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FULLERENES: ORAL TOXICITY AND BIOLOGICAL EFFECTS

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Among the various products of the nano industry, fullerenes occupy a special place. Fullerenes have many applications, including pharmacology, biosensors, packaging composites, plant protection products, etc. Fullerenes and their polyhydroxylated derivatives have pronounced antioxidant, hepatoprotective, radioprotective, and other types of protective action on the human body. However, the introduction into the circulation of products containing fullerenes is hindered by the ambiguity of the properties exhibited, consisting of the presence of signs of nanotoxicity for biological systems *in vitro* and *in vivo*. **This study aimed** to evaluate the oral toxicity and biological effects of the fullerene C_{60} and its water-soluble derivative $C_{60}(OH)_{24}$ at their daily doses from 0.1 to 10 mg/kg body weight (bw) in the long-term experiments on Wistar rats.

Nanomaterials

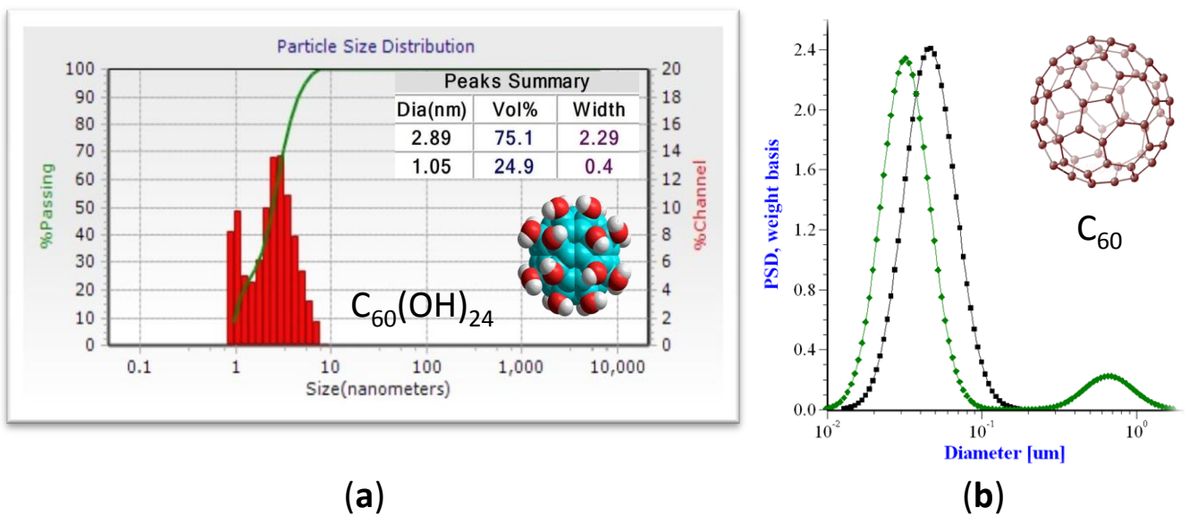
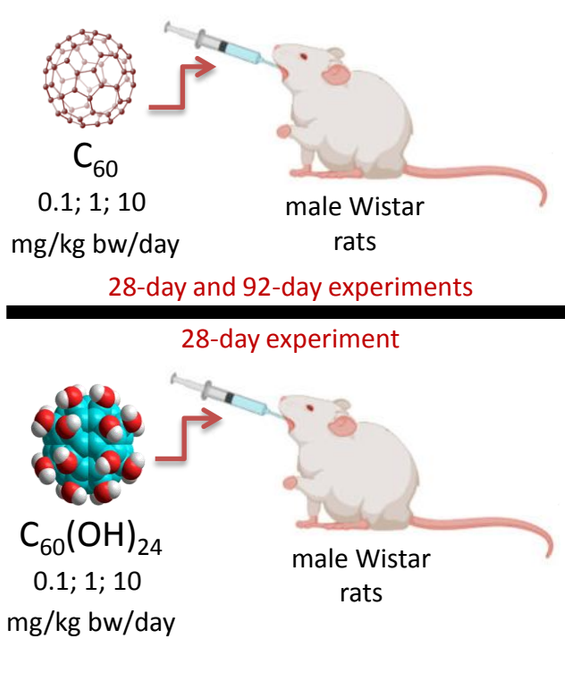


Fig. 1. *Fullerenes size distribution. (**a**) DLS of $C_{60}(OH)_{24}$ water solution (75.1% represented by particles with average diameter of ~2.89 nm and 24.9% represented by particles with diameter of ~1.05 nm. (**b**) Spectroacoustic study of water colloidal dispersion of fullerene C_{60} in 2% starch solution (75% represented by ~30 nm particles and 25% by ~600 nm).*

Study Design



Studied Indicators Set

- ✓ Integral (body weight gain, mass of internal organs)
- ✓ Biochemical indicators
- ✓ Hematological indicators
- ✓ Non-protein liver thiols (reduced glutathione)
- ✓ Selenium status (Microfluorimetric method)
- ✓ The state of the protective barrier function of the small intestine (ELISA)
- ✓ Liver morphology (laser confocal fluorescence microscopy)
- ✓ Bio-distribution of C_{60} in animal organs and tissues (HPLC)

C_{60} Toxicity Signs

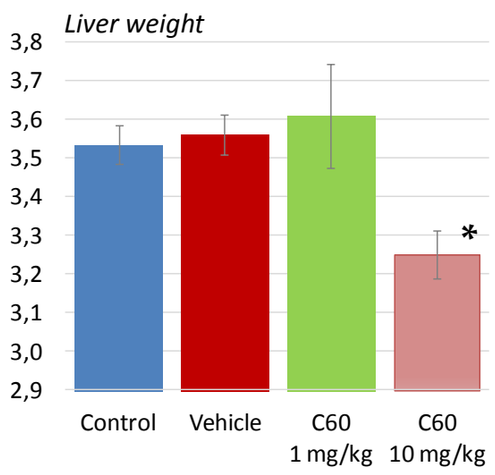


Fig. 2. *Relative weight of the rat liver at the end of the 28-day experiment., % of body, M±S.E.M. * - the difference with control groups is significant, P<0.05*

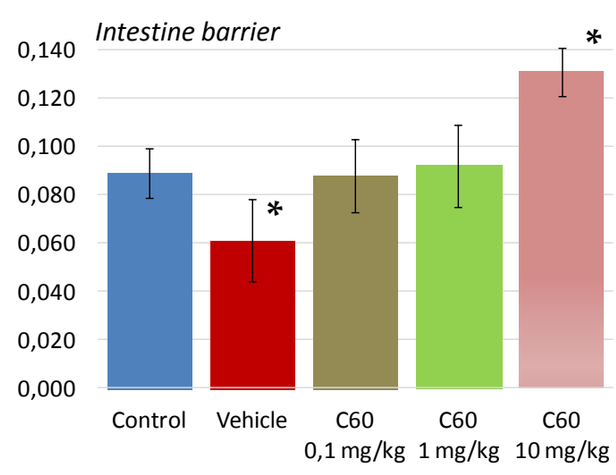


Fig. 3. *Absorption of the antigenic ovalbumin protein into the blood of animals, % of the administered dose at the end of the 92-day experiment, M±S.E.M. The groups marked with * differ significantly, P<0.05*

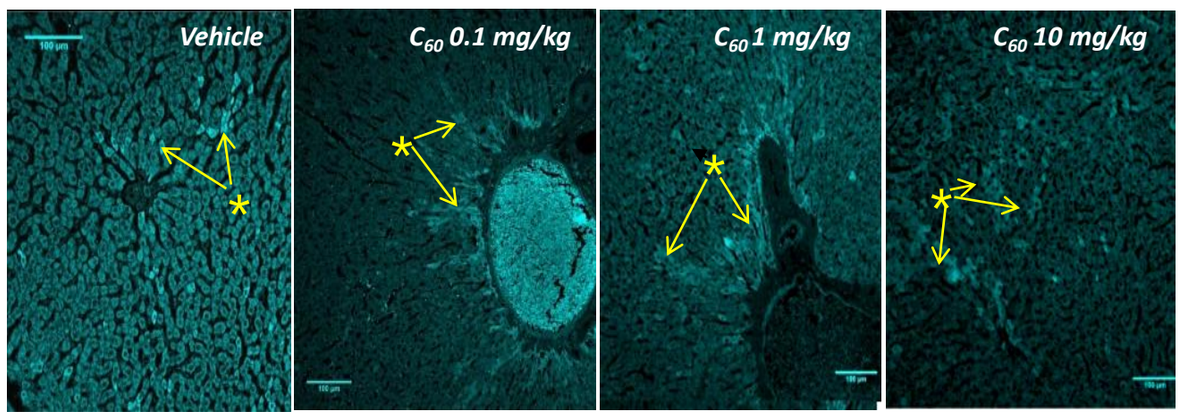


Fig. 4. *Comparison of confocal images of the liver stained with AT to CD106 (92-day experiment). The position of CD106+ cells morphologically similar to Kupfer macrophages was noted *. Magnification ×400*

$C_{60}(OH)_{24}$ Toxicity Signs

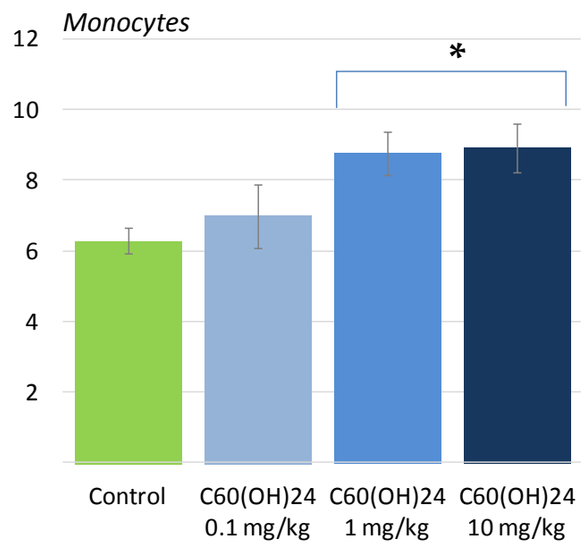


Fig. 5. *The average content of monocytes in the blood of rats on the 28th day of the experiment. * - the difference with control group is significant, P<0.05*

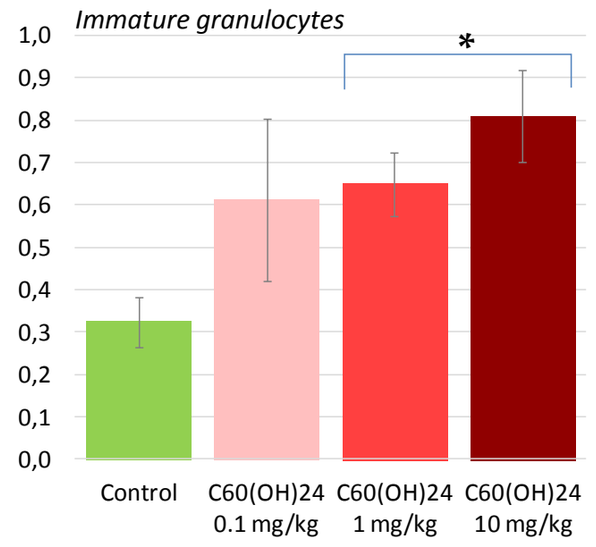


Fig. 6. *The average content of immature granulocytes in the blood of rats on the 28th day of the experiment. * - the difference with control group is significant, P<0.05*

Conclusion. As a result of daily intragastric administration of nanoscale dispersion of C_{60} to rats for 28 and 92 days at doses studied, changes in endpoints were revealed indicating the presence of a general toxic effect on the animal body, including a dose-dependent decrease in the relative weight of the liver, an increase in the permeability of the small intestine barrier for protein macromolecules by 100%, an increase in the number of CD_{106+} granular cells in the liver parenchyma. It should be noted that there is no reason to interpret the identified dose-depended effect of selenium accumulation in the brain as unfavorable (toxic), taking into account the role of selenium compounds as indirect antioxidants. Based on the analysis of the data obtained, the estimated NOAEL of C_{60} at subacute oral administration is in the range of 1-10 mg/kg bw/day. A 28-day subacute experiment with $C_{60}(OH)_{24}$ also demonstrated the presence of signs of a general toxic effect on the body of animals, based on the analysis of which the estimated NOAEL of $C_{60}(OH)_{24}$ is in the range of 0.1 to 1.0 mg/kg bw/day. The results obtained indicate the presence of risks associated with the effects of fullerenes on the human body during the oral route of intake and indicate the need for their regulation in consumer products (including food products) and environmental objects.

C_{60} and Selenium in Brain

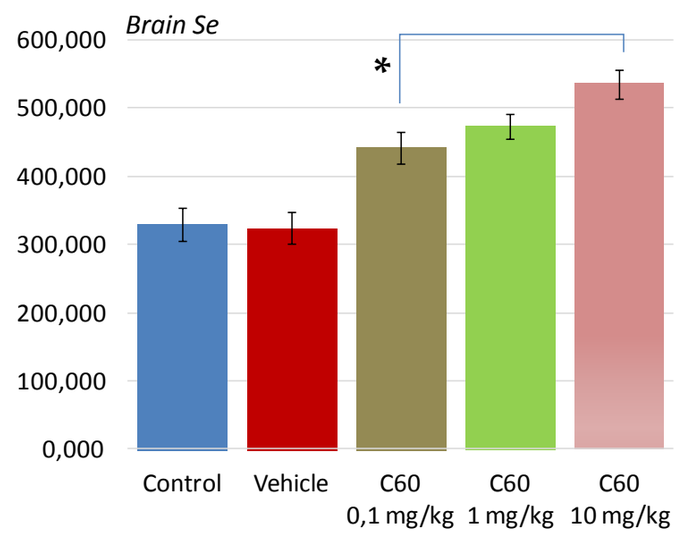


Fig. 7. *The average (M±SD) selenium content in the brain of rats treated with C_{60} for 92 days. * - differences between experimental groups and control groups are significant, P<0.05*