_L$, where m~8, n~12, L~1 [196]. In that there was alteration of the tertiary structure of HSA in the direction of larger compactness together with elevation of content of α-helices and β-strands and increase of polarity of microenvironment of Trp residue. Hence, HSA may provide delivery of nanoparticles to organs and tissues. However, simultaneously a competition is established regarding other physiologically important components due to changes of conformational state of the molecule and a simple competition.

It is still known a little regarding real effects of fullerenes on structure and functions of proteins moreover, despite some proteins interact with fullerenes, no crystal structure of such complexes was obtained to the date. However, it was demonstrated using docking [195] a high similarity between physico-chemical properties and geometry of the surface for sites of binding of fullerene with HIV-protease, BSA and HSA (Fig.6).

Carboxyfullerene forms a complex with β-lactoglobulin (a typical representative of a family of proteins of barrier fluid) [197], and a possibility of carboxyfullerene transfer from this complex to albumin was shown that expands our understanding of a mode of nanoparticles transport in a biological system.

During direct determination of mitochondrial Mg^{2+}-ATPase activity, it was revealed that the enzyme is inhibited by fullerol with IC_{50} =7,1 ± 0,3 μmole/L [198] and this process is a concentration-dependent one.

Usage of water-soluble hexasulfonate derivatives of fullerene C_{60} decreased concentration of lactate dehydrogenase in the blood [172].

Fullerolpyrrolidines are non-competitive inhibitors in relation to acetylcholinesterase, IC_{50} varied in a range 15.6-31.4 μmole/L [199].

Combined carboxyfullerene-C_{60} exhibited inhibitory activity against cysteine and serine proteinases. IC_{50} were equal: against calpain – 3.6 μmole/L; cathepsin – 10.5 μmole/L; papain – 43 μmole/L; trypsin – 5.6 μmole/L; plasmin – 3.2 μmole/L. Inhibition of thrombin was equal to 24% in concentration of preparation of 10 μmole/L [67,180]. As inhibitors, such fullerenes may be used in treatment of burns and as radioprotectors, when a strong activation of proteinases takes place.

Water-soluble fullerenes that have, as a side radical, alcoholic, amine or amino acid ones act as inhibitors of Zn-containing enzyme, carboanhydrase (CAs) [200]. 13 isoforms of CAs showed different inhibition profile by these compounds. The mechanism is linked with corking of the entrance to the active center of the enzyme by the fullerene grid (the same size ~1 nm in both cases), while side fragments interact with amino acid residues of the active center, including His64, His94, His96, Val121 and Thr200.

C_{60} is a non-competitive inhibitor of GST in relation to etacrynic acid with K_i=48.8±0.25 μmole/l [201]. Under the same conditions, Gsr is effectively inhibited by only carboxyl derivatives of fullerene [187].

An uracil adduct of C_{60} was obtained [202] that is able to bind complementarily with adenine,

adenosine and ATP. Also, porphyrin-fullerenes may exhibit various properties, for example, forming metallocomplexes. They are able to incorporate into proteins, for example, apo-myoglobin, with preparation of C_{60}-myoglobin [203**].**

DNA

One of the most known apoptosis pathways runs through DNA damages that activates p53-signaling pathway [204].

Water-soluble derivatives of C_{60} may sharply increase efficiency of polymerase reaction under relatively low DNA concentration [205] that is able to disturb a norm replication of DNA in vivo and initiate different signaling pathways of apoptosis.

Mono- and bis-methane phosphonates of C_{60} act in some cases as inhibitors of DNA- restriction endonucleases [15]. Inhibition of DNA-endonuclease Exo III by bis-methane phosphonate-C_{60} (BMPF) depends clearly on the fullerene dose and inhibition of PCR (polymerase chain reaction) with Taq DNA-polymerase (IC_{50}=2.7 μmole/l) with help of BMPF was decreased with increasing of concentration of Taq polymerase in PCR system [206]. It is suggested that this process does not correlate with ROS and depends on the binding of the fullerene adduct with the enzyme and not with DNA.

Investigation of binding of bacterial DNA with nanoC_{60} and fullerol showed [207] that at pH<9 the fullerol size is suitable for binding with DNA. In this case elevation of thermal and enzymatic (in relation to DNAaзe I and Hind III restrictase) DNA stability in a dose-dependent manner takes place. Necessary for protection concentration of fullerol was equal to 50-500 ng/μL. In the same time, a concentration of not less than 500 ng/μL was required to provide a protection from enzymatic cleavage during biding of DNA with nanoC_{60}. Also dependence between effect of fullerene nanoparticles size on the result of impact on DNA and toxicity was observed. For example, nanoC_{60} in size of 100 nm are unsuitable for binding with DNA.

DNA-fullerene binding is able to change a tertiary structure of DNA molecules and complicate their recognition by proteins because this process is based on the certain shape of the DNA molecule [208]. Seemingly, further it must affect the signaling pathway of apoptosis that involves p53.

Certain changes were demonstrated in [209] on the complex $C_{60}(OH)_{24}$-DNA, where fullerol bound strongly to phosphates outside the native DNA chain and to nitrogen bases pairs in the main channel of DNA double helix.

It is known that $C_{60}(OH)_{24}$ only in concentration of ~0.71 μmole/L begins to demonstrate an ability to inhibit DNA synthesis, while under lesser concentrations it inhibits proliferation. Thus, its effect is more cytostatic than cytotoxic. To understand various effects of fullerols and physical and chemical mechanism of their action, different components of fullerol were separated by isoelectric focusing [210]. Four fractions were identified with a general formulae $C_{60}(OH)_m(O)_n$, where m and n values may vary, according to their isoelectric point. Experiments, performed in vitro, showed that fullerols possess low toxicity. However, a fraction with the greatest density of the negative charge [(-1.913±0.008) 10^{-4} C] and smaller size (3.92±0.71 nm) causes DNA damage. In that, a free negative surface charge is determined by a degree of C@O functionalization. Hence, to obtain good biocompatibility, it is necessary to perform separation and purification of the raw fullerol.

Antivirus activity of fullerenes

Fullerene derivatives are able to be accommodated inside hydrophobic cavity of HIV-protease, thereby preventing access of substrates into catalytic center of the enzyme. Relatively long ago it was found [138] that a derivative fenetylaminosuccinate-C_{60} possess anti-HIV activity with K_{inh}=5.3 μmole/L. Dendrite derivatives of fullerene [83] showed EC_{50} equal to 0.22 μmole/L in lymphocytes of a patient with HIV-1 acute phase. To degrade selectively the HIV-1 protease, C_{60}-carbohydrate hybrid was used [211**]**. A docking was performed to analyze interactions of mono- and bis-adducts of fullerene C_{60} in order to investigate the binding of fullerene based inhibitors to the HIV-1 protease [212].

A number of works has shown [213,214] that prerequisites for antiviral activity in relation to HIV-1 and HIV-2 strains are, possibly, specific relative position of two substitutes and positive charges in the neighborhood of the carbon grid. This enhances attention of researchers to studying structure/activity relationships in C_{60} derivatives to reveal anti-HIV activity. It was found that only trans-2-isomers are prospective ones and presence of quaternary pyrrolidone nitrogen affect solubility [214]. Positive charges near C_{60}-framework may increase antivirus activity, while extension of solubilizing chains induces cytoxicity. Trans-isomer of bis-fulleropyrolydine-C_{60} showed interesting antivirus properties in relation to HIV, and no regiostereomers of this compound exhibited inhibitory activity in relation to DNA or RNA of viruses different from HIV.

A mechanism of HIV reversed transcriptase inhibition was registered for some fullerene derivatives [215]. However, at the moment it is hardly to talk about specificity of anti-HIV mechanism.

Recently due to development of conjugates synthesis, C_{60}-Curdlan (linear 1,3-β-glucan) sulfate

[216] was obtained in order combine anti-HIV activity of both components [217].

Adduct of fullerene with polyvinylpyrrolidone possesses antivirus effect in relation to influenza A and B virus [218]. Under effective dose of C_{60} ~5 μg/mL, its effect is stable during all cycle of the virus amplification.

IV. FULLERENES AND GENOTOXICITY

Oligonucleotide microchips were used identifying and profiling of gene expression in rat lungs after inhalation of C_{60} **[**219**]** and up-regulation of genes linked with inflammatory response, oxidative stress, apoptosis and metalloendonuclease activity was observed. Moreover, some genes, linked with immune system are subjected to up-regulation. In general, no severe pulmonary toxicity was observed. Fullerenes in lungs [220,221] are captured by alveolar macrophages, which, in such a manner, execute their protective role.

C_{60} in doses from 0 to 200 μg/mL and long exposition did not cause apoptosis of epithelial cells of murine lungs and mutations in CII gene, however, proliferation was slowed down (in G1 phase), DNA breaks are occurred, but amount of mutations was insufficient [222].

Comparative gene microchip analysis firstly showed on zebrafish that hydroxylated fullerenes causes de-regulation of circadian rhythm gene and also alter the regulation of genes, participating in activity of kinases, vesicular transport and immune response [223].

Emergence of genotoxic effect of fullerenes was registered at concentration of 2.24 μg/mL of medium in Drosophila melanogaster larvae [93] and human lymphocytes culture [74], where the strict concentration dependence was observed. It is suggested that the genotoxicity is a result of the lipid peroxidation induction.

Changes in the profile of expression of genes after intratracheal instillation with C_{60} in various dosages were characterized. In particles dose of 1 mg the next genes: Cxcl2, Cxcl6, Orm1 and Spp1 participate in the «inflammatory reaction» and Mmp7 and Mmp12 genes were highly expressed for more than 6 months in matrix metalloprotease activity **[**220]. Expression of some genes (predominantly, «inflammatory») correlated with the dose of introduced drug that makes it possible to use them as biomarkers.

Mechanism of immunotoxicity was studied [224] on murine BAL cells. In instillation of n-C_{60} elevation of pro-inflammatory cytokines such as IL-1, TNF-α and IL-6, and also Th1-cytokines (IL-12 and IFN-γ) in BAL-culture took place. Moreover, expression of MHC (major histocompatibility complex) of class II (H2-Eb1) molecules was stronger than those for MHC of class I (H2-T23). Increase of T-cell dissemination, cellular infiltration and damage of a tissue, linked with genes expression in the pulmonary tissue were also observed in the experimental period that indicates inflammatory response to appearance of nanoparticles. However, fine dispergated fullerenes in size of 33 nm and in amount of 0.1-0.2 mg during intratracheal instillation did not cause increase of inflammatory neutrophils level that was observed in a small amount after introduction of 1 mg of nanoC_{60} [87]. Also in these cases there was no significant elevation of expression of CINC-1,-2αβ and -3 (cytokine-induced neutrophil chemoattractant) in lungs.

According of [225] fullerene C_{60} (water-dispersive) adversely affects on cell activity of nonspecific immunity link by inhibiting the enzymatic activity of myeloperoxidase and the expression of molecules CD54. Hence this is the impact of C_{60} on the various phases and mechanisms of phagocytosis.

Modulating effect of fullerene in the combined molecules was demonstrated under usage of fullerene C_{60} conjugates with immunomodulating peptide Thr-Lys-Pro-Arg (TA) in the form of NH_2-TA-C_{60} (161 nm) and C_{60}-TA-COOH (132 nm) in concentration of 2-20 μmole/L at murine model in vitro. In comparison with the peptide TA enhancement of phagocytosis, chemotaxis activity and expression of MHC of class II. Conjugates were resistant in relation to degradation by leucine aminopeptidase, did not exhibit toxicity in relation to macrophages and on all parameters are the candidates for vaccine adjuvant [226]. Immunoactivation was observed in the case of nanocomposites of fullerene C_{60}-PVP and C_{60}-Tween-80 (0.01-0.1% solutions) [227] that showed a brightly expressed anti-inflammatory effect.

Gene modulating effect of fullerols $C_{60}(OH)_x$ (20 ppm) in comparison with other (non-carbon) nanoparticles was studied on human primary skin fibroblasts (HDF) [228]. The greatest changes of gene expression (in times in relation to control) were observed for TLR3 (2.59), TLR6 (1.84), IL1RAP (1.66), IKBKB (1.2), NFKB2 (1.29), CCL2 (0.62), NLRC4 (0.52), however, smaller changes were visible regarding expression of other genes. Thus, fullerols greatly influence on cytokines balance and, seemingly, increasing immunity in these conditions. In the same time, there were phosphorylation of p38 and JNK (MAPK) that leads to NF-κB activation and inflammatory response. This cascade is a result of ROS action and IL-6 up-regulation. It is obvious that the balance of cytokines may shift to any direction under changes of nanoparticles parameters or concentration.

Stable C_{60} nanoparticles, prepared in the form of suspensions with help of 0.1% sodium

carboxymethylcellulose or 0,1% water solution of Tween-80, did not demonstrate genotoxic ability in bacterial reversible mutation analysis, in vitro analysis of chromosomal aberrations and in vivo micro-nuclear analysis [78]. However, usage of fullerol $C_{60}(OH)_{24}$ indirectly in some cases caused decreasing of chromosomal aberrations frequency [229]. In the meantime, recent investigations showed that fullerols are perspective for inhibition of enzymes involved in processes of DNA replication, transcription etc., and leading to dysfunction of DNA with subsequent increasing of the mutation rate [207]. Authors suggest that the direct damage of DNA by fullerene derivatives is not great, but emerging ROS induce inflammatory processes and genetic damages [230]. In that, namely, peroxynitrite represented a signal event for genotoxicity and emergence of mutations (deletions) in gpt delta transgenic mouse primary embryo fibroblasts [168**]**.

It is necessary to remember that all these processes are dose- and size (morphology)-dependent ones.

V. ANTITUMOR EFFEICIENCY OF FULLERENE DERIVATIVES

Due to the ability to cause under definite conditions cell death, fullerenes are potential antitumor agents. However, predicting of pro- and antitumor properties of various derivatives of fullerenes, moreover, for different types of cells, is still a hard task. In this connection, computer approaches and DFT method for calculation of physico-chemical properties of fullerene derivatives are actively utilized. Calculations by method of DFT of stabilization of ortho-, meta- and para- substitutes in relation to aldehyde group in a series of 1-(4,5, and 6 –selenyl-derivatives of 3-formyl-phenyl) pyrrolidine fullerene molecules C_{60}-C_2H_4N-[3-$(CHO)C_6H_3SeX$], where X= CN, $CH_2CH(NH_2)CO_2H$ and $CH_2CH_2CH(NH_2)CO_2H$, in order to determine effect of such structural changes on electronic structure of fullerene derivatives [231] determining their oxidative properties, may serve as an example. In case of selen-cyanide systems, general tendency that ortho-structure is more stable was kept. Similar picture is observed in the case of selen-methionine group. However, in the case of selen-cysteine the para-structure was the most low energy one, probably due to close position of a proximal NH_2-group to a point of interaction Se-O. Such fullerene systems may be effective molecular acceptors of free electrons in biological systems.

Some forms of fullerols demonstrated antitumor activity in vivo in relation of hepatocarcinoma H22 [163] and in vitro cytoxicity against human liver carcinoma cells (HepG2) [91,154]. The effect depended on the dose and size of particles. It was shown through two lysosomal enzymatic markers (arginase and acid phosphatase of peritoneal macrophages, which were obtained from animals, treated in vivo) [163] that usage of fullerol $C_{60}(OH)_x$ stimulates significant activation of macrophages and inhibits the tumor growth. Production of TNF-α by fullerol-stimulated macrophages is sufficiently increased under action of $C_{60}(OH)_x$ in the dose range of 0.2-2 mg/kg. In that, no acute toxicity was observed at concentrations up to 5 mg/kg.

Daily doses of 0.08 and 0.4 mg/mL were used during investigation of fullerol $C_{60}(OH)_{20}$ for antitumor and antimetastatic activity [232] on EMT-6, metastatic model of breast cancer the average size of nanoparticles at pH 7 varied from 223 to 364 nm, correspondingly. In addition to expected modulation of oxidative stress, decreasing of expression of a few angiogenic factors in tumor tissues was observed. In particular, expression of CD-31 (PECAM-1 – molecule of adhesion of endothelial cells thrombocytes) and vascular density was decreased in tumors treated by fullerol. By this mode $C_{60}(OH)_{20}$ inhibits a tumor growth and suppresses metastasizing through signaling pathway linked with tyrosine kinase.

Bis-(N,N-dimethyl-pyrrolidin iodide)-C_{60} [233] demonstrated cytoxicity in relation to pro-myeloleukemic cells (HL-C60).

Endofullerenes are of special interest regarding cancer therapeutics. At present, antitumor effect of hydroxylated metallofullerene, containing gadolinium [$Gd@C_{82}(OH)_X$], which action is linked with accumulation of immune cells, was studied in detail **[**14**]**. However, presence of this compound in the tumor in vitro was not practically detected that suggests interrelationship of tumor growth inhibition and antitumor immunity activation [234]. It is known that up-regulated immune response in vivo is a favorable strategy for clinical treatment of cancer.

$Gd@C_{82}(OH)_{22}$ [235,236] of 2 nm in size and with mean size of its aggregates of 100 nm [14] possesses immunomodulating activity in vivo and in vitro. It may stimulate macrophages and T-cells to release of a few cytokines IL-2, IL-4, IL-5, TNF-α and IFN-γ that promote inhibition of tumor growth in vivo. Specific immunomodulating effects on T-cells and macrophages include polarization of cytokine balance to Th1 (T-helper cellular type 1) cytokines by decrease of Th2 cytokines production (IL-4, IL-5 and IL-6). Amount of Th1 cytokines (IL-2 , IFN-γ and TNF-α) in serum samples are increased. Modulation depends on a drug dose. Under low concentrations nanoparticles of $Gd@C_{82}(OH)_{22}$ slightly influence activity of immune cells in vitro. In high concentrations they notably increase immune responses and stimulate release of cytokines that facilitates removal of abnormal cells. In particular, increasing of TNF-α level that plays key role in cellular immune processes is observed. Gd @ $C_{82}(OH)_{22}$-nanoparticles are more effective than some clinical antitumor preparations in inhibition of

tumor growth in mice.

Many tumor cells (in particular, murine hepatoma H22 cells) have pro-coagulant activity that promotes local activation of the coagulation system. So, changes in blood coagulation were assessed after introduction of $[Gd@C_{82}(OH)_{22}]$ to mice. Elevation of APTT (activated partial thromboplastin time) and decrease of PT (protrombin time) in comparison with control group was revealed. Moreover, an elevated concentration of fibrinogen was observed in the blood plasma after introduction of $[Gd@C_{82}(OH)_{22}]$-nanoparticles [234]. Thus, this drug decreased in vivo blood supply of the tumor [166] and simultaneously down-regulated more than 10 angiogenic factors at mRNA level that was further confirmed at the protein level [237]. In that, all indicators on activity of enzymes linked with oxidative stress: Gpx, SOD, GST; CAT – demonstrated tendency of approaching normal level. In the same time, reduction of MDA level took place. This indicates high antioxidant properties of Gd-containing fullerene [238]. Moreover, the preparation promotes activation of dendrite cells enhancing the immune response [166]. Nanoparticles of $[Gd@C_{82}(OH)_{22}]_{\mathbf{n}}$ are the first fullerene derivative promoting maturation of dendrite cells as well as antigen-specific immune response.

Experiments on transplantation of malignant tumors to group of mice demonstrated efficiency of C_{60} usage to inhibit growth of such tumors [239]. This is linked not only with antioxidant activity of C_{60}, but also with blockage of specific cell receptors, in particular, endothelia growth factor.

A review [240] was devoted to possible use of C_{60} and C_{70}-fullero-pyrrolidines that include antitumor as well as antioxidant drugs [27].

Water-soluble co-polymer fullerene-acrylamide demonstrated in vitro activity against bone marrow tumor cells [241].

As concerned biodistribution of metal-containing fullerols, then, after intravenous injection to mice, $Gd@C_{82}(OH)_{40}$ was accumulated, predominantly, in kidney, liver, lungs and spleen [242]. $[Gd@C_{82}(OH)_{22}]$-nanoparticles were accumulated in bone tissue, pancreas, kidney, spleen and liver and only very small amount was directed to lungs [234]. Fullerol, containing holmium, $^{166}Ho@C_{82}(OH)_{\mathbf{y}}$ was distributed among different organs and tissues with exclusion of brain and adipocytes after 1 hour from its administration into the organism [117].

Using ^{99m}Tc, biodistribution of $C_{60}(OH)_{\mathbf{x}}(O)_{\mathbf{y}}$. was studied [243]. The compound was fastly absorbed by tissues, especially by coronal bone, breastbone, spine, liver and spleen. Its clearance was slow in all tissues with exception of the brain.

In the last time, conjugates of fullerenes with known drugs for enhancement and/or deliverance of drugs became a widespread event. For example, the fullerene-doxorubicin was used [244]. However, uptake of conjugates, containing fullerenes, and their biodistribution often substantially differs from those for free molecules of the drugs that require a detailed investigation. For example, DOX is localized in a cell nucleus, but its conjugate with fullerene is in a cytoplasm.

Comparative study of nC_{60} and nC_{60}(Nd) as agents that modify proliferation in HeLa cancer cells was performed [245]. Nanoparticles of nC_{60}(Nd) elevated chemotherapeutics susceptibility of cancer cells, and the mechanism of these processes included not only common for nC_{60} ROS-attacks, but also enhancing of autophagy. Elevation of chemotherapeutic activity proceeded already at low dose of the preparation without significant cytotoxicity. It is suggested that, while entering cells, the nanoparticles are captured by aytophagosomes, however, their inability to be degraded leads to block of the way after autofagosome/lysosome fusion due to autolysosomes accumulation. However, this needs an experimental confirmation.

VI. PORPHYRIN-FULLERENES AND TARGETED DELIVERY OF DRUGS

Over the last years a great attention is paid to using different fullerenes for drug transport. It is still relatively novel, although extensively developing field in the fullerene chemistry and their usage that needs new ideas and thorough investigations. Some contemporary examples of the drug delivery [246] and also a general strategy of nanoparticles utilization as transporters [34] have been described.

Concerning fullerenes, the most attractive conception is contained in the idea that there is a multiunit with properties of transporter and a few attached medicinal parts (for example, photosensibilizator) and also there is a lead unit possessing selectivity to target cells [247]. In another variant, an additional sensibilizing compound may be used as a transporter. In that, nanoparticles must be hydro- and lipophilic ones and be free of acute toxicity.

One of the prospective approaches in this field is the use of porphyrinfullerenes. Fullerenes are known as excellent electron acceptors due to their low energy of reorganization. A direct interaction of porphyrins and fullerene **[**248,249**]** and a strong interaction of bis-porphyrins with fullerenes in the solution are known. There are two methodologies for the system of electron transfer of photoexcited state of porphyrin and fullerene: covalent **[**250**]** and coordination **[**251**]** ones. Porphyrins, in turn, possess properties of receptors and are able to form complexes with metals cations yielding

metalloporphyrins. A class of dendrite porphyrins, containing a central atom of zinc inside and 32 ammonia groups, was a strongest singlet oxygen inducing cytotoxic agent [252]. It was possible to form various supramolecular complexes of fullerenes and metalloporphyrins such as, for example, were shown on Fig.7a **[**37]. A constant of association of relative flexible bis-porphyrins with C_{60} approximately is equal to 5 10^3 $mole^{-1}$ (in toluene) **[**253] and is varied in dependence on the central metal ion. For example, in the case of Rh(III) the association constant is equal to 2.5 10^7 $mole^{-1}$. In general, this value is greater for C_{70} than for C_{60} due to alteration of fullerene "ball" conformation [37**]** and associated differences in symmetry and a number of non-equivalent bonds **[**19,254**]**. Such supramolecules, in addition to their own modulating effects on cells, may serve as transporters for targeting delivery of fullerene conjugates (and fullerenes themselves) to biological targets in the organism. To perform a targeting transport of different drugs [85] a high electro negativity of fullerene molecules (C_{60} and C_{70}) are exploited.

Moreover, porphyrinfullerenes are exclusively attractive carriers for targeting delivery of drugs to organs and tissues, because they under a certain design possess an elevated bioavailability and non-toxic degradation products.

Porphyrinfullerene derivative PMC16 (Fig.7b) [255] was used for delivery of magnetic nuclei of ^{25}Mg that may increase more than two times the ATP yield [256] (that is very important in conditions of hypoxia-induced acidosis). PMC16 decreased the acidosis consequences, arisen during chemotherapy, and did not exhibit toxicity in a wide range of concentrations. After introduction into the organism, PMC16 was preferably accumulated in the myocardium and in a less degree in lymphocytes and brain. For comparison: accumulation of nC_{60} is observed, mainly, in the liver and spleen and sufficiently lower in other organs [257]. Being a cation exchanger, PMC16 prolonged release of metal ions in acidosis conditions only. PMC16 was also used for delivery of zinc isotopes to lymphocytes of healthy donors and patients with ALL-T, ALL-B and AML [142] that led in case of ALL-B and AML to increasing of apoptosis of cancer cells in specific conditions.

Construction of supramolecul, where fullerene derivatives or their complexes are used as guest molecules, is a relatively new scientific field in the drug delivery. In vitro supramolecules demonstrated themselves as good thermo-reacting co-polymer of poly- (N – isopropylacrylamide)–CD as a host molecule and adamantyl-C_{60} as a guest molecule [259]. Due to fullerene, these molecules possess acceptor ability in relation to OH-radicals and effectively inhibited oxidative damages of mitochondria.

Cationic micelles of block-copolymer poly (N-vinylcaprolactam)-C_{60} delivered fullerene to cells for further utilization in PDT **[**260].

Amphiphilic derivatives of C_{70}, in rational way packed into lipid bilayers with loading up to 65%, represent a new system of drug delivery [261]. In particular, lyposomal malonyl-fullerenes-C_{70} (ALM) were used. ALM have been effective quenching agents for superoxide and hydroxyl radicals and inhibited lipid peroxidation, while maintaining an integrity of lipid bilayer structure.

Use of fullerols as drug transporters may bring positive results in cancer therapy. So, fullerol ($C_{60}(OH)_8$)-DOX conjugates inhibited proliferation of cancer cell lines in vitro through blocking of G2/M stage of cell cycle [262]. Fullerols may serve as transporters of radioactive nuclides in vivo. $C_{60}(OH)_{20}$, labeled by $^{99m}Tc(CO)_3$ [263] as a complex was delivered quickly to all tissues, excepting the brain, and was kept their without loss of activity during 3 h. Rate of radioactivity clearance took place during 24 h. It is suggested to use in future a fullerol platform for cisplatin delivery.

To transport through ophthalmologic barrier, fullerols $C_{60}(OH)_{22-26}$ are used, however, it is necessary to remember that water-soluble fullerenes demonstrated cytotoxicity in relation to epithelial cells of human retina (HLE-B-3) [264,265]. However, $C_{60}(OH)_{22-24}$–nanoparticles are considered as transporters of photosensibilizators to eye (and skin) cells in PDT of tumors [265-267].

VII. PHOTOTOXICITY OF FULLERENES. PHOTODYNAMIC THERAPY

During light absorption fullerenes may actively generate ROS that make them possible agent in PDT. Depending on functional groups introduced into the molecule, fullerenes may effectively perform photoinactivation of pathogenic microbial cells and malignant cancer cells. However, under certain conditions many fullerenes are able to protect cells from UV and other irradiation. To determine a role of fullerenes in PDT, physical and chemical properties of a certain derivative as well as experimental conditions: duration and intensity of irradiation, concentration of a preparation, size of nanoparticles, aggregation are of great meaning.

Large amount of model investigations of fullerene phototoxicity are executed in frames of ecological investigations on some fish and invertebrates species in model water systems at simultaneous environmental level of UV. It is necessary to take into account the presence of organic substances, in particular, polycyclic aromatic hydrocarbons (PAHs), which bioavailability may altered by fullerenes [268]. For example, under short-term

expositions C_{60} protects cell components (mitochondria, microvilli, basal inclusions) from UV+fluoranthen (model PAHs) phototoxicity. However, long-term effects (21 days) even at low concentrations of C_{60} lead to cells damage in gastrointestinal tract of Daphnia Magna. This demonstrates an exclusive importance of interactions between stress agents and water nanoparticles in water medium. Such synergism must be accounted in medical usage of fullerenes.

The method of PDT is widely used in cancer treatment (for example, zinc-containing photosensibilizators are well-known [43]). Two types of effects are distinguished in PDT [269], where acting agents are preferably superoxide radicals or singlet oxygen (Fig.2**).** For fullerenes the method is based on the selective accumulation of photosensibilizator in tumor cells and its ability to generate both agents (singlet oxygen as well as superoxide radical) under irradiation with light beam of definite wavelength. The ability of fullerene to generate in these conditions ROS with rate of 10 nmole mL^{-1} min^{-1} was confirmed by EPR method [270].

In the present time, photosensibilizators on the basis of carbon nanostructures did not pass clinical trials and are not allowed for their practical use [271]. Nevertheless, investigations are widely carried out with hope for their further usage.

Incubation of tumor cells with fullerenes with subsequent irradiation by light causes apoptosis in different types of cancer through 4-6 hours after irradiation [272]. Mono-adducts of C_{60} (in comparison with bis- or tris-adducts) demonstrated the greatest activity in relation to cancer cells due to their high cell uptake and enhanced localization in mitochondria.

C_{60} with a few polyester chains are also prefer to be accumulated in cancer cells and under irradiation at λ=400-505 nm cause a tumor necrosis [273].

The next derivatives phenylalanine-C_{60}, folic acid-C_{60}, L-arginine-C_{60} in concentration of 5 μg/mL did not cause cytotoxicity in the dark during long time and possessed selectivity regarding tumor cells (HeLa) [274]. Decrease of mitochondrial membrane potential, cells viability and activity of SOD, CAT, Gpx and also increase of MDA were observed after irradiation by visible light. Finally, the apoptosis proceeded through enhancement of caspase-3 activity.

C_{60}-pyrofeoforbids with different amount of substitutes showed different phototoxicity in relation to leukemic human T-lymphocytes (Jurkat cells) [247]. Effects were determined by difference in their physical and chemical properties and, as consequence, by different intracellular uptakes.

Photoinduced cleavage of super-helix DNA pBR322 predominantly at guanine bases [269] was observed after incubation with carboxyfullerenes-C_{60} and irradiation by visible light (but no in the darkness). Triads tetraphenylporphyrin (TPP)-PVP-C_{60} [275] demonstrated good results in PDT. No dark cytotoxicity in relation of human lymphoblast cell line (K562, chronic leukemia) was observed under use of 1 μmole/L of sensibilizator. However, apoptosis of cancer cells without participation of caspase-3 took place under triad concentrations of 0.05-5μmole/L with irradiation by light at λ=436 nm (1000 mJ/sm^2, 20-200 mW/sm^2

PEG-fullerene-C_{60} demonstrated phototoxicity (λ=400-600 nm, 140 J/cm^2) in relation to human fibrosarcoma cells HT1080, significantly decreasing their viability (from 50 to 30% in dependence on the conditions). Normal fibroblasts in the same conditions kept viability of 85-93%. It is considered that PEG-fullerenes C_{60} possess good potential to be used in PDT with very small side effects for normal cells [276]. PEG-conjugated fullerenes, containing Gd^{3+} ion, were used for photodynamic therapy in combination with magnetic resonance tomography [277].

Co-polymers of C_{60}-N-vinylpyrrolidon demonstrated the best phototoxicity in relation to HeLa and murine osteogenic sarcoma cells under irradiation by light in comparison with other complexes of fullerene [278]. Cell apoptosis is already observed under low concentrations (5μg/mL) of such a copolymer and more than 30% of cells perished at concentration of 100 μg/ml. A cell membrane was a target for damages. It is considered that calcium as a secondary messenger participates in this photo-induced process.

Fullerol $C_{60}(OH)_{24}$) is a powerful photosensibilizator [279] at the expense of superoxide radicals and singlet oxygen generation through effective resonance transfer of energy [280]. $C_{60}(OH)_{24}$ is used in PDT in ophthalmology, because it is able to overcome eye barriers and some correlation between its intracellular distribution and progression in damage of human lens and retina in vivo is observed [281**]**.

Fullerol ($C_{60}(OH)_{19}(ONA)_{17}18H_2O$) also exhibited in water solutions a high phototoxicity in relation to cells and cellular compounds [282,283] that was explained by authors [279] as a result of possible accumulation of ROS-products.

Photosensibilizing and photoprotector role of fullerenes are intersected. Some works are devoted to joint role of fullerene as pro-oxidant as well as antioxidant in UVB-induced damages of different tissues, i.e. synergic or cumulative effects in PDT **[**13**]**. This problem is very important in production of cosmetic anti-sunburn means and also at some skin

diseases. It is known that under UV-irradiation a set of events, leading to pro-apoptotic alterations (generation of ROS, cell rounding, bubbling of its surface etc.) and anoikis, is observed at the cellular level [284]. In mice sebaceous glands fulfill a role of a main site for ROS generation in UV-irradiation [285]. Use of C_{60} did not lead to emergence of toxicity, but index of ROS and index of apoptosis were decreased. More significant decrease was detected at simultaneous use of ascorbic acid (AA) and fullerene that, possibly, is provided by binding of fullerene with AA and decreasing of the Fenton reaction yield due to intercalation of AA to the heme pocket. Thus, use of a sum of fullerene+AA in combination with UV-irradiation is an effective remedy against oxidative damage of a skin.

C_{60}, incorporated into phospholipid membrane (74.5 nm, C=150 ppm), in the case of its introduction before or after UVA irradiation (10 J/cm^2), restores viability of cells, decreasing at 30% the level of ROS [286]. Quick excretion of the drug is its shortage. Liposome-fullerene (250 ppm, with C= 0.75 ppm C_{60}) under full absence of own toxicity significantly inhibited damage caused by chronic UVA irradiation of skin (by 4 κJ/cm^2, in total 76 J/cm^2) [287]. Carboxyfullerenes sufficiently decreased human keratinocytes proliferation blocking induced by UVB-irradiation [288], simultaneously decreasing amount of cells with depolarized mitochondria. The mechanism of action included interference of the preparation to the process of ROS generation by depolarized mitochondria, however, without participation of Bcl-2. In the same time, a cationic adduct of C_{60} **(**Fig.7c,d) incorporated into liposome demonstrated high efficiency of HeLa cells damage in PDT [257].

Water-soluble nanoparticles containing fullerene-C_{60} incorporated into liposomes (LPF, 75.6 nm, up to 0.3% C_{60} by weight) showed dose-dependent protective effect HaCaT cells against OH-radicals, emerging under UVA- (12 J/cm^2) and UVB- (500mJ/cm^2) irradiation. Prevention of cell morphology degeneration was observed and any protective effect took place in the presence of C_{60} only [289].

C3 is able to protect selectively cells against intracellular and/or membrane changes in UV-irradiation **[**152**]**. It suggested that protection of epithelial cells A431 is linked with ability of, namely, this compound to maintain a network of cytoskeleton components and the integrity of coordination linkage, but only in the case, when fullerene derivative presents during irradiation. It is not excluded that the ability of a preparation to capture the superoxide radical before its conversion into OH- radical is a substantial component of the antioxidant action. However, C3 have been localized in the cell membrane.

Skin keratinocytes (HaCaT) were used for probating of different fullerols: $C_{60}(OH)_{44}$ $8H_2O$ (SHH-F), $C_{60}(OH)_{6\text{-}12}$ (LH-F) and $C_{60}(OH)_{32\text{-}34}$ $7H_2O$ (HH-F) [290] in conditions of UVA and UVB-irradiation. Acceptor activity in relation to ROS was higher for HH-F and SHH-F, than for LH-F that determined a degree of their cytoprotector effect, which was greater in the case of SHH-F. In that, protective effect of SHH-F in relation to UVB- induced damages was higher than those in relation to UVA. Thus, SHH-F is a highly effective cytoprotector under UV-irradiation.

Water-soluble derivative $(\gamma\text{-CD})_2/C_{60}$ is used in two ways: as drug transporter through eye barriers and photosensibilizator in PDT for tumors treatment **[**291**]**. 2 μmole/L of $(\gamma\text{-CD})_2/C_{60}$ have already been toxic for HLE B-3 cells in UVA irradiation. However, the effect was not observed under irradiation by visible light and in the darkness. In the meantime, aggregated nanoparticles did not provide such an effect even at 30 μmole/L. Namely singlet oxygen is an important intermediate product of phototoxicity of monomer $(\gamma\text{-CD})_2/C_{60}$ and its production decreases with particles aggregation degree growth. Photodynamic activity of C_{70}-γ-cyclodextrine complex was sufficiently greater than those for C_{60} [15]. Similar picture was observed in comparison of photodynamic activity (λ>400 nm) of C_{60} and C_{70} incorporated into lipid membrane in relation to HeLa cells [292]. Authors consider that this is linked with a simple difference in their ability to generate singlet oxygen, due to asymmetry of C_{70}.

Investigation of [293] phototoxicity of three fullerene hexa-cis-adducts in combination with different amount of introduced photosensibilizators: bis (3^1,3^2-didehydrophytochlorine) fullerene [5:1]-hexa-adduct (FHP1), fullerene [5:1]-hexa-adduct with six 3^1,3^2- didehydrophytochlorine groups (FHP6) and fullerene[6:0]-hexa-adduct with 12-3^1,3^2- didehydrophytochlorine units (FHP12) was performed and FHP6 was the most prospective one. The degree of intracellular uptake, which was depended on the size and asymmetry of the fullerene complex, that affected the singlet oxygen quantum yield, had the greatest meaning.

Some fullerols cause phototoxicity of human retina pigment epithelial cells [114]. Early apoptosis proceeds already at concentrations >5 μmole/L and a dose of 8.5 J/cm^2 of visible light (quantum yield of singlet oxygen is 0.05).

High phototoxicity was observed under action of 1 μmole/L of diad porphyrin-C_{60} (P-C_{60}), incorporated into liposomes, on the cell line of human larynx carcinoma Hep-2. Death of 80% of cells was observed under 54 J/cm^2. [294]. There is a first case, when a high ability of such compounds to form a photo-induced state with isolated (separated) charge was stressed. The cells viability depended on the

light level. High cytotoxic effect was kept even in the argon atmosphere. Damages were caused through the mechanism of $^1O_2$ – mediated photoreaction process, or through ROS attack under low oxygen concentration in dependence on sensibilizator localization site micro-environment. Caspase-3 pathway-dependent apoptosis (58% of apoptotic cells) was substituted by predominance of necrotic events under anaerobic conditions.

A fullerene-carbohydrate hybrid that did not require any additions was used for selective degradation of a target protein, HIV-1 protease, under irradiation by UV or visible light [211]. Carbohydrate-C_{60} acts through generation of singlet oxygen during laser irradiation with λ=355 nm [295]. PDT did not reveal cytotoxicity in usage of fullerene glyco-conjugates against normal fibroblasts targeting, namely, cancer cells [296]. In that, carbohydrate-substituted C_{60} inhibited lipid peroxidation in the blood plasma [297].

Cationic micelles of block-copolymers of poly(N-vinylcaprolactam)-C_{60} demonstrated themselves as a potential antivirus drug [298] and, simultaneously, strong photosensibilizator under UV-irradiation [260].

Using BMPF (4 μmole/L, irradiation by green light) and HeLa cells, it was shown [299] that ROS are involved in the process of sensibilization of apoptosis and necrosis together with calcium ions. Simultaneously, BMPF enhances lipid peroxidation increasing the MDA level in dependence on dose and duration of irradiation [269]. Presence of extracellular calcium promotes activity of fullerene derivatives, but its removal does not interrupt their membrane damaging activity that indicates for existence of both calcium-dependent and calcium-independent ways in the process.

Simultaneous action of C_{60} (12-50 nm, 50 μmole/L) colloid solution and irradiation in UV- and visible light range caused cytotoxic effects on leukemic T-lymphocytes and Jurkat cell line (but not thymocytes) [300]. The process was accompanied by elevated activation of caspase-3 and depended on C_{60} concentration.

A hypothesis regarding usage of fullerenes to mediate PDT of intraperitoneal carcinomatosis was checked [301], applying N-methyl-pyrrolidine-C_{60}, placed into Cremophore-EL-micelles, and illumination by white light through the abdominal wall. Domination of necrotic events over apoptosis was observed.

Dendrite C_{60} [11] inhibited growth of cells in the darkness and was slightly phototoxic under UV-irradiation due to independent formation of aggregates. A method of preparation of fullerene nanoparticles played a great role in its phototoxic activity [260].

PVP–C_{60} [302] repressed the changes, caused by UVA HaCaT cells in the form of translocations of the transcription factor NF-κB into cytoplasm to the nucleus of keratinocytes. Protective effect and apoptosis abnormal signaling pathways blocking were observed.

Thus, photosensibilizing action of fullerene derivatives may be performed at the expense of $^1O_2$ (C_{60}) and ROS enhancing ($C_{60}(OH)_{18}$). In that it is necessary to take into account the result of differential interaction with various structures, for example, binding to molecules of the lipid membrane, increasing of OH-generation etc. The effect may be additionally enhanced by using of light gathering antenna molecule [273]. The greatest phototoxicity is characteristic for mono-substituted C_{60} adducts that have no an ability to self-aggregation, especially in the presence of calcium ions. The process is a dose- and concentration-dependent and the method of preparation of fullerene nanoparticles is of a great importance.

It is necessary to account that fullerenes may be more effective in PDT of hypoxia tumors (where the oxygen level is low), because they are able to change a mechanism of cell damage.
In the recent works [303] an idea of fullerene association with porphyrin structures in order to develop new photosensibilizators with increased generation of singlet oxygen and improved penetration into tumors is discussed. Some modern aspects of fullerene-mediated PDT, in particular, therapeutic perspectives of their use, are considered in the review [304]**.** In particular, using of this method for rescuing of mice, whose wounds were infected by gram-negative bacteria, was demonstrated.

I. IONIZING RADIATION AND FULLERENES

It is known that impact of radiation in great degree is determined by generation of larger amounts of ROS. Cytotoxic or, on the contrary, antioxidant effects of fullerenes may play a substantial role in these conditions, increasing or compensating impact of ionizing radiation on the organism. Moreover, properties of the fullerenes may also be changed under action of ionizing radiation.

NanoC_{60} in certain conditions inhibit tumor cells growth, expressing properties of a sensibilizator under radiotherapy, enhancing apoptosis [305].

Radioprotective (anti-radical) activity of hydrated fullerene C_{60}HyFn and its labile nanosize clusters at concentrations of 10^{-11}-10^{-6} mole/L was developed under X-ray irradiation of DNA (1-7 Gy in vitro) **[**306**]**. Using 8-oxoguanine as a marker of DNA

oxidative damage, it was shown that C_{60}HyFn at concentrations of 10^{-7}-10^{-6} mole/L protects nucleic acids against radical-induced damage. An optimal radioprotective concentration of C_{60}HyFn was equal to 1 mg/kg in vivo (mice, intraperitoneally, 1 hour before or 15 min. after irradiation) at the lethal dose of 7 Gy. Lysine-C_{60} did not express visible toxicity in relation to human lymphoblastic cells AHH-1 and was used for preliminary treatment of cells before γ-irradiation (>400 mg/L). This sufficiently increased the cell survival after irradiation, decreasing the apoptosis level in a dose-dependent manner [307].

Dendro-C_{60}-fullerene – the fullerene derivative, containing 18 carboxyl groups (C_{60}DF) [308], is able to protect human lymphocytes and intestine cells from consequences of impact of high doses of γ-irradiation. The process includes decrease of ROS level, inhibition of radiation-induced apoptosis and cells necrosis, DNA damages, oxidative stress. However, the process is not selective, because no difference between modest protective effect of the dendro-fullerene on normal fibroblasts and tumor cells was observed in vivo. Dose modifying factor (DMF) was equal of 1.1 [309]. $LD_{50/30}$ for mice, received 300 mg/kg of the dendro-fullerene before irradiation, was equal to 10.09 Gy in comparison with 8.29 Gy for control group. No protective effect was described for a dose of the drug of 200 mg/kg. Protective effect, linked with antioxidant effects of C_{60}DF in more wide range of usage, was observed under irradiation of Danio rerio embryos in a dose of 20 Gy and 40 Gy [310].

γ-Irradiation is able to influence on cytotoxicity of n-C_{60} (THF) **[**7**]**. Irradiated fullerene not only did not cause oxidative stress and induce ERK-dependent death of different mammalian cells, but, on the contrary, protected cells against oxidative stress, induced by starting THF-nC_{60} or hydrogen peroxide. Thus, γ-irradiation is able to alter physical and chemical properties of n-C_{60}, leading to full loss of its cytotoxicity and transforming it into a cytoprotective agent. In this case, it is not possible to exclude a possibility of functionalization of fullerene surface by products of water radiolysis that, in addition to a possible role of the residual THF in cytotoxicity, is able to cause the loss of cytotoxicity and acquisition of new properties by the fullerene.

Observed protective effect of polyhydroxylated derivatives of fullerene attracts great attention, however, the mechanism of action is not clarified to the moment, excluding its antioxidant action. It is known [311,312] that fullerene derivatives, predominantly, linked with mitochondria. It is also possible that nanosize particles may be captured by reticule-endothelial cells [313]. Namely, localization of one or another fullerene derivatives, may serve as decisive factor of their effector activity. In the next work [314] $C_{60}(OH)_{24}$ was utilized in a dose of 40 mg/kg for 2 weeks before irradiation of the whole body of mice with a lethal dose of γ-irradiation (^{60}Co). In comparison with control group animals receiving the drug demonstrated decrease of mortality due to elevation of immunity, decrease of oxidative damages and improvement of mitochondria functioning (restoration of mitochondrial membrane potential).

Fullerols, exhibiting protective effect in relation to heart and liver against chronic toxicity induced by doxorubicin [315], possessed also radioprotective effect during X-ray irradiation of animals (8 Gy) [316].

C_{60}-PVP and γ-CD-C_{60}, acting as antioxidants, are able to be stabilizers of radioprotective properties of β-carotene, preventing its oxidation [317] that increases the interest to them as compensating drugs during cancer treatment using radiotherapy.

There is information [318] about the possibility of combined action sulfa-containing drugs as radioprotectors and derivatives of C_{60}, which in some cases results to reduce the side effects of the original drug (amifostine).

CONCLUSION

To utilize fullerenes in pharmaceutics, it is necessary to have a full understanding about their effects on processes of production/extinguishing of ROS, because in most cases they form the basis for biological effects of fullerenes, including corresponding signaling pathways in apoptosis. It is also necessary to take into account the factors that modify these processes and alter their correlation. Among them are: methods of preparation and conditions for fullerenes action and also spontaneous processes of their modification in some cases, for example, under irradiation by ionizing radiation. Comprehensive investigation of these inter-relationships is necessary to strictly control ROS-dependent biological effects of different fullerenes and present their potential for therapeutic use. In some cases, it is necessary, firstly to perform theoretical analysis of preparations. For this purpose, a method of QNAR was developed that is concluded in the analysis of nanostructure-activity relationship on analogy with the method of QSAR [319]. It is obvious that nanoparticle size selection is a one of the most important factors responsible for their cytotoxicity or, on the contrary, absence of the toxicity. Total assessment of all parameters, able to affect signaling pathways of apoptosis, represents the serious problem in nanotechnology, including nanocarbon materials. Some effects of fullerenes on components of apoptosis signaling pathways are depicted on Fig.8.

One of important aspects of nanobiotechnology is linked with immunoreactivity of the organism to nanomaterials. Being powerful antioxidant, fullerene

is able to directly interfered cellular processes, where ROS are involved. This concerns processes, linked with inflammation: neurodegenerative diseases, ischemia, allergy etc. So, one important question is arising – is the immune system able to recognize the pure carbon framework of the fullerene or not? In a few studies it was demonstrated that neither fullerene nor its derivatives are able to generate C_{60}-specific antibodies and are not allergens. Expression of system anaphylaxis in sensibilized mice, treated by nano-C_{60}, is reliably lower in comparison with the control group. However, such works are rare and there are contradictions.

It is also necessary to take into account that in every subsequent doubling of a dose of drugs on the basis of nanosubstances their positive effect may be less appreciable, but the cytotoxic effect may significantly increase [85].

In the same time, it is necessary to note that fullerenes as drugs transporters, in some cases, are much suitable than carbon nanotubes, possessing different (depending on shape and size), but significant and sustainable toxicity, in particular, to lungs **[**147,320**]**.

It is very important that a system may be developed with fullerenes participation, when a single molecule combines acting component (for example, fullerene as generator of singlet oxygen), and a system of its targeting delivery to the target molecule (for example, cationic groups of side radical bind to anionic groups in DNA). So, it is absolutely necessary to develop new approaches to design preparations as well as experiments on nanomaterials assessment on animals.

Use of fullerenes in photo- and radio-therapy of cancer seems to be very perspective. In addition, searching of anti-tumor drugs among fullerenes is successfully continued.

A large amount of fullerene derivatives applications in medicine was described in [321]. At present, there are enough patents on concrete use of fullerene derivatives, for example, for treatment of granule cells and basophiles –mediated disease [322].

As a whole, active application of any nanoparticles in medicine must be under strict control till all their consequences (including remote ones) for the organism will be revealed in detail. One of the main research fields is revealing of preparation effects on apoptosis signaling pathways. At present, there are data regarding undoubtedly positive possibilities of fullerene nanoparticles as well as their potentially dangerous properties **[**323**]**. For example, neurons stopped to react on chemical signals and enter latent state in the presence of magnetic nanoparticles of less than 10 nm in size. Fullerenes in some conditions in vitro are able to kill liver, skin and brain cells [324,325]. Accumulation of nanoparticles in a cell medium under biodegradation is dangerous that may disrupt organelles integrity and even cause genetic mutations **[**323**]**. In the meantime, use of fullerene nanoparticles may bring a serious success today in therapy of such complicated diseases as cancer, HIV, AD or PD. Seemingly the greatest progress in near future will be seen in the field of construction of supramolecular nanoplatforms with filling by differently acting drugs and drug delivery with developing of targeted therapy and personalized medicine.

FIGURE LEGENDS

Fig.1. Hydroxylated fullerene (a), spheric cluster $(C_{60}@\{H_2O\}_n)_m$ (b), C_{60}-folic acid (c).

Fig.2. Mechanisms of singlet oxygen and superoxide radical generation by fullerenes.

Fig.3. C_{60}-derivative and adenosine receptors in SK-N-MC cell line of human neuroepithelioma. Copy from [88].

Fig.4. A scheme of events in CMECs, according to **[**119**]**, induced by hydrogen peroxide and treatment by $C_{60}(C(COOH)_2)_2$ nanoparticles. Changes are mediated by decreasing of JNK phosphorylation and inhibition of ROS production. There is down-regulation of the signaling pathway with decreasing of c-Jun and caspase-3 activation and inhibition of PARP cleavage and release of a mitochondrial cytochrome C.

Fig.5. The effect of $C_{60}(C(COOH)_2)_2$ on lysosomal and mitochondrial apoptotic pathway, according [158].

Fig.6. A site of carboxyfullerene binding with HSA, predicted by docking. Copy from [195].

Fig.7. (a**)-** Structure of supramolecular aggregate, octaamidoporphyrin with fullerene C_{60}. **(**b**)-** bakminsterfullerene (C_{60}) – 2 – (butadiene – 1- yl) тетра (о – γ –amino butyryl–о-phtalyl) ferroporphyrin (PMC16), containing 4 ions of magnetic isotope of ^{25}Mg, (c)- Complex of C_{60} with a liposome, possessing, due to compounds 1-4 (d), different surface charge, according to [258].

Fig.8 Effects of fullerenes (Fs) on some signaling pathways of apoptosis.

ABREVIATIONS

AA –ascorbic acid
AD – Alzheimer`s disease
ALM – liposomal malonyl fullerene-C_{70}
AMPA – 2-amino-3(3-hydroxy-5-methylisoksazol-4-yl)methyl isopropionic acid
AMPK – AMP-activated protein kinases

AP1 –activator protein 1 – transcription factor (leucine zipper)
APTT – activated partial thromboplastin time
BBB – blood brain barrier
BMPF – bis-methanophosphonate-C_{60}
BSA – bovine serum albumin
CAs – carbonic anhydrases
CAT – catalase
C3 – tris-malonyl-C_{60}
CD – cyclodexrin
C_{60}-DF – C_{60}-dendrofullerene with 18 carboxyl groups
CINC – cytokine-induced neutrophil chemoattractant
CMECs- brain microvessel endothelial cells
Cyt C – cytochrome C
Curdlan – linear 1,3β-glucan
DFT – density functional theory
DMF – dose modifying factor
DOX – doxorubicin
ERK – signal regulated kinases
ER – endoplasmatic reticulum
FMD – C_{60}-methionine
GSH/GSSG – reduced/oxidized glutathione
GluR – glutamate receptors
Gpx – glutathione peroxidase
GST – glutathione-S-transferase
Gsr – glutathione reductase
HAS – human serum albumin
HH-F – $C_{60}(OH)_{32-34}$ $7H_2O$
HIF – hypoxia-inducible factor responsible for the reaction to the lack of oxygen
Hsp70 – molecular shaperon
ID4 – inhibitor of differentiation 4
IL12; p70; IFN-γ; IL1β; IL2; IL6 – cytokins
JNK – c-Jun amino terminal kinases
KA – kainate
LH-F – $C_{60}(OH)_{6-12}$
MES – solvent exchange method
MMP-1; MMP-3; MMP-13 – matrix matalloproteinases
MDA – malonic dialdehyde
MPTP – 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MAPK – mitogen activated protein kinases
MHC – major histocompatibility complex
NADH/NAD^+ - reduced/oxidized nicotinamide adenine
NAC – N-acetyl-L-cysteine
NMDA – N-methyl-D-aspartate
NF-κB – nuclear factor kappa light-chain-enhancer of activated B cells (transcription factor)
NOS – NO-synthases
PAHs – polycyclic aromatic hydrocarbons
PARP – poly(ADP-ribose)polymerase
PCR – polymerase chain reaction
PD – Parkinson`s disease
PDT – photodynamic therapy
PEG – polyethylene glycol
PEGAM 1 (CD31) – platelet/endothelian cell adhesion molecule 1
PMC16 – Buckminster fullerene(C_{60})-2-(butadiene-1-yl) tetra-(o-γ-amino-butyryl-o-phtalyl) ferroporphyrin
POX – poly(2-alkyl-2-oxazoline)
PTX – pentoxifylline
PT – protrombin time
PVP – polyvinylpyrrolidone
RANK – receptor activator NF-κB
ROS – reactive oxidative species
SNP – sodium nitroferricyanide
SHH-F – $C_{60}(OH)_{44}$ $8H_2O$
SOD – superoxide dismutase
STZ – streptozotocin
TA – peptide Thr-Lys-Pro-Arg
TGF-β – transforming growth factor β
TNF-α – tumor necrosis factor α

ACKNOWLEDGMENT

This work was supported by RFBR grant № 10-08-00680. We wish to thank Professor Kuznetsov D.A. for valuable advice and Arkhangelsky S.E. – for the technical assistance.

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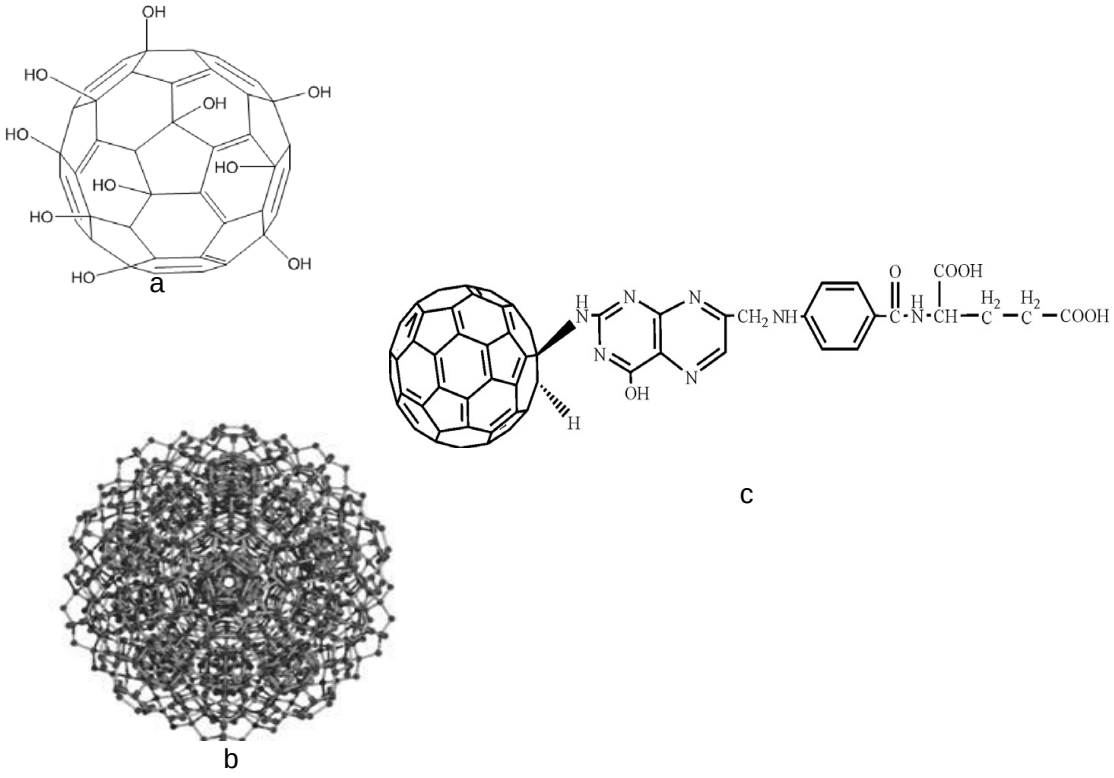
Fig. 1.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CH2 NH
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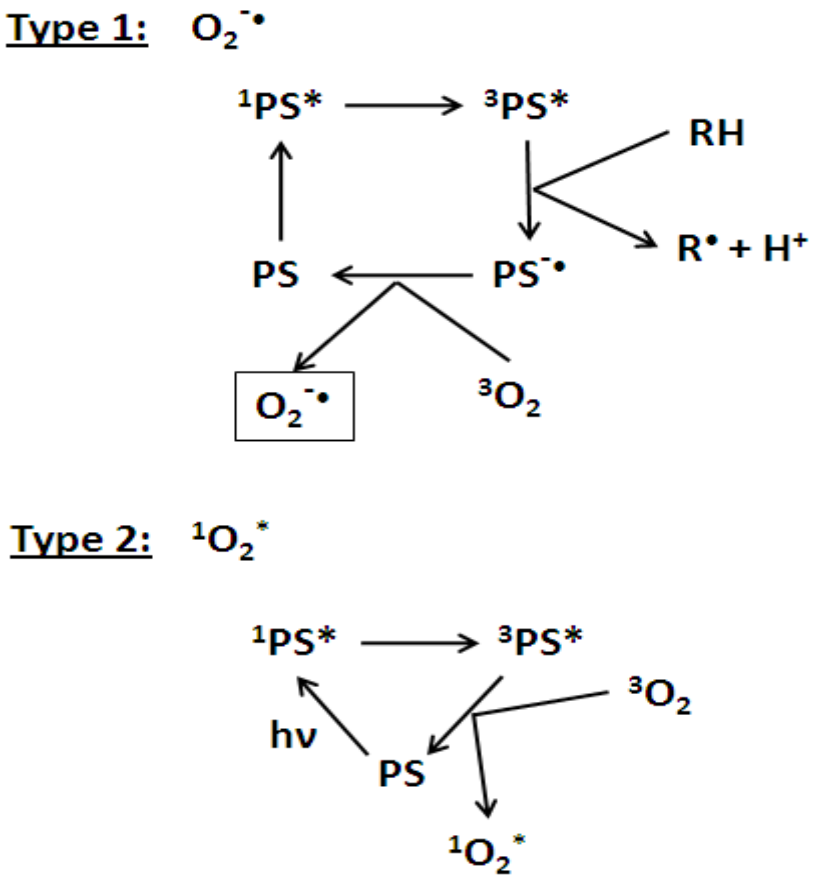
Fig. 2.


Type 1: $O_2^{-\bullet}$
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RH
$R^\bullet + H^+$
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Fig. 3.

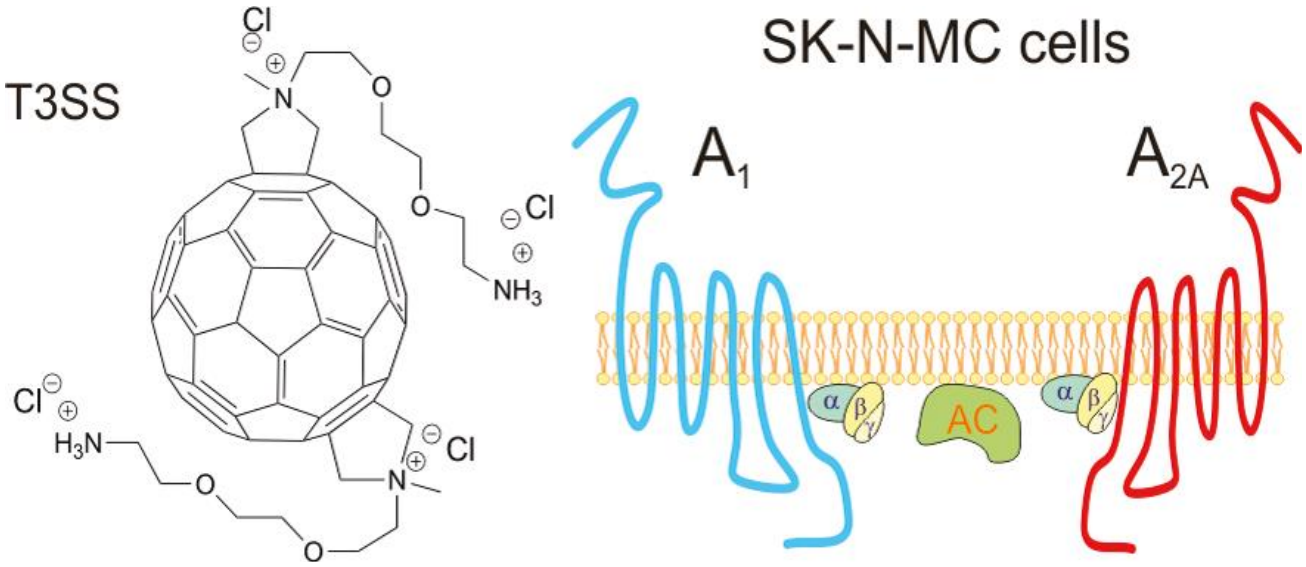
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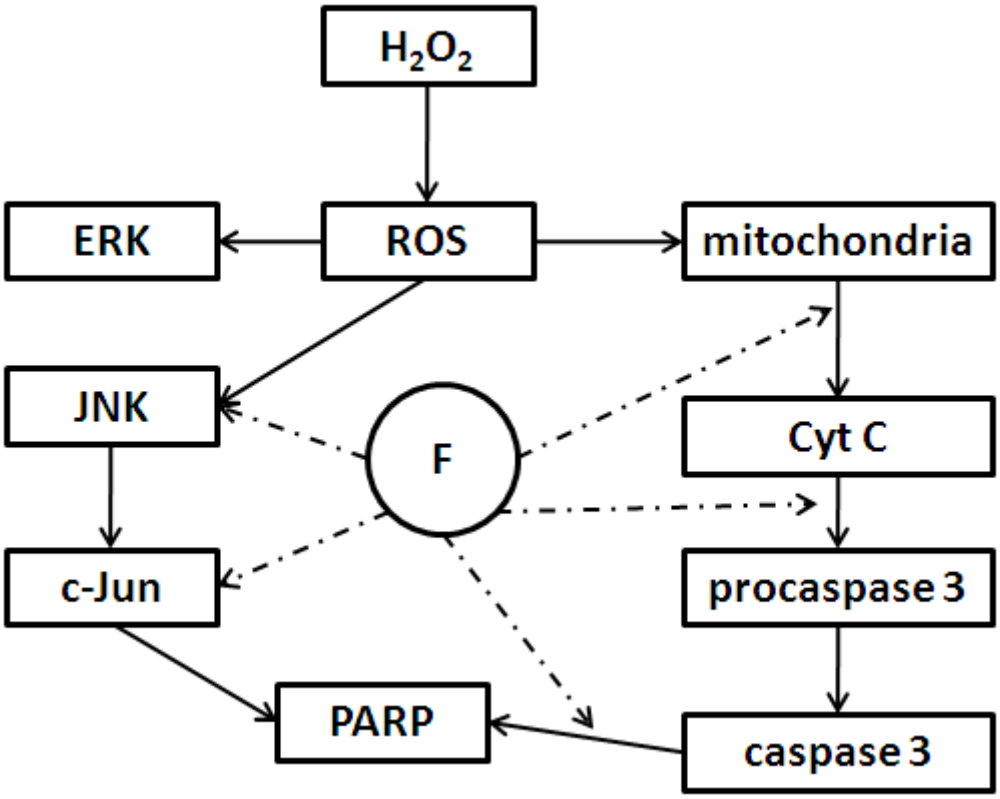
Fig. 4.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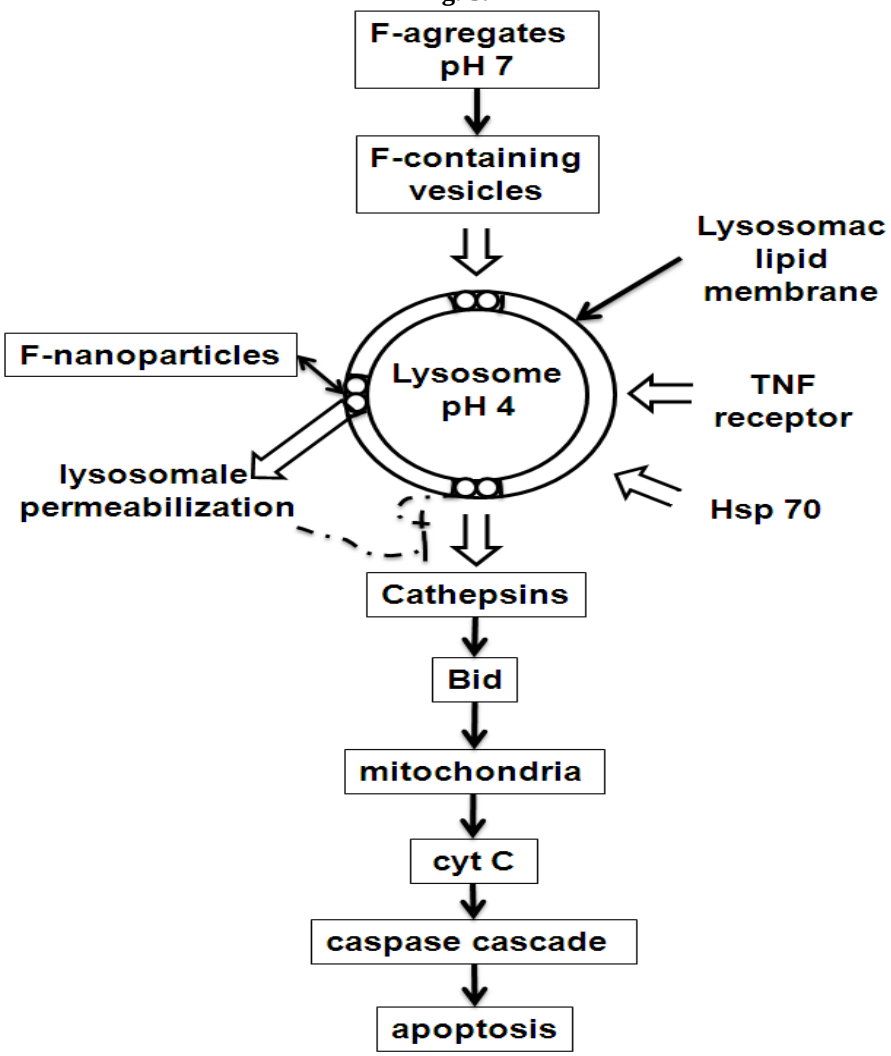
Cyt C
c-Jun
procaspase 3
PARP
caspase 3

Fig. 5.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caspase cascade
apoptosis

Fig. 6.

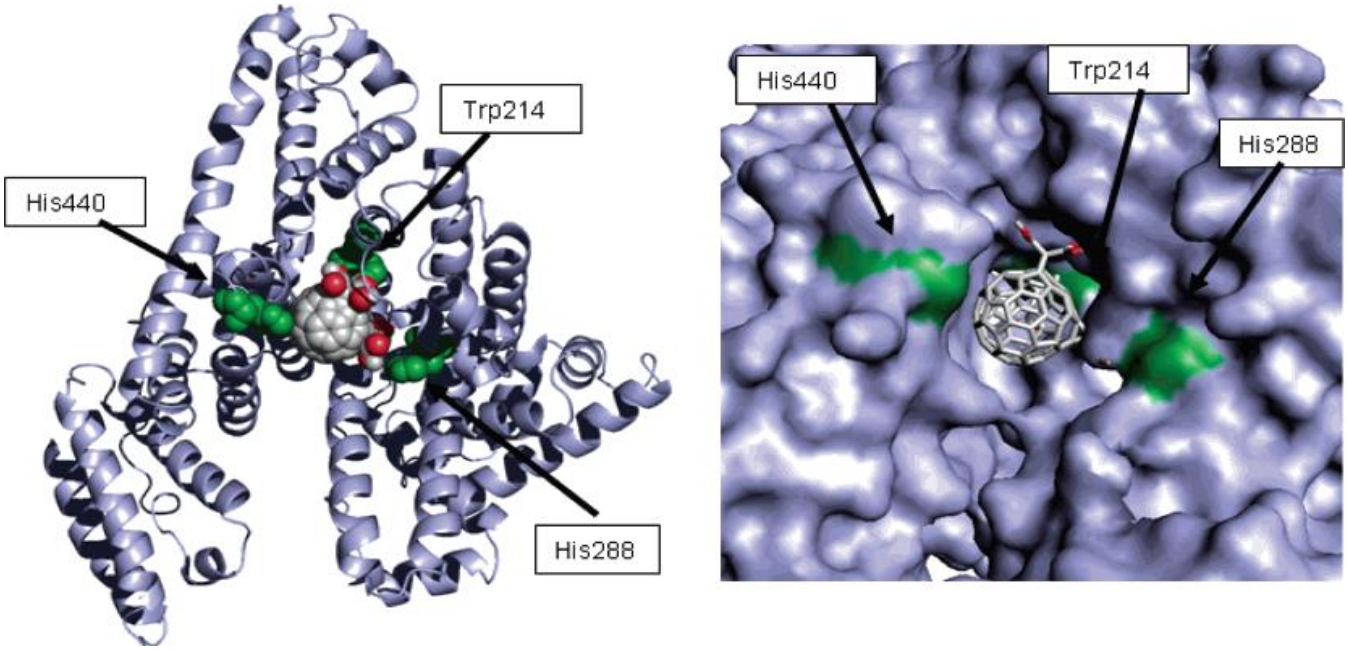
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Fig. 7

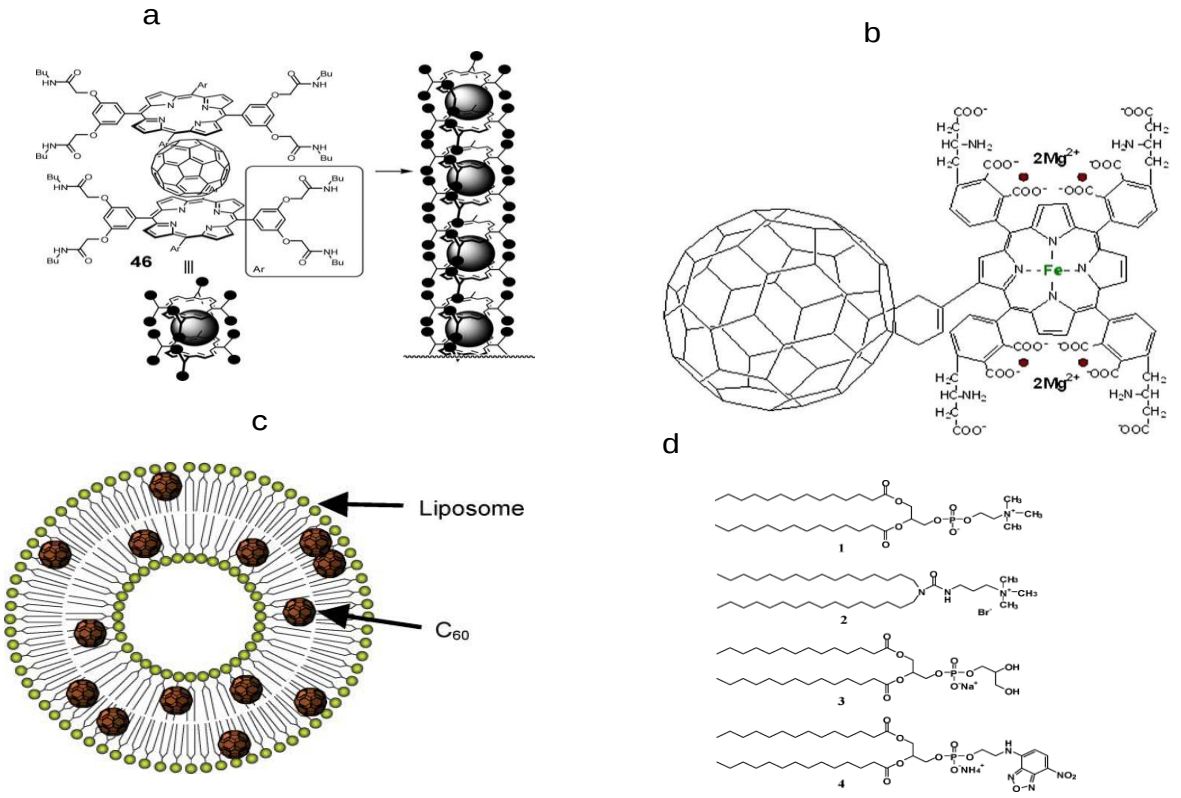
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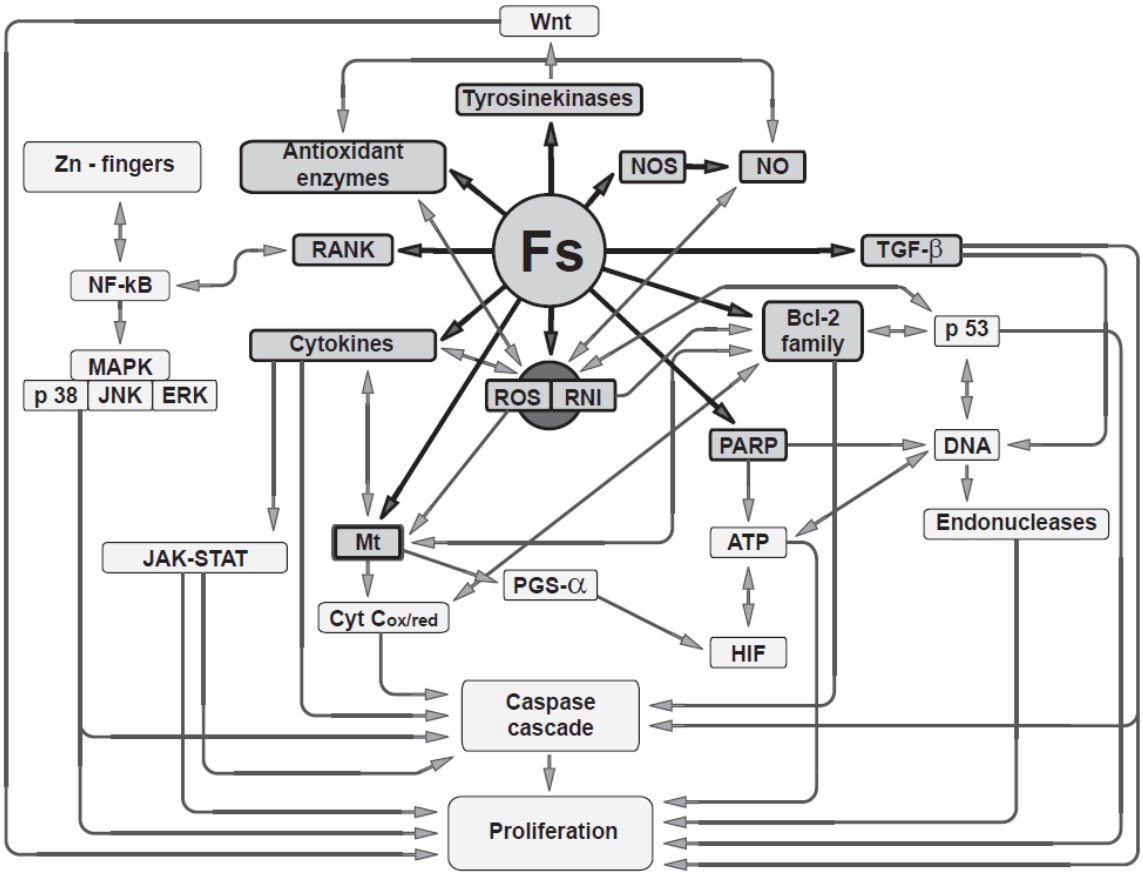
Fig. 8.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Antioxidant enzymes
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TGF-β
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Cytokines
Bcl-2 family
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MAPK
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DNA
Endonucleases
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Mt
ATP
PGS-α
Cyt Cox/red
HIF
Caspase cascade
Proliferation