

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

Original

Tannic-acid-mediated synthesis and characterization of magnetite-gold nanoplatforms for photothermal therapy / Miola, M.; Multari, C.; Kostevsek, N.; Gerbaldo, R.; Laviano, F.; Verne, Enrica.. - In: NANOMEDICINE. - ISSN 1748-6963. - 18:20(2023), pp. 1331-1342. [10.2217/nnm-2023-0134]

Availability:

This version is available at: 11583/2988867 since: 2024-05-20T15:24:50Z

Publisher:

Taylor & Francis

Published

DOI:10.2217/nnm-2023-0134

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright

(Article begins on next page)

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

30

31 **Structured Abstract**

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

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

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

41

42 **Keywords**

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

45

46 **1. Introduction**

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

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

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

72 The aim of this work is to synthesize MNPs and GNPs creating a magneto-plasmonic
73 nanoplatform (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
75 stabilize HNPs without using any other toxic chemicals. This method faces up to the need
76 to develop more environmentally friendly approaches in order to avoid the problems that
77 chemical and physical NPs synthesis procedures usually present, such as the use of toxic
78 chemicals that can lead to both health and environmental issues as well as the high
79 exposure risk of the operator [30,31]. This new awareness can be achieved by using a
80 wide range of biological resources, which could bring various advantages in the NPs
81 synthesis, such as simplicity, low-cost, non-toxic procedures and compatibility for
82 biomedical and pharmaceutical applications [32,33].

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

93 A further aim of this work is to characterize the synthesized HNPs from different points
94 of view, including size, morphology, composition, magnetic and plasmonic properties,
95 ability to generate heating under laser irradiation. Moreover, it is well known that NPs
96 can easily access blood cells, influencing their function and resulting in potentially toxic
97 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 engineered
99 nanoplatfoms for biomedical applications.

100

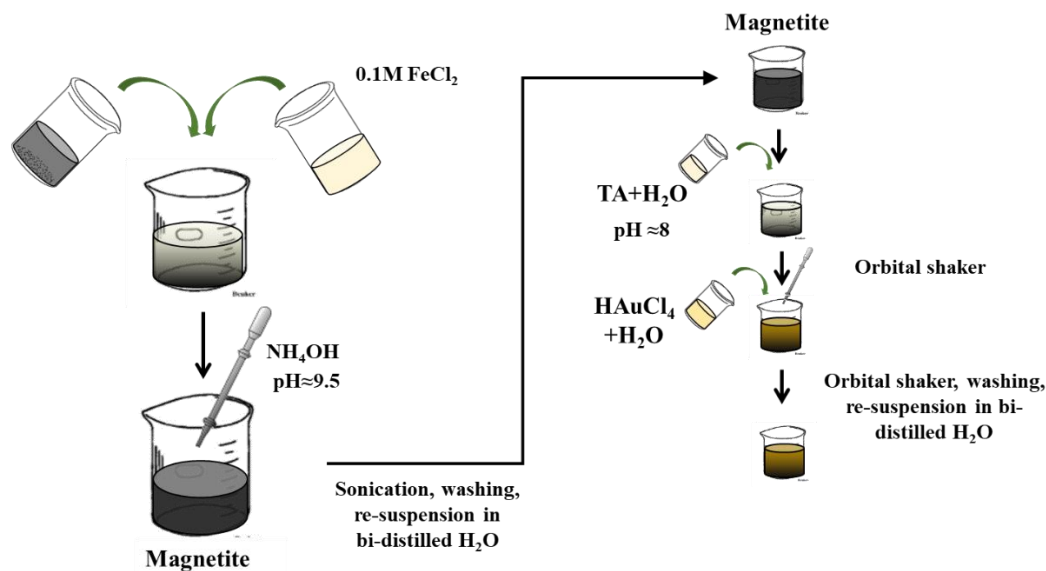
101 **2. Materials and methods**

102 **2.1 HNPs synthesis**

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

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

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

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

138 To verify the effective functionalization and perform elemental analysis a JASCO 4000

139 Fourier transform infrared spectroscopy (FT-IR) was used, spectra were acquired from

140 4000 to 500 cm^{-1} , to perform FT-IR analysis, the solution was left at room temperature
141 until the powder were completely dried.

142

143 *2.2.2 Optical characterization*

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

148

149 *2.2.3 Magnetic characterization*

150 The magnetic properties of HNPs were investigated by means of a DC magnetometer
151 (LakeShore 7225) equipped with a Cryogen-Free Magnet, useful to study the
152 superparamagnetic behavior of the MNPs and the ability of the sample to be activated
153 with an external magnetic field by means of an induction heating system (FELMI-EGMA
154 6-10.15 REV.01). Magnetic hysteresis cycle measurements were performed at room
155 temperature in quasi static condition using an applied magnetic field up to 800 kA/m
156 using the samples in form of powder.

157

158 *2.2.4. Plasmonic behavior under laser irradiation*

159 The HNPs were subjected to a 10 minutes NIR laser irradiation of 808 nm (model FC-808,
160 CNI Optoelectronics Tech, Changchun, China) in order to detect their ability to be
161 activated with an external light stimulus and exploit their SPR effect of increasing
162 temperature. The HNPs concentration used for the analysis was 0.1 mg/ml (determined
163 using ICP-MS analysis) in a total volume of 1 ml. The laser power used was set at 1 W/cm^2
164 and the spot size of the laser beam was 1 cm in order to irradiate the entire volume of the

165 vial. Temperature of the samples was monitored in real time using a J-type Teflon
166 thermocouple.

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

169

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 µg/ml (determined via ICP-MS analysis) were
174 put in contact with red blood cells for 5 hours.

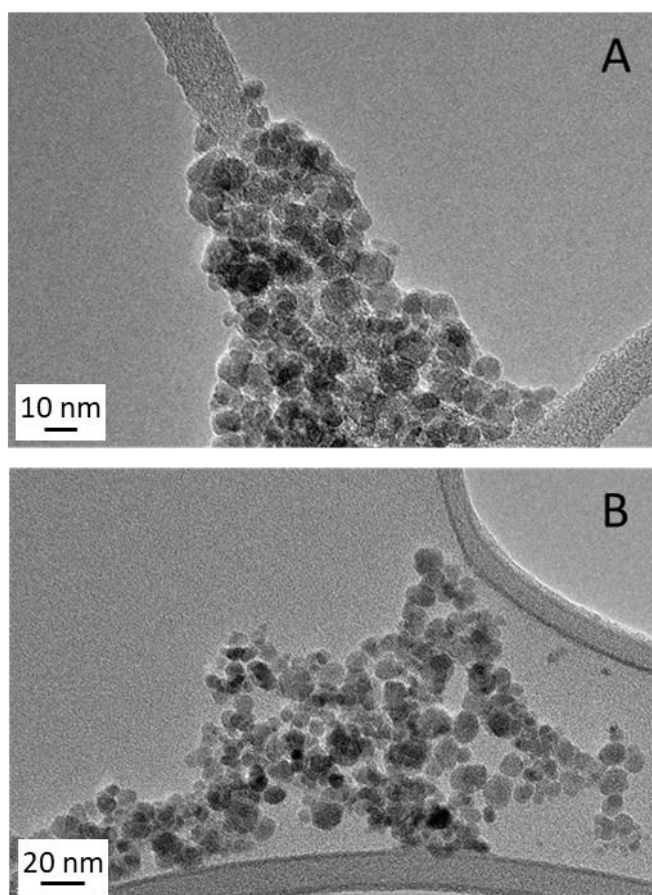
175 For the hemolysis study, red blood cells were isolated from the whole sheep blood,
176 supplied by the Veterinary Faculty (University of Ljubljana, Slovenia) in Alsever's medium
177 (TCS Biosciences Ltd, UK) and used within one week. Red blood cells were isolated via
178 centrifugation (2500 rpm/10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

190

191 3. Results and discussion

192 In this paragraph, the morphological, compositional and chemical characterizations concerning
193 the HNPs are described. In particular, a preliminary characterization on bare iron oxide
194 nanoparticles was firstly performed in order to verify the correct formation of MNPs followed
195 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
198 is visible their pseudo-spherical shape and a dimensional range between 5-15 nm.

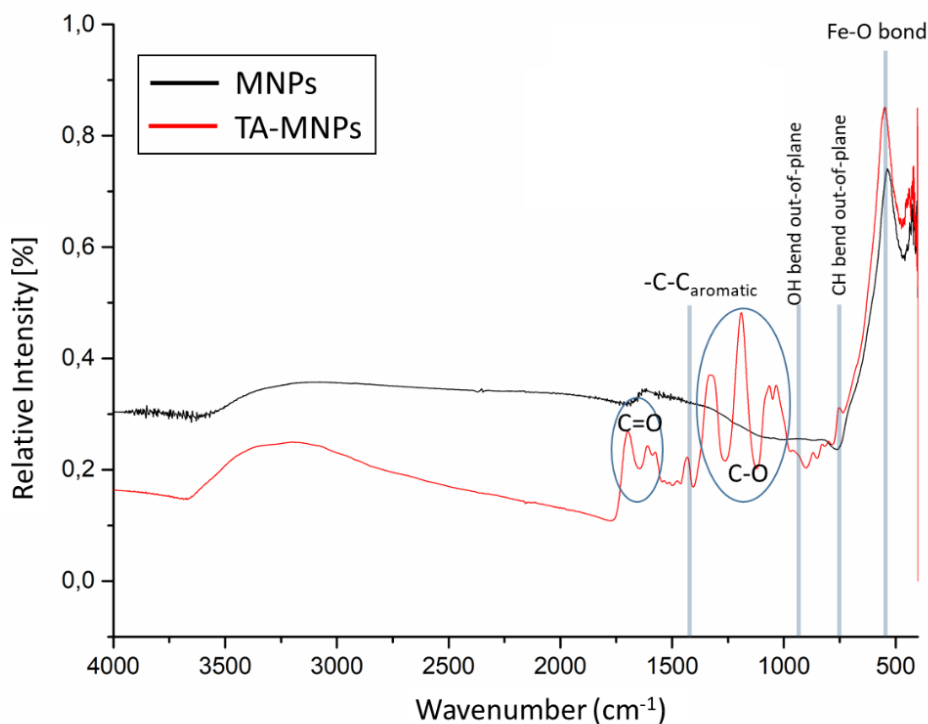


199

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

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

203 (figure 3), the patterns of MNPs and TA functionalized MNPs are shown. Both spectra
204 display the strong vibrational modes of Fe-O bonds of magnetite located at 585 cm^{-1}
205 [44,45], while from the TA-MNPs pattern (red line) the main characteristic peaks of TA
206 [46] are visible, in particular, the 758 cm^{-1} peak indicates out of plane CH bending of
207 phenyl groups, the peak at 923 cm^{-1} is referred to OH out of plane bending of acid groups,
208 the C=O stretching vibration at $1730\text{-}1705\text{ cm}^{-1}$ and C-O at $1100\text{-}1300\text{ cm}^{-1}$, while around
209 1452 cm^{-1} the stretching vibrations of -C-C aromatic groups appear. Moreover, as
210 confirmation of correct functionalization of MNPs with TA, the broad peak at 3400 cm^{-1} ,
211 which represent the hydroxyl groups and surface-adsorbed water molecules, is visible
212 together with the vibrational modes of Fe-O bonds of magnetite
213



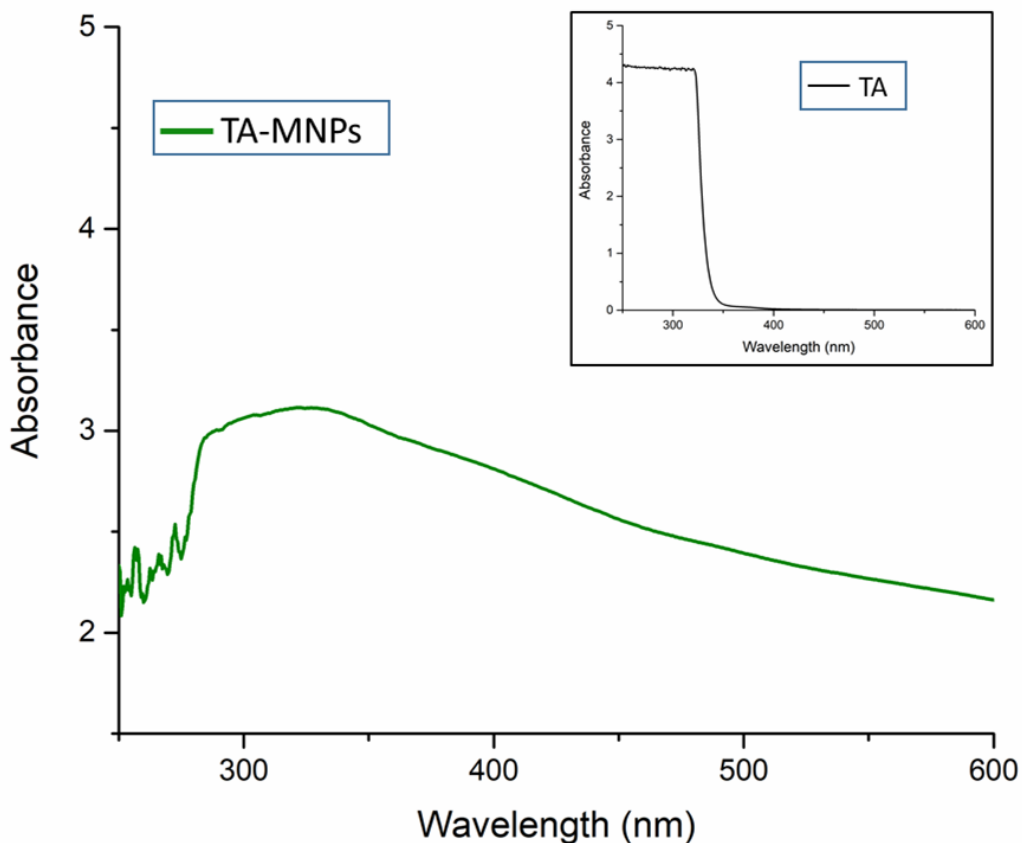
214

215

Figure 3: FTIR spectra of MNPs and TA-MNPs

216

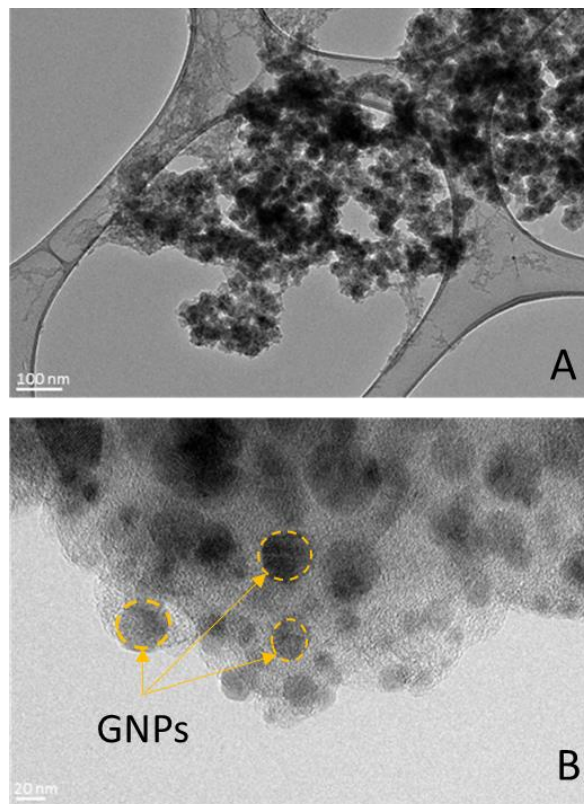
217 Figure 4 reports the UV-Vis analysis in which the peak associated to the tannic acid at
218 around 300 nm is visible. This result corroborates the outcomes obtained from FT-IR and
219 confirms the correct binding of tannic acid on MNPs surface, thus confirming that TA can
220 be grafted onto the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



222
223 **Figure 4:** UV-Vis spectra of TA-MNPs. In the inset: UV-Vis spectra of TA alone.

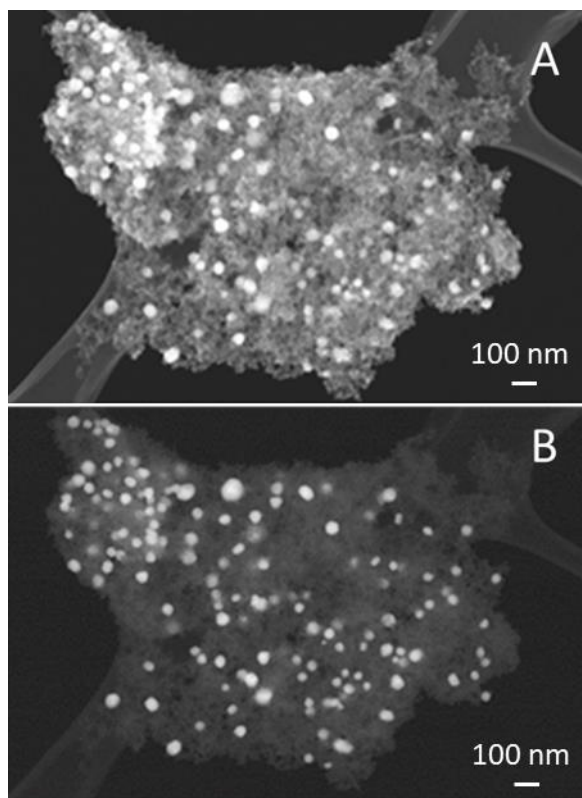
224
225 Once attested the correct functionalization with TA, the TEM analysis was used to verify
226 the size and morphology of HNPs, as well as to attest the correct attachment of GNPs on
227 iron oxide core. Figure 5 shows the TEM images of HNPs, in which the GNPs are visible;
228 they appear darker than MNPs due to their higher atomic number and electron density.
229 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.



232
233 **Figure 5:** TEM image of HNPs. In figure 4 (B) GNPs are evidenced. Scale bar: figure A
234 100 nm; figure B 20 nm.

235
236 In figure 6 the STEM images acquired in dark field mode are shown, in which high mass
237 materials (such as gold) appear bright. The figure shows the morphological aspect of
238 HNPs, in which the GNPs result to be homogeneous and well-dispersed on magnetite
239 surface. This analysis corroborates the TEM results previously obtained, in which it is
240 possible to observe a high concentration of GNPs attached to the MNPs with a dimensional
241 range between 10 nm and 20 nm. The correct reduction of GNPs on MNPs is also
242 supported by the EDS analysis (figure 7), that evidence the presence of all the elements
243 characteristic of MNPs and GNPs.

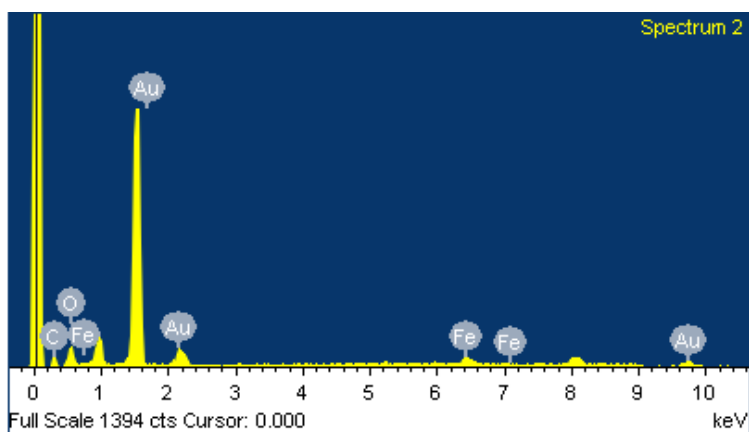


244

245

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

246



247

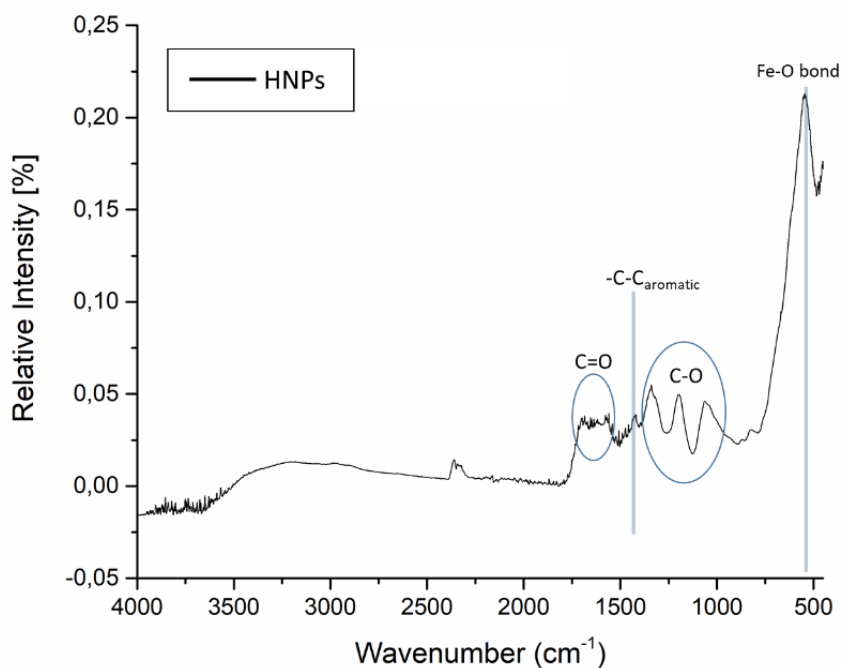
248

Figure 7: EDS analysis of HNPs.

249

250 Moreover, in order to identify the functional groups present in the TA, which is
251 responsible for the reduction of GNPs and stabilization of HNPs, FT-IR measurement of
252 the final HNPs solution was carried out as shown in figure 8. In the image it is possible to

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



263

264

Figure 8: FT-IR spectra of HNPs

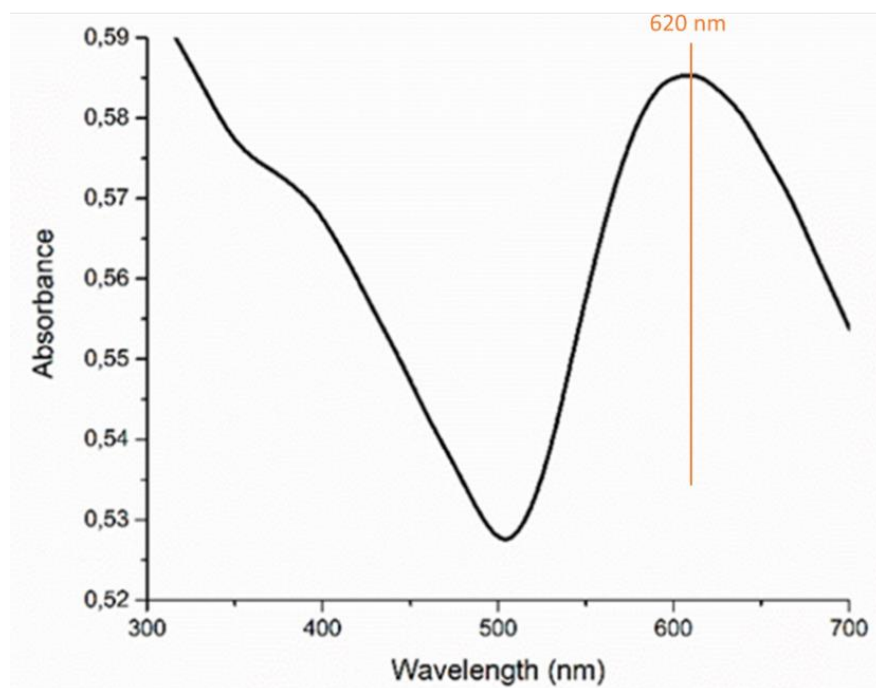
265

266 Once attested the correct HNPs formation and the correct role of TA to work as reducing
267 and stabilizing agent, the UV-Visible spectrophotometry was employed to identify at

268 which wavelength the HNPs are able to absorb. The graph in figure 9 shows a high signal
269 in the GNPs absorbing window with sharp absorbing peak at 620 nm. This analysis is
270 useful to attest the great ability of GNPs to absorb light as well as to confirm the high
271 concentration, homogeneous dimension and very good dispersion of GNPs in the solution
272 [11]: this is confirmed by the broad gold extinction peak which in case of aggregation it
273 would show a decrease in intensity (due to the depletion of stable nanoparticles) and a
274 wider peak towards longer wavelengths (due to the formation of aggregates) [49].

275

276



277

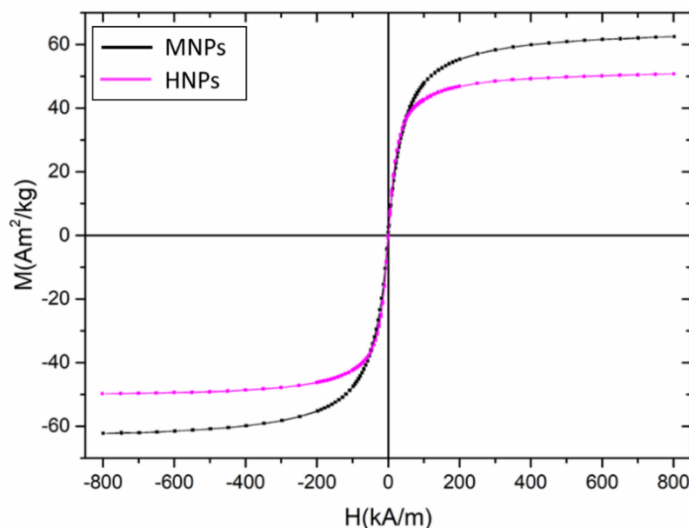
278

Figure 9: UV-Vis of HNPs.

279

280 With the aim to determine the effect that GNPs have on the magnetic properties of pure
281 MNPs, the magnetic properties of the suspension were evaluated by means of
282 magnetization measurements system and induction heating system. In fact, it is important

283 to consider that the ability to manage the HNPs using a magnetic field is one of the main
284 reasons for utilizing Fe_3O_4 NPs as support for GNPs.
285 In particular, in figure 10 magnetic hysteresis cycle curves at room temperature of bare
286 MNPs (black curve) and the as synthesized HNPs (pink curve) are reported. Here it is
287 possible to observe that both the samples exhibit a superparamagnetic behaviour as
288 confirmed by the negligible coercive field and remanence magnetization [50]. The higher
289 magnetization values of MNPs with respect to HNPs, could be linkable to its lack of any
290 additional element that lower these properties (such as the TA and GNPs); in fact, the
291 decrease in the saturation magnetizations of HNPs, could be due to the diamagnetic
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,
294 indicating that GNPs are not influencing excessively the magnetic properties of the
295 precursor [51].



296

297

Figure 10: Magnetic hysteresis cycles of MNPs and HNPs.

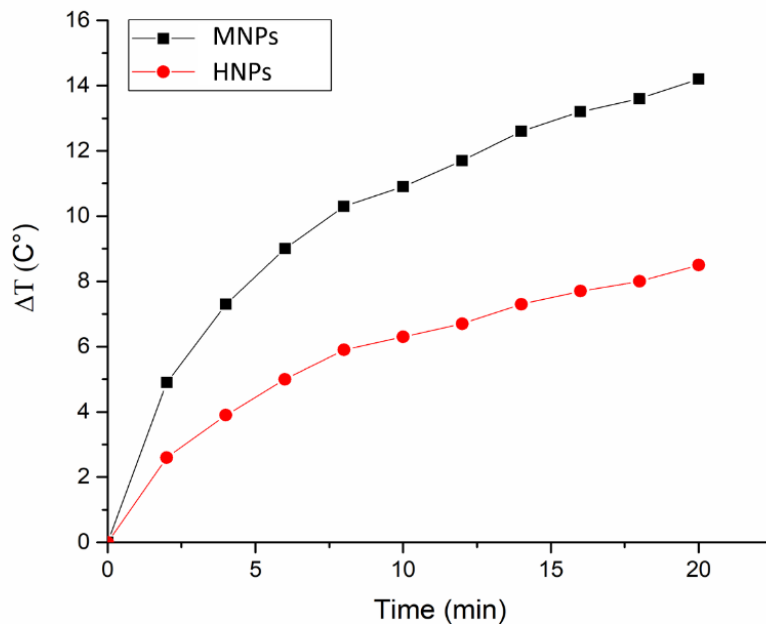
298

299

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

300 sample to be activated with an external mediator. In particular, it is possible to notice that
301 MNPs (black curve) are able to produce higher heating than HNPs (red curve), due to the
302 same reasons for which the magnetization appeared lower in figure 10. Despite this, the
303 synthesized HNPs are able to be externally activated with the applied magnetic field: this
304 means that the GNPs decoration is not influencing the magnetic properties of HNPs,
305 corroborating the magnetization measurement results previously obtained.

306



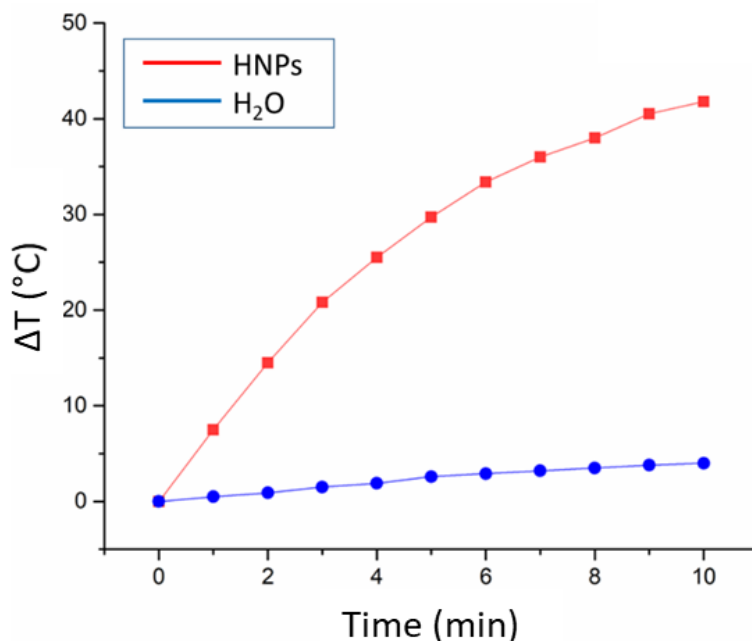
307

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

310

311 Finally, the HNPs were subjected to a laser irradiation in order to detect their ability to be
312 activated with an external light stimulus and to exploit their SPR effect increasing their
313 temperature. This analysis is useful to study their ability to be used as photothermal agent
314 in cancer treatment. The same test was performed both with HNPs dispersed in water at

315 concentration of 0.1 mg/ml than with only water, to observe the difference between the
316 two solutions. In figure 12, it is visible that after 10 minutes of laser irradiation, the HNPs
317 are able to raise a temperature of 40/45°C ascribable to the high absorption spectra of
318 GNPs at the characteristic wavelength of the irradiation showed in UV-Vis graph (figure
319 9), while, as expected, the water is not showing any effect when irradiated. This result
320 confirms the excellent ability of GNPs to exploit SPR effect demonstrating the ability of
321 the synthesized HNPs to be used in photothermal therapy.
322

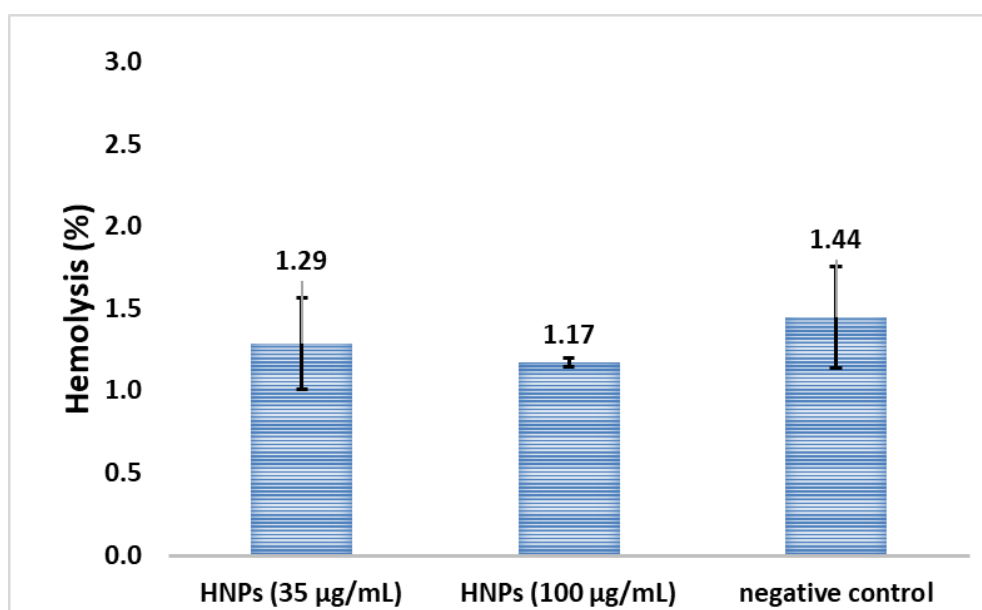


323
324 **Figure 12:** Photothermal results of nanocomposites after 10 minutes of laser
325 irradiation. HNPs concentration: 0.1 mg/ml; Laser power: 1 W/cm².
326

327 Once characterized the sample in terms of size, morphology, chemical, magnetic and
328 optical properties, a preliminary hemotoxicological analysis was performed in order to
329 evaluate the toxicological effect of the nanocomposites in contact with red blood cells
330 (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
332 incubation with nanoparticles. The results concerning the RBCs hemolysis after
333 incubation with 35 and 100 $\mu\text{g/ml}$ concentration of HNPs, are shown in figure 13 in which
334 it is possible to notice that after 5 h incubation, the HNPs did not show any hemotoxicity,
335 which is comparable to that of the negative control sample. In fact, for each sample of RBC
336 it is observed that the hemolysis is very low (lower than 1.4%), which means that the NPs
337 hemotoxicity at these concentrations is negligible and therefore they are potentially
338 usable for biomedical applications [52,53].

339



340

341 **Figure 13:** Hemotoxicity results. Cell viability of RBCs was evaluated after 5 h
342 incubation at 37 $^{\circ}\text{C}$ (n=3). Data analysis revealed no statistically significant difference in
343 cell viability values between tested groups ($p < 0.05$).

344

345 4. Conclusions

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

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

357

358 **Acknowledgements**

359 Authors are grateful for financial support from the Slovenian Research Agency ARRS
360 (project number P2-0084) and to Elisa Bertone (DISAT) for FTIR and UV-Vis facilities.

361

362 **Summary Points**

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

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

374

375 **References**

- 376 [1] Jabir NR, Tabrez S, Ashraf GM, Shakil S, Damanhour GA, Kamal MA.
377 Nanotechnology-based approaches in anticancer research. *Int J Nanomedicin*, 7,
378 4391–408 (2012).
- 379 [2] Boisseau P, Loubaton B. Nanomedicine, nanotechnology in medicine. *Comptes*
380 *Rendus Phys.* 12(7), 620–36 (2011).
381 <http://dx.doi.org/10.1016/j.crhy.2011.06.001>
- 382 [3] Saini R, Saini S, Sharma S. Nanotechnology: the future medicine. *J Cutan Aesthet*
383 *Surg.* 3(1), 32–3 (2010). <https://www.ncbi.nlm.nih.gov/pubmed/20606992>
- 384 [4] Holm BA, Bergey EJ, De T, Rodman DJ, Kapoor R, Levy L, et al. Nanotechnology in
385 Bio Medical Applications. *Molecular Crystals and Liquid Crystals.* 374(1), 589-
386 598 (2002) DOI: 10.1080/713738279
- 387 [5] Nikalje AP. Nanotechnology and its Applications in Medicine. *Med chem.* 5(2),
388 081-089 (2015).
- 389 [6] Boisseau P, Loubaton B. Nanomedicine, nanotechnology in medicine. *Comptes*
390 *Rendus Phys.* 12(7),620–36 (2011).
391 <http://www.sciencedirect.com/science/article/pii/S1631070511001538>
- 392 [7] Soares S, Sousa J, Pais A, Vitorino C. Nanomedicine: principles, properties, and
393 regulatory issues. *Front Chem.* Article ID 6, 360, 15 pages (2018).
- 394 [8] Hwu JR, Lin YS, Josephrajan T, Hsu M, Cheng F. Targeted Paclitaxel by
395 Conjugation to Iron Oxide and Gold Nanoparticles. *J. Am. Chem. Soc.* 131(1), 66–
396 68 (2009).

- 397 [9] Kumar A, Boruah B, Liang X-J. Gold Nanoparticles: Promising Nanomaterials for
398 the Diagnosis of Cancer and HIV/AIDS. *J Nanomater.* Article ID 202187, 17 pages
399 (2011). <https://doi.org/10.1155/2011/202187>
- 400 [10] Shilpi S, Khatri K. Gold Nanoparticles as Carrier(s) for Drug Targeting and
401 Imaging. *Pharm Nanotechnol.* 3(3),154-170 (2015).
- 402 [11] Huang X, El-Sayed MA. Gold nanoparticles: Optical properties and
403 implementations in cancer diagnosis and photothermal therapy. *J Adv Res.*
404 1(1),13-28 (2010).
- 405 [12] Multari C, Miola M, Laviano F, Gerbaldo R, Pezzotti G, Debellis D, et al.
406 Magnetoplasmonic nanoparticles for photothermal therapy. *Nanotechnology*
407 30(25), 255705 (2019). <http://dx.doi.org/10.1088/1361-6528/ab08f7>
- 408 [13] Gul S, Khan SB, Rehman IU, Khan MA, Khan MI. A comprehensive review of
409 magnetic nanomaterials modern day theranostics. *Front Mater.* 6, Article179, 15
410 pages (2019).
- 411 [14] Bansal SA, Kumar V, Karimi J, Singh AP, Kumar S. Role of gold
412 nanoparticles in advanced biomedical applications. *Nanoscale Adv.* 2(9), 3764-87
413 (2020).
- 414 [15] Kumar CSSR, Mohammad F. Magnetic nanomaterials for hyperthermia-
415 based therapy and controlled drug delivery. *Adv Drug Deliv Rev.* 63(9), 789-808
416 (2011) <http://dx.doi.org/10.1016/j.addr.2011.03.008>
- 417 [16] Lodhia J, Mandarano G, Ferris N, Eu P, Cowell S. Development and use of
418 iron oxide nanoparticles (Part 1): Synthesis of iron oxide nanoparticles for MRI.
419 *Biomed Imaging Interv J.* 6, e12 (2010).

- 420 [17] Babes L, Denizot B, Tanguy G, Le Jeune JJ, Jallet P. Synthesis of iron oxide
421 nanoparticles used as MRI contrast agents: a parametric study. *J Colloid Interface*
422 *Sci.* 212(2), 474–82 (1999).
- 423 [18] Gobbo OL, Sjaastad K, Radomski MW, Volkov Y, Prina-Mello A.
424 Theranostics Magnetic Nanoparticles in Cancer *Theranostics.* 5(11), 1249-63
425 (2015).
- 426 [19] Yoo D, Lee J-H, Shin T-H, Cheon J. Theranostic magnetic nanoparticles. *Acc*
427 *Chem Res.* 44(10), 863–74 (2011).
- 428 [20] Chang D, Lim M, Goos JACM, Qiao R, Ng YY, Mansfeld FM, et al. Biologically
429 Targeted Magnetic Hyperthermia: Potential and Limitations. *Front Pharmacol*; 9,
430 Article 831, 20 pages (2018).
- 431 [21] Cheraghipour E, Javadpour S, Mehdizadeh A. Citrate capped
432 superparamagnetic iron oxide nanoparticles used for hyperthermia therapy. *J*
433 *Biomed Sci Eng.* 5(12), 715–719 (2012).
- 434 [22] Indira T. Magnetic Nanoparticles: A Review. *Int J Pharm.* 3(3), 1035–1042
435 (2010).
- 436 [23] Mahmoudi M, Serpooshan V, Laurent S. Engineered nanoparticles for
437 biomolecular imaging. *Nanoscale.* 3(8), 3007–3026 (2011).
438 <http://dx.doi.org/10.1039/C1NR10326A>
- 439 [24] Vinod M, Jayasree RS, Gopchandran KG. Synthesis of pure and
440 biocompatible gold nanoparticles using laser ablation method for SERS and
441 photothermal applications. *Curr Appl Phys.* 17(11), 1430–1438 (2017).
- 442 [25] Lucky SS, Soo KC, Zhang Y. Nanoparticles in Photodynamic Therapy. *Chem*
443 *Rev.* 115(4), 1990–2042 (2015).

- 444 [26] Jain PK, Huang X, El-Sayed IH, El-Sayed MA. Noble metals on the nanoscale:
445 optical and photothermal properties and some applications in imaging, sensing,
446 biology, and medicine. *Acc Chem Res.* 41(12), 1578–1586 (2008).
- 447 [27] Zhang Y, Zhan X, Xiong J, Peng S, Huang W, Joshi R, et al. Temperature-
448 dependent cell death patterns induced by functionalized gold nanoparticle
449 photothermal therapy in melanoma cells. *Sci Rep.* 8(1), 8720 (2018).
450 <https://doi.org/10.1038/s41598-018-26978-1>.
- 451 [28] Miola M, Ferraris S, Pirani F, Multari C, Bertone E, Žužek Rožman K, et al.
452 Reductant-free synthesis of magnetoplasmonic iron oxide-gold nanoparticles.
453 *Ceram Int.* 43(17),15258–65 (2017).
- 454 [29] de la Encarnación C, Lenzi E, Henriksen-Lacey M, Molina B, Jenkinson K,
455 Herrero A, et al., Hybrid Magnetic–Plasmonic Nanoparticle Probes for Multimodal
456 Bioimaging, *The Journal of Physical Chemistry C.* 126 (45), 19519-19531 (2022).
457 DOI: 10.1021/acs.jpcc.2c06299
- 458 [30] Miola M, Multari C and a Vernè E, Iron oxide-Au magneto-plasmonic
459 heterostructures: advances in their eco-friendly synthesis,
- 460 [31] *Materials.* 15, 7036 (2022). <https://doi.org/10.3390/ma15197036>
- 461 [32] Jadoun S, Arif R, Jangid NK, Meena RK. Green synthesis of nanoparticles
462 using plant extracts: a review. *Environ Chem Lett.* 19(1), 355–74 (2021).
463 <https://doi.org/10.1007/s10311-020-01074-x>
- 464 [33] Gupta H, Paul P, Kumar N, Baxi S, Das DP. One pot synthesis of water-
465 dispersible dehydroascorbic acid coated Fe₃O₄ nanoparticles under atmospheric
466 air: blood cell compatibility and enhanced magnetic resonance imaging. *J Colloid*
467 *Interface Sci.* 430, 221–228 (2014). <http://dx.doi.org/10.1016/j.jcis.2014.05.043>

- 468 [34] Dahl JA, Maddux BLS, Hutchison JE. Toward greener nanosynthesis. *Chem*
469 *Rev.* 107(6), 2228–69 (2007).
- 470 [35] Gülçin İ, Huyut Z, Elmastas M, Aboul-enein HY. Radical scavenging and
471 antioxidant activity of tannic acid. *Arabian Journal of Chemistry*, 3 (1), 43-53
472 (2010).
- 473 [36] Miola M, Multari C, Debellis D, Laviano F, Gerbaldo R, Vernè E, Magneto-
474 plasmonic heterodimers: Evaluation of different synthesis approaches, *J Am*
475 *Ceram Soc.* 105,1276–1285 (2022). DOI: 10.1111/jace.18190
- 476 [37] Ahmad T. Reviewing the Tannic Acid Mediated Synthesis of Metal
477 Nanoparticles. Thundat T, editor. *J Nanotechnol.* 2014, 954206 (2014).
478 <https://doi.org/10.1155/2014/954206>
- 479 [38] Gülçin İ, Huyut Z, Elmastaş M, Aboul-Enein HY. Radical scavenging and
480 antioxidant activity of tannic acid. *Arab J Chem.*3(1),43–53 (2010).
- 481 [39] Dong G, Liu H, Yu X, Zhang X, Lu H, Zhou T, et al. Antimicrobial and anti-
482 biofilm activity of tannic acid against *Staphylococcus aureus*. *Nat Prod Res.*
483 32(18),2225–2228 (2018). <https://doi.org/10.1080/14786419.2017.1366485>
- 484 [40] Martínez-Castañon GA, Nino-Martinez N, Martinez-Gutierrez F, Martinez-
485 Mendoza JR, Ruiz F. Synthesis and antibacterial activity of silver nanoparticles
486 with different sizes. *J nanoparticle Res.* 10(8), 1343–1348 (2008).
- 487 [41] Daduang J, Palasap A, Daduang S, Boonsiri P, Suwannalert P, Limpai boon T.
488 Gallic acid enhancement of gold nanoparticle anticancer activity in cervical
489 cancer cells. *Asian Pac J Cancer Prev.* 16(1),169–74 (2015).
- 490 [42] de la Harpe KM, Kondiah PPD, Choonara YE, Marimuthu T, du Toit LC,
491 Pillay V. The Hemocompatibility of Nanoparticles: A Review of Cell-Nanoparticle

- 492 Interactions and Hemostasis. *Cells*. 8(10),1209 (2019). doi:
493 10.3390/cells8101209.
- 494 [43] Borroni E, Miola M, Ferraris S, Ricci G, Kristina Z, Kostevšek N, et al. Tumor
495 targeting by lentiviral vectors combined with magnetic nanoparticles in mice.
496 *Acta Biomaterialia*. 59, 303–316 (2017).
- 497 [44] Multari C, Miola M, Ferraris S, Movia D, Žužek Rožman K, Kostevšek N, et
498 al. Synthesis and characterization of silica-coated superparamagnetic iron oxide
499 nanoparticles and interaction with pancreatic cancer cells. *Int J Appl Ceram*
500 *Technol*. 15(4), 947–60 (2018).
- 501 [45] Bruce IJ, Taylor J, Todd M, Davies MJ, Borioni E, Sangregorio C, et al.
502 Synthesis, characterisation and application of silica-magnetite nanocomposites. *J*
503 *Magn. Magn. Mater*. 284,145–160 (2004).
- 504 [46] Singh RK, Kim T-H, Patel KD, Knowles JC, Kim H-W. Biocompatible
505 magnetite nanoparticles with varying silica-coating layer for use in biomedicine:
506 Physicochemical and magnetic properties, and cellular compatibility. *J Biomed*
507 *Mater Res Part A*. 100A (7),1734–1742 (2012).
508 <https://doi.org/10.1002/jbm.a.34140>
- 509 [47] Pantoja M, González-Rodríguez H. Study by infrared spectroscopy and
510 thermogravimetric analysis of Tannins and Tannic acid. *Rev Latinoam química*.
511 39,107–12 (2010).
- 512 [48] Veisi H, Moradi SB, Saljooqi A, Safarimehr P. Silver nanoparticle-decorated
513 on tannic acid-modified magnetite nanoparticles (Fe₃O₄@TA/Ag) for highly
514 active catalytic reduction of 4-nitrophenol, Rhodamine B and Methylene blue.
515 *Mater Sci Eng C*. 100, 445–52 (2019).

- 516 [49] Aromal SA, Philip D. Facile one-pot synthesis of gold nanoparticles using
517 tannic acid and its application in catalysis. *Phys E Low-dimensional Syst*
518 *Nanostructures*. 44(7-8),1692-1696 (2012)
519 <http://dx.doi.org/10.1016/j.physe.2012.04.022>
- 520 [50] Gold-nanoparticles-optical-properties.
521 <https://nanocomposix.com/pages/gold-nanoparticles-optical-properties>. Cited
522 04/05/2023
- 523 [51] Correa JR, Bordallo E, Canetti D, León V, Otero-Díaz LC, Negro C, et al.
524 Structure and superparamagnetic behaviour of magnetite nanoparticles in
525 cellulose beads. *Mater Res Bull*. 45(8),946-53 (2010).
- 526 [52] Simmons M, Wiles C, Rocher V, Francesconi MG, Watts P. The preparation
527 of magnetic iron oxide nanoparticles in microreactors. *J Flow Chem*. 3(1), 7-10
528 (2013).
- 529 [53] Ajdary M, Moosavi MA, Rahmati M, Falahati M, Mahboubi M, Mandegary A,
530 et al. Health Concerns of Various Nanoparticles: A Review of Their in Vitro and in
531 Vivo Toxicity. *Nanomater*. 8(9), 634 (2018).
- 532 [54] Yao Y, Zang Y, Qu J, Tang M, Zhang T. The Toxicity of Metallic Nanoparticles
533 on Liver: The Subcellular Damages, Mechanisms, And Outcomes. *Int J*
534 *Nanomedicine*. 14, 8787-804 (2019).