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Tannic-acid-mediated synthesis and characterization of magnetite-gold nanoplatforms for photothermal therapy

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1	Tannic acid mediated synthesis and characterization of magnetite-gold
2	nanoplatforms for photothermal therapy
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19	Abstract
20	Magnetite (MNPs) and gold (GNPs) nanoparticles attracted attention because of their
21	potentialities in cancer treatment. In this paper, an original synthesis of MNPs and GNPs
22	was designed through the innovative use of tannic acid (TA), which allows the synthesis
23	and the stabilization of eco-friendly hybrid nanoplatforms (HNPs) avoiding toxic
24	chemicals. HNPs were characterized in terms of size, morphology, composition, magnetic
25	and plasmonic properties, ability to generate heating under laser irradiation and their

hemotoxicity. The results revealed that the TA allowed the production of HNPs through a
new, simple and green synthesis method. The HNPs preserved the peculiar properties of
each nanomaterial, and did not show any hemotoxic effect, thus representing an
innovative approach for magneto-photothermal therapy of cancer.

30

31 Structured Abstract

Aim: the design of new hybrid nanoplatforms (HNPs) through the innovative and eco-friendly use of tannic acid (TA) for the synthesis and the stabilization of the NPs.

Materials & Methods: the size, morphology, composition as well as magnetic and plasmonic properties of HNPs were investigated together with their ability of HNPs to generate heating under laser irradiation and the hemotoxicity to explore their potential use for biomedical applications.

Results and Conclusions: the use of TA allowed the synthesis of the HNPs by adopting a
simple and green method. The HNPs preserved the peculiar properties of both magnetic and
plasmonic nanoparticles and did not show any hemotoxic effect.

41

42 Keywords

43 Magnetite nanoparticles; gold nanoparticles; magneto-plasmonic nanoparticles; phothermal
44 therapy; tannic acid;

45

46 **1. Introduction**

In recent years, many studies have been focused on new applications of nanotechnologyin biomedical field. Nowadays one of the main applications of nanotechnology in

biomedicine is the use of nanoparticles [1-7]. In particular, magnetite and gold 49 nanoparticles (MNPs and GNPs respectively) have attracted a lot of interest in the 50 51 scientific community thanks to the possibility to use them in different research fields [8-14]. MNPs have been considered as contrast agents for magnetic resonance imaging, heat 52 sources for hyperthermia and vectors for drug delivery, especially in cancer therapy [15-53 21]. Moreover, they show low toxicity, high biocompatibility and great stability [22]. GNPs 54 have attracted huge interest due to their easiness of synthesis and surface modification, 55 high stability and excellent biocompatibility; in fact, they present very low toxicity even 56 at high concentration [10-23]. Furthermore, GNPs possess a unique photo-physical 57 phenomenon which is not present in massive metal: localized surface plasmon resonance 58 (LSPR) [11,24-26]. The LSPR effect is the result of the nanoparticles interaction with light 59 radiation in a specific wavelength, in fact, GNPs are able to transform the received light 60 61 into thermal energy by producing heat. This could bring the cancer cells to apoptosis as a consequence of their high heat sensitivity [27]. Thus, GNPs are one of the most promising 62 63 tools for photothermal therapy [11].

Combining MNPs and GNPs together, is possible to create a hybrid nanoplatform which 64 preserves the specific properties of each nanomaterial, thus creating an innovative 65 approach for magneto-photothermal therapy of cancer [28]. Indeed, magnetoplasmonic 66 HNPs could be driven in a specific tumour site due to their ability to be activated through 67 an external magnetic field while acting as photothermal system by exploiting the SPR 68 69 effect when irradiated with a laser light. Moreover, it has been recently reported that the combined magnetic and optical properties of magneto-plasmonic HNPs could be 70 71 successfully exploited in multimodal imaging techniques [29].

The aim of this work is to synthetize MNPs and GNPs creating a magneto-plasmonicnanoplatform (HNPs) through an innovative and eco-friendly synthesis of GNPs, which

74 uses tannic acid (TA) as the unique reagent able, at the same time, to reduce GNPs and stabilize HNPs without using any other toxic chemicals. This method faces up to the need 75 76 to develop more environmentally friendly approaches in order to avoid the problems that chemical and physical NPs synthesis procedures usually present, such as the use of toxic 77 chemicals that can lead to both health and environmental issues as well as the high 78 exposure risk of the operator [30,31]. This new awareness can be achieved by using a 79 wide range of biological resources, which could bring various advantages in the NPs 80 synthesis, such as simplicity, low-cost, non-toxic procedures and compatibility for 81 biomedical and pharmaceutical applications [32,33]. 82

Tannic acid was selected since it is a polyphenolic compound extracted from plants [34] 83 84 and can be used as stabilizing and reducing agent [12,35] avoiding the use of all other hazardous chemicals, creating a green and non-toxic synthesis of HNPs [36]. Moreover, 85 TA is well known for its natural antioxidant, anti-inflammatory, antitumoral and 86 antimicrobial properties [37,38]. This organic compound was used to allow GNPs 87 nucleation directly on MNPs surface due to its high reducing power [36]. Furthermore, 88 working under mild-acidic/basic condition, a partial hydrolyzation of TA take place 89 generating glucose and gallic acid [39]: the glucose guarantee the property of being a good 90 stabilizing agent while the gallic acid induces the formation of GNPs at room temperature 91 92 thanks to its well-known reducing power [39,40].

A further aim of this work is to characterize the synthetized HNPs from different points
of view, including size, morphology, composition, magnetic and plasmonic properties,
ability to generate heating under laser irradiation. Moreover, it is well known that NPs
can easily access blood cells, influencing their function and resulting in potentially toxic
effects [41]. Therefore, a preliminary study on hemotoxicity of HNPs in contact with red

98 blood cells has been performed to attest the possibility to use the newly engineered99 nanoplatforms for biomedical applications.

100

101 2. Materials and methods

102 **2.1 HNPs synthesis**

103 HNPs were prepared by improving a synthesis route reported in our previous papers [12,35]. The syntheses differ from each other because in the previous ones the MNPs were 104 105 stabilized with citric acid and functionalized with APTES (3-Aminopropyltriethoxysilane) to promote the GNPs attachment, while in the synthesis here described, 106 107 the TA was used as unique benign reagent that works both as stabilizing and reducing agent. Briefly, Fe₃O₄ NPs were firstly synthetized by the co-precipitation method in which 108 37.5 ml of 0.1 M FeCl₂ and 50 ml of 0.1 M FeCl₃ were mixed together until the salts were 109 completely dissolved. To induce the magnetite formation, NH₄OH was added drop by drop 110 111 until the pH reached a value of 9.5 and the suspension turned black, indicating the precipitation of MNPs. Then the suspension was sonicated in an ultrasonic bath (SONICA 112 113 Ultrasonic Cleaner) for 20 minutes and washed two times before re-suspended in 100 ml of bi-distilled water [42,43]. 114

115 TA solution was prepared by dissolving 2.55 mg of TA in 1.2 ml of bi-distilled water and buffered at pH= 8 in order to improve its reducing power. Then the TA solution was added 116 117 to the MNPs dispersion with a ratio TA(ml) : MNPs(ml) of 0.3 and left at 70 °C for 5 minutes under agitation to allow the TA binding on NPs. All the steps were carried out 118 rapidly in order to avoid the Fe₃O₄ NPs aggregation. Finally, 60 mg of HAuCl₄ were 119 dissolved in 12 ml of bi-distilled water and added to the TA-MNPs suspension and left 120 under continuous stirring at 70 °C for 5 minutes. This step would allow the GNPs 121 nucleation directly on MNPs surface. All the reactants were purchased by Sigma Aldrich®. 122

123 The obtained HNPs were then characterized in terms of size, morphology, composition,

124 magnetic and plasmonic properties. Figure 1 reports schematically the above-mentioned

125 synthesis steps.



126

127

Figure 1. Experimental procedure for the HNPs synthesis.

128 2.2 HNPs characterization

129 2.2.1 Morphological and compositional characterization

In order to assess the dimension, the shape and the morphology of the as-synthetized 130 HNPs, electron microscopes FESEM (Zeiss supra 40 GEMINI Field Emission Scanning 131 Electron Microscopy) and - TEM (FEI Tecnai F20 TWIN transmission electron microscope 132 with a Schottky emitter operated at 200 KV) were used; the chemical composition and the 133 correct reduction of GNPs on MNPs were detected by Zeiss supra 40 GEMINI X-ray 134 spectroscopy (EDS). For these analyses 5µl of sample solution were placed on a Lacey 135 carbon coated 200 mesh copper grid and then located on the appropriate support for the 136 analysis. 137

To verify the effective functionalization and perform elemental analysis a JASCO 4000
Fourier transform infrared spectroscopy (FT-IR) was used, spectra were acquired from

4000 to 500 cm⁻¹, to perform FT-IR analysis, the solution was left at room temperature
until the powder were completely dried.

142

143 2.2.2 Optical characterization

The UV-Visible spectrophotometry, UV-2600 Shimadzu (UV-VIS) was employed to identify at which wavelength the HNPs are able to absorb and to provide information on their size and aggregation, for this analysis the HNPs were maintained in their original water suspension.

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149 2.2.3 Magnetic characterization

The magnetic properties of HNPs were investigated by means of a DC magnetometer (LakeShore 7225) equipped with a Cryogen-Free Magnet, useful to study the superparamagnetic behavior of the MNPs and the ability of the sample to be activated with an external magnetic field by means of an induction heating system (FELMI-EGMA 6-10.15 REV.01). Magnetic hysteresis cycle measurements were performed at room temperature in quasi static condition using an applied magnetic field up to 800 kA/m using the samples in form of powder.

157

158 2.2.4. Plasmonic behavior under laser irradiation

The HNPs were subjected to a 10 minutes NIR laser irradiation of 808 nm (model FC-808, CNI Optoelectronics Tech, Changchun, China) in order to detect their ability to be activated with an external light stimulus and exploit their SPR effect of increasing temperature. The HNPs concentration used for the analysis was 0.1 mg/ml (determined using ICP-MS analysis) in a total volume of 1 ml. The laser power used was set at 1 W/cm² and the spot size of the laser beam was 1 cm in order to irradiate the entire volume of the vial. Temperature of the samples was monitored in real time using a J-type Teflonthermocouple.

This analysis is useful to study their ability to be used as photothermal agent in cancer
treatment, for this reason, the HNPs were maintained in their original water suspension.

170 2.2.5 In-vitro hemotoxicological analysis

171 Once attested all the physical, chemical, magnetic and optical properties, a preliminary in-172 vitro cytotoxicity evaluation of the as-produced HNPs was performed, in which a 173 nanoplatforms concentration of 35 and 100 μ g/ml (determined via ICP-MS analysis) were 174 put in contact with red blood cells for 5 hours.

For the hemolysis study, red blood cells were isolated from the whole sheep blood, 175 supplied by the Veterinary Faculty (University of Ljubljana, Slovenia) in Alsever's medium 176 177 (TCS Biosciences Ltd, UK) and used within one week. Red blood cells were isolated via centrifugation (2500 rpm/10 min) and washed 3-times with phosphate-buffered saline 178 179 (PBS) buffer (tablets, Sigma Aldrich). Nanoparticles suspended in PBS were incubated with 5 vol.% of red blood cells (pH 7.4) for 5 h at 37 °C with constant orbital shaking in 180 1.5 ml tubesEppendorfof, Germany, volume of samples 1 mL, all samples in triplicates). 181 After incubation, tubes were centrifuged (1500 rpm/4 min) to sediment cells and 182 supernatant was analyzed in triplicates. Hemolysis was evaluated by measuring released 183 hemoglobin absorbance (A) at 541 nm using a plate reader (Synergy H4, BioTek, 184 185 Winooski, VT, USA). Samples representing positive control (100% dead) were prepared by lysing control samples with deionized water via hypotonic osmotic shock. Percent 186 hemolysis was then calculated as follows: Hemolysis (%)=100·(Asample – Acontrol)/(187 A100% dead – Acontrol). One-way ANOVA and Student's t-test was used for our statistical 188 189 analysis. The data were presented as mean ± SD for all experiments.

190

191 **3. Results and discussion**

In this paragraph, the morphological, compositional and chemical characterizations concerning the HNPs are described. In particular, a preliminary characterization on bare iron oxide nanoparticles was firstly performed in order to verify the correct formation of MNPs followed by the analyses achieved to attest the correct binding of TA on MNPs.

- 196 To verify the size and morphology of MNPs, they were firstly characterized by means of
- 197 TEM analysis. In figure 2 TEM images of bare iron oxide nanoparticles are shown, in which
- is visible their pseudo-spherical shape and a dimensional range between 5-15 nm.



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Figure 2: TEM image of MNPs. Scale bar: figure A 10 nm; figure B 20 nm

In order to confirm the correct binding of TA on MNPs surface, the FT-IR and UV-Visanalyses were performed as shown in figure 3 and figure 4 respectively. In FT-IR graph

(figure 3), the patterns of MNPs and TA functionalized MNPs are shown. Both spectra 203 display the strong vibrational modes of Fe-O bonds of magnetite located at 585 cm⁻¹ 204 205 [44,45], while from the TA-MNPs pattern (red line) the main characteristic peaks of TA [46] are visible, in particular, the 758 cm⁻¹ peak indicates out of plane CH bending of 206 phenyl groups, the peak at 923 cm⁻¹ is referred to OH out of plane bending of acid groups, 207 the C=O stretching vibration at 1730-1705 cm⁻¹ and C-O at 1100-1300 cm⁻¹, while around 208 1452 cm⁻¹ the stretching vibrations of -C-C aromatic groups appear. Moreover, as 209 confirmation of correct functionalization of MNPs with TA, the broad peak at 3400 cm⁻¹, 210 which represent the hydroxyl groups and surface-adsorbed water molecules, is visible 211 together with the vibrational modes of Fe-O bonds of magnetite 212

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Figure 3: FTIR spectra of MNPs and TA-MNPs

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Figure 4 reports the UV-Vis analysis in which the peak associated to the tannic acid at around 300 nm is visible. This result corroborates the outcomes obtained from FT-IR and confirms the correct binding of tannic acid on MNPs surface, thus confirming that TA can be grafted onto the surface of magnetic particles, without interposing other spacer molecules (e.g. APTES).







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Once attested the correct functionalization with TA, the TEM analysis was used to verify the size and morphology of HNPs, as well as to attest the correct attachment of GNPs on iron oxide core. Figure 5 shows the TEM images of HNPs, in which the GNPs are visible; they appear darker than MNPs due to their higher atomic number and electron density. GNPs show an approximately spherical shape and a dimension around 10-20 nm,

- 230 confirming the presence of GNPs on MNPs core creating a sort of nano-dumbbell
- 231 structures.



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Figure 5: TEM image of HNPs. In figure 4 (B) GNPs are evidenced. Scale bar: figure A
 100 nm; figure B 20 nm.

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In figure 6 the STEM images acquired in dark field mode are shown, in which high mass 236 237 materials (such as gold) appear bright. The figure shows the morphological aspect of HNPs, in which the GNPs result to be homogeneous and well-dispersed on magnetite 238 239 surface. This analysis corroborates the TEM results previously obtained, in which it is possible to observe a high concentration of GNPs attached to the MNPs with a dimensional 240 241 range between 10 nm and 20 nm. The correct reduction of GNPs on MNPs is also supported by the EDS analysis (figure 7), that evidence the presence of all the elements 242 243 characteristic of MNPs and GNPs.



Figure 6: STEM images of HNPs. Scale bar: 100 nm.



Figure 7: EDS analysis of HNPs.



253 observe an altered intensity and position of the TA peaks with respect to the FT-IR of TA-MNPs (figure 3) as indication of the correct reduction of GNPs. In particular, the shift of 254 the broad peak from 3400 cm⁻¹ to lower wavenumber suggests the involvement of OH 255 functional groups in the reduction process as well as the altered intensity of CO groups 256 and C-C aromatic rings, which indicate the involvement of TA-MNPs in immobilization of 257 GNPs (47). On the basis of data, it could be inferred that the TA remains bound to the HNPs 258 surface and that the TA phenolic hydroxyls may be responsible for the reduction of metal 259 ions. During the metal reduction process, the COO- group present in the TA, together with 260 the rest of the molecule, can works as surfactant on the HNPs surface stabilizing them 261 through electrosteric stabilization (48). 262



263

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Figure 8: FT-IR spectra of HNPs

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which wavelength the HNPs are able to absorb. The graph in figure 9 shows a high signal in the GNPs absorbing window with sharp absorbing peak at 620 nm. This analysis is useful to attest the great ability of GNPs to absorb light as well as to confirm the high concentration, homogeneous dimension and very good dispersion of GNPs in the solution [11]: this is confirmed by the broad gold extinction peak which in case of aggregation it would show a decrease in intensity (due to the depletion of stable nanoparticles) and a wider peak towards longer wavelengths (due to the formation of aggregates) [49].

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Figure 9: UV-Vis of HNPs.

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With the aim to determine the effect that GNPs have on the magnetic properties of pure MNPs, the magnetic properties of the suspension were evaluated by means of magnetization measurements system and induction heating system. In fact, it is important to consider that the ability to manage the HNPs using a magnetic field is one of the main
 reasons for utilizing Fe₃O₄ NPs as support for GNPs.

285 In particular, in figure 10 magnetic hysteresis cycle curves at room temperature of bare MNPs (black curve) and the as synthetized HNPs (pink curve) are reported. Here it is 286 possible to observe that both the samples exhibit a superparamagnetic behaviour as 287 confirmed by the negligible coercive field and remanence magnetization [50]. The higher 288 magnetization values of MNPs with respect to HNPs, could be linkable to its lack of any 289 additional element that lower these properties (such as the TA and GNPs); in fact, the 290 decrease in the saturation magnetizations of HNPs, could be due to the diamagnetic 291 292 nature of GNPs anchored on MNPs surface, as well as the minor amount of magnetic NPs 293 in the sample in which gold is also present. Despite this, the HNPs show no hysteresis, indicating that GNPs are not influencing excessively the magnetic properties of the 294 295 precursor [51].



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Figure 10: Magnetic hysteresis cycles of MNPs and HNPs.

In figure 11, the temperature-time curves obtained by submitting the samples to an external magnetic field are reported. This analysis is useful to attest the ability of the sample to be activated with an external mediator. In particular, it is possible to notice that
MNPs (black curve) are able to produce higher heating than HNPs (red curve), due to the
same reasons for which the magnetization appeared lower in figure 10. Despite this, the
synthetized HNPs are able to be externally activated with the applied magnetic field: this
means that the GNPs decoration is not influencing the magnetic properties of HNPs,
corroborating the magnetization measurement results previously obtained.

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Figure 11: Temperature-Time curve of MNPs and HNPs after 20 min of an external magnetic field application. Applied magnetic field: 800 kA/m.

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Finally, the HNPs were subjected to a laser irradiation in order to detect their ability to be activated with an external light stimulus and to exploit their SPR effect increasing their temperature. This analysis is useful to study their ability to be used as photothermal agent in cancer treatment. The same test was performed both with HNPs dispersed in water at concentration of 0.1 mg/ml than with only water, to observe the difference between the
two solutions. In figure 12, it is visible that after 10 minutes of laser irradiation, the HNPs
are able to raise a temperature of 40/45°C ascribable to the high absorption spectra of
GNPs at the characteristic wavelength of the irradiation showed in UV-Vis graph (figure
9), while, as expected, the water is not showing any effect when irradiated. This result
confirms the excellent ability of GNPs to exploit SPR effect demonstrating the ability of
the synthetized HNPs to be used in photothermal therapy.

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Once characterized the sample in terms of size, morphology, chemical, magnetic and optical properties, a preliminary hemotoxicological analysis was performed in order to evaluate the toxicological effect of the nanocomposites in contact with red blood cells (RBCs). With this analysis it is possible to evaluate the hemoglobin absorbance using a 331 spectrophotometer, which is useful to detect the RBCs hemolysis before and after incubation with nanoparticles. The results concerning the RBCs hemolysis after 332 333 incubation with 35 and 100 μ g/ml concentration of HNPs, are shown in figure 13 in which it is possible to notice that after 5 h incubation, the HNPs did not show any hemotoxicity, 334 which is comparable to that of the negative control sample. In fact, for each sample of RBC 335 it is observed that the hemolysis is very low (lower than 1.4%), which means that the NPs 336 hemotoxicity at these concentrations is negligible and therefore they are potentially 337 usable for biomedical applications [52,53]. 338

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Figure 13: Hemotoxicity results. Cell viability of RBCs was evaluated after 5 h
 incubation at 37 °C (n=3). Data analysis revealed no statistically significant difference in
 cell viability values between tested groups (p<0.05).

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345 **4. Conclusions**

In this this work a facile and reproducible synthesis method was optimized and used to
 develop new hybrid nanoplatforms composed by magnetic core and GNPs decoration. The

main goal was to prepare the HNPs through a green and simple synthesis by means of the 348 innovative use of tannic acid, a polyphenolic compound as both reducing and stabilising 349 350 agent. This approach allowed to prepare the HNPs without using any toxic chemical in the process, thus improving the synthesis procedure in terms of number of reagents used, 351 properties, scalability, cost-efficiency and eco-sustainability. Further, another aim of the 352 research was the complete characterization of the obtained HNPs including a preliminary 353 hemotoxicological evaluation. The obtained structures are able to preserve the peculiar 354 properties of each nanomaterial and display negligible hemotoxicity, creating a novel 355 approach for magneto-photothermal therapy of cancer. 356

357

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361

362 Summary Points

- A facile and reproducible synthesis method was developed to prepare new hybrid
 nanoplatforms (HNPs) composed by magnetic core and gold nanoparticle
 decoration.
- The innovative use of tannic acid as both reducing and stabilising agent was used
 to prepare the HNPs
- The HNPs were prepared without any toxic chemical in the process.
- A complete characterization revealed that the obtained HNPs are able to preserve
 the peculiar properties of each nanomaterial.
- The obtained HNPs display negligible hemotoxicity.

- The obtained HNPs represent a novel approach for magneto-photothermal
 therapy of cancer.
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