Taxus baccata Aril-Mediated Green Synthesis of Fe_3O_4 Nanoparticles for Lung Cancer: Antiproliferative Effects, Respiratory Safety Assessment, and Hyperthermia Potential

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1. Background and Aim

Green-synthesized magnetic iron oxide nanoparticles combine bioactive surface functionalization with magnetic responsiveness. *Taxus baccata* aril, rich in phenolics and carotenoids such as rhodoxanthin, is a promising plant source for green nanosynthesis. This study aimed to synthesize Tb-aril-mediated Fe_3O_4 NPs and evaluate their antiproliferative activity, respiratory biocompatibility, and magnetic hyperthermia potential.

Tb-aril → Green synthesis (Fe^{3+}:Fe^{2+} = 2:1 • alkaline precipitation • 80–82°C) → Fe_3O_4-NPs → A549 / EpiAirway™ → Biological and magnetic evaluation

2. Results and Discussion

Across complementary biological endpoints, Fe_3O_4-NPs consistently produced stronger concentration-dependent effects on A549 cells than Tb-aril alone, while EpiAirway™ viability remained above 70% at the tested concentrations.

2.1. Antiproliferative effects

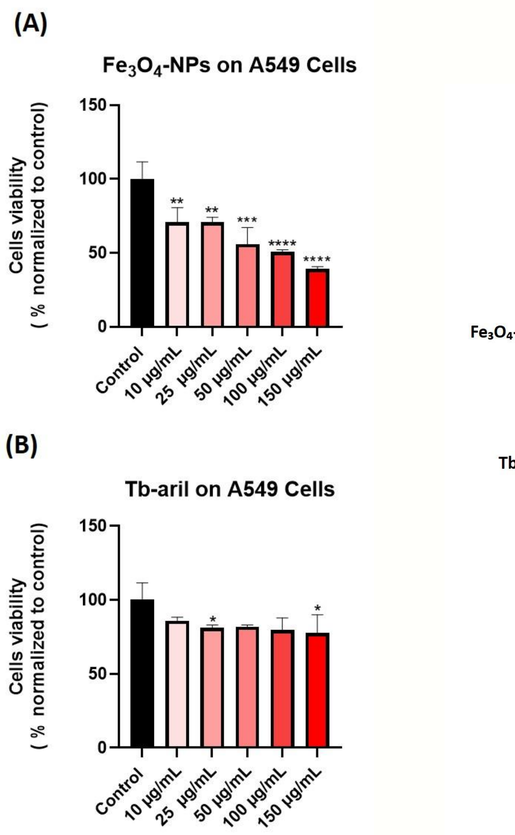


Figure 1. A549 cell viability after 24 h of exposure to Fe_3O_4-NPs (A) or Tb-aril (B), showing a stronger concentration-dependent reduction following Fe_3O_4-NP treatment.

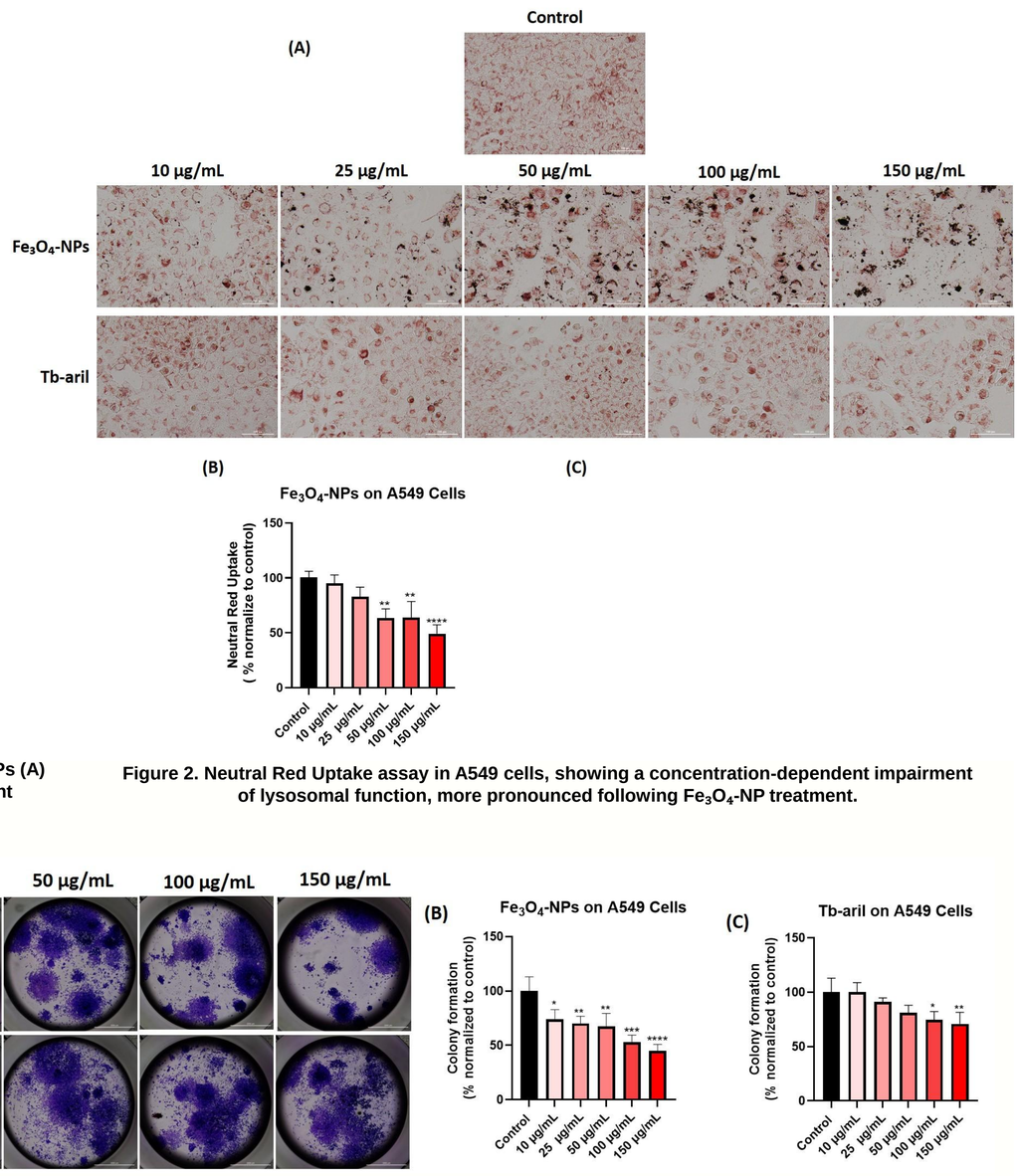


Figure 2. Neutral Red Uptake assay in A549 cells, showing a concentration-dependent impairment of lysosomal function, more pronounced following Fe_3O_4-NP treatment.

Figure 3. Colony formation assay showing a persistent concentration-dependent inhibition of A549 clonogenic capacity, stronger following Fe_3O_4-NP treatment.

2.2. Mechanisms of cellular injury

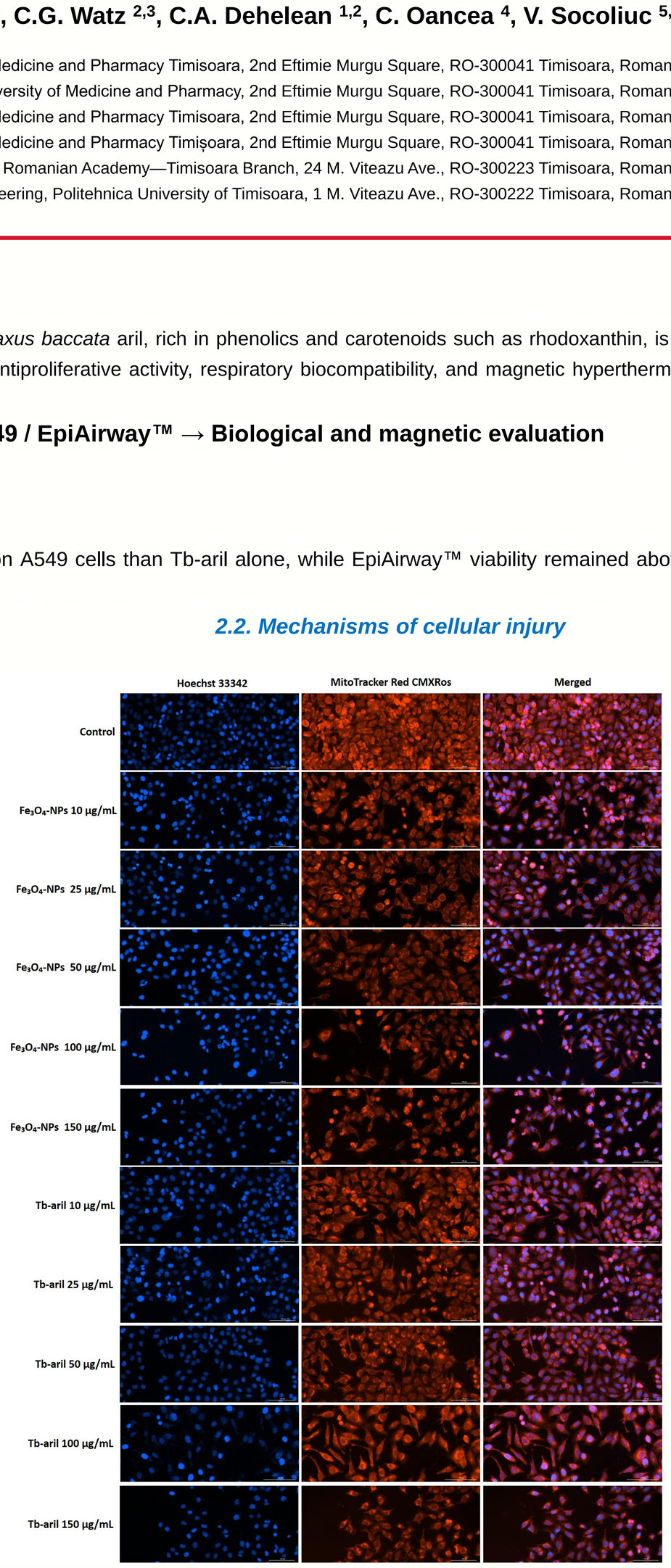


Figure 4. Hoechst 33342 / MitoTracker Red staining of A549 cells showing progressive nuclear alterations and disruption of the mitochondrial network, particularly after Fe_3O_4-NP exposure.

2.3. Respiratory safety & hyperthermia potential

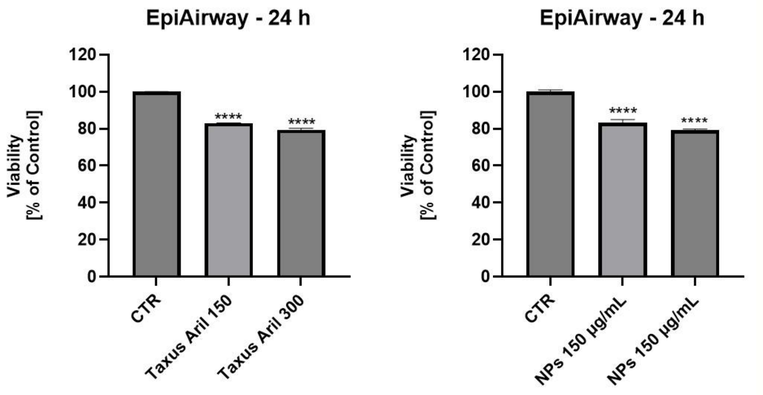


Figure 6. Viability of EpiAirway™ 3D bronchial microtissues after 24 h of exposure to Tb-aril or Fe_3O_4-NPs; viability remained above 70% at the tested concentrations.

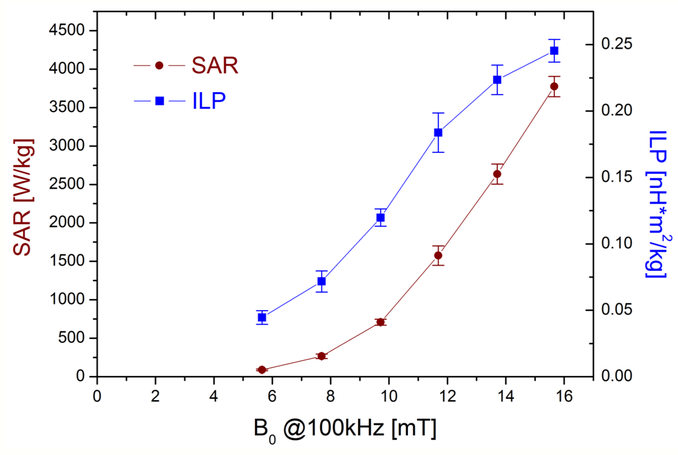


Figure 7. SAR and ILP of the Fe_3O_4-NPs as a function of the 100kHz applied magnetic field amplitude B_0.

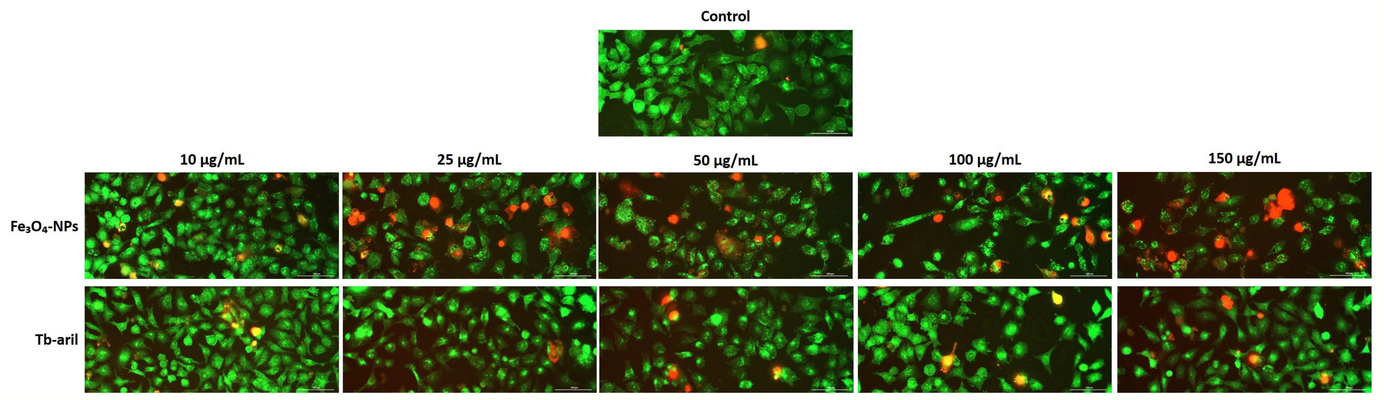


Figure 5. AO/PI double staining of A549 cells showing a concentration-dependent increase in apoptotic/late-apoptotic or necrotic features, more pronounced for Fe_3O_4-NPs.

Phase-contrast microscopy further confirmed a concentration-dependent loss of cell confluence and cell-to-cell contacts, with increased cellular debris and fragmentation, particularly following exposure to 100–150 µg/mL Fe_3O_4-NPs.

3. Conclusions

- Tb-aril-mediated Fe_3O_4-NPs exerted stronger and more persistent antiproliferative effects on A549 cells than Tb-aril alone, involving lysosomal and mitochondrial dysfunction, nuclear alterations, apoptotic/necrotic changes, and reduced clonogenic capacity.
- Despite their pronounced activity in A549 cells, EpiAirway™ viability remained above 70%, supporting an acceptable short-term respiratory biocompatibility profile.
- Together with their efficient magnetic heating and favorable SAR profile, these findings support further investigation of Tb-aril-mediated Fe_3O_4-NPs for lung cancer applications, including magnetic hyperthermia.

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