RSC Advances

rsc.li/rsc-advances

ISSN 2046-2069

ROYAL SOCIETY OF CHEMISTRY

RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2018, **8**, 38376

Bamboo leaf-based carbon dots for efficient tumor imaging and therapy†

Mochamad Zakki Fahmi, *[a] Abdul Haris,[a] Ahmadi Jaya Permana,[a] Denika Liyan Nor Wibowo,[a] Bambang Purwanto,[b] Yatim Lailun Nikmah[c] and Adi Idris[d]

In this study, carbon dots synthesized from bamboo leaf cellulose were used simultaneously as a staining agent and for doxorubicin delivery to target cancer cells. Owing to their nontoxic properties, the production of carbon dots from bamboo leaves is a green approach involving optimized application of bamboo tree waste. For multifunctional applications, the carbon dots were modified with 4-carboxybenzylboronic acid and doxorubicin to improve target specificity and drug delivery to HeLa tumor cells. The resulting modified carbon dots were characterized using different analytical techniques, which showed that they were biocompatible, nontoxic, and highly stable over a wide range of pH values and at high ionic strengths. Furthermore, *in vitro* confocal microscopy studies demonstrated their blue fluorescence and cellular pathway for entering HeLa cells *via* folate receptor-mediated endocytosis. Cell viability data and flow cytometry results also confirmed the selective uptake of the carbon dots by HeLa cells, which significantly enhanced cell cytotoxicity.

Received 25th September 2018
Accepted 26th October 2018

DOI: 10.1039/c8ra07944g

rsc.li/rsc-advances

Introduction

The development of ecofriendly and nontoxic nanomaterials has been rapid following extensive investigations into nanotechnology in the last two decades.[1–3] The versatile and attractive properties of nanomaterials are the main factors promoting their study, especially in the medical field. To date, the biomedical utilization of nanomaterial has resulted in achievements in detection and the treatment of diseases resulting from tumors,[4–6] viruses,[7–9] and bacteria.[10,11] Emerging carbon-based nanomaterials are of much research interest owing to toxicity issues in the medical application of nanoparticles. Several carbon-based nanomaterials, such as carbon nanotubes,[12] nanodiamonds,[13] carbon nanofibers,[14] and carbon dots,[15] have recently been introduced and pursued for medical use owing to their green approach, low toxicity, environmental friendliness, and biocompatibility.

Among these carbon-based materials, carbon dots (CDs), or graphene quantum dots, have recently been discovered. CDs have received attention owing to their additional luminescent properties, which are comparable to those of quantum dots,[16] and specific hydrophobic sites that allow simultaneously improved diagnostics and therapy.[17] In the pursuit of synthetic methods for preparing carbon dots, using both bottom-up and top-down approaches,[18] many carbon sources have been applied, including citric acid,[9] carbohydrate and glucose,[19,20] amino acid,[21] grass,[22] acetic acid,[23] protein,[24] egg,[25] and fruit waste.[26] The synthetic methods and reactants used have been found to influence the properties of the resulting carbon dots.

Despite extensive study, the development of effective and efficient methods for synthesizing carbon dots remains challenging. Investigations into using commercial or unused materials as carbon dot precursors have received interest owing to the potential advantages of the resulting carbon dots. Organic waste material can be considered an alternative material. There are many sources of natural organic materials, including plant leaves, among which waste bamboo leaves are produced in abundance and underutilized. Several reports have confirmed the antioxidant,[27,28] antimicrobial, and antibacterial activities of bamboo leaves.[29,30] Furthermore, the potential application of bamboo leaves as precursors of carbon dots used as the base material for copper ion detection has been reported.[31] However, the application of carbon dots from waste bamboo leaves in both tumor detection and therapy has yet to be reported.

Using nanomaterials for tumor labelling and therapy has been proposed to overcome the problems of complicated syntheses, expensive precursors, and emission losses, which are the major factors preventing the specific targeting of tumor cells instead of normal cells. In this study, improvements in the synthesis of carbon dots from waste bamboo leaves and their

[a]*Department of Chemistry, Universitas Airlangga, Surabaya 61115, Indonesia. E-mail: m.zakki.fahmi@fst.unair.ac.id*

[b]*Department of Physiology, Department of Medical Biochemistry, Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia*

[c]*Department of Chemistry, Faculty of Natural Science, Sepuluh Nopember Institute of Technology, Keputih, Sukolilo, Surabaya 60111, Indonesia*

[d]*Menzies Health Institute Queensland, School of Medical Science, Griffith University, Southport, Queensland, Australia*

† Electronic supplementary information (ESI) available: Reaction mechanism of CD and IC_{50} cytotoxicity. See DOI: 10.1039/c8ra07944g

modification to obtain specific targeting of HeLa tumor cells are reported. The abundance of folate receptors overexpressed on the surface of HeLa tumor cells motivated our selection of targeting agent CBBA (4-carboxybenzylboronic acid) for attachment to the synthesized carbon dots. Furthermore, tumor drug doxorubicin was attached to carbon dots to afford a drug delivery ability. In addition to characterization, stability, toxicity, and *in vitro* assays of HeLa tumor cells taken up on this material were performed to confirm that these multifunctional carbon dots can be used for tumor detection and therapy.

Experimental section

Materials

Bamboo leaves from *Gigantochloa apus* were collected near Airlangga University, Indonesia. Sodium hydroxide, sodium hypochlorite (NaOCl), *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI, 97%), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, 97.5%), 4-dimethylaminopyridine (DMAP, 98%), doxorubicin (Dox, 98%), and 4-carboxybenzylboronic acid (CBBA, 98%) were purchased from Sigma Aldrich (Milwaukee, WI, USA). Citric acid was purchased from Bratachem Co. Ltd. (Jakarta, Indonesia). All chemicals were used directly without further purification.

Synthesis of carbon dots

Bamboo leaves, as the carbon dot (CD) precursor, were first cleaned and dried at 120 °C for 2 h. The dried leaves were sliced to give 2 kg of sliced leaves and then refluxed with 1 M NaOH (10 mL) at 60 °C for 4 h. After rinsing with DI water, the leaves were further immersed in NaOCl solution (10 mL, 5% (v/v)) for bleaching. The obtained cellulose was precipitated by centrifugation at 2000 rpm for 15 min and pyrolyzed at 250 °C for 30 min in a furnace. The resulting CDs stacked at the reactor wall were dissolved in 0.5 M NaOH and filtered through a syringe (0.22 μm) to remove larger particles. The CDs were then dialyzed using a cellulose dialysis bag (MWCO, 1000 Da) for 24 h to separate smaller particles and unreacted reagent. The obtained CDs were used in the next step.

Attaching CBBA to CD(CBBA-CD) and Dox loading

The attachment of CBBA onto CDs was achieved using the DMAP/EDCI mechanism. CBBA (13.3 mg) was dissolved in DI water (10 mL) and EDCI (23.7 mg) was added under stirring to afford a homogenous solution. Meanwhile, to a solution of CDs (5 mL, 0.5 mg mL^{-1}) was added DMAP, followed by treatment using an ultrasonic probe (JY-9211DN, Ningbo Scientz Biotechnology, Co. Ltd., China) operated at 20 Hz and 130 W power for 2 min to accelerate DMAP dissolution. The two solutions were mixed at pH 6 using a magnetic stirrer for 24 h. The resulting mixture was then dialyzed using a cellulose membrane (MWCO, 1000 Da) for 24 h to remove unreacted substrates and byproducts. This dialyzed solution was used for further experiments.

Tumor drug Dox was loaded onto CBBA-CDs by adding Dox (about 5 mg) to CBBA-CD solution (15 mL) with stirring for 24 h. Unconjugated Dox was separated from Dox-loaded CBBA-CDs (Dox/CBBA-CDs) by dialysis for 24 h using similar conditions to the previous dialysis process. The amount of Dox stacked on CBBA-CD was further assessed by its absorption at 482 nm compared with the standard concentration. The loading efficiency and loading amount were measured using eqn (1) and (2).

$$\text{Percentage of loading efficiency (\%)} = \frac{\text{mass of Dox on CBBA-CD}}{\text{mass of Dox in feed}} \times 100 \quad (1)$$

$$\text{Percentage of loading amount (\%)} = \frac{\text{mass of Dox on CBBA-CD}}{\text{mass of CBBA-CD}} \times 100 \quad (2)$$

Dox release pattern

The pattern of Dox release was assessed by dialyzing Dox/CBBA-CDs using a cellulose membrane (MWCO, 1000 Da) immersed in an outer PBS aqueous solution. Aliquots (about 1 mL) of the PBS solution were removed at certain times, while the volume of the PBS buffer was kept at 50 mL. The Dox concentration released into the outer solution was measured by tracking Dox absorbance and corrected using eqn (3):

$$Ct' = Ct + \frac{v}{V}\sum_{0}^{i-t} Ct \quad (3)$$

where Ct' is the corrected concentration at time t, Ct is the apparent concentration at time t, v is the volume of aliquots taken, and V is the total buffer volume. The effect of pH on Dox release was investigated by adjusting the pH value of the outer solution to 5.0, 7.4, and 9.0.

Cell culture

For culturing human cervical (HeLa) tumor cells, Eagle's minimum essential medium (containing 1.5 g L^{-1} sodium bicarbonate) supplemented with 1% L-glutamine, 1% antibiotic antimycotic formulation, 1% non-essential amino acid, 1% sodium pyruvate, and 10% fetal bovine serum was used as medium. The cells were then stored in a humidified 5% CO_2 incubator maintained at 37 °C.

Cytotoxicity assessment

Cell viability was quantified using an MTT assay in HeLa tumor cells. HeLa cells previously cultured in Eagle's minimum essential medium, as described above, were placed in 12-well plate (25 000 cells per well) for 24 h. After washing with phosphate-buffered saline (PBS, UniRegion Biotech, Taiwan), the proliferated cells were further washed with PBS and incubated with adjusted samples for 24 h. After washing the plate twice with PBS, MTT reagent (1 mL, 500 mg mL^{-1}) was added and incubated for

4 h. To dissolve formazan crystals, dimethyl sulfoxide (1 mL) was added to each well and the absorbance of the crystals was measured at 570 nm using an Elisa reader (Biotech Powerwave XS). The absorbance intensity was related to the amount of formazan and was proportional to the number of live cells.

Confocal imaging observation

The HeLa cells were first seeded in a 6-well plate in culturing medium (2 mL) and cultured for 24 h. After incubating with sample (300 μL) for 60 min, the cells were washed three times with PBS solution and then fixed with 70% alcohol for 10 min. Fluorescence images of HeLa cells were acquired using a Leica TCS SP2 inverted confocal microscope (Leica Microsystems) equipped with a 63 × 1.32 NA oil immersion objective. Confocal images were obtained by illuminating the samples with inline Ar (488 nm) and He–Ne (503–680 nm and 588 nm) lasers.

Flow cytometry analysis

Approx. 3×10^5 cells were individually cultured in a cell flask with medium (5 mL) for 24 h. The medium was then replaced with fresh medium (5 mL) containing different concentrations of samples, with PBS-treated cells used as control. After incubating for 1 h, the treated cells were rinsed with PBS, trypsinized, centrifuged, and suspended in binding buffer. The cells were then stained with Annexin V-FITC (5 μL) for 15 min, washed with binding buffer, and stained with propidium iodide (10 μL). The samples were analyzed on a Guava easyCyte Flow Cytometer equipped with an argon laser (488 nm).

Characterization

High resolution-transmission electron microscopy (HR-TEM) images were obtained on a Philips Tecnai G2 F20 microscope (Philips, Holland) and assigned using energy-dispersive X-ray spectroscopy (EDS) at 200 kV. Powder X-ray diffraction (XRD) patterns were obtained using a Rigaku 18 kW rotating anode source X-ray diffractometer with Cu $K_{\alpha 1}$ line radiation ($\lambda = 1.54$ Å). UV-Vis absorption spectra were measured using a JASCO V-670 spectrometer. PL spectra were measured using a PerkinElmer LS 55 spectrofluorometer equipped with a 20 kW xenon lamp. Atomic force microscopy[12] images were acquired using a scanning probe AFM5500M instrument (Hitachi Co., Japan) at ambient temperature. Raman analysis was performed using a MRS-320 Raman Instrument system (Horiba Ltd., Japan).

Statistical analysis

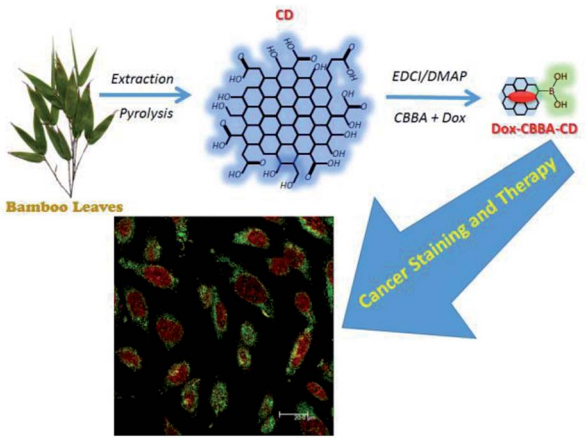
Statistical analysis, including the cytotoxic concentration causing a 50% decrease in cell viability (CC_{50}), was performed using dose–response mode on the nonlinear fitting curve in Origin software (version 8.0724, OriginLab Inc., Northampton, MA). All data were obtained in triplicate, and means were compared using a paired-sample *t*-test.

Results and discussion

CD preparation

CDs were synthesized by pyrolyzing cellulose in bamboo leaves, as shown in Scheme 1. Several treatments, including the addition NaOH and NaOCl solutions, were performed to collect cellulose from lignin and bleach the collected cellulose, respectively. Extraction was conducted for 2 h until the NaOH changed color to black and the bamboo leaf color faded. The extraction process aimed to degrade lignin in bamboo leaves, because lignin compounds can interfere with the synthesis of carbon dots obtained as the result of the pyrolysis of cellulose in bamboo leaves. The collected cellulose was then heated to 250 °C. This process allowed carbonation of cellulose, which both reconstructed and combined the polysaccharides, resulting in a graphene oxide structure. As shown in previous studies, incomplete carbonation will drive cellulose to form CDs.[31,32]

CD formation was first confirmed by XRD. The crystallinity of the CDs was confirmed by a certain peak observed in the 2θ range diffractogram 20–25°. The XRD results for CDs synthesized at 300 °C are shown in Fig. 1. The signal of crystalline CDs



Scheme 1 Synthesis and modification of bamboo leaf-based carbon dots.

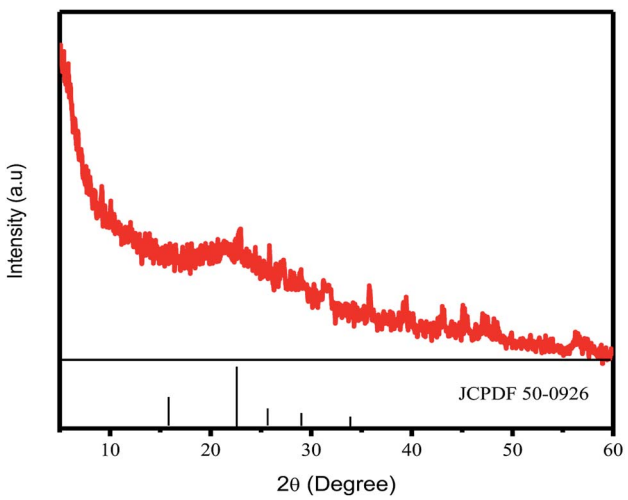


Fig. 1 XRD pattern of CDs.

was observed at 22.7° Prasannan *et al.* reported that crystalline CDs were observed at a 2θ value of 22.7°.[26] The XRD results also indicated the size of the crystalline CDs, with the 2θ position at 22.7° corresponding to an FWHM value of about 604 948, which was converted to a carbon nanoparticle size of about 0.24 nm using the Scherrer equation.

Furthermore, optical analysis of the prepared CDs by UV-Vis spectrophotometry (Fig. 2a) showed a shoulder peak at 360 nm, attributed to the particular exciton of CDs. As supported by our previous report, this indicated CD formation in the carbonation process.[9] CD luminescence was characterized by PL spectroscopy (Fig. 2a). By varying the temperature of pyrolysis, the CD emissions showed insignificant luminescence emission at wavelengths of around 425–475 nm. These differences showed the graphene-like structure of CDs prepared from the carbonization of bamboo leaves. The difference in the maximum emission peak was around 5 nm. Zhu *et al.* reported that CD emission in the range 425–475 nm confirmed a CD size of below 5 nm, which emitted blue luminescence.[33]

The AFM results (Fig. 2b) indicated that the size of CDs from bamboo leaves averaged 2 nm, with some CDs having sizes of over 4 nm. High-magnification HR-TEM (Fig. 2c) systematically showed the carbon structures, confirming the formation of a graphene-like structure in the CDs. Furthermore, Raman spectra (Fig. 2d) showed the G-band peak of CDs at 1582 cm^{-1} and a D-band peak at 1332 cm^{-1}, attributed to the vibration of sp^2-hybridized and sp^3-hybridized carbon atoms at the edge of the crystal, respectively. This peak supported that the CDs formed a graphene-like crystal structure. Furthermore, a higher D-band intensity supported the formation of more amorphous phase at the terminal end of the carbon plane, which was responsible for the water solubility of the CDs rather than the CD emission.

Conjugation of CBBA onto CDs (CBBA-CDs)

CDs were modified with CBBA to afford CD that specifically target tumor cells. Previous research has shown that boronic acids have a high affinity for *cis*-diol moieties in sialic acid, which generally exists on the membrane of tumor cells.[34] Therefore, CBBA can specifically guide CDs to tumor cells. However, the addition of CBBA to the CDs required a specific catalyst, namely the Steglich catalyst. This catalyst was used for esterification between carboxylic acid groups in CBBA and alcohol groups in the CDs. The mechanism of the Steglich reaction is shown in Fig. S1 (ESI†). In this esterification reaction, EDCI acts as a cross-linker, making the reaction irreversible. To evaluate the change in CD size before and after CBBA modification, AFM images of CBBA-CDs and their size distributions were measured, as shown in Fig. S2 (ESI†). The histogram data showed an insignificant increase in the size distribution of CBBA-CDs, with average sizes of about 2.5 nm.

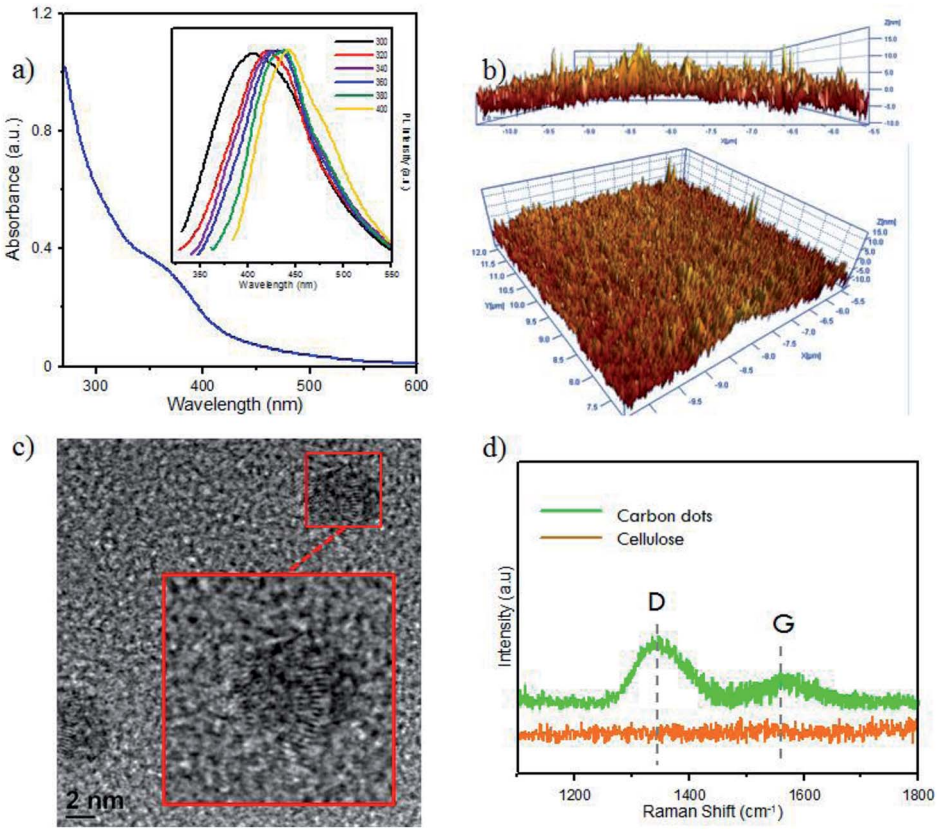


Fig. 2 (a) UV-Vis spectra of CDs. Inset: PL spectra at varied temperatures, namely 200 °C (red), 250 °C (green), 300 °C (blue), 350 °C (pink), 400 °C (brown). (b) AFM images of CDs in vertical and diagonal views. (c) HR-TEM images of CDs with high magnification image on adjusted square. (d) Raman spectra of CDs and raw cellulose. Inset: Photograph of CDs compared with water under UV lamp (365 nm).

This showed that modification with CBBA maintained the original CD size.

FTIR was also used to assess the presence of CBBA on the CDs (Fig. 3). For CBBA-CDs, boron dihydroxy (O–B–O) bond vibrations were observed at 1266 cm^{-1} (asymmetric stretching), 1215 cm^{-1} (deformation), and 507 cm^{-1} (bending vibration), along with a B–O–H stretching band at 1083 cm^{-1}.[35] Other bands at 745 and 670 cm^{-1} were attributed to bending vibrations of B–O–H.[36] Furthermore, pristine CDs also showed bands at 713, 874, and 1083 cm^{-1}, which were attributed to vibrations of C–H aromatic groups.

Loading of Dox onto CBBA-CDs (Dox/CBBA-CDs)

As-prepared CBBA-CDs were physically conjugated with tumor cell drug Doxorubicin (Dox) using the procedure described in Scheme 1 to determine the Dox delivery ability of the CDs. In this procedure, Dox was loaded onto CBBA-CDs through electrostatic interactions. As reported previously, Dox can stack on graphene-like structures through π–π interactions among benzene structures.[5] Therefore, DOX exhibited a high affinity for negatively charged BSA (isoelectric point, pH = 5.4).

To investigate the Dox delivery potential of the CDs, we evaluated the cellular uptake of CDs on HeLa tumor cells using confocal laser scanning microscopy (CLSM). CLSM is a powerful method for observing the internalization of CDs, CBBA-CDs, and Dox/CBBA-CDs into HeLa tumor cells (Fig. 4). Significant green fluorescence was observed from CBBA-CDs on the cytoplasm of HeLa tumor cells after 1 h of incubation. Compared with CDs, which did not show green emission (Fig. 4a), the existence of green fluorescence confirmed that CDs were readily taken up by the cells *via* endocytosis (Fig. 4b). These findings also showed that boronic acids were good targeting agents for CDs onto tumor cells. Furthermore, Dox delivery was successfully achieved using CBBA-CDs, with red fluorescence, the characteristic emission of Dox, observed in the nuclei of cells treated with Dox/CBBA-CDs. Dox operates as a tumor drug by disturbing the DNA helix structure in the cell nucleus. Therefore, the appearance of red fluorescence in the cell nucleus after incubation with Dox confirmed that the drug had been successfully delivered to the target.

Cytotoxicity assessment of CDs was conducted using an MTT assay. After incubation for 24 h, the MTT results (Fig. 5) showed excellent cell viability (over 80%) for both CDs and CBBA-CDs. This strongly suggested that CDs and CBBA-CDs had low toxicity, even when the CD concentration was increased to 400 μg mL^{-1}. However, toxicity was observed after loading Dox onto the CDs (Dox/CBBA-CDs). Starting at a low concentration (10 μg mL^{-1}), Dox decreased the cell viability. Furthermore, half-maximal inhibitory concentration (IC_{50}) values were determined using dose–response graphs obtained after treating HeLa cells with free Dox and Dox/CBBA-CDs (Fig. S3, ESI†). Analysis showed that free Dox resulted in lower IC_{50} values (52.3 mg mL^{-1}) than Dox/CBBA-CDs (68.2 mg mL^{-1}). This suggested that CBBA-CDs successfully achieved delivery of Dox to the target cells.

Further *in vitro* assessments of the obtained CDs were directed toward measuring the characteristic emission on HeLa cells *via* flow cytometry analysis. This method can detect the fluorescence of materials accumulated on microorganisms, such as HeLa cells. The graph in Fig. 6 shows the intensity of green fluorescence in cells treated with CDs and CBBA-CDs after incubation for 1 h. Compared with untreated cells and CD-treated cells as control, the fluorescence of cells treated with CBBA-CDs was significantly higher. These data were supported by the previous CLSM results, which indicated that CBBA worked well to deliver CDs specifically to HeLa cells. The formation of tetravalent complexes between the boronic acid sites and *cis*-diols in sialic acid on the outer cell membrane was key to the insertion of CDs into the cell cytoplasm. Further flow cytometry analysis was focused on improving the cytotoxicity of CDs by assessing the number of apoptotic cells affected by CDs (Fig. 7a–d). In this study, Annexin V-FITC and propidium iodide were used as the kit package for detecting apoptosis and necrosis, respectively.

Annexin has a high affinity for phosphatidylserine expressed on the outer membrane once cell apoptosis has occurred and

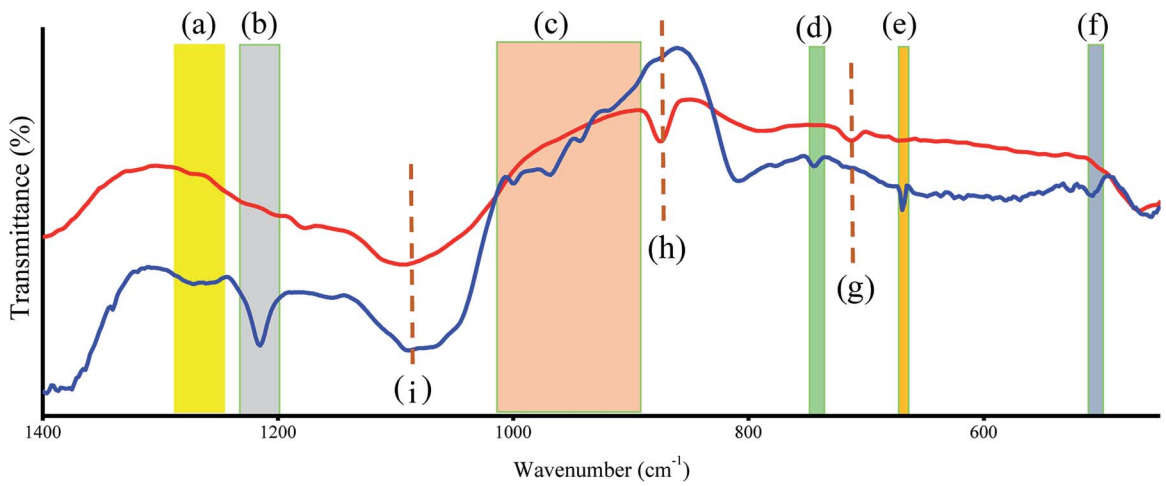


Fig. 3 FTIR spectra of CD (red line) and CBBA-CD (blue line). (a) to (f) refer to existence of CBBA site and (g) to (i) refer to CD vibration.

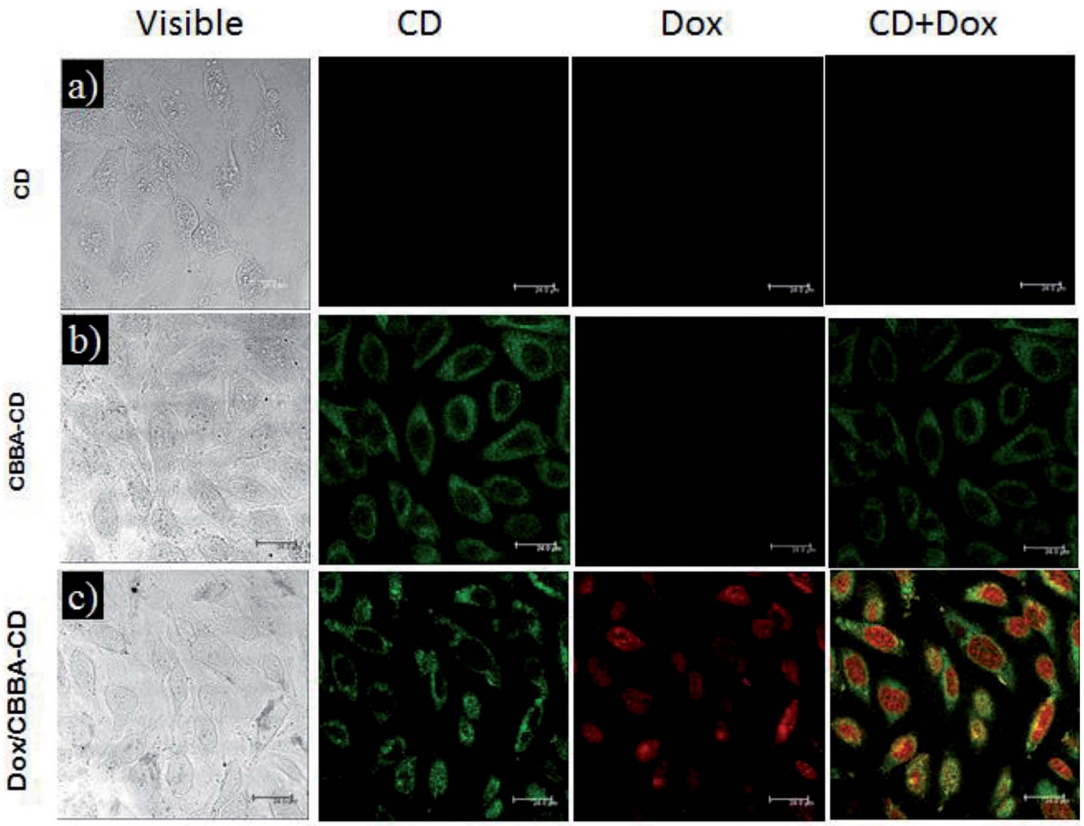


Fig. 4 CLSM images of (a) CDs, (b) CBBA-CDs, and (c) Dox/CBBA-CDs after incubation for 1 h with HeLa cells at 37 °C. Scale bars represent 24 μm.

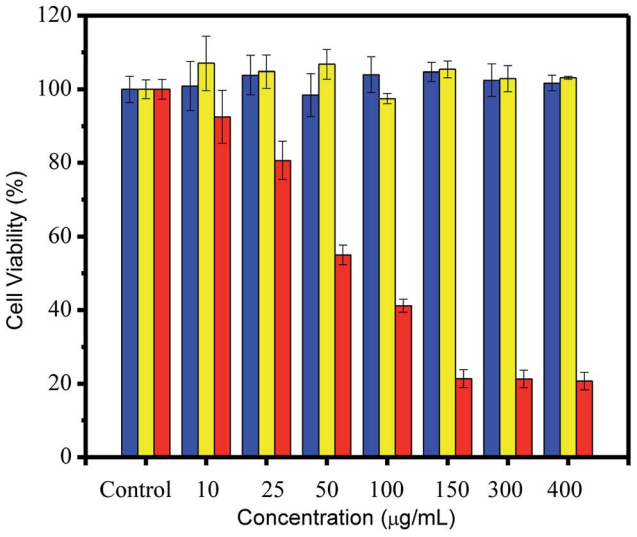


Fig. 5 Cell viability study through MTT assay of HeLa cells after 24 h of treatment with CDs (blue), CBBA-CDs (yellow), and Dox/CBBA-CDs (red). All MTT data are shown as means ± SD ($n = 3$).

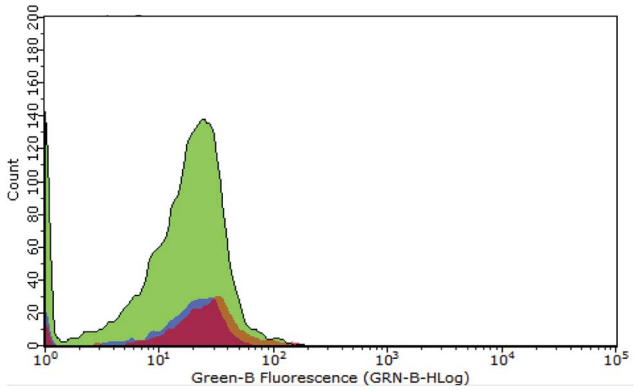


Fig. 6 Flow cytometry data representing fluorescence distribution of untreated cells (purple area), CD-treated cells (orange area), and CBBA-CD-treated cells (green area).

green fluorescence emerging from connected FITC. In contrast, propidium iodide, which shows red fluorescence, conjugates to cell DNA during necrosis. The flow cytometry quadrant data of untreated cells (Fig. 7a) was established as the control, in which all cells existed in quadrant 1 (Annexin, negative; PI, negative). The addition of CDs onto cell did not have a toxic effect upon living cells, while the absence of CDs on the cell cytoplasm resulted in the cell performing like the control cells or untreated cells; therefore, almost all cells were in quadrant 1 (Fig. 7b). Furthermore, the presence of CBBA on CDs resulted in some cells (23.5%) undergoing necrosis in quadrant 3 (Annexin, negative; PI, positive), which is a form of uncontrolled or pathological death cell and cannot be claimed as proof of CD

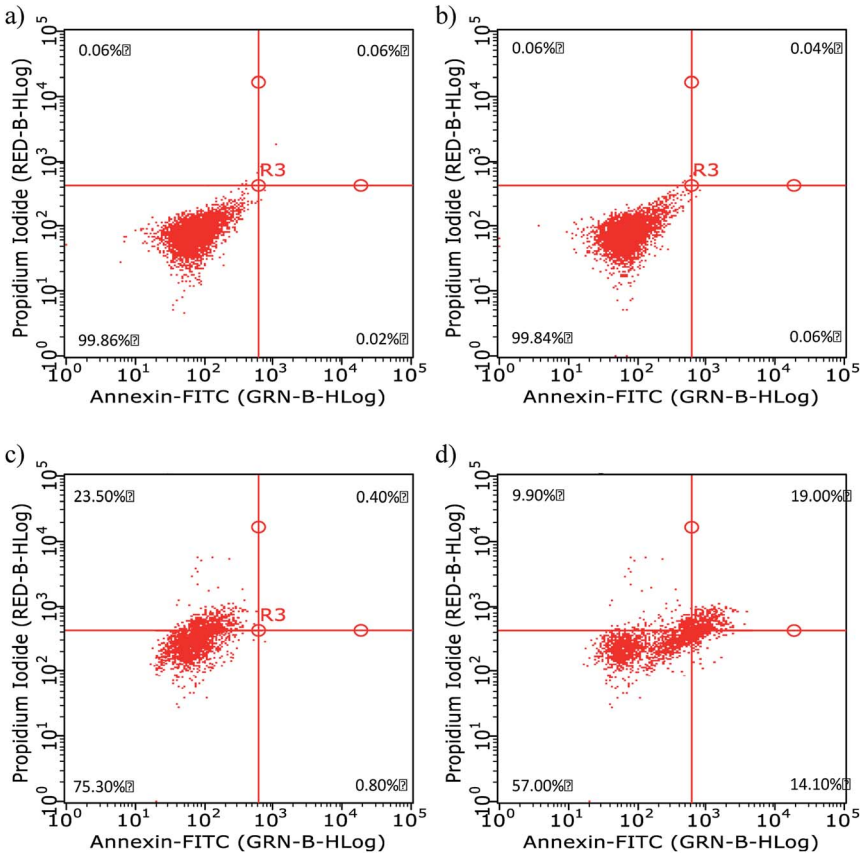


Fig. 7 Apoptosis data of HeLa cells (a) before and (b–d) after 1 h of incubation with (b) CDs, (c) CBBA-CDs, and (d) Dox/CBBA-CDs.

toxicity (Fig. 7c). In contrast, cells treated with Dox/CBBA-CDs showed 14.1% early apoptosis (Annexin, positive; PI, negative) and 19% late apoptosis (Annexin, positive; PI, positive). Apoptosis is a programmed form of cell death, caused in this case by Dox damaging DNA formation in the cell (Fig. 7d). This findings demonstrated that CBBA-CDs and Dox can successfully deliver drugs and kill the targeted cell, respectively.

Conclusions

We have demonstrated the application of cellulose from bamboo leaves as a raw material for the synthesis of CDs for imaging and drug delivery. The resulting CDs were nontoxic, biocompatible, and exhibited a graphene-like structure that accommodated tumor drug Dox. This method was used to construct multifunctional nanoparticle for imaging and drug delivery by conjugation of CBBA and Dox onto the CDs, respectively. CBBA acts as a targeting agent and stabilizes the CDs. An efficient method for preparing CDs valuable against tumor cells was achieved by conjugation with Dox. Cytotoxicity investigations *via* MTT and flow cytometry showed the toxic effects of this type of nanomaterial after binding with Dox. The design of modified CDs can hopefully motivate the future development of novel approaches for preparing multi-purpose nanomaterials.

Conflicts of interest

There are no conflicts to declare.

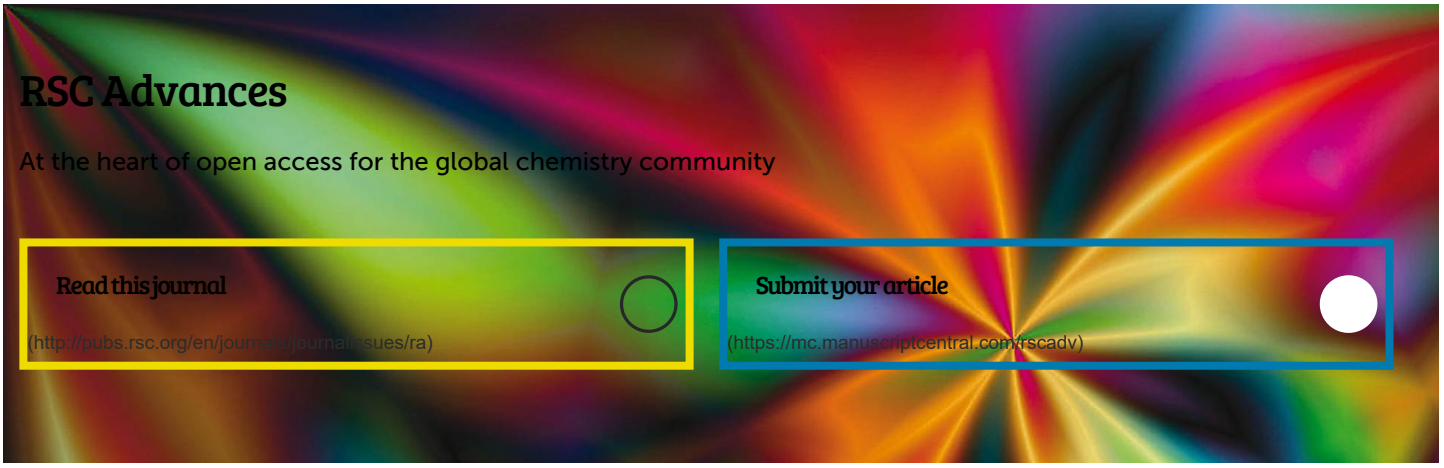
Acknowledgements

The authors thank the Ministry of Research and Technology, Republic of Indonesia, for full support of this study, and the SATU Joint Research Program and Universitas Airlangga for providing research facilities.

Notes and references

1 C. Lherm, R. H. Müller, F. Puisieux and P. Couvreur, *Int. J. Pharm.*, 1992, **84**, 13–22.
2 J. S. Tsuji, A. D. Maynard, P. C. Howard, J. T. James, C.-w. Lam, D. B. Warheit and A. B. Santamaria, *Toxicol. Sci.*, 2006, **89**, 42–50.
3 N. Savage and M. S. Diallo, *J. Nanopart. Res.*, 2005, **7**, 331–342.
4 C. Andreou, V. Neuschmelting, D.-F. Tschaharganeh, C.-H. Huang, A. Oseledchyk, P. Iacono, H. Karabeber, R. R. Colen, L. Mannelli and S. W. Lowe, *ACS Nano*, 2016, **10**, 5015–5026.
5 M. Z. Fahmi, K.-L. Ou, J.-K. Chen, M.-H. Ho, S.-H. Tzing and J.-Y. Chang, *RSC Adv.*, 2014, **4**, 32762–32772.

6 W. M. Girma, M. Z. Fahmi, A. Permadi, M. A. Abate and J.-Y. Chang, *J. Mater. Chem. B*, 2017, **5**, 6193–6216.
7 H. J. Park, E. J. Jeon, J. S. Lee, S. H. Hong, A. N. Cho, J. Lee, J. S. Moon, K. E. Jung, J. W. Oh and H. Lee, *Advanced Healthcare Materials*, 2016.
8 G. Ortega, J. Zuaznabar-Gardona, O. Morales-Tarré and E. Reguera, *RSC Adv.*, 2016, **6**, 98457–98465.
9 M. Z. Fahmi, W. Sukmayani, S. Q. khairunisa, a. m. witaningrum, d. w. indriati, m. q. y. matondang, J.-Y. Chang, T. Kotaki and M. Kameoka, *RSC Adv.*, **6**(95), 92996–93002.
10 Y. H. Lim, K. M. Tiemann, D. A. Hunstad, M. Elsabahy and K. L. Wooley, *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 2016.
11 M. Latha, M. Priyanka, P. Rajasekar, R. Manikandan and N. Prabhu, *Microb. Pathog.*, 2016, **93**, 88–94.
12 H. A. Hassan, L. Smyth, J. T.-W. Wang, P. M. Costa, K. Ratnasothy, S. S. Diebold, G. Lombardi and K. T. Al-Jamal, *Biomaterials*, 2016, **104**, 310–322.
13 Y. Zhang, Z. Cui, H. Kong, K. Xia, L. Pan, J. Li, Y. Sun, J. Shi, L. Wang and Y. Zhu, *Adv. Mater.*, 2016, **28**(14), 2699–2708.
14 D. Naskar, P. Bhattacharjee, A. K. Ghosh, M. Mandal and S. C. Kundu, *ACS Appl. Mater. Interfaces*, 2016, **9**(23), 19356–19370.
15 T. Feng, X. Ai, G. An, P. Yang and Y. Zhao, *ACS Nano*, 2016, **10**(4), 4410–4420.
16 L. Cao, S.-T. Yang, X. Wang, P. G. Luo, J.-H. Liu, S. Sahu, Y. Liu and Y.-P. Sun, *Theranostics*, 2012, **2**, 295–301.
17 S. Y. Choi, S. H. Baek, S.-J. Chang, Y. Song, R. Rafique, K. T. Lee and T. J. Park, *Biosens. Bioelectron.*, 2017, **93**, 267–273.
18 J. C. E. da Silva and H. M. Gonçalves, *TrAC, Trends Anal. Chem.*, 2011, **30**, 1327–1336.
19 S. K. Bhunia, A. Saha, A. R. Maity, S. C. Ray and N. R. Jana, *Sci. Rep.*, 2013, **3**, 1473.
20 H. Peng, Y. Li, C. Jiang, C. Luo, R. Qi, R. Huang, C.-G. Duan and J. Travas-Sejdic, *Carbon*, 2016, **100**, 386–394.
21 J. Jiang, Y. He, S. Li and H. Cui, *Chem. Commun.*, 2012, **48**, 9634–9636.
22 S. Liu, J. Tian, L. Wang, Y. Zhang, X. Qin, Y. Luo, A. M. Asiri, A. O. Al-Youbi and X. Sun, *Adv. Mater.*, 2012, **24**, 2037–2041.
23 Y. Fang, S. Guo, D. Li, C. Zhu, W. Ren, S. Dong and E. Wang, *ACS Nano*, 2011, **6**, 400–409.
24 Z. Zhang, J. Hao, J. Zhang, B. Zhang and J. Tang, *RSC Adv.*, 2012, **2**, 8599–8601.
25 J. Wang, C. F. Wang and S. Chen, *Angew. Chem.*, 2012, **124**, 9431–9435.
26 A. Prasannan and T. Imae, *Ind. Eng. Chem. Res.*, 2013, **52**, 15673–15678.
27 X. Ma, E. Wang, Y. Lu, Y. Wang, S. Ou and R. Yan, *PLoS One*, 2015, **10**, e0130680.
28 B. Lu, X. Wu, X. Tie, Y. Zhang and Y. Zhang, *Food Chem. Toxicol.*, 2005, **43**, 783–792.
29 D.-K. Chung and R.-N. Yu, *Korean J. Food Sci. Technol.*, 1995, **27**, 1035–1038.
30 M. Kim, M. Byun and M. Jang, *J. Korean Soc. Food Nutr.*, 1996, **25**(1), 135–142.
31 Y. Liu, Y. Zhao and Y. Zhang, *Sens. Actuators, B*, 2014, **196**, 647–652.
32 P. Shen, J. Gao, J. Cong, Z. Liu, C. Li and J. Yao, *ChemistrySelect*, 2016, **1**, 1314–1317.
33 S. Zhu, Y. Song, X. Zhao, J. Shao, J. Zhang and B. Yang, *Nano Res.*, 2015, **8**, 355–381.
34 L. Liang and Z. Liu, *Chem. Commun.*, 2011, **47**, 2255–2257.
35 D. Buc, I. Bello, M. Caplovicova, M. Mikula, J. Kovac, I. Hotovy, Y. M. Chong and G. G. Siu, *Thin Solid Films*, 2007, **515**, 8723–8727.
36 J. Datka and M. Kawałek, *Collect. Czech. Chem. Commun.*, 1992, **57**, 745–749.



Supporting our community through Covid-19

We know that this is a very challenging time for everyone, for many different reasons. If any aspect of the publishing process is worrying you – for example you think you may struggle to meet a pre-determined deadline – please let us know, and we will work out an answer together.

Setting up remote access to RSC content

You can find details about how to access information remotely in this step-by-step guide (/covid-19-response/publishing-remote-access/). The guide will also help if for any reason you have difficulty accessing the content you want.

RSC Advances publishes advances in chemistry, and in topics of interest to the chemistry community.

Thoughts from our Editor-in-chief

"Scientific publishing is entering an exciting period when high ethical standards, visibility and impact are all important to authors. I'm honoured to be chairing the board of *RSC Advances* which has already pioneered an open access publishing model for the benefit of authors and readers."

Russell J Cox, Editor-in-chief.

As the largest gold open access journal dedicated to the chemical sciences, we are here for everyone who wants to publish quality chemistry research and share it with the world.

We are here for everyone who needs access to work in every area of the chemical sciences and related disciplines.

And as part of the Royal Society of Chemistry, we are at the heart of open, international research dissemination for the chemistry community.

Great science matters. We make sure the world knows it.

> Impact factor: 3.119*
> Indexed in Scopus, Web of Science and DOAJ

Breadth

We publish work in all areas of chemistry and reach a global readership

Affordability

Low APCs, discounts and waivers make publishing open access achievable and sustainable

Quality

Research to advance the chemical sciences undergoes rigorous peer review for a trusted, society-run journal

Community

Led by active researchers, we publish quality work from scientists at every career stage, and from all countries

RSC Advances in numbers

An impact factor above **3**

Submissions from **100+** countries in 2020

An average of **30** days from submission to first decision

An average acceptance rate of **46**%

Associate editors in **25+** countries

20,000+ articles free to access and growing

Scope

RSC Advances papers should provide an insight that advances the chemistry field. Papers that contain little or no chemistry and are not considered to be of interest or relevance to the chemistry community are not within the scope of the journal.

The criteria for publication are that the work must be high quality, well conducted and advance the development of the field. Articles submitted to the journal are evaluated by our international team of associate editors and reviewers for the overall quality and accuracy of the science presented.

Download our full list of subject categories (/globalassets/05-journals-books-databases/our-journals/rsc-advances/full-list-of-subject-categories-for-rsc-advances.pdf) to see the range of topics we publish in *RSC Advances*.

Please ensure you have considered the following points before submitting your manuscript.

- Does the work present a significant advance over the existing literature? **Please supply a covering letter with your submission to demonstrate how the work is advancing the field over the existing literature.**
- Have you provided sufficient evidence/data to support your conclusions?
- Have you provided adequate characterisation data for your materials/compounds? (Please check the supporting information section to ensure that the necessary requirements have been met and copies of relevant spectra have been provided where necessary.)
- Are the results discussed in the context of the literature?
- Are the references relevant and do they appropriately reflect the existing literature?

Article processing charges and licensing

Following our peer review process, if the article is accepted, the article processing charges below will be applied to your article. There are no submission charges for *RSC Advances*.

	Article processing charge
Full price	£750 (+local taxes if applicable)*
Corresponding authors from India, Indonesia and Philippines	£500 (+local taxes if applicable)
Corresponding authors from Research4Life (https://www.research4life.org/access/eligibility/) Group A & Group B	Full APC waiver

*15% RSC member and R&P Institution (/journals-books-databases/open-access/read-and-publish/community/) discount available. Applicable to full price only.

Discounts and waivers are also available on an individual basis. Find out more about applying for a waiver (/journals-books-databases/open-access/gold-open-access/).

Corresponding authors who pay an APC and are not already members of the Royal Society of Chemistry are entitled to one year's Affiliate membership as part of their APC. Find out more about our member benefits (/membership-and-community/join/#benefits).

As part of the submission process, authors will be asked to agree to the *RSC Advances* open access terms & conditions.

We offer *RSC Advances* authors a choice of two Creative Commons licences, CC-BY or CC-BY-NC. Publication under these licenses means that authors retain copyright of their article, but allows users to read, download, copy, distribute, print, search, or link to the full texts of articles, or use them for any other lawful purpose, without asking prior permission from the publisher or the author. Read our open access statement (/journals-books-databases/open-access/open-access-info/#hide1) for further information.

All published articles are deposited with LOCKSS, CLOCKSS, Portico and the British Library for archiving.

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_cox) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_cox)

Russell Cox (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_cox)

Editor-in-chief: *Leibniz Universität Hannover, Germany*

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_batteas) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_batteas)

James Batteas (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_batteas)

Editorial Board Member: *Texas A&M University, USA*

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_faulds) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_faulds)

Karen Faulds (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_faulds)

Editorial Board Member: *University of Strathclyde, UK*

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_jun) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_jun)

Young-Shin Jun (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_jun)

Editorial Board Member: *Washington University in St Louis*

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_maji) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_maji)

Tapas Kumar Maji (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_maji)

Editorial Board Member: *JNCASR, India*

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_Piedade) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_Piedade)

Manuel Minas da Piedade (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_Piedade)

Washington University in St Louis, USA

JNCASR, India

Editorial Board Member: *University of Lisbon, Portugal*

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_nakagaki) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_nakagaki)

Shirley Nakagaki (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_nakagaki)

Editorial Board Member:*Universidade Federal do Paraná, Brazil*

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_pastore) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_pastore)

Heloise Oliveira Pastore (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_pastore)

Editorial Board Member: *UNICAMP, Brazil*

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_shibata) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_shibata)

Norio Shibata (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_shibata)

Editorial Board Member: *Nagoya Institute of Technology, Japan*

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_turner) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_turner)

Charlotta Turner (/journals-books-databases/about-journals/rsc-

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_wetmore) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_wetmore)

Stacey Wetmore (/journals-books-databases/about-journals/rsc-

(/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_zheng) (/journals-books-databases/about-journals/rsc-advances/editorial-board-members/#ra_zheng)

Qingdong Zheng (/journals-books-databases/about-journals/rsc-

databases/about-journals/rsc-advances/editorial-board-members/#ra_turner)
Editorial Board Member: *Lund University, Sweden*

databases/about-journals/rsc-advances/editorial-board-members/#ra_wetmore)
Editorial Board Member: *University of Lethbridge, Canada*

databases/about-journals/rsc-advances/editorial-board-members/#ra_zheng)
Editorial Board Member: *Chinese Academy of Sciences, China*

Emerging Investigators series

We are delighted to announce the start of an Emerging Investigators series! This series will showcase some of the best research from scientists in the early stages of their independent careers. The series will be guest edited by Professor James Batteas (Texas A&M University), and articles in the series will be accepted and published throughout the year. In addition, an Editorial article featuring recent researchers in the issue will be published annually.

Read more about this series +

Outstanding Student Paper Awards

We are delighted to announce *RSC Advances* Outstanding Student Paper Awards in 2021. These awards recognise outstanding work published in the journal, for which a substantial component of the research was conducted by a student. Winning papers will be selected by the Editorial Board and Associate Editors in 2022. Winning students receive a framed certificate and will be invited by *RSC Advances* to give a virtual talk about their research to an international audience.

Read more about these awards +

Article types

RSC Advances publishes:

- Full papers
- Reviews
- Comments

RSC Advances

COUNTRY

United Kingdom

Universities and research institutions in United Kingdom

SUBJECT AREA AND CATEGORY

Chemical Engineering
Chemical Engineering (miscellaneous)

Chemistry
Chemistry (miscellaneous)

PUBLISHER

Royal Society of Chemistry

H-INDEX

128

PUBLICATION TYPE

Journals

ISSN

20462069

COVERAGE

2011-2020

INFORMATION

Homepage

How to publish in this journal

Contact

SCOPE

RSC Advances papers should provide an insight that advances the chemistry field. Papers that contain little or no chemistry and are not considered to be of interest or relevance to the chemistry community are not within the scope of the journal. The criteria for publication are that the work must be high quality, well conducted and advance the development of the field. Articles submitted to the journal are evaluated by our international team of associate editors and reviewers for the overall quality and accuracy of the science presented.

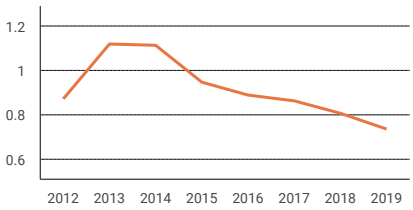
Quartiles

FIND SIMILAR JOURNALS

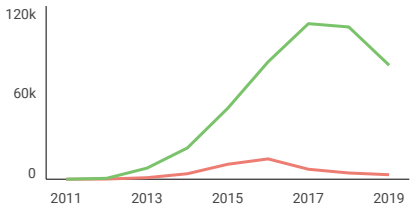
options

1	2	3	4	5
ACS Omega	**Frontiers in Chemistry**	**Chemical Research in Chinese Universities**	**Progress in Chemistry**	**Materials Today Chemistry**
USA	CHE	CHE	CHN	GBR
88%	**81%**	**77%**	**77%**	**77%**
similarity	similarity	similarity	similarity	similarity

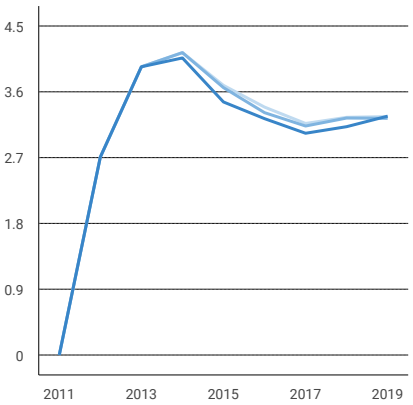
SJR



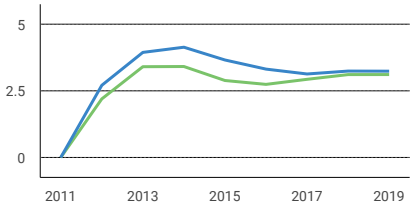
Total Cites Self-Cites



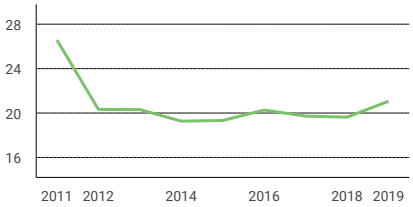
Citations per document



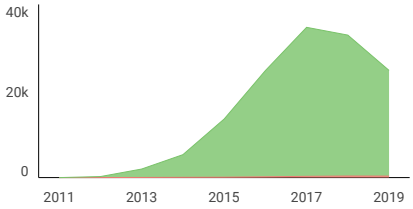
External Cites per Doc Cites per Doc



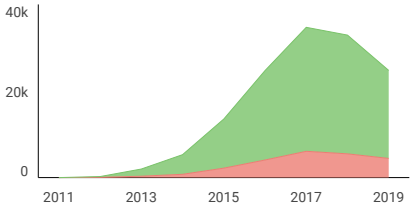
% International Collaboration



Citable documents Non-citable documents



Cited documents Uncited documents



RSC Advances

Q1

Chemical Engineering (miscellaneous)

best quartile

SJR 2019

0.74

powered by scimagojr.com

← Show this widget in your own website

Just copy the code below and paste within your html code:

<a href="https://www.scima

Metrics based on Scopus® data as of April 2020

Decision on submission to RSC Advances - RA-ART-09-2018-007944

1 message

RSC Advances <onbehalfof@manuscriptcentral.com> Fri, Oct 19, 2018 at 8:58 PM
Reply-To: advances@rsc.org
To: m.zakki.fahmi@fst.unair.ac.id, zakkifahmi@gmail.com

19-Oct-2018

Dear Mr Fahmi:

Manuscript ID: RA-ART-09-2018-007944
TITLE: Bamboo Leaves Based Carbon Dots as an Efficient Tumor Imaging and Therapy

Thank you for your submission to RSC Advances, published by the Royal Society of Chemistry. I sent your manuscript to reviewers and I have now received their reports which are copied below.

I have carefully evaluated your manuscript and the reviewers' reports, and the reports indicate that major revisions are necessary.

Please submit a revised manuscript which addresses all of the reviewers' comments. Further peer review of your revised manuscript may be needed. When you submit your revised manuscript please include a point by point response to the reviewers' comments and highlight the changes you have made. Full details of the files you need to submit are listed at the end of this email.

Please submit your revised manuscript as soon as possible using this link:

*** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/rscadv?URL_MASK=86189260fd844aa9b45c242a4e41ca04

(This link goes straight to your account, without the need to log on to the system. For your account security you should not share this link with others.)

Alternatively, you can log in to your account (https://mc.manuscriptcentral.com/rscadv) where you will need your case-sensitive user ID and password details.

You should submit your revised manuscript as soon as possible; please note you will receive a series of automatic reminders. If your revisions will take a significant length of time, please contact me.

The Royal Society of Chemistry requires the submitting author to provide their ORCID iD when they submit a revised manuscript. This is quick and easy to do as part of the revised manuscript submission process. We will publish this information with the article, and you may choose to have your ORCID record updated automatically with details of the publication.

Please also encourage your co-authors to sign up for their own ORCID account and associate it with their account on our manuscript submission system. Please note that we are unable to do this on behalf of your co-authors. For further information see: http://www.rsc.org/journals-books-databases/journal-authors-reviewers/processes-policies/#attribution-id.

I look forward to receiving your revised manuscript.

Yours sincerely,
Professor Suprakas Sinha Ray
Associate Editor, RSC Advances

****
REVIEWER REPORT(S):
Referee: 1

Recommendation: Minor revisions

Comments:
This is a well organized scientifically sound work on imaging and therapy and advancing current of this field.
The only minor comment-the authors must do proper language check during revision.

Additional Questions:
Does the work significantly advance the understanding or development in this field?: Yes

Are the conclusions of the work convincing and sufficiently supported by experimental evidence?: Yes

Is the experimental section sufficiently detailed to allow others to reproduce the work?: Yes

Are the reported claims adequately discussed in the context of the literature?: Yes

Are the number of tables and figures in the manuscript appropriate and clear?: Yes

Referee: 2

Recommendation: Major revisions

Comments:
The manuscript presents the synthesis of carbon dots from a bamboo leaves as a eco-friendly source. These CD have been decorated with boronic groups in order to provide selectivity against HeLa cells and additionally, doxorubicine has been adsorbed on the particle surface for achieving the tumoral cell destruction. The topic is not really novel considering the wide number of systems described in the literature but the system is interesting considering the cheap and Green source of the materials and the good results obtained. In any case, the manuscript should be extensively revised before to publish it. The English have to be polished because there are many incorrections and tipos. Additionally other issues should be corrected or clarified:

1) The authors employed carbodiimide chemistry for attaching the carboxy-boronic acid on the particle surface. This strategy could cause cross-linking between the carbon particles becasue they exhibit carboxylic as well as hydroxyl groups on their surface. The size of the particles should be measured by DLS before and after the boronic anchoring.

2) The boronic attachment should be studied with more detail. FTIR analysis is very poor. The authors should explain more properly the Fig 3.

3) The analysis of the celular uptake should be carried out with more experiments. The authors employed only CLSM which provide cualitative information about the uptake but it do not provide cuantitative information. Flow cytometry should be employed in order to obtain cuantitative data about the uptake of each type of particle. Fig 4 is very confusing. More details are needed.

Additional Questions:
Does the work significantly advance the understanding or development in this field?: Yes

Are the conclusions of the work convincing and sufficiently supported by experimental evidence?: No

Is the experimental section sufficiently detailed to allow others to reproduce the work?: No

Are the reported claims adequately discussed in the context of the literature?: Yes

Are the number of tables and figures in the manuscript appropriate and clear?: No

****
FILES TO PROVIDE WITH YOUR REVISED MANUSCRIPT:
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission. Please carefully check the spelling and format of all author names, affiliations and funding information. If your paper is accepted for publication, it is important this information is accurate to ensure your article is correctly indexed, which may affect citations and future funding evaluation.

- A point-by-point response to the comments made by the reviewer(s)
- Your revised manuscript with any changes clearly marked (.doc(x) or.pdf file)
- Your revised manuscript as a .doc(x) file including figures, without highlighting, track changes, etc. (If providing in TeX format instead, please also provide a final PDF version including figures). Please note that we cannot proceed with publication using a .pdf file only.

High quality figures
EITHER
embedded in a doc(x) file
OR

as numbered figures in separate files in .tif, or .eps format, with a resolution of 600 dpi or greater and structures preferably as ChemDraw files. Chemwindow files (.cwg/.cw2), ISIS/Draw exported in sketch format (.skc) and ChemSketch exported in ChemDraw format (.cdx) may also be supplied.

AND

• A table of contents entry: graphic maximum size 8 cm x 4 cm and one sentence of text, maximum 20 words, highlighting the novelty of the work
• Your revised Electronic Supplementary Information (if any)
• Your revised CheckCIF reports (if any). Please ensure that any revised cif files have been deposited with the Cambridge Crystallographic Data Centre (CCDC) via https://deposit.ccdc.cam.ac.uk/ before you submit your revised manuscript.

For Feature Articles/Review-type articles only:
• A photograph and biography of yourself and your co-authors. Separate photographs of each author may be supplied or if you prefer, a group photograph, saved as a .tif, .pdf or .jpeg file. The resolution of the photographs should be 600 dpi or higher. The dimensions of the photograph in the printed journal will be 4 cm wide x 5 cm high (individual photograph) or 8.3 cm wide x 5 cm high (group photograph). Individual photographs should be accompanied by a maximum of 100 words; a group photograph by a maximum of 200 words. There can be a maximum of 6 individual biographies per article.
• Copies of permissions required from other publishers to reproduce figures. Please ensure that necessary permissions are acknowledged in the figure captions in accordance with the publishers' instruction. Information on how to obtain permissions and rights that we require are given on our website at http://www.rsc.org/journals-books-databases/journal-authors-reviewers/licences-copyright-permissions/

****
If you need to contact the journal, please use the email address advances@rsc.org

****

Your RSC Advances article page numbers are now available

3 messages

advances@rsc.org <advances@rsc.org> Wed, Nov 14, 2018 at 6:26 PM
To: m.zakki.fahmi@fst.unair.ac.id

Follow us and stay in touch

Dear Mr Mochamad Zakki Zakki Fahmi

Bamboo Leaves Based Carbon Dots as an Efficient Tumor Imaging and Therapy

We have published your *RSC Advances* article in an issue on pages 38376 - 38383.

It can now be cited as:

RSC Advances, 2018, **8**, 38376 - 38383

Access your PDF reprints here

Manuscript ID: C8RA07944G

Password: 605349 (this link will expire in 60 days)

You can now access the enhanced HTML version of your article here

We encourage you to share your article with the chemical sciences community. Share your article easily among colleagues, peers or students by downloading your free PDF reprint or by purchasing paper reprints here. Find out more about your deposition and sharing rights.

You can see all the latest papers published in RSC Advances by signing up to our email alerts service here

Thank you for publishing with *RSC Advances*, a journal published by the Royal Society of Chemistry - the world's leading chemistry community, advancing excellence in the chemical sciences.

With best wishes,
From the Editors of *RSC Advances*
Royal Society of Chemistry
advances@rsc.org

Mochamad Zakki Fahmi <m.zakki.fahmi@fst.unair.ac.id> Thu, Nov 15, 2018 at 9:39 AM
To: ahmadi jaya permana <ahmadi-j-permana@fst.unair.ac.id>, Yatim Nikmah <yatimnikmah@gmail.com>, Adi Idris <a.idris@griffith.edu.au>, Haris Biotek Prima Indoplus <haris.biotekprimaindoplus@gmail.com>, bambang purwanto <bambang-purwanto@fk.unair.ac.id>, denika liyannw <denikaliyannw@gmail.com>

Salam Everyone,

Alhamdulillah the manuscript became a paper on RSC Advance, please find link on the forwarded email below for the paper. Thanks a lot for all of your contribution. Thank you

Best Regards,

Mochamad Zakki Fahmi, Ph.D (張家其)
Assistant Professor, Departement of Chemistry
Universitas Airlangga
Phone : +62-838-32901697

Email : m.zakki.fahmi@fst.unair.ac.id

[Quoted text hidden]

Adi Idris <a.idris@griffith.edu.au> Thu, Nov 15, 2018 at 9:43 AM
To: Mochamad Zakki Fahmi <m.zakki.fahmi@fst.unair.ac.id>, ahmadi jaya permana <ahmadi-j-permana@fst.unair.ac.id>, Yatim Nikmah <yatimnikmah@gmail.com>, Haris Biotek Prima Indoplus <haris.biotekprimaindoplus@gmail.com>, bambang purwanto <bambang-purwanto@fk.unair.ac.id>, denika liyannw <denikaliyannw@gmail.com>

Thank you all. Looks great!

Dr Adi Idris | **Research Fellow**

Menzies Health Institute Queensland
Griffith University | Gold Coast campus | QLD 4222 | School of Medical Science (G05) Room 3.37a
T +61 7 555 27709 | E a.idris@griffith.edu.au

Scientific Research Consultant | Kaifeng Central Hospital | China

---

From: Mochamad Zakki Fahmi <m.zakki.fahmi@fst.unair.ac.id>
Date: Wednesday, 14 November 2018 at 9:39 pm
To: ahmadi jaya permana <ahmadi-j-permana@fst.unair.ac.id>, Yatim Nikmah <yatimnikmah@gmail.com>, Adi Idris <a.idris@griffith.edu.au>, Haris Biotek Prima Indoplus <haris.biotekprimaindoplus@gmail.com>, bambang purwanto <bambang-purwanto@fk.unair.ac.id>, denika liyannw <denikaliyannw@gmail.com>
Subject: Fwd: Your RSC Advances article page numbers are now available

Salam Everyone,

Alhamdulillah the manuscript became a paper on RSC Advance, please find link on the forwarded email below for the paper. Thanks a lot for all of your contribution. Thank you

Best Regards,

Mochamad Zakki Fahmi, Ph.D (張家其)

Assistant Professor, Departement of Chemistry

Universitas Airlangga

Phone : +62-838-32901697

Email : m.zakki.fahmi@fst.unair.ac.id

---------- Forwarded message ---------
From: <advances@rsc.org>
Date: Rab, 14 Nov 2018 pukul 18.26
Subject: Your RSC Advances article page numbers are now available
To: <m.zakki.fahmi@fst.unair.ac.id>

Follow us and stay in touch

Dear Mr Mochamad Zakki Zakki Fahmi

Bamboo Leaves Based Carbon Dots as an Efficient Tumor Imaging and Therapy

We have published your *RSC Advances* article in an issue on pages 38376 - 38383.

It can now be cited as:

RSC Advances, 2018, **8**, 38376 - 38383

Access your PDF reprints here

Manuscript ID: C8RA07944G

Password: 605349 (this link will expire in 60 days)

You can now access the enhanced HTML version of your article here

We encourage you to share your article with the chemical sciences community. Share your article easily among colleagues, peers or students by downloading your free PDF reprint or by purchasing paper reprints here. Find out more about your deposition and sharing rights.

You can see all the latest papers published in RSC Advances by signing up to our email alerts service here

Thank you for publishing with *RSC Advances*, a journal published by the Royal Society of Chemistry - the world's leading chemistry community, advancing excellence in the chemical sciences.

With best wishes,
From the Editors of *RSC Advances*
Royal Society of Chemistry
advances@rsc.org

www.rsc.org
Registered charity number 207890

You have been sent this message because you have submitted an article to *RSC Advances*. If you feel that you have received this in error, please contact advances@rsc.org

[Quoted text hidden]

Mochamad Zakki <m.zakki.fahmi@fst.unair.ac.id>

Decision on submission to RSC Advances - RA-ART-09-2018-007944.R1

6 messages

RSC Advances <onbehalfof@manuscriptcentral.com> Sat, Oct 27, 2018 at 4:08 AM
Reply-To: advances@rsc.org
To: m.zakki.fahmi@fst.unair.ac.id, zakkifahmi@gmail.com

26-Oct-2018

Dear Mr Fahmi:

Manuscript ID: RA-ART-09-2018-007944.R1
TITLE: Bamboo Leaves Based Carbon Dots as an Efficient Tumor Imaging and Therapy

Thank you for submitting your revised manuscript to RSC Advances. After considering the changes you have made, I am pleased to accept your manuscript for publication in its current form.

You will shortly receive a separate email from us requesting you to submit a licence to publish for your article, so that we can proceed with publication of your manuscript.

RSC Advances is a gold open access journal. Your manuscript will be published open access and the article will be subject to the appropriate article processing charge (APC). Discounted APCs and full APC waivers for corresponding authors in certain countries are available. All authors can apply for an ad hoc APC waiver - please see the following URL for more details: http://www.rsc.org/journals-books-databases/about-journals/rsc-advances

Please note that RSC Advances no longer publishes 'Just Accepted' manuscripts; the time between acceptance and final publication is typically less than 10 days and therefore we no longer feel this provides a significant benefit to our authors. Instead, articles are published following editing and proofing and once the final, paginated PDF is ready for publication.

We will email you information on how to access your RSC Advances article proofs shortly.

As an author you are entitled to a 25% discount on books published by the Royal Society of Chemistry. To receive this discount, enter the promotional code JLTH25 when purchasing from our online bookshop (pubs.rsc.org/bookshop). Please contact booksales@rsc.org if you have any problems.

Discover more Royal Society of Chemistry author services and benefits here:

http://www.rsc.org/journals-books-databases/about-journals/benefits-of-publishing-with-us/

Thank you for publishing with RSC Advances, a journal published by the Royal Society of Chemistry – the world's leading chemistry community, advancing excellence in the chemical sciences.

With best wishes,

Professor Suprakas Sinha Ray
Associate Editor, RSC Advances

******

If you need to contact the journal, please use the email address advances@rsc.org

****

Chemistry.

Mochamad Zakki Fahmi <m.zakki.fahmi@fst.unair.ac.id> Tue, Oct 30, 2018 at 9:27 AM
To: Haris Biotek Prima Indoplus <haris.biotekprimaindoplus@gmail.com>, ahmadi jaya permana <ahmadi-j-permana@fst.unair.ac.id>, bambang purwanto <bambang-purwanto@fk.unair.ac.id>, Yatim Nikmah <yatimnikmah@gmail.com>, Dr Adi Yusri bin Dato Paduka Hj Idris <yusri.idris@ubd.edu.bn>, Adi Idris <adi.diris@gmail.com>

Dear Dr. Bambang Purwanto (**bambang-purwanto@fk.unair.ac.id**)
Dr. Adi Idris (**yusri.idris@ubd.edu.bn**)
Dr. Nikmah (**yatimnikmah@gmail.com**)
Dr. Ahmadi J Permana (**ahmadi-j-permana@fst.unair.ac.id**)
Abdul Haris(**haris.biotekprimaindoplus@gmail.com**)

I hope all of you on great health and doing well. I sent this email to inform you that our manuscript on application of bamboo leaves as carbon dots was accepted by RSC Advances with some revisions, Alhamdulillah.

Moreover, on the revised manuscript I added Denika Liyan Nor Wibowo as co-Author due to she contributed some data for the revised manuscript. By this process, RSC Advances editors ask me and all of my co-Author to sent them an email as approval statement. Therefor, please all of you send email to RSC Advances Editor (**rsc_editorial_office@spi-global.com**) using your email (mentioned above) that confirm your approval Denika as new co-Author for the manuscript.

On your Email, please input paragraph below as main body of your email, beside you can add more information:

Dear RSC Advances Editor,
Regarding your request on Manuscript ID RA-ART-09-2018-007944.R1, I as co-Author for the manuscript confirm my approval for adding Denika Liyan nor Wibowo as new co-Author. Her contribution was significantly appear on preparing data for the revised manuscript.

I hope this condition not interfere the online pubication of manuscript so much. Thank you.

Best Regards,

Mochamad Zakki Fahmi, Ph.D (張家其)
Assistant Professor, Departement of Chemistry
Universitas Airlangga
Phone : +62-838-32901697
Email : m.zakki.fahmi@fst.unair.ac.id

[Quoted text hidden]

Adi Idris <adi.diris@gmail.com> Tue, Oct 30, 2018 at 4:51 PM
To: Mochamad Zakki Fahmi <m.zakki.fahmi@fst.unair.ac.id>

Salam Zaki

Hope you are well. This is great news. However, I do not work at UBD anymore. Im at Griffith University, Australia. Could I change my affiliation during the final galley proofing process?

Do you mind aending me a copy of the submitted paper?

My new work email is
a.idris@griffith.edu.au

Dr Adi Idris, *PhD (UQ)*
[Quoted text hidden]

Mochamad Zakki Fahmi <m.zakki.fahmi@fst.unair.ac.id> Tue, Oct 30, 2018 at 7:24 PM
To: Adi Idris <adi.diris@gmail.com>

Oh sure. Thank you for the information
[Quoted text hidden]
--
Best Regards,

Mochamad Zakki Fahmi, Ph.D (張家其)
Assistant Professor, Departement of Chemistry
Airlangga University
Phone : +62-838-32901697
Email : m.zakki.fahmi@fst.unair.ac.id

Adi Idris <adi.diris@gmail.com> Wed, Oct 31, 2018 at 12:55 AM
To: Mochamad Zakki Fahmi <m.zakki.fahmi@fst.unair.ac.id>

Could I please have a copy of the submitted manuscript?
[Quoted text hidden]

Mochamad Zakki Fahmi <m.zakki.fahmi@fst.unair.ac.id> Wed, Oct 31, 2018 at 7:48 AM
To: Adi Idris <adi.diris@gmail.com>

Sorry for my late response, please find the manuscript on the attached file. Thank you
Best Regards,

Mochamad Zakki Fahmi, Ph.D (張家其)
Assistant Professor, Departement of Chemistry
Universitas Airlangga
Phone : +62-838-32901697
Email : m.zakki.fahmi@fst.unair.ac.id

[Quoted text hidden]

_system_appendPDF_proof_hi.pdf
3502K

Request for consent for addition of a co-author - RA-ART-09-2018-007944.R1

2 messages

RSC Advances <onbehalfof@manuscriptcentral.com> Mon, Oct 29, 2018 at 7:04 PM
Reply-To: rsc_editorial_office@spi-global.com
To: m.zakki.fahmi@fst.unair.ac.id, zakkifahmi@gmail.com

29-Oct-2018

Dear Mr Fahmi:

Manuscript ID: RA-ART-09-2018-007944.R1
TITLE: Bamboo Leaves Based Carbon Dots as an Efficient Tumor Imaging and Therapy

Thank you for your recently accepted manuscript to RSC Advances. I am about to pass this on to our production team but have noticed that a co-authors (Dr. Denika Liyan Nor Wibowo) have been added in revised paper.

In accordance with our guidelines and as a member of the Committee on Publication Ethics (http://publicationethics.org), please could you inform me of the contribution that Dr. Denika Liyan Nor Wibowo made in the preparation of the manuscript?

I would be grateful if you could reply to this email explaining the reasons for the addition of this new co-author, and ask all co-authors listed on this paper to email us to confirm that they agree with the addition of the author.

Please could you also ask Dr. Denika Liyan Nor Wibowo to contact us at rsc_editorial_office@spi-global.com to confirm that he/she agree to be added in the paper as an author.

My apologies that this was not picked up sooner, we would normally hope to ask for this information during the review process to avoid any delays to publication.

We look forward to hearing from you soon.

Yours sincerely,

Marrizz M. Esperanza
Publishing Assistant
Royal Society of Chemistry - RSC Advances
****

Mochamad Zakki Fahmi <m.zakki.fahmi@fst.unair.ac.id> Tue, Oct 30, 2018 at 8:43 AM
To: rsc_editorial_office@spi-global.com

Dear RSC Advances Editor,

Thank you for the previous email and I am sorry for the updating my co-Author for manuscript ID RA-ART-09-2018-007944.R1
The reason for add Dr Denika Liyan Nor Wibowo is based on her contribution on preparing and improving AFM data of CBBA-CD for the revised manuscript. We hope this condition not interferes the manuscript process so much and I will inform all of my co-Author for their approval also Dr. Denika as well. Thank you
[Quoted text hidden]

Decision on submission to RSC Advances - RA-ART-09-2018-007944

1 message

RSC Advances <onbehalfof@manuscriptcentral.com> Fri, Oct 19, 2018 at 8:58 PM
Reply-To: advances@rsc.org
To: m.zakki.fahmi@fst.unair.ac.id, zakkifahmi@gmail.com

19-Oct-2018

Dear Mr Fahmi:

Manuscript ID: RA-ART-09-2018-007944
TITLE: Bamboo Leaves Based Carbon Dots as an Efficient Tumor Imaging and Therapy

Thank you for your submission to RSC Advances, published by the Royal Society of Chemistry. I sent your manuscript to reviewers and I have now received their reports which are copied below.

I have carefully evaluated your manuscript and the reviewers' reports, and the reports indicate that major revisions are necessary.

Please submit a revised manuscript which addresses all of the reviewers' comments. Further peer review of your revised manuscript may be needed. When you submit your revised manuscript please include a point by point response to the reviewers' comments and highlight the changes you have made. Full details of the files you need to submit are listed at the end of this email.

Please submit your revised manuscript as soon as possible using this link:

*** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/rscadv?URL_MASK=86189260fd844aa9b45c242a4e41ca04

(This link goes straight to your account, without the need to log on to the system. For your account security you should not share this link with others.)

Alternatively, you can log in to your account (https://mc.manuscriptcentral.com/rscadv) where you will need your case-sensitive user ID and password details.

You should submit your revised manuscript as soon as possible; please note you will receive a series of automatic reminders. If your revisions will take a significant length of time, please contact me.

The Royal Society of Chemistry requires the submitting author to provide their ORCID iD when they submit a revised manuscript. This is quick and easy to do as part of the revised manuscript submission process. We will publish this information with the article, and you may choose to have your ORCID record updated automatically with details of the publication.

Please also encourage your co-authors to sign up for their own ORCID account and associate it with their account on our manuscript submission system. Please note that we are unable to do this on behalf of your co-authors. For further information see: http://www.rsc.org/journals-books-databases/journal-authors-reviewers/processes-policies/#attribution-id.

I look forward to receiving your revised manuscript.

Yours sincerely,
Professor Suprakas Sinha Ray
Associate Editor, RSC Advances

****
REVIEWER REPORT(S):
Referee: 1

Recommendation: Minor revisions

Comments:
This is a well organized scientifically sound work on imaging and therapy and advancing current of this field.
The only minor comment-the authors must do proper language check during revision.

Additional Questions:
Does the work significantly advance the understanding or development in this field?: Yes

Are the conclusions of the work convincing and sufficiently supported by experimental evidence?: Yes

Is the experimental section sufficiently detailed to allow others to reproduce the work?: Yes

Are the reported claims adequately discussed in the context of the literature?: Yes

Are the number of tables and figures in the manuscript appropriate and clear?: Yes

Referee: 2

Recommendation: Major revisions

Comments:
The manuscript presents the synthesis of carbon dots from a bamboo leaves as a eco-friendly source. These CD have been decorated with boronic groups in order to provide selectivity against HeLa cells and additionally, doxorubicine has been adsorbed on the particle surface for achieving the tumoral cell destruction. The topic is not really novel considering the wide number of systems described in the literature but the system is interesting considering the cheap and Green source of the materials and the good results obtained. In any case, the manuscript should be extensively revised before to publish it. The English have to be polished because there are many incorrections and tipos. Additionally other issues should be corrected or clarified:

1) The authors employed carbodiimide chemistry for attaching the carboxy-boronic acid on the particle surface. This strategy could cause cross-linking between the carbon particles becasue they exhibit carboxylic as well as hydroxyl groups on their surface. The size of the particles should be measured by DLS before and after the boronic anchoring.

2) The boronic attachment should be studied with more detail. FTIR analysis is very poor. The authors should explain more properly the Fig 3.

3) The analysis of the celular uptake should be carried out with more experiments. The authors employed only CLSM which provide cualitative information about the uptake but it do not provide cuantitative information. Flow cytometry should be employed in order to obtain cuantitative data about the uptake of each type of particle. Fig 4 is very confusing. More details are needed.

Additional Questions:
Does the work significantly advance the understanding or development in this field?: Yes

Are the conclusions of the work convincing and sufficiently supported by experimental evidence?: No

Is the experimental section sufficiently detailed to allow others to reproduce the work?: No

Are the reported claims adequately discussed in the context of the literature?: Yes

Are the number of tables and figures in the manuscript appropriate and clear?: No

****
FILES TO PROVIDE WITH YOUR REVISED MANUSCRIPT:
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission. Please carefully check the spelling and format of all author names, affiliations and funding information. If your paper is accepted for publication, it is important this information is accurate to ensure your article is correctly indexed, which may affect citations and future funding evaluation.

- A point-by-point response to the comments made by the reviewer(s)
- Your revised manuscript with any changes clearly marked (.doc(x) or.pdf file)
- Your revised manuscript as a .doc(x) file including figures, without highlighting, track changes, etc. (If providing in TeX format instead, please also provide a final PDF version including figures). Please note that we cannot proceed with publication using a .pdf file only.

High quality figures
EITHER
embedded in a doc(x) file
OR

as numbered figures in separate files in .tif, or .eps format, with a resolution of 600 dpi or greater and structures preferably as ChemDraw files. Chemwindow files (.cwg/.cw2), ISIS/Draw exported in sketch format (.skc) and ChemSketch exported in ChemDraw format (.cdx) may also be supplied.

AND

• A table of contents entry: graphic maximum size 8 cm x 4 cm and one sentence of text, maximum 20 words, highlighting the novelty of the work
• Your revised Electronic Supplementary Information (if any)
• Your revised CheckCIF reports (if any). Please ensure that any revised cif files have been deposited with the Cambridge Crystallographic Data Centre (CCDC) via https://deposit.ccdc.cam.ac.uk/ before you submit your revised manuscript.

For Feature Articles/Review-type articles only:
• A photograph and biography of yourself and your co-authors. Separate photographs of each author may be supplied or if you prefer, a group photograph, saved as a .tif, .pdf or .jpeg file. The resolution of the photographs should be 600 dpi or higher. The dimensions of the photograph in the printed journal will be 4 cm wide x 5 cm high (individual photograph) or 8.3 cm wide x 5 cm high (group photograph). Individual photographs should be accompanied by a maximum of 100 words; a group photograph by a maximum of 200 words. There can be a maximum of 6 individual biographies per article.
• Copies of permissions required from other publishers to reproduce figures. Please ensure that necessary permissions are acknowledged in the figure captions in accordance with the publishers' instruction. Information on how to obtain permissions and rights that we require are given on our website at http://www.rsc.org/journals-books-databases/journal-authors-reviewers/licences-copyright-permissions/

****
If you need to contact the journal, please use the email address advances@rsc.org

****

Mochamad Zakki <m.zakki.fahmi@fst.unair.ac.id>

Decision on submission to RSC Advances - RA-ART-09-2018-007944.R1

RSC Advances <onbehalfof@manuscriptcentral.com> 27 Oktober 2018 04.08
Balas Ke: advances@rsc.org
Kepada: m.zakki.fahmi@fst.unair.ac.id, zakkifahmi@gmail.com

26-Oct-2018

Dear Mr Fahmi:

Manuscript ID: RA-ART-09-2018-007944.R1
TITLE: Bamboo Leaves Based Carbon Dots as an Efficient Tumor Imaging and Therapy

Thank you for submitting your revised manuscript to RSC Advances. After considering the changes you have made, I am pleased to accept your manuscript for publication in its current form.

You will shortly receive a separate email from us requesting you to submit a licence to publish for your article, so that we can proceed with publication of your manuscript.

RSC Advances is a gold open access journal. Your manuscript will be published open access and the article will be subject to the appropriate article processing charge (APC). Discounted APCs and full APC waivers for corresponding authors in certain countries are available. All authors can apply for an ad hoc APC waiver - please see the following URL for more details: http://www.rsc.org/journals-books-databases/about-journals/rsc-advances

Please note that RSC Advances no longer publishes 'Just Accepted' manuscripts; the time between acceptance and final publication is typically less than 10 days and therefore we no longer feel this provides a significant benefit to our authors. Instead, articles are published following editing and proofing and once the final, paginated PDF is ready for publication.

We will email you information on how to access your RSC Advances article proofs shortly.

As an author you are entitled to a 25% discount on books published by the Royal Society of Chemistry. To receive this discount, enter the promotional code JLTH25 when purchasing from our online bookshop (pubs.rsc.org/bookshop). Please contact booksales@rsc.org if you have any problems.

Discover more Royal Society of Chemistry author services and benefits here:

http://www.rsc.org/journals-books-databases/about-journals/benefits-of-publishing-with-us/

Thank you for publishing with RSC Advances, a journal published by the Royal Society of Chemistry – the world's leading chemistry community, advancing excellence in the chemical sciences.

With best wishes,

Professor Suprakas Sinha Ray
Associate Editor, RSC Advances

******

If you need to contact the journal, please use the email address advances@rsc.org

****