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Opinion

Fullerene Trend in Biomedicine: Expectations and Reality

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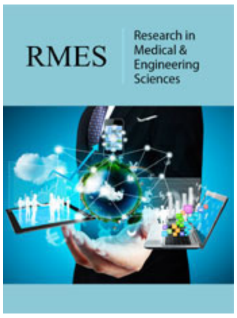

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Opinion

Fullerenes are the third allotropic form of carbon, along with diamond and graphite, where carbon atoms are situated in vertices of the closed shells (cages) [1]. Since their discovery in 1985, fullerenes have attracted an attention of scientists not only because of their unique and beautiful structure but also as the materials for possible applications in engineering and medicine. Lots of fullerenes with hollow carbon cages were synthesized and chemically functionalized. Biomedical effects of such "empty" fullerenes are mostly defined by the chemical groups attached to the fullerene cage [1,2]. Besides, there are the so-called endohedral metallofullerenes (EMF) molecules of which contain one or more atoms, among them lanthanides or heavy elements like Pb or Bi trapped inside the carbon cage [3,4]. The goal of this editorial is to summarize the ideas of using fullerenes for biomedicine and express our opinion concerning the prospects of their application for therapeutic purposes.

The discovery of fullerenes has inspired the searching of novel fullerene-based drugs. Over the last three and a half decades, lots of so-called chemically functionalized fullerenes, with carbon cages containing up to 132 carbon atoms, were synthesized and tested in biomedical experiments. Some of these compounds have indeed displayed the beneficial medical effects, among them antioxidant properties and neuroprotective effects, healing tendencies against hepatitis C, antibacterial and anti-viral properties, even anti-HIV. There are the evidences regarding prospects of the fullerene derivatives in oncology and anti-aging medicine [2,5-15]. Some fullerenes, under the action of UV light, produce singlet oxygen and other reactive oxygen species and, thus, they can be used, for example, in the photodynamic therapy of cancer. Moreover, the beneficial effects of the fullerene derivatives against diabetes (type 2 diabetes mellitus) and Alzheimer disease were revealed in the experiments with rats [14,15]. Usual laboratory Wistar rats do not suffer from Diabetes Type II or Alzheimer disease, but the fullerene enthusiasm has apparently brought the Russian scientists out of the routine knowledge.

Endohedral metallofullerenes also appear to have a considerable promise in biomedicine. It has been suggested that EMF with the appropriate particle-emitting radionuclides inside, among them β-emitting ^{89}Sr, ^{90}Y, ^{47}Sc, ^{64}Cu, ^{149}Pr, ^{153}Sm, ^{166}Ho, and ^{177}Lu show promise for radiation medicine while the advances in the molecular biotechnology provide targeting vectors to deliver therapeutic doses of the ionizing radiation with high specificity to the metastatic cancer cells thereby decreasing irradiation of healthy tissues [16]. Recently, the radioactive Pb-EMF and Bi-EMF, with β-emitting ^{212}Pb and α-emitting ^{212}Bi inside the cage, and there malonic ester derivatives were prepared for the first time [17]. The anti-cancer effects of ^{212}Pb, despite the favorable decay characteristics of this radionuclide, are usually limited because of the myelotoxicity resulting from accumulation of ^{212}Pb in the bone marrow. In the experiments with mice it was found that ^{212}Pb did not accumulate in the bone marrow after being administered within the endohedral fullerene, in contrast to the results with conventional poly amino carboxylate chelators for ^{212}Pb. The EMF molecules encapsulate radionuclides more stably and, thus, could potentially play a valuable role in radioimmunotherapy [17].

It is well known that Gd(III)-based chelates are in current clinical use as contrast agents for magnetic-resonance imaging (MRI). Meanwhile, the "spin leakage" of the fullerene shell of EMF may provide the more effective relaxation mechanism through the contact coupling of the delocalized electron spin with the nuclear spins of the solvent, as it was suggested in [4,16]. Indeed, the water proton relativity of Gd@C82(OH)n has turned out to be 20 times higher than that of the commercial contrast agent magnevist (gadolinium-diethylenetri-aminepentaacetic acid) [18]. The idea of using EMF as contrast agents for MRI appears to have considerable promise. For example, the derivatives of Gd-EMF functionalized with special cytokines increase their selectivity to the markers of chronic post-traumatic osteomyelitis [19] while the additional amino-groups can allow to use the Gd-EMF in imaging the glioblastoma tumor cells [20]. Moreover, the noninvasive imaging approach to detect and clinically differentiate chronic post-traumatic osteomyelitis from aseptic inflammation using the targeted metallofullerene MRI probe has been developed [21]. Thus, there are the grounds to believe that EMF, due to their unique physical and chemical properties, can provide prospects for designing the novel relaxants for MRI as well as the effective pharmaceuticals for radiation medicine in the new millennium.

Summing up the fullerene trend in biomedicine, one should take into account that all fullerenes are the artificial compounds. As such, they are extraneous to the living Nature. Therefore, no wonder that fullerenes were proved to be, in a greater or lesser degree, toxic [2,22,23]. Meanwhile, favorable biological responses of cells and multi-cellular organisms to low-dose exposures to toxins have long been known. This is a well-known phenomenon, the so-called hormesis. As it was said by Paracelsus, all things are poison, and nothing is without poison, the dosage alone makes it, so a thing is not a poison [24]. Therefore, it is little wonder that some derivates of empty fullerenes as well as some derivates of endohedral metallofullerenes, when being used at the relevantly low doses, display the above-mentioned therapeutic effects. For example, the commercially available creams, based on the C60-fullerenes can be found on the market [25]. Yet, negative side effects of long-range using of such compounds can hardly be excluded.

In summary, it should be recognized that, in spite of all the exciting ideas of using fullerenes in biomedicine proposed in the last years, most of them have already lost their charm.

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