Self-assembled Nanostructures of Biomolecules for Sensing, UV-protection, Bioimaging and Drug Delivery

Thesis submitted in partial fulfillment for the
Award of Degree

DOCTOR OF PHILOSOPHY

By

KANCHAN YADAV

Department of Physics
Indian Institute of Technology
(Banaras Hindu University)
Varanasi-221005
India

Roll No. 16171502 **2022**

Chapter-7

7 References

1. Khan, I., Saeed, K. & Khan, I. Nanoparticles: Properties, applications and toxicities. *Arab. J. Chem.* **12**, 908–931 (2019).

2. Patel, K. D., Singh, R. K. & Kim, H. W. Carbon-based nanomaterials as an emerging platform for theranostics. *Mater. Horizons* **6**, 434–469 (2019).

3. LeCroy, G. E. *et al.* Functionalized carbon nanoparticles: Syntheses and applications in optical bioimaging and energy conversion. *Coordination Chemistry Reviews* vols 320–321 (2016).

4. Rao, N., Singh, R. & Bashambu, L. Carbon-based nanomaterials: Synthesis and prospective applications. *Mater. Today Proc.* **44**, 608–614 (2021).

5. Aranda-Garcia, D. *et al.* Simulating Time-Resolved Dynamics of Biomolecular Systems. *Ref. Modul. Biomed. Sci.* (2022) doi:10.1016/B978-0-12-820472-6.00214-0.

6. Nagamune, T. Biomolecular engineering for nanobio/bionanotechnology. *Nano Converg. 2017 41* **4**, 1–56 (2017).

7. Knowles, T. P. J., Vendruscolo, M. & Dobson, C. M. The amyloid state and its association with protein misfolding diseases. *Nat. Rev. Mol. Cell Biol. 2014 156* **15**, 384–396 (2014).

8. Dumetz, A. C., Chockla, A. M., Kaler, E. W. & Lenhoff, A. M. Protein Phase Behavior in Aqueous Solutions: Crystallization, Liquid-Liquid Phase Separation, Gels, and Aggregates. *Biophys. J.* **94**, 570–583 (2008).

9. McManus, J. J., Charbonneau, P., Zaccarelli, E. & Asherie, N. The physics of protein self-assembly. *Curr. Opin. Colloid Interface Sci.* **22**, 73–79 (2016).

10. Pignataro, M. F., Herrera, M. G. & Dodero, V. I. Evaluation of Peptide/Protein Self-Assembly and Aggregation by Spectroscopic Methods. *Mol. 2020, Vol. 25, Page 4854* **25**, 4854 (2020).

11. McManus, J. J., Charbonneau, P., Zaccarelli, E. & Asherie, N. The physics of protein self-assembly. *Curr. Opin. Colloid Interface Sci.* **22**, 73–79 (2016).

12. Sun, H., Li, Y., Yu, S. & Liu, J. Hierarchical Self-Assembly of Proteins Through Rationally Designed Supramolecular Interfaces. *Front. Bioeng. Biotechnol.* **8**, 295 (2020).

13. Kirchner, E.-M. & Hirsch, T. Recent developments in carbon-based two-dimensional materials: synthesis and modification aspects for electrochemical sensors. *Microchim. Acta 2020 1878* **187**, 1–21 (2020).

14. Jelinek, R. Characterization and physical properties of carbon-dots. *Carbon Nanostructures* **0**, 29–46 (2017).

15. Lim, S. Y., Shen, W. & Gao, Z. Carbon quantum dots and their applications. *Chem. Soc. Rev.* **44**, 362–381 (2014).

16. Xu, X. *et al.* Electrophoretic analysis and purification of fluorescent single-walled carbon nanotube fragments. *J. Am. Chem. Soc.* **126**, 12736–12737 (2004).

17. Zhou, W. & Coleman, J. J. Semiconductor quantum dots. *Curr. Opin. Solid State Mater. Sci.* **20**, 352–360 (2016).

18. Resch-Genger, U., Grabolle, M., Cavaliere-Jaricot, S., Nitschke, R. & Nann, T. Quantum dots versus organic dyes as fluorescent labels. *Nat. Methods 2008 59* **5**, 763–775 (2008).

19. Lin, P. *et al.* Computational and ultrastructural toxicology of a nanoparticle, Quantum Dot 705, in mice. *Environ. Sci. Technol.* **42**, 6264–6270 (2008).

20. Liu, J., Li, R. & Yang, B. Carbon Dots: A New Type of Carbon-Based Nanomaterial with Wide Applications. *ACS Cent. Sci.* **6**, 2179–2195 (2020).

21. Koutsogiannis, P., Thomou, E., Stamatis, H., Gournis, D. & Rudolf, P. Advances in fluorescent carbon dots for biomedical applications. *Adv. Phys. X* **5**, (2020).

22. Gude, V. Synthesis of hydrophobic photoluminescent carbon nanodots by using L-tyrosine and citric acid through a thermal oxidation route. *Beilstein J. Nanotechnol. 5164* **5**, 1513–1522 (2014).

23. Papaioannou, N. *et al.* Structure and solvents effects on the optical properties of sugar-derived carbon nanodots. *Sci. Reports 2018 81* **8**, 1–10 (2018).

24. Peng, Z., Ji, C., Zhou, Y., Zhao, T. & Leblanc, R. M. Polyethylene glycol (PEG) derived carbon dots: Preparation and applications. *Appl. Mater. Today* **20**, 100677 (2020).

25. Zulfajri, M. *et al.* Plant Part-Derived Carbon Dots for Biosensing. *Biosensors* **10**, (2020).

26. Kang, C., Huang, Y., Yang, H., Yan, X. F. & Chen, Z. P. A review of carbon dots produced from biomass wastes. *Nanomaterials* **10**, 1–24 (2020).

27. Jiang, J., He, Y., Li, S. & Cui, H. Amino acids as the source for producing carbon nanodots: Microwave assisted one-step synthesis, intrinsic photoluminescence

property and intense chemiluminescence enhancement. *Chem. Commun.* **48**, 9634–9636 (2012).

28. Sai, L. *et al.* Protein-derived carbon nanodots with an ethylenediamine-modulated structure as sensitive fluorescent probes for Cu 2+ detection. *RSC Adv.* **7**, 16608–16615 (2017).

29. Liu, T. *et al.* Carbon quantum dots prepared with polyethyleneimine as both reducing agent and stabilizer for synthesis of Ag/CQDs composite for Hg2+ ions detection. *J. Hazard. Mater.* **322**, 430–436 (2017).

30. Song, J. *et al.* Carbon Quantum Dots Prepared with Chitosan for Synthesis of CQDs/AuNPs for Iodine Ions Detection. *Nanomaterials* **8**, (2018).

31. Sciortino, A., Cannizzo, A. & Messina, F. Carbon Nanodots: A Review—From the Current Understanding of the Fundamental Photophysics to the Full Control of the Optical Response. *C* **4**, 67 (2018).

32. Thongpool, V., Asanithi, P. & Limsuwan, P. Synthesis of Carbon Particles using Laser Ablation in Ethanol. *Procedia Eng.* **32**, 1054–1060 (2012).

33. Deng, J. *et al.* Electrochemical Synthesis of Carbon Nanodots Directly from Alcohols. *Chem. – A Eur. J.* **20**, 4993–4999 (2014).

34. Chao-Mujica, F. J. *et al.* Carbon quantum dots by submerged arc discharge in water: Synthesis, characterization, and mechanism of formation. *J. Appl. Phys.* **129**, (2021).

35. Wei, Q. *et al.* Small-Molecule Emitters with High Quantum Efficiency: Mechanisms, Structures, and Applications in OLED Devices. *Adv. Opt. Mater.* **6**, 1800512 (2018).

36. Smagulova, S., Egorova, M. & Tomskaya, A. Investigation of the properties of carbon quantum dots synthesized by the hydrothermal method. *IOP Conf. Ser. Mater. Sci. Eng.* **693**, (2019).

37. De Medeiros, T. V. *et al.* Microwave-assisted synthesis of carbon dots and their applications. *J. Mater. Chem. C* **7**, 7175–7195 (2019).

38. Shaik, S. A., Sengupta, S., Varma, R. S., Gawande, M. B. & Goswami, A. Syntheses of N-Doped Carbon Quantum Dots (NCQDs) from Bioderived Precursors: A Timely Update. *ACS Sustain. Chem. Eng.* **9**, 3–49 (2021).

39. Zhu, S. *et al.* Photoluminescence mechanism in graphene quantum dots: Quantum confinement effect and surface/edge state. *Nano Today* **13**, 10–14 (2017).

40. Emam, A. N., Loutfy, S. A., Mostafa, A. A., Awad, H. & Mohamed, M. B. Cyto-toxicity, biocompatibility and cellular response of carbon dots–plasmonic based nano-hybrids for bioimaging. *RSC Adv.* **7**, 23502–23514 (2017).

41. Dimos, K. Carbon Quantum Dots: Surface Passivation and Functionalization. *Curr. Org. Chem.* **20**, 682–695 (2016).

42. Bhunia, S. K., Saha, A., Maity, A. R., Ray, S. C. & Jana, N. R. Carbon nanoparticle-based fluorescent bioimaging probes. *Sci. Rep.* **3**, (2013).

43. Deng, Y. *et al.* Visible-Ultraviolet Upconversion Carbon Quantum Dots for Enhancement of the Photocatalytic Activity of Titanium Dioxide. *ACS omega* **6**, 4247–4254 (2021).

44. Li, M. *et al.* Synthesis and upconversion luminescence of N-doped graphene quantum dots. *Appl. Phys. Lett.* **101**, 103107 (2012).

45. Zhuo, S., Shao, M. & Lee, S. T. Upconversion and downconversion fluorescent graphene quantum dots: Ultrasonic preparation and photocatalysis. *ACS Nano* **6**, 1059–1064 (2012).

46. Yoo, D., Park, Y., Cheon, B. & Park, M. H. Carbon Dots as an Effective Fluorescent Sensing Platform for Metal Ion Detection. *Nanoscale Res. Lett.* **14**, 1–13 (2019).

47. Yan, F. *et al.* The fluorescence mechanism of carbon dots, and methods for tuning their emission color: a review. *Microchim. Acta* **186**, 1–37 (2019).

48. El-Shafey, A. M. Carbon dots: Discovery, structure, fluorescent properties, and applications. *Green Process. Synth.* **10**, 134–156 (2021).

49. Li, H. *et al.* Water-soluble fluorescent carbon quantum dots and photocatalyst design. *Angew. Chemie - Int. Ed.* **49**, 4430–4434 (2010).

50. Hola, K. *et al.* Photoluminescence effects of graphitic core size and surface functional groups in carbon dots: COO- induced red-shift emission. *Carbon N. Y.* **70**, 279–286 (2014).

51. Mai, X. D., Phan, Y. T. H. & Nguyen, V. Q. Excitation-Independent Emission of Carbon Quantum Dot Solids. *Adv. Mater. Sci. Eng.* **2020**, (2020).

52. Zhang, Q., Wang, R., Feng, B., Zhong, X. & Ostrikov, K. (Ken). Photoluminescence mechanism of carbon dots: triggering high-color-purity red fluorescence emission through edge amino protonation. *Nat. Commun. 2021 121* **12**, 1–13 (2021).

53. Xu, J., Tao, J., Su, L., Wang, J. & Jiao, T. A critical review of carbon quantum dots: From synthesis toward applications in electrochemical biosensors for the determination of a depression-related neurotransmitter. *Materials (Basel).* **14**, (2021).

54. Wang, Y. *et al.* Carbon dots of different composition and surface functionalization: cytotoxicity issues relevant to fluorescence cell imaging. *Exp. Biol. Med.*

(Maywood). **236**, 1231–1238 (2011).

55. Yang, S. T. *et al.* Carbon dots as nontoxic and high-performance fluorescence imaging agents. *J. Phys. Chem. C* **113**, 18110–18114 (2009).

56. Shereema, R. M., Sankar, V., Raghu, K. G., Rao, T. P. & Shankar, S. S. One Step Green Synthesis Of Carbon Quantum Dots And Its Application Towards The Bioelectroanalytical And Biolabeling Studies. *Electrochim. Acta* **182**, 588–595 (2015).

57. Xue, B. *et al.* Photoluminescent lignin hybridized carbon quantum dots composites for bioimaging applications. *Int. J. Biol. Macromol.* **122**, 954–961 (2019).

58. Huang, C. *et al.* Synthesis of Carbon Quantum Dot Nanoparticles Derived from Byproducts in Bio-Refinery Process for Cell Imaging and In Vivo Bioimaging. *Nanomaterials* **9**, (2019).

59. Ji, C., Zhou, Y., Leblanc, R. M. & Peng, Z. Recent Developments of Carbon Dots in Biosensing: A Review. *ACS Sensors* **5**, 2724–2741 (2020).

60. Li, H., Zhang, Y., Wang, L., Tian, J. & Sun, X. Nucleic acid detection using carbon nanoparticles as a fluorescent sensing platform. *Chem. Commun.* **47**, 961–963 (2010).

61. Bhattacharya, S., Sarkar, R., Nandi, S., Porgador, A. & Jelinek, R. Detection of Reactive Oxygen Species by a Carbon-Dot-Ascorbic Acid Hydrogel. *Anal. Chem.* **89**, 830–836 (2017).

62. Lu, S. *et al.* Facile and ultrasensitive fluorescence sensor platform for tumor invasive biomaker β-glucuronidase detection and inhibitor evaluation with carbon quantum dots based on inner-filter effect. *Biosens. Bioelectron.* **85**, 358–362 (2016).

63. Kong, B. *et al.* Carbon dot-based inorganic-organic nanosystem for two-photon imaging and biosensing of pH variation in living cells and tissues. *Adv. Mater.* **24**, 5844–5848 (2012).

64. Liu, X., Zhang, N., Bing, T. & Shangguan, D. Carbon dots based dual-emission silica nanoparticles as a ratiometric nanosensor for Cu2+. *Anal. Chem.* **86**, 2289–2296 (2014).

65. Mintz, K. J., Zhou, Y. & Leblanc, R. M. Recent development of carbon quantum dots regarding their optical properties, photoluminescence mechanism, and core structure. *Nanoscale* **11**, 4634–4652 (2019).

66. Li, X., Rui, M., Song, J., Shen, Z. & Zeng, H. Carbon and Graphene Quantum Dots for Optoelectronic and Energy Devices: A Review. *Adv. Funct. Mater.* **25**, 4929–4947 (2015).

67. Hoang, V. C., Dave, K. & Gomes, V. G. Carbon quantum dot-based composites for

energy storage and electrocatalysis: Mechanism, applications and future prospects. *Nano Energy* **66**, 104093 (2019).

68. Chen, D. *et al.* Preparation of highly sensitive Pt nanoparticles-carbon quantum dots/ionic liquid functionalized graphene oxide nanocomposites and application for H2O2 detection. *Sensors Actuators B Chem.* **255**, 1500–1506 (2018).

69. Matea, C. T. *et al.* Quantum dots in imaging, drug delivery and sensor applications. *Int. J. Nanomedicine* **12**, 5421–5431 (2017).

70. Li, X. *et al.* Functional gold nanoparticles as potent antimicrobial agents against multi-drug-resistant bacteria. *ACS Nano* **8**, 10682–10686 (2014).

71. Jia, X. *et al.* PEGylated Oxidized Alginate-DOX Prodrug Conjugate Nanoparticles Cross-Linked with Fluorescent Carbon Dots for Tumor Theranostics. *ACS Biomater. Sci. Eng.* **2**, 1641–1648 (2016).

72. Xu, G., Mahajan, S., Roy, I. & Yong, K. T. Theranostic quantum dots for crossing blood-brain barrier in vitro and providing therapy of HIV-associated encephalopathy. *Front. Pharmacol.* **4**, (2013).

73. Li, N. *et al.* Biodistribution study of carbogenic dots in cells and in vivo for optical imaging. *J. Nanoparticle Res.* **14**, 1–9 (2012).

74. Wang, D. Y. *et al.* Quantum dot light-emitting diode using solution-processable graphene oxide as the anode interfacial layer. *J. Phys. Chem. C* **116**, 10181–10185 (2012).

75. Biswal, M. R. & Bhatia, S. Carbon Dot Nanoparticles: Exploring the Potential Use for Gene Delivery in Ophthalmic Diseases. *Nanomaterials* **11**, (2021).

76. Li, S. *et al.* Nontoxic carbon dots potently inhibit human insulin fibrillation. *Chem. Mater.* **27**, 1764–1771 (2015).

77. Jian, H. J. *et al.* Super-Cationic Carbon Quantum Dots Synthesized from Spermidine as an Eye Drop Formulation for Topical Treatment of Bacterial Keratitis. *ACS Nano* **11**, 6703–6716 (2017).

78. Cao, X. *et al.* Photoluminescent Cationic Carbon Dots as efficient Non-Viral Delivery of Plasmid SOX9 and Chondrogenesis of Fibroblasts. *Sci. Reports 2018 81* **8**, 1–11 (2018).

79. Liu, H. *et al.* Physically flexible, rapid-response gas sensor based on colloidal quantum dot solids. *Adv. Mater.* **26**, 2718–2724 (2014).

80. Zhang, M. *et al.* Magnetofluorescent Fe3O4/carbon quantum dots coated single-walled carbon nanotubes as dual-modal targeted imaging and chemo/photodynamic/photothermal triple-modal therapeutic agents. *Chem. Eng. J.*

338, 526–538 (2018).

81. Reineck, P. & Gibson, B. C. Near-Infrared Fluorescent Nanomaterials for Bioimaging and Sensing. *Adv. Opt. Mater.* **5**, 1600446 (2017).

82. Hassanvand, Z., Jalali, F., Nazari, M., Parnianchi, F. & Santoro, C. Carbon Nanodots in Electrochemical Sensors and Biosensors: A Review. *ChemElectroChem* **8**, 15–35 (2021).

83. Chu, C. S., Hsieh, M. W. & Su, Z. R. Hydrogen peroxide sensing based on carbon quantum dots. *MATEC Web Conf.* **59**, (2016).

84. Ring, L. C. *et al.* Synthesis of curcumin quantum dots and their antimicrobial activity on necrotizing fasciitis causing bacteria. *Mater. Today Proc.* **31**, 31–35 (2020).
85. Azam, N., Najabat Ali, M. & Javaid Khan, T. Carbon Quantum Dots for Biomedical Applications: Review and Analysis. *Front. Mater.* **8**, 272 (2021).

86. Ahmed, E. M. Hydrogel: Preparation, characterization, and applications: A review. *J. Adv. Res.* **6**, 105–121 (2015).

87. Caló, E. & Khutoryanskiy, V. V. Biomedical applications of hydrogels: A review of patents and commercial products. *Eur. Polym. J.* **65**, 252–267 (2015).

88. Chimisso, V., Aleman Garcia, M. A., Yorulmaz Avsar, S., Dinu, I. A. & Palivan, C. G. Design of Bio-Conjugated Hydrogels for Regenerative Medicine Applications: From Polymer Scaffold to Biomolecule Choice. *Mol. 2020, Vol. 25, Page 4090* **25**, 4090 (2020).

89. Kohane, D. S. & Langer, R. Polymeric Biomaterials in Tissue Engineering. *Pediatr. Res. 2008 635* **63**, 487–491 (2008).

90. Totosaus, A., Montejano, J. G., Salazar, J. A. & Guerrero, I. A review of physical and chemical protein-gel induction. *Int. J. Food Sci. Technol.* **37**, 589–601 (2002).

91. Bao, Z. *et al.* Natural Polymer-Based Hydrogels with Enhanced Mechanical Performances: Preparation, Structure, and Property. *Adv. Healthc. Mater.* **8**, 1900670 (2019).

92. Silva, R., Fabry, B. & Boccaccini, A. R. Fibrous protein-based hydrogels for cell encapsulation. *Biomaterials* **35**, 6727–6738 (2014).

93. Fisher, S. A., Baker, A. E. G. & Shoichet, M. S. Designing Peptide and Protein Modified Hydrogels: Selecting the Optimal Conjugation Strategy. *J. Am. Chem. Soc.* **139**, 7416–7427 (2017).

94. Olechnovič, K. & Olechnovič Andčeslovasandˇandčeslovas Venclovas, O. VoroMQA web server for assessing three-dimensional structures of proteins and protein complexes. *Nucleic Acids Res.* **47**, W437–W442 (2019).

95. Le, X. T., Rioux, L. E. & Turgeon, S. L. Formation and functional properties of protein–polysaccharide electrostatic hydrogels in comparison to protein or polysaccharide hydrogels. *Adv. Colloid Interface Sci.* **239**, 127–135 (2017).

96. Davari, N. *et al.* Protein-Based Hydrogels: Promising Materials for Tissue Engineering. *Polym. 2022, Vol. 14, Page 986* **14**, 986 (2022).

97. Pickel, B. & Schaller, A. Dirigent proteins: molecular characteristics and potential biotechnological applications. *Appl. Microbiol. Biotechnol.* **97**, 8427–8438 (2013).

98. Huang, H., Qi, X., Chen, Y. & Wu, Z. Thermo-sensitive hydrogels for delivering biotherapeutic molecules: A review. *Saudi Pharm. J. SPJ Off. Publ. Saudi Pharm. Soc.* **27**, 990–999 (2019).

99. Berger, J. *et al.* Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications. *Eur. J. Pharm. Biopharm.* **57**, 19–34 (2004).

100. Parhi, R. Cross-Linked Hydrogel for Pharmaceutical Applications: A Review. *Adv. Pharm. Bull.* **7**, 515 (2017).

101. Jonker, A. M., Lö Wik, D. W. P. M. & Van Hest, J. C. M. Peptide-and Protein-Based Hydrogels. (2011) doi:10.1021/cm202640w.

102. Homaeigohar, S., Monavari, M., Koenen, B. & Boccaccini, A. R. Biomimetic biohybrid nanofibers containing bovine serum albumin as a bioactive moiety for wound dressing. *Mater. Sci. Eng. C* **123**, 111965 (2021).

103. Yang, X. *et al.* Collagen-alginate as bioink for three-dimensional (3D) cell printing based cartilage tissue engineering. *Mater. Sci. Eng. C. Mater. Biol. Appl.* **83**, 195–201 (2018).

104. Balakrishnan, B., Joshi, N., Jayakrishnan, A. & Banerjee, R. Self-crosslinked oxidized alginate/gelatin hydrogel as injectable, adhesive biomimetic scaffolds for cartilage regeneration. *Acta Biomater.* **10**, 3650–3663 (2014).

105. Zhao, X. *et al.* Photocrosslinkable Gelatin Hydrogel for Epidermal Tissue Engineering. *Adv. Healthc. Mater.* **5**, 108–118 (2016).

106. Yuan, H. *et al.* A novel bovine serum albumin and sodium alginate hydrogel scaffold doped with hydroxyapatite nanowires for cartilage defects repair. *Colloids Surfaces B Biointerfaces* **192**, 111041 (2020).

107. Liu, W. *et al.* Multifunctional injectable protein-based hydrogel for bone regeneration. *Chem. Eng. J.* **394**, 124875 (2020).

108. Wang, X., Ali, M. S. & Lacerda, C. M. R. A Three-Dimensional Collagen-Elastin Scaffold for Heart Valve Tissue Engineering. *Bioeng. (Basel, Switzerland)* **5**, (2018).

109. Veerasubramanian, P. K. *et al.* An investigation of konjac glucomannan-keratin hydrogel scaffold loaded with Avena sativa extracts for diabetic wound healing. *Colloids Surf. B. Biointerfaces* **165**, 92–102 (2018).

110. Chen, Y. *et al.* Glucose-triggered in situ forming keratin hydrogel for the treatment of diabetic wounds. *Acta Biomater.* **125**, 208–218 (2021).

111. Hong, H. *et al.* Digital light processing 3D printed silk fibroin hydrogel for cartilage tissue engineering. *Biomaterials* **232**, 119679 (2020).

112. Pankongadisak, P. & Suwantong, O. Enhanced properties of injectable chitosan-based thermogelling hydrogels by silk fibroin and longan seed extract for bone tissue engineering. *Int. J. Biol. Macromol.* **138**, 412–424 (2019).

113. El-Sherbiny, I. M. & Yacoub, M. H. Hydrogel scaffolds for tissue engineering: Progress and challenges. *Glob. Cardiol. Sci. Pract.* **2013**, 316 (2013).

114. Mahmood, A., Patel, D., Hickson, B., Desrochers, J. & Hu, X. Recent Progress in Biopolymer-Based Hydrogel Materials for Biomedical Applications. *Int. J. Mol. Sci.* **23**, 23 (2022).

115. Li, J., Wu, C., Chu, P. K. & Gelinsky, M. 3D printing of hydrogels: Rational design strategies and emerging biomedical applications. *Mater. Sci. Eng. R Reports* **140**, 100543 (2020).

116. Henrot, P. *et al.* A Method for Isolating and Culturing Skin Cells: Application to Endothelial Cells, Fibroblasts, Keratinocytes, and Melanocytes From Punch Biopsies in Systemic Sclerosis Skin. *Front. Immunol.* **11**, (2020).

117. Yadav, K. *et al.* Synthesis and characterization of novel protein nanodots as drug delivery carriers with an enhanced biological efficacy of melatonin in breast cancer cells. *RSC Adv.* **11**, 9076–9085 (2021).

118. Wu, M. S. *et al.* Nanodiamonds protect skin from ultraviolet B-induced damage in mice. *J. Nanobiotechnology* **13**, 1–12 (2015).

119. Shukla, D. *et al.* Sandalwood-derived carbon quantum dots as bioimaging tools to investigate the toxicological effects of malachite green in model organisms. *Chemosphere* **248**, (2020).

120. Rangel, R. *et al.* Advantages of hydrothermal synthesis to produce tunable TiO2 nanomicro sized photocatalysts and their effect in lignin degradation. *Nano* **10**, (2015).

121. Shukla, D. *et al.* Understanding the In Situ Mechanistic Control of Plant-Derived Carbon Quantum Dots on the Synthesis of Gold Nanoparticles. *ChemistrySelect* **4**, 13677–13688 (2019).

122. Li, Y. *et al.* Melatonin for the prevention and treatment of cancer. *Oncotarget* **8**, 39896–39921 (2017).

123. Yadav, S. K. *et al.* Nanomelatonin triggers superior anticancer functionality in a human malignant glioblastoma cell line. *Nanotechnology* **28**, 365102 (2017).

124. Shukla, D. *et al.* Sandalwood-derived carbon quantum dots as bioimaging tools to investigate the toxicological effects of malachite green in model organisms. *Chemosphere* **248**, 125998 (2020).

125. Justus, C. R., Leffler, N., Ruiz-Echevarria, M. & Yang, L. V. In vitro cell migration and invasion assays. *J. Vis. Exp.* (2014) doi:10.3791/51046.

126. Leong, Y. S. *et al.* UV-Vis Spectroscopy: A New Approach for Assessing the Color Index of Transformer Insulating Oil. *Sensors 2018, Vol. 18, Page 2175* **18**, 2175 (2018).

127. Gomes, A. J., Lunardi, C. N., Rocha, F. S. & Patience, G. S. Experimental methods in chemical engineering: Fluorescence emission spectroscopy. *Can. J. Chem. Eng.* **97**, 2168–2175 (2019).

128. Panowicz, R., Miedzińska, D., Pałka, N. & Niezgoda, T. The initial results of THz spectroscopy non-destructive investigations of epoxy-glass composite structure. 2–3 (2011).

129. Zeta potential :: Anton Paar Wiki. https://wiki.anton-paar.com/en/zeta-potential/.
130. Seyama, H., Soma, M. & Theng, B. K. G. X-Ray Photoelectron Spectroscopy. *Dev. Clay Sci.* **5**, 161–176 (2013).

131. Li, J. *et al.* Application of the small-angle X-ray scattering technique for structural analysis studies: A review. *J. Mol. Struct.* **1165**, 391–400 (2018).

132. Das, P. Optical Properties of Low Dimensional Structures Using Cathodoluminescence in a High Resolution Scanning Electron Microscope. 166 (2014).

133. Sharma, S., Jaiswal, S., Duffy, B. & Jaiswal, A. K. Nanostructured Materials for Food Applications: Spectroscopy, Microscopy and Physical Properties. *Bioeng. 2019, Vol. 6, Page 26* **6**, 26 (2019).

134. Schmidt, M. A., Goodwin, T. & Cuttino, M. Personalized Medicine in Space Flight, Part II: Personalized Precision Medicine Approaches. *Princ. Gender-Specific Med. Gend. Genomic Era Third Ed.* 673–693 (2017) doi:10.1016/B978-0-12-803506-1.00064-4.

135. Elliott, A. D. Confocal Microscopy: Principles and Modern Practices. *Curr. Protoc. Cytom.* **92**, e68 (2020).

136. Ferraris, C. F. & Martys, N. S. Concrete rheometers. *Underst. Rheol. Concr.* 63–82 (2012) doi:10.1533/9780857095282.1.63.

137. Mahshid, S. *et al.* Carbon-Pt nanoparticles modified TiO 2 nanotubes for simultaneous detection of dopamine and uric acid. *J. Nanosci. Nanotechnol.* **11**, 6668–6675 (2011).

138. D'Orazio, J., Jarrett, S., Amaro-Ortiz, A. & Scott, T. UV radiation and the skin. *Int. J. Mol. Sci.* **14**, 12222–12248 (2013).

139. Sanford, J. A. & Gallo, R. L. Functions of the skin microbiota in health and disease. *Semin. Immunol.* **25**, 370 (2013).

140. Med, C. C. Ultraviolet Radiation Exposure and Its Impact on Skin Cancer Risk. **40**, 1291–1296 (2015).

141. Teresa, M., Petersen, S. & Prakash, G. UV Light Effects on Proteins: From Photochemistry to Nanomedicine. *Mol. Photochem. - Var. Asp.* (2012) doi:10.5772/37947.

142. Harrison, S. C. & Bergfeld, W. F. Ultraviolet light and skin cancer in athletes. *Sports Health* **1**, 335–340 (2009).

143. Craig, S., Earnshaw, C. H. & Virós, A. Ultraviolet light and melanoma. *J. Pathol.* **244**, 578–585 (2018).

144. Fontanillas, P. *et al.* Disease risk scores for skin cancers. *Nat. Commun. 2021 121* **12**, 1–13 (2021).

145. Siegel, R. L., Miller, K. D., Fuchs, H. E. & Jemal, A. Cancer Statistics, 2021. *CA. Cancer J. Clin.* **71**, 7–33 (2021).

146. Nehal, K. S. & Bichakjian, C. K. Update on Keratinocyte Carcinomas. *N. Engl. J. Med.* **379**, 363–374 (2018).

147. Diepgen, T. L. & Mahler, V. The epidemiology of skin cancer. *Br. J. Dermatol.* **146**, 1–6 (2002).

148. Xu, L. *et al.* Microencapsulated sunblock nanoparticles based on zeolitic imidazole frameworks for safe and effective UV protection. *RSC Adv.* **8**, 12315–12321 (2018).

149. Tang, J. Q. *et al.* Recent developments in nanomedicine for melanoma treatment. *Int. J. Cancer* **141**, 646–653 (2017).

150. Jose, J. & Netto, G. Role of solid lipid nanoparticles as photoprotective agents in cosmetics. *J. Cosmet. Dermatol.* **18**, 315–321 (2019).

151. Lu, P. J. *et al.* Characterization of titanium dioxide and zinc oxide nanoparticles in

sunscreen powder by comparing different measurement methods. *J. Food Drug Anal.* **26**, 1192–1200 (2018).

152. Singh, P. & Nanda, A. Enhanced sun protection of nano-sized metal oxide particles over conventional metal oxide particles: An in vitro comparative study. *Int. J. Cosmet. Sci.* **36**, 273–283 (2014).

153. Vitiello, G. *et al.* Bioinspired hybrid eumelanin-TiO2 antimicrobial nanostructures: the key role of organo-inorganic frameworks in tuning eumelanin's biocide action mechanism through membrane interaction. *RSC Adv.* **8**, 28275–28283 (2018).

154. Vishnubhakthula, S., Elupula, R. & Durán-Lara, E. F. Recent Advances in Hydrogel-Based Drug Delivery for Melanoma Cancer Therapy: A Mini Review. *J. Drug Deliv.* **2017**, 1–9 (2017).

155. Rigon, R. B. *et al.* Nanotechnology-based drug delivery systems for melanoma antitumoral therapy: A review. *Biomed Res. Int.* **2015**, 16–20 (2015).

156. Vyas, A. *et al.* Recent Nanoparticuulate approches of drug delivery for skin cancer. *Trends in Applied Science Research* 620–635 (2012).

157. Chang, Z. *et al.* Self-healable and biodegradable soy protein-based protective functional film with low cytotoxicity and high mechanical strength. *Chem. Eng. J.* **404**, 126505 (2021).

158. Kumar, M. *et al.* Designer Protein-Based Performance Materials. *Biomacromolecules* **7**, 2543–2551 (2006).

159. Debele, T. A. & Su, W. P. Polysaccharide and protein-based functional wound dressing materials and applications. (2020).

160. Zhang, D. & Wang, Y. Functional Protein-Based Bioinspired Nanomaterials: From Coupled Proteins, Synthetic Approaches, Nanostructures to Applications. *Int. J. Mol. Sci. 2019, Vol. 20, Page 3054* **20**, 3054 (2019).

161. Mahler, A., Reches, M., Rechter, M., Cohen, S. & Gazit, E. Rigid, Self-assembled Hydrogel Composed of a Modified Aromatic Dipeptide. *Adv. Mater.* **18**, 1365–1370 (2006).

162. Nagarajan, S. *et al.* Overview of Protein-Based Biopolymers for Biomedical Application. *Macromol. Chem. Phys.* **220**, 1900126 (2019).

163. Xiang, B. *et al.* Self-assembled DNA Hydrogel Based on Enzymatically Polymerized DNA for Protein Encapsulation and Enzyme/DNAzyme Hybrid Cascade Reaction. *ACS Appl. Mater. Interfaces* **8**, 22801–22807 (2016).

164. Arabi, S. H. *et al.* Biomaterials Science rsc.li/biomaterials-science Serum albumin hydrogels in broad pH and temperature ranges: characterization of their self-

assembled structures and nanoscopic and macroscopic properties †. *Cite this Biomater. Sci* **6**, 478 (2018).

165. Su, T. J., Lu, J. R., Thomas, R. K., Cui, Z. F. & Penfold, J. The Conformational Structure of Bovine Serum Albumin Layers Adsorbed at the Silica−Water Interface. *J. Phys. Chem. B* **102**, 8100–8108 (1998).

166. Jayabharathi, J., Thanikachalam, V. & Venkatesh Perumal, M. Mechanistic investigation on binding interaction of bioactive imidazole with protein bovine serum albumin—A biophysical study. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **79**, 502–507 (2011).

167. Wu, X., Lv, L., Han, X. & Li, C. Bovine serum albumin fibrous biofilm template synthesis of metallic nanomeshes for surface-enhanced Raman scattering and electrocatalytic detection. *Mater. Des.* **192**, 108777 (2020).

168. Zewde, B., Atoyebi, O., Gugssa, A., Gaskell, K. J. & Raghavan, D. An Investigation of the Interaction between Bovine Serum Albumin-Conjugated Silver Nanoparticles and the Hydrogel in Hydrogel Nanocomposites. *ACS Omega* **6**, 11614–11627 (2021).

169. Upadhyay, A., Narula, A. & Rao, C. P. Copper-Based Metallogel of Bovine Serum Albumin and Its Derived Hybrid Biomaterials as Aerogel and Sheet: Comparative Study of the Adsorption and Reduction of Dyes and Nitroaromatics. *ACS Appl. Bio Mater.* **3**, 8619–8626 (2020).

170. Phan, V. H. G. *et al.* Development of bioresorbable smart injectable hydrogels based on thermo-responsive copolymer integrated bovine serum albumin bioconjugates for accelerated healing of excisional wounds. *J. Ind. Eng. Chem.* **96**, 345–355 (2021).

171. Jiang, B., Jain, A., Lu, Y. & Hoag, S. W. Probing Thermal Stability of Proteins with Temperature Scanning Viscometer. *Mol. Pharm.* **16**, 3687–3693 (2019).

172. Michnik, A., Michalik, K. & Drzazga, Z. Stability of bovine serum albumin at different pH. *J. Therm. Anal. Calorim.* **80**, 399–406 (2005).

173. Molodenskiy, D. *et al.* Thermally induced conformational changes and protein–protein interactions of bovine serum albumin in aqueous solution under different pH and ionic strengths as revealed by SAXS measurements. *Phys. Chem. Chem. Phys.* **19**, 17143–17155 (2017).

174. Arabi, S. H. *et al.* Serum albumin hydrogels in broad pH and temperature ranges: characterization of their self-assembled structures and nanoscopic and macroscopic properties. *Biomater. Sci.* **6**, 478–492 (2018).

175. Shibayama, M., Tanaka, T. & Han, C. C. Small angle neutron scattering study on poly(N-isopropyl acrylamide) gels near their volume-phase transition temperature. *J. Chem. Phys.* **97**, 6829 (1998).

176. Bodenberger, N. *et al.* Evaluation of methods for pore generation and their influence on physio-chemical properties of a protein based hydrogel. *Biotechnol. Reports* **12**, 6–12 (2016).

177. De Maria, S., Ferrari, G. & Maresca, P. Rheological Characterization Bovine Serum Albumin Gels Induced by High Hydrostatic Pressure. *Food Nutr. Sci.* **06**, 770–779 (2015).

178. Chen, J. *et al.* Self-healing of thermally-induced, biocompatible and biodegradable protein hydrogel. *RSC Adv.* **6**, 56183–56192 (2016).

179. Allen, M. Post Hoc Tests: Tukey Honestly Significant Difference Test. *SAGE Encycl. Commun. Res. Methods* (2017).

180. Zisapel, N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. *Br. J. Pharmacol.* **175**, 3190 (2018).

181. Grivas, T. B. & Savvidou, O. D. Melatonin the 'light of night' in human biology and adolescent idiopathic scoliosis. *Scoliosis* **2**, 1–14 (2007).

182. Carcangiu, V. *et al.* Daily rhythm of blood melatonin concentrations in sheep of different ages. *Biol. Rhythm Res.* **44**, 908–915 (2013).

183. Srinivasan, V. *et al.* Melatonin in mood disorders. *World J. Biol. Psychiatry* **7**, 138–151 (2006).

184. Boafo, A. *et al.* Could long-term administration of melatonin to prepubertal children affect timing of puberty? A clinician's perspective. *Nat. Sci. Sleep* **11**, 1 (2019).

185. Tamarkin, L., Almeida, O. F. & Danforth, D. N. Melatonin and malignant disease. *Ciba Found. Symp.* **117**, 284–299 (1985).

186. Kotlarczyk, M. P. *et al.* Melatonin osteoporosis prevention study (MOPS): A randomized, double-blind, placebo-controlled study examining the effects of melatonin on bone health and quality of life in perimenopausal women. *J. Pineal Res.* **52**, 414–426 (2012).

187. Altun, A. & Ugur-Altun, B. Melatonin: therapeutic and clinical utilization. *Int. J. Clin. Pract.* **61**, 835–845 (2007).

188. Zisapel, N. The use of melatonin for the treatment of insomnia. *Biol. Signals Recept.* **8**, 84–89 (1999).

189. Kleszczyński, K., Slominski, A. T., Steinbrink, K. & Reiter, R. J. Clinical Trials for Use of Melatonin to Fight against COVID-19 Are Urgently Needed. *Nutr. 2020, Vol. 12, Page 2561* **12**, 2561 (2020).

190. Castillo, R. R. *et al.* Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series. *Melatonin Res.* **3**, 297–310 (2020).

191. Andersen, L. P. H., Gögenur, I., Rosenberg, J. & Reiter, R. J. The Safety of Melatonin in Humans. *Clin. Drug Investig. 2015 363* **36**, 169–175 (2015).

192. Gitto, E., Aversa, S., Reiter, R. J., Barberi, I. & Pellegrino, S. Update on the use of melatonin in pediatrics. *J. Pineal Res.* **50**, 21–28 (2011).

193. Besag, F. M. C., Vasey, M. J., Lao, K. S. J. & Wong, I. C. K. Adverse Events Associated with Melatonin for the Treatment of Primary or Secondary Sleep Disorders: A Systematic Review. *CNS Drugs* **33**, 1167–1186 (2019).

194. Anghel, L. *et al.* Benefits and adverse events of melatonin use in the elderly (Review). *Exp. Ther. Med.* **23**, 219 (2022).

195. Moderie, C., Boudreau, P., Shechter, A., Lespérance, P. & Boivin, D. B. Effects of exogenous melatonin on sleep and circadian rhythms in women with premenstrual dysphoric disorder. *Sleep* **44**, (2021).

196. Sadak, M. S., Abdalla, A. M., Abd Elhamid, E. M. & Ezzo, M. I. Role of melatonin in improving growth, yield quantity and quality of Moringa oleifera L. plant under drought stress. *Bull. Natl. Res. Cent. 2020 441* **44**, 1–13 (2020).

197. Asif, M., Pervez, A., Irshad, U., Mehmood, Q. & Ahmad, R. Melatonin and plant growth-promoting rhizobacteria alleviate the cadmium and arsenic stresses and increase the growth of Spinacia oleracea L. *Plant, Soil Environ.* **66 (2020)**, 234–241 (2020).

198. Hardeland, R. Melatonin, Its Metabolites and Their Interference with Reactive Nitrogen Compounds. *Molecules* **26**, (2021).

199. Vitale, A. A., Ferrari, C. C., Aldana, H. & Affanni, J. M. Highly sensitive method for the determination of melatonin by normal-phase high-performance liquid chromatography with fluorometric detection. *J. Chromatogr. B. Biomed. Appl.* **681**, 381–384 (1996).

200. Kennaway, D. J. Measuring melatonin by immunoassay. *J. Pineal Res.* **69**, (2020).

201. Gazy, A. A., Abdine, H. H. & Abdel-Hay, M. H. Colorimetric and Spectrofluorimetric Methods for the Determination of Melatonin in Tablets and Serum. **31**, 177–197 (2006).

202. Schotten, C. *et al.* Making electrochemistry easily accessible to the synthetic chemist. *Green Chem.* **22**, 3358–3375 (2020).

203. Apetrei, I. M. & Apetrei, C. Voltammetric determination of melatonin using a

graphene-based sensor in pharmaceutical products. *Int. J. Nanomedicine* **11**, 1859 (2016).

204. Kumar, N., Rosy & Goyal, R. N. Nanopalladium grained polymer nanocomposite based sensor for the sensitive determination of Melatonin. *undefined* **211**, 18–26 (2016).

205. Cincotto, F. H. *et al.* A nano-magnetic electrochemical sensor for the determination of mood disorder related substances. *RSC Adv.* **8**, 14040–14047 (2018).

206. Molaakbari, E., Mostafavi, A. & Beitollahi, H. Simultaneous electrochemical determination of dopamine, melatonin, methionine and caffeine. *Sensors Actuators, B Chem.* **208**, 195–203 (2015).

207. Thomas, A. & Kumar, K. G. Acetylene black-chitosan mediated electro-oxidation of serotonin and melatonin: an efficient platform for simultaneous voltammetric sensing. *Ionics (Kiel).* **25**, 2337–2349 (2019).

208. Levent, A. Electrochemical determination of melatonin hormone using a boron-doped diamond electrode. *Diam. Relat. Mater.* **21**, 114–119 (2012).

209. Rajkumar, C., Veerakumar, P., Chen, S. M., Thirumalraj, B. & Liu, S. Bin. Facile and novel synthesis of palladium nanoparticles supported on a carbon aerogel for ultrasensitive electrochemical sensing of biomolecules. *Nanoscale* **9**, 6486–6496 (2017).

210. Liu, H., Ge, J., Ma, E. & Yang, L. Advanced biomaterials for biosensor and theranostics. *Biomater. Transl. Med. A Biomater. Approach* 213–255 (2018) doi:10.1016/B978-0-12-813477-1.00010-4.

211. Parashar, P. *et al.* Gelatin-based nanomaterials in drug delivery and biomedical applications. *Biopolym. Nanomater. Drug Deliv. Biomed. Appl.* 407–426 (2021) doi:10.1016/B978-0-12-820874-8.00020-8.

212. Rong, J., Niu, Z., Lee, L. A. & Wang, Q. Chemistry and Materials Development of Protein-Based Nanoparticles. *Compr. Nanosci. Technol.* **1–5**, 153–174 (2011).

213. Crookes-Goodson, W. J., Slocik, J. M. & Naik, R. R. Bio-directed synthesis and assembly of nanomaterials. *Chem. Soc. Rev.* **37**, 2403–2412 (2008).

214. Wang, Y. & Hu, A. Carbon quantum dots: synthesis, properties and applications. *J. Mater. Chem. C* **2**, 6921–6939 (2014).

215. Yadav, K. *et al.* Synthesis and characterization of novel protein nanodots as drug delivery carriers with an enhanced biological efficacy of melatonin in breast cancer cells. *RSC Adv.* **11**, 9076–9085 (2021).

216. Kang, Y. F. *et al.* Carbon Quantum Dots for Zebrafish Fluorescence Imaging. *Sci.*

Rep. **5**, (2015).

217. Singh, S., Jain, D. V. S. & Singla, M. L. One step electrochemical synthesis of gold-nanoparticles-polypyrrole composite for application in catechin electrochemical biosensor. *Anal. Methods* **5**, 1024–1032 (2013).

218. Gou, H. *et al.* A Highly Effective Electrochemical Chiral Sensor of Tryptophan Enantiomers Based on Covalently Functionalize Reduced Graphene Oxide with L-Lysine. *J. Electrochem. Soc.* **163**, B272–B279 (2016).

219. Frenzel, N., Hartley, J. & Frisch, G. Voltammetric and spectroscopic study of ferrocene and hexacyanoferrate and the suitability of their redox couples as internal standards in ionic liquids. *Phys. Chem. Chem. Phys.* **19**, 28841–28852 (2017).

220. Ferrari, A. G. M., Foster, C. W., Kelly, P. J., Brownson, D. A. C. & Banks, C. E. Determination of the Electrochemical Area of Screen-Printed Electrochemical Sensing Platforms. *Biosens. 2018, Vol. 8, Page 53* **8**, 53 (2018).

221. Tadayon, F. & Sepehri, Z. A new electrochemical sensor based on a nitrogen-doped graphene/CuCo2O4 nanocomposite for simultaneous determination of dopamine, melatonin and tryptophan. *RSC Adv.* **5**, 65560–65568 (2015).

222. Rosy & Goyal, R. N. Estimation of Amoxicillin in Presence of High Concentration of Uric Acid and Other Urinary Metabolites Using an Unmodified Pyrolytic Graphite Sensor. *J. Electrochem. Soc.* **162**, G8–G13 (2015).

223. Ngamchuea, K., Tharat, B., Hirunsit, P. & Suthirakun, S. Electrochemical oxidation of resorcinol: mechanistic insights from experimental and computational studies. *RSC Adv.* **10**, 28454–28463 (2020).

224. Benítez-King, G. Melatonin as a cytoskeletal modulator: Implications for cell physiology and disease. *Journal of Pineal Research* vol. 40 1–9 (2006).

225. Hill, S. M. *et al.* Melatonin and associated signaling pathways that control normal breast epithelium and breast cancer. *J. Mammary Gland Biol. Neoplasia* **16**, 235–245 (2011).

226. Blask, D. E., Dauchy, R. T. & Sauer, L. A. Putting cancer to sleep at night: The neuroendocrine/circadian melatonin signal. *Endocrine* vol. 27 179–188 (2005).

227. Tamarkin, L. *et al.* Decreased nocturnal plasma melatonin peak in patients with estrogen receptor positive breast cancer. *Science (80-.).* **216**, 1003–1005 (1982).

228. Wang, J. *et al.* Simultaneous modulation of COX-2, p300, Akt, and Apaf-1 signaling by melatonin to inhibit proliferation and induce apoptosis in breast cancer cells. *J. Pineal Res.* **53**, 77–90 (2012).

229. Reiter, R. J., Paredes, S. D., Manchester, L. C. & Tan, D. X. Reducing oxidative/nitrosative stress: A newly-discovered genre for melatonin melatonin as

an antioxidant R. J. Reiter et al. *Critical Reviews in Biochemistry and Molecular Biology* vol. 44 175–200 (2009).

230. Yuan, X., Li, B., Li, H. & Xiu, R. Melatonin inhibits IL-1β-induced monolayer permeability of human umbilical vein endothelial cells via Rac activation. *J. Pineal Res.* **51**, 220–225 (2011).

231. Grant, S. G., Melan, M. A., Latimer, J. J. & Witt-Enderby, P. A. Melatonin and breast cancer: Cellular mechanisms, clinical studies and future perspectives. *Expert Reviews in Molecular Medicine* vol. 11 e5 (2009).

232. Dominguez-Rodriguez, A. & Abreu-Gonzalez, P. Melatonin: Still a forgotten antioxidant. *Int. J. Cardiol.* **149**, 382 (2011).

233. Padillo, F. J. *et al.* Melatonin and celecoxib improve the outcomes in hamsters with experimental pancreatic cancer. *J. Pineal Res.* **49**, 264–270 (2010).

234. Srinivasan, V., Spence, D. W., Pandi-Perumal, S. R., Trakht, I. & Cardinali, D. P. Therapeutic actions of melatonin in cancer: Possible mechanisms. *Integrative Cancer Therapies* vol. 7 189–203 (2008).

235. Korkmaz, A. *et al.* Melatonin: An established antioxidant worthy of use in clinical trials. *Molecular Medicine* vol. 15 43–50 (2009).

236. Galano, A., Tan, D. X. & Reiter, R. J. Melatonin as a natural ally against oxidative stress: A physicochemical examination. *Journal of Pineal Research* vol. 51 1–16 (2011).

237. Bonnefont-Rousselot, D., Collin, F., Jore, D. & Gardès-Albert, M. Reaction mechanism of melatonin oxidation by reactive oxygen species in vitro. *J. Pineal Res.* **50**, 328–335 (2011).

238. REITER, R. J. *et al.* Melatonin As a Free Radical Scavenger: Implications for Aging and Age-Related Diseases. *Ann. N. Y. Acad. Sci.* **719**, 1–12 (1994).

239. POEGGELER, B. *et al.* Melatonin—A Highly Potent Endogenous Radical Scavenger and Electron Donor: New Aspects of the Oxidation Chemistry of this Indole Accessed in vitro. *Ann. N. Y. Acad. Sci.* **738**, 419–420 (1994).

240. Um, H. J., Park, J. W. & Kwon, T. K. Melatonin sensitizes Caki renal cancer cells to kahweol-induced apoptosis through CHOP-mediated up-regulation of PUMA. *J. Pineal Res.* **50**, 359–366 (2011).

241. Proietti, S. *et al.* Melatonin and vitamin D 3 synergistically down-regulate Akt and MDM2 leading to TGFβ-1-dependent growth inhibition of breast cancer cells. *J. Pineal Res.* **50**, 150–158 (2011).

242. Shokrzadeh, M. & Ghassemi-Barghi, N. Melatonin Loading Chitosan-

Tripolyphosphate Nanoparticles: Application in Attenuating Etoposide-Induced Genotoxicity in HepG2 Cells. *Pharmacology* **102**, 74–80 (2018).

243. Mirhoseini, M. *et al.* Protective effects of melatonin solid lipid nanoparticles on testis histology after testicular trauma in rats. *Res. Pharm. Sci.* **14**, 201–208 (2019).

244. Hara, C. D. C. P., Honorio-França, A. C., Fagundes, D. L. G., Guimarães, P. C. L. & França, E. L. Melatonin nanoparticles adsorbed to polyethylene glycol microspheres as activators of human colostrum macrophages. *J. Nanomater.* **2013**, (2013).

245. Kumar Yadav, S. *et al.* Nanomelatonin triggers superior anticancer functionality in a human malignant glioblastoma cell line. *Nanotechnology* **28**, 365102 (2017).

246. Rosli, N. S., Rahman, A. A., Aziz, A. A., Shamsuddin, S. & Zakaria, N. S. Effects of the gold nanoparticles (AuNPs) on the proliferation and morphological characteristics of human breast cancer cells (MCF-7) in culture. in *Solid State Phenomena* vol. 268 SSP 254–258 (2017).

247. Martins, L. G., khalil, N. M. & Mainardes, R. M. PLGA Nanoparticles and Polysorbate-80-Coated PLGA Nanoparticles Increase the In vitro Antioxidant Activity of Melatonin. *Curr. Drug Deliv.* **15**, 554–563 (2018).

248. Mirakabad, F. S. T. *et al.* PLGA-based nanoparticles as cancer drug delivery systems. *Asian Pacific Journal of Cancer Prevention* vol. 15 517–535 (2014).

249. Rao, J. P. & Geckeler, K. E. Polymer nanoparticles: Preparation techniques and size-control parameters. *Progress in Polymer Science (Oxford)* vol. 36 887–913 (2011).

250. Danhier, F., Feron, O. & Préat, V. To exploit the tumor microenvironment: Passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. *Journal of Controlled Release* vol. 148 135–146 (2010).

251. Sharma, S., Parmar, A., Kori, S. & Sandhir, R. PLGA-based nanoparticles: A new paradigm in biomedical applications. *TrAC - Trends in Analytical Chemistry* vol. 80 30–40 (2016).

252. Knop, K., Hoogenboom, R., Fischer, D. & Schubert, U. S. Poly(ethylene glycol) in drug delivery: Pros and cons as well as potential alternatives. *Angewandte Chemie - International Edition* vol. 49 6288–6308 (2010).

253. Wolfbeis, O. S. An overview of nanoparticles commonly used in fluorescent bioimaging. *Chem. Soc. Rev.* **44**, 4743–4768 (2015).

254. Zuo, J. *et al.* Preparation and Application of Fluorescent Carbon Dots. *J. Nanomater.* **2015**, 1–13 (2015).

255. Caponetti, V. *et al.* Self-assembled Biocompatible Fluorescent Nanoparticles for

Bioimaging. *Front. Chem.* **7**, 168 (2019).

256. Shukla, D. *et al.* Label-Free Fluorometric Detection of Adulterant Malachite Green Using Carbon Dots Derived from the Medicinal Plant Source *Ocimum tenuiflorum*. *ChemistrySelect* **4**, 4839–4847 (2019).

257. Pramanik, S., Chatterjee, S., Suresh Kumar, G. & Sujatha Devi, P. Egg-shell derived carbon dots for base pair selective DNA binding and recognition. *Phys. Chem. Chem. Phys.* **20**, 20476–20488 (2018).

258. Olmez, T. T. *et al.* Autonomous Synthesis of Fluorescent Silica Biodots Using Engineered Fusion Proteins. *ACS Omega* **3**, 585–594 (2018).

259. Atabaev, T. S. Doped carbon dots for sensing and bioimaging applications: A minireview. *Nanomaterials* vol. 8 (2018).

260. Dong, Y. *et al.* Polyamine-functionalized carbon quantum dots for chemical sensing. *Carbon N. Y.* **50**, 2810–2815 (2012).

261. Robson, A. L. *et al.* Advantages and limitations of current imaging techniques for characterizing liposome morphology. *Frontiers in Pharmacology* vol. 9 (2018).

262. Derfus, A. M., Chan, W. C. W. & Bhatia, S. N. Probing the Cytotoxicity of Semiconductor Quantum Dots. *Nano Lett.* **4**, 11–18 (2004).

263. Jensen, E. C. Use of Fluorescent Probes: Their Effect on Cell Biology and Limitations. *Anat. Rec. Adv. Integr. Anat. Evol. Biol.* **295**, 2031–2036 (2012).

264. Guo, C. X. *et al.* A new class of fluorescent-dots: long luminescent lifetime bio-dots self-assembled from DNA at low temperatures. *Sci. Rep.* **3**, 2957 (2013).

265. Jha, A. *et al.* DNA biodots based targeted theranostic nanomedicine for the imaging and treatment of non-small cell lung cancer. *Int. J. Biol. Macromol.* **150**, 413–425 (2020).

266. Liu, H. *et al.* Lysosome-targeted carbon dots for ratiometric imaging of formaldehyde in living cells. *Nanoscale* **11**, 8458–8463 (2019).

267. Hu, X., Dong, C., Su, R., Xu, Q. & Dinu, C. Z. Protein self-assembly onto nanodots leads to formation of conductive bio-based hybrids. *Sci. Rep.* **6**, 1–13 (2016).

268. Ozkan, A. D., Tekinay, A. B., Guler, M. O. & Tekin, E. D. Effects of temperature, pH and counterions on the stability of peptide amphiphile nanofiber structures. *RSC Adv.* **6**, 104201–104214 (2016).

269. Sarkar, S., Banerjee, D., Ghorai, U. K., Das, N. S. & Chattopadhyay, K. K. Size dependent photoluminescence property of hydrothermally synthesized crystalline carbon quantum dots. *J. Lumin.* **178**, 314–323 (2016).

270. Song, S.-H. *et al.* Size and pH dependent photoluminescence of graphene quantum dots with low oxygen content. *RSC Adv.* **6**, 97990–97994 (2016).

271. Su, T. J., Lu, J. R., Thomas, R. K., Cui, Z. F. & Penfold, J. The effect of solution pH on the structure of lysozyme layers adsorbed at the silica-water interface studied by neutron reflection. *Langmuir* **14**, 438–445 (1998).

272. Deka, M. J. *et al.* Carbon dots derived from water hyacinth and their application as a sensor for pretilachlor. *Heliyon* **5**, e01985 (2019).

273. Mehta, V. N., Jha, S., Basu, H., Singhal, R. K. & Kailasa, S. K. One-step hydrothermal approach to fabricate carbon dots from apple juice for imaging of mycobacterium and fungal cells. *Sensors Actuators, B Chem.* **213**, 434–443 (2015).

274. Zhou, J., Sheng, Z., Han, H., Zou, M. & Li, C. Facile synthesis of fluorescent carbon dots using watermelon peel as a carbon source. *Mater. Lett.* **66**, 222–224 (2012).

275. Hess, S. C. *et al.* Direct synthesis of carbon quantum dots in aqueous polymer solution: one-pot reaction and preparation of transparent UV-blocking films. *J. Mater. Chem. A* **5**, 5187–5194 (2017).

276. Xu, Y. *et al.* Nitrogen-doped carbon dots: A facile and general preparation method, photoluminescence investigation, and imaging applications. *Chem. - A Eur. J.* **19**, 2276–2283 (2013).

277. Ramanan, V. *et al.* Outright green synthesis of fluorescent carbon dots from eutrophic algal blooms for in vitro imaging. *ACS Sustain. Chem. Eng.* **4**, 4724–4731 (2016).

278. Bhattacharya, D., Mishra, M. K. & De, G. Carbon Dots from a Single Source Exhibiting Tunable Luminescent Colors through the Modification of Surface Functional Groups in ORMOSIL Films. *J. Phys. Chem. C* **121**, 28106–28116 (2017).

279. Parmar, A. S. & Muschol, M. Hydration and hydrodynamic interactions of lysozyme: Effects of chaotropic versus kosmotropic ions. *Biophys. J.* **97**, 590–598 (2009).

280. Yamamoto, T. *et al.* Transfer of photoenergy in π-Conjugated polymers. Two types of photoluminescence that involve energy transfer along a polymer chain. *J. Phys. Chem. B* **109**, 10605–10610 (2005).

281. Sun, Y. *et al.* The Cost-Effective Preparation of Green Fluorescent Carbon Dots for Bioimaging and Enhanced Intracellular Drug Delivery. *Nanoscale Res. Lett.* **15**, 1–9 (2020).

282. Altindal, D. Ç. & Gumusderelioglu, M. Melatonin releasing PLGA micro/nanoparticles and their effect on osteosarcoma cells. *J. Microencapsul.* **33**, 53–63 (2016).

283. Ferreira, L. C. *et al.* The role of melatonin on miRNAs modulation in triple-negative breast cancer cells. *PLoS One* **15**, (2020).

284. Mao, L. & Hill, S. M. Inhibition of cell proliferation and blockade of cell invasion by melatonin in human breast cancer cells mediated through multiple signaling pathways. *Cancer Res.* **65**, (2005).