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Bioinspired Carbon Dots-Based Fluorescent Sensor for the Selective Determination of a Potent Anti-Inflammatory Drug in the Presence of Its Photodegradation Products

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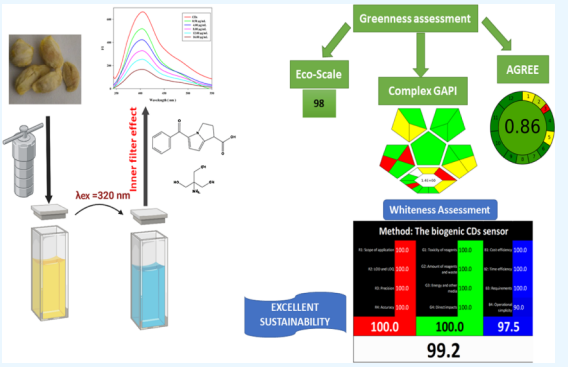
ABSTRACT: Herein, we synthesized biogenic carbon dots (CDs) with blue-shifted maximum excitation ($\lambda_{ex}/\lambda_{em}$ of 320/404 nm) from largely wasted tangerine seeds for the first time via a one-step hydrothermal method. The biogenic CDs exhibit a maximum excitation wavelength that overlaps with the absorption spectrum of ketorolac tromethamine (KETO) at 320 nm. The developed CDs serve as a turn-off fluorescent probe via an inner filter effect (IFE) quenching mechanism. The resulting CDs have high quantum yield (QY) (39% ± 2.89%, n = 5) and exhibited great performance toward KETO over a concentration range of 0.50−16.00 μg/mL with a limit of detection (LOD) = 0.17 μg/mL. The nanoprobe achieved a high % recovery in assaying KETO in tablet dosage form and had not been significantly affected by various interferents including co-formulated and co-administered drugs. The nanoprobe shows selectivity toward KETO, even in the presence of its photocatalytic degradation products. It can effectively investigate the elimination of KETO from aquatic systems and test its stability in pharmaceutical preparations. The developed nanoprobe underwent a comprehensive evaluation of its environmental impact using analytical eco-scale (AES), complex green analytical procedure index (Complex GAPI), and the Analytical GREEnness calculator (AGREE). The sustainability of the developed nano sensor was assessed and compared to the reported metal-based quantum dots probe for KETO using the innovative RGB 12 model, considering 12 white analytical chemistry (WAC) perspectives.



1. INTRODUCTION

Nowadays, carbon dots (CDs) are considered the magic star for constructing myriad eco-friendly fluorescent-based sensing platforms. They have a size of less than 10 nm and contain plenty of different functional groups attached to their surface, making them react selectively with different analytes via different mechanisms. CDs are primarily prepared via two well-reported approaches: bottom-up and top-down. Bottom-up is considered the most common approach for preparing CDs from different biowaste and chemical precursors. CDs are prepared using different methods that are located under the umbrella of the bottom-up approach, but the most common methods used in the literature are the hydrothermal and microwave-assisted synthesis techniques since they are economically saving, facile, and can be scaled up easily. Most notably, modifications including doping are accomplished using facile and mild conditions.[1,2]

Approximately 1.3 billion tons of food waste is disposed of every year, leading to resource wastage and environmental harm.[3] Traditional methods of managing food waste, such as composting and landfilling, have proven to be ineffective. However, recent developments have focused on converting food waste into valuable products, including biochar, bioactive compounds, enzymes, exopolysaccharides,[3−5] and fluorescent CDs.[6] CDs synthesized from food waste[6] have found applications in environmental and pharmaceutical analysis, as well as bioimaging, due to their water solubility, stability, and biocompatibility.

Citrus fruits generate substantial waste, with global production exceeding 40 million tons annually.[7] Tangerine seeds, solid waste of *Citrus reticulata blanco* and its cultivated varieties, contain active constituents like polyphenols, flavonoids, and tannins.[8] Tangerine seeds are mostly discarded or minimally utilized.[9] So, in this study, tangerine seeds were rationally selected as a cost-effective and abundant biogenic precursor for the synthesis of highly fluorescent biogenic CDs

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using a one-step hydrothermal method. As the active constituents of tangerine seeds contain plenty of oxygen-containing functional groups, we predicted that the resulting CDs would be rich in oxygen-containing groups. Although CDs have been applied to detect various drugs, CDs are limited mainly to the drugs having UV absorption spectra with λ_{max} between 340 and 400 nm that quench the CDs' fluorescence by the IFE mechanism. Upon carefully surveying the literature, we observed that CDs that are synthesized from natural precursors rich in oxygen containing function groups have a hypsochromic shift in their excitation wavelength compared to the traditional doped one[10−13] and hence could be employed to detect drugs that have UV absorption spectra with λ_{max} between 300 and 330 nm. So, the challenge in this work is to carefully select an affordable and widely available natural precursor that is rich in oxygen to give pristine CDs with reasonably high QY to avoid the need for doping common atoms such as nitrogen or sulfur to enhance the resulted QY, as these doped atoms had been well reported to cause bathochromic shift to the maximum excitation wavelength of the resulted CDs[14,15] which is not well fitted with its application in analysis of the non-fluorescent drugs that strongly absorb near the middle UV region via the IFE quenching mechanism.

The literature was surveyed to guide and support our hypothesis for the optimal selection of the used precursor, and we found that Liu et al.[10] reported a facile one-pot hydrothermal method for the synthesis of oxygen-rich CDs from chocolate as it is well-known that it contains large amount of polyphenols which endowed the resulted CDs rich in oxygen groups and the reported CDs have ($\lambda_{ex}/\lambda_{em}$ of 280/354 nm), also Xue et al.[11] reported a simple one-step pyrolysis method for synthesis of oxygen-rich CDs from peanut shells which composed of plenty of oxygen-rich chemical compounds as this precursor contains 40.5% cellulose, 14.7% hemicellulose, and 26.4% lignin,[16] which produced CDs rich in oxygen groups and have ($\lambda_{ex}/\lambda_{em}$ of 320/440 nm). Hu and Gao[12] reported an H_2O_2-assisted hydrothermal method for the preparation of oxygen-rich CDs from wasted chewing gum made of polymeric hydrocarbons, the resulting CDs have abundant oxygenous groups with ($\lambda_{ex}/\lambda_{em}$ of 320/431 nm). Zhang et al.[13] reported the synthesis of oxygen-rich CDs from the phenolic compounds extracted from coffee bean shells, the resulting CDs have numerous oxygen-rich groups with ($\lambda_{ex}/\lambda_{em}$ of 320/380 nm). It was noticed from the reported methods that oxygen-rich group CDs have a hypsochromic shift in their maximum excitation wavelength in comparison to the nitrogen- and sulfur-doped CDs, so oxygen-rich group CDs are promising to detect the non-fluorescent drugs that strongly absorb near the middle UV region (300−330 nm) via the IFE quenching mechanism. Fortunately, the developed tangerine seeds-derived CDs were found to be rich in oxygen containing function groups and their maximum excitation wavelength was found to be 320 nm (very near to the middle UV region) which is completely overlapped with the KETO absorption spectrum (λ_{max}= 320 nm). This enabled the sensitive and highly selective determination of KETO in the presence of common interfering substances in different matrices.

Ketorolac tromethamine (KETO) belongs to the group of nonsteroidal anti-inflammatory drugs (NSAIDs) and is known for its strong ability to inhibit the cyclooxygenase (COX) enzyme. As a result, it demonstrates remarkable anti-inflammatory and analgesic effects. It is used mainly to reduce the postoperative pain.[17] Numerous analytical techniques had been described in the literature for the estimation of bare and KETO salt in different matrices such as spectroscopic methods,[18,19] chromatographic methods,[20,21] and electrochemical methods.[22]

Pharmaceuticals are biologically active, long-lasting substances that are recognized as emerging contaminants and a constant threat to the environment. Each year, tons of drugs are produced and consumed, making them susceptible to leakage into the aquatic ecosystem through wastewater discharge from the municipal, healthcare, and pharmaceutical industries, livestock treatments, improper drug removal, and aquaculture practices. Accordingly, numerous methods had been reported for the benign elimination of KETO from aquatic ecosystems based on its photodegradation using various metals as a photocatalytic reagent.[23] Most of the reported analytical techniques for KETO are time-consuming and use hazardous reagents and solvents, such as most chromatographic methods. Moreover, the recently published UV−vis spectroscopic method[18] had achieved lower sensitivity, in addition to using tedious steps and hazardous solvents and reagents to synthesize the molecular imprinted polymer to achieve reasonable selectivity for the analysis of the studied drug. So, it is important to construct an ecofriendly, rapid, selective, sensitive, and cost-effective fluorescent probe to determine KETO in the presence of its different interferents, including its photocatalytic degradation products, to further enable monitoring KETO stability in different pharmaceuticals in addition to investigating its complete elimination from the aquatic ecosystems via different photocatalytic reagents. Owing to its simplicity, high sensitivity, and low cost, CDs-based probes have become the magic star for the analysis of many drugs in different matrices,[24−27] in addition to their application in the bioimaging[28] field as a biocompatible and cost-effective alternative to the classical quantum dots including graphene quantum dots.[29]

As far as we know, no biowaste-derived CDs-based fluorescent probe has been reported for the analysis of the studied drug alone or in the presence of its photodegradation products, so the developed biowasted tangerine seeds-derived CDs are employed as a simple and highly selective sensor for the analysis of KETO in the presence of different interfering substances including its photodegradation products.

2. MATERIALS AND METHODS

2.1. Instruments. The intruments used are illustrated in details in Supporting Information.

2.2. Chemicals and Reagents. The chemicals and reagents used are illustrated in detail in Supporting Information.

2.3. Synthesis of Biogenic CDs. Tangerine seeds were collected and peeled; then, they were well dried in open air, and after that the seeds were crushed into fine powder through the grinder. The resulting fine powder (0.60 g) was dispersed in 30 mL of distilled water, and the resulting suspension was carefully transferred into a 50 mL Teflon-lined stainless-steel autoclave reactor. The hydrothermal reactor was incubated at 200 °C for 12 h; then, it was cooled to room temperature, and the resulting brownish solution was collected. Finally, the collected brownish solution was centrifuged and filtered through a 0.22 μm syringe filter. The resulting clear solution was freeze-dried to obtain a biogenic CDs powder. The

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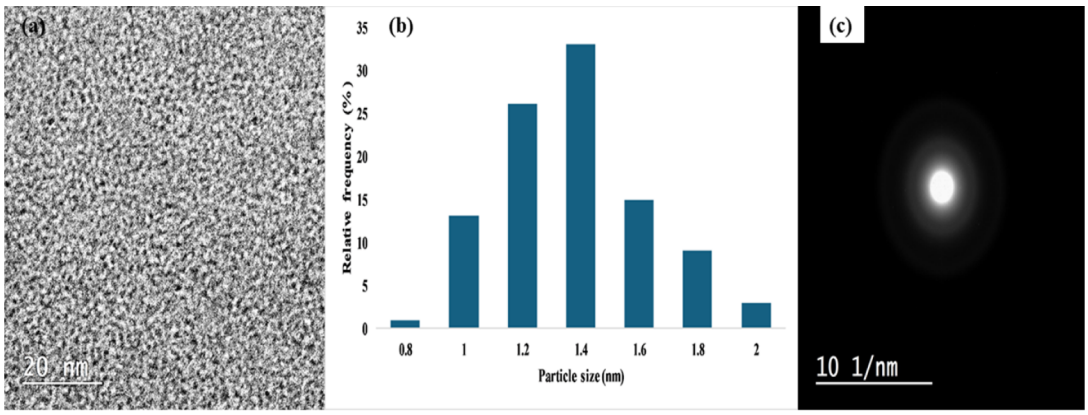

Figure 1. (a) HRTEM of CDs, (b) particle size distribution histogram as analyzed from the HRTEM, and (c) SAED pattern of the CDs.

obtained CDs was stored in well-sealed amber-colored bottle in the refrigerator at 4 °C.

2.4. Calculation of the Quantum Yield. The quantum yield (Q) was estimated by applying the following equation:

$$Q = Q_{ref} \times \frac{I}{I_{ref}} \times \frac{A_{ref}}{A} \times \frac{n^2}{n_{ref}^2}$$

where I is the resulted integrated fluorescence, A is the obtained absorbance value, and n is the refractive index of the solvent (for both solvents n equals 1.33).[30] The reference fluorophore used is quinine sulfate in 0.1 M H_2SO_4. Q_{ref} value is 0.54. The sign (ref) represents the standard quinine sulfate.

2.5. Analytical Procedures for Assaying KETO. 40.0 μL from the prepared CDs solution (2.00 mg/mL) was transferred into a series of 10 mL volumetric flasks followed by transferring different aliquots from the stock solution of KETO (100.00 μg/mL) and the volume was completed to the mark with the same solvent (distilled water). All fluorescent intensity (FI) measurements were recorded at λ_{em} = 404 nm using λ_{ex} = 320 nm.

2.6. Analytical Procedures for the Analysis of KETO in Real Samples. *2.6.1. Analytical Procedures for the Analysis of KETO in Commercial Tablets.* Ten Ketolac tablets each labeled to contain 10 mg of KETO were separately weighed, ground to fine powder, and an amount of the powder equivalent to 10 mg of KETO was accurately weighed and transferred into 100 mL light-protected volumetric flask by 50 mL of distilled water for extraction using ultrasonication; the volume was completed to the mark with the same solvent and filtered using 0.45 μm syringe filter. Different aliquots were withdrawn and transferred into a series of light-protected 10 mL volumetric flasks, each containing 40.0 μL of the prepared biogenic CDs solution and completed to the mark with the same solvent to give the desired concentration. Each sample was investigated as mentioned in Section 2.5.

2.6.2. Photostability Study of KETO in Commercial Tablets. The same procedures mentioned under Section 2.6.1 were followed for the preparation of a KETO solution which claimed to contain 100.00 μg/mL KETO. The prepared solution was subjected to direct sunlight and after 4 days, 1.2 mL was withdrawn and transferred into light protected 10 mL volumetric flask containing 40.0 μL of the prepared biogenic CDs solution, and the volume was completed to the mark with distilled water. After another 2 days, 1.2 mL was withdrawn and the same procedures were followed. Each sample was investigated as mentioned in Section 2.5.

3. RESULTS AND DISCUSSION

3.1. Optimization of the Synthesis Conditions. The hydrothermal method is widely employed as a bottom-up synthetic approach to produce CDs with a narrow size distribution and well-defined shapes. The two crucial factors, photoluminescence behavior and QY, of the produced CDs can be effectively controlled by manipulating the particle size in addition to their surface states. The hydrothermal method is particularly favored for biomass utilization due to its advantageous characteristics such as being solvent-free, easy to operate, scalable, and utilizing abundant and cost-effective biomass sources. Moreover, this method overcomes the limitations imposed by the moisture content of the raw materials. By employing a batch reactor, the hydrothermal method can withstand the high temperatures required for carbonization while securely containing all of the vapors generated during the reaction, thereby increasing the pressure. The autogenous high pressures enhance the efficiency of organic material digestion and enable longer heating durations without loss of volume through evaporation.[31] The most important rationale for using the hydrothermal method is the high photoluminescence QY of the produced CDs which is considered a crucial parameter that determines the efficiency of the generated CDs. Since the reaction temperature and time have a significant effect on the photoluminescent QY of the resulting CDs, it should be studied carefully and optimized. By carefully surveying the literature, it was found that the temperature range of 120−240 °C, and reaction time of 3−24 h had been used for preparing CDs from most natural sources.[31] Accordingly, different temperatures were investigated ranging from 120 to 240 °C (using constant heating time). The obtained results revealed that 200 °C is the optimal temperature that gives CDs with the highest QY (Figure S1a). Additionally, the effect of different heating time intervals ranging from 3 to 14 h was investigated (using 200 °C as a heating temperature). It was found that 12 h is the optimal heating time that gives CDs with the highest QY (Figure S1b). Moreover, our study investigated the impact of different batches sourced from various places of tangerine seed waste on the FI and hence the QY of biogenic CDs. The results illustrated in Figure S1c indicated that there were no significant differences in the FI and hence the QY (39% ± 2.89%, n = 5) among the five different places. These findings suggest that the FI and QY of CDs derived from tangerine seed waste remain consistent regardless of the collection place, emphasizing the

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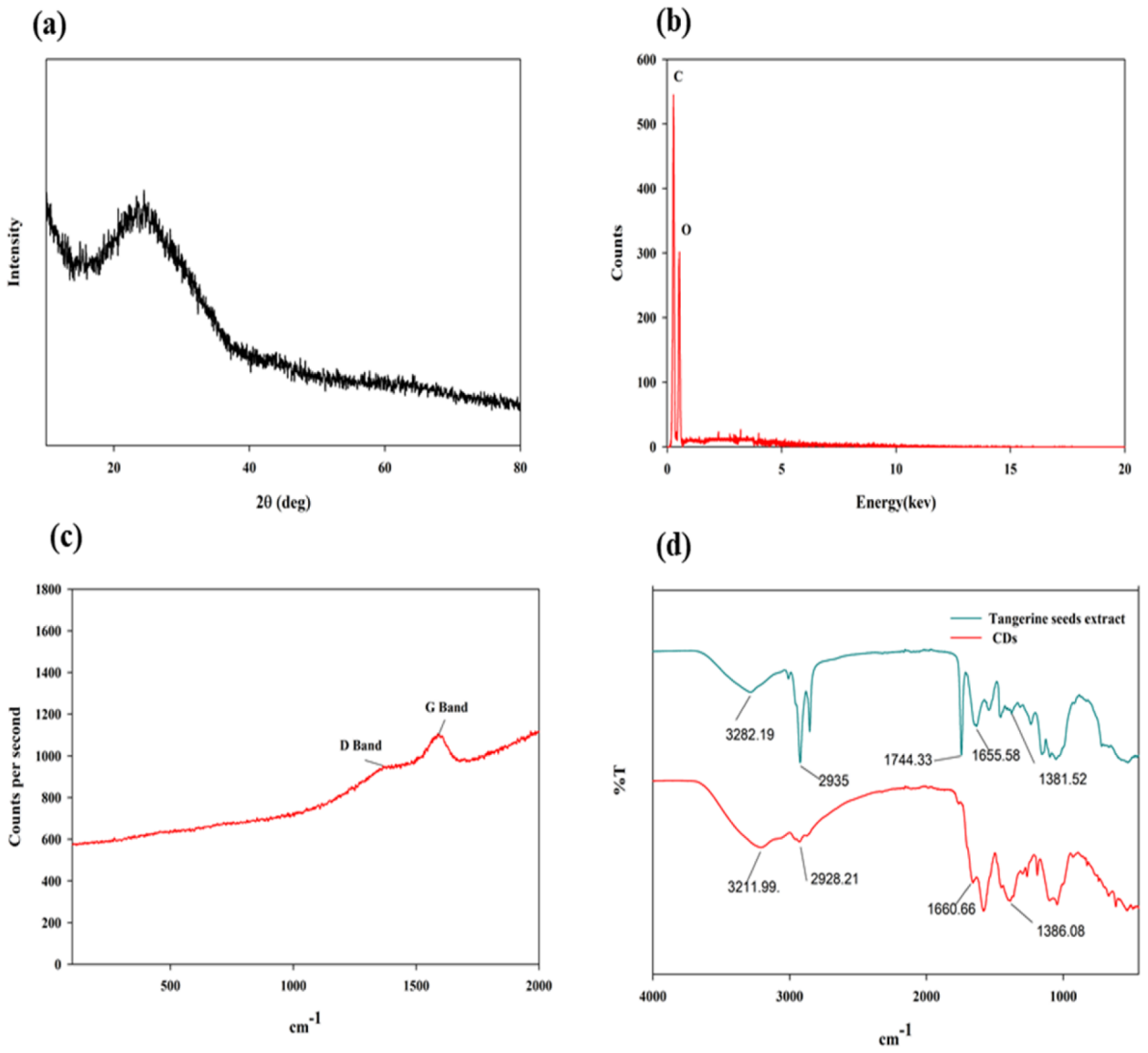

Figure 2. (a) XRD pattern of the prepared CDs, (b) EDX analysis of the prepared CDs, (c) Raman spectrum of the developed CDs, and (d) FTIR spectra of tangerine seeds extract and CDs.

robustness and reliability of the synthesis process for biogenic CDs.

3.2. Characterization and Optical Properties of the Biogenic CDs. As shown in (Figure S2), the synthesized biogenic CDs solution gives a bright blue color under the long UV light (365 nm) and its FI was stable for up to 6 months. HRTEM image (Figure 1a) confirms that the particles of the prepared biogenic CDs are homogeneously distributed with no obvious aggregates, also the particle size distribution histogram was drawn (Figure 1b) and the average particle size was calculated statistically, and it was found to be 1.276 nm with amorphous morphology as confirmed by the selected area electron diffraction (SAED) pattern (Figure 1c). The XRD pattern of the synthesized CDs (Figure 2a) confirmed the results of the SAED pattern as the XRD pattern has a broad hump centered around $\sim 2\theta = 23.4°$. Such a hump has been widely observed in XRD patterns of amorphous carbon.[32] EDX analysis had been performed to study the elemental composition of the developed CDs, as illustrated in Figure 2b, the resulting CDs were found to be mainly made up of C (55.28%) and O (44.72%). The Raman spectrum (Figure 2c) was investigated, and the resulting spectrum exhibited two broad peaks, with peak positions centered at 1370 and 1592 cm^{-1}, which were assigned to the defect band (D band) and graphitic band (G band), respectively. The presence of these peaks in the Raman spectral data confirms the existence of both sp3 (D band) and sp2 (G band) carbon defects within the synthesized CDs.[33] Moreover, the function groups that attached to the surface of the prepared biogenic CDs were characterized by FT-IR and compared with that of the precursor (tangerine seeds extract). The comparison of the two FT-IR spectra (Figure 2d), revealed that the prepared biogenic CDs retained the same function groups of the precursor,[34] most importantly the oxygen rich function groups. These results confirmed that there are plenty of oxygen-rich groups attached to the surfaces of the prepared biogenic CDs. The absorption bands that are detected within the range of 1000−1700 cm^{-1} and 1000−1300 cm^{-1} typically are associated with vibration of C−O stretching and C−O−C bending modes, respectively. Moreover, the absorption bands

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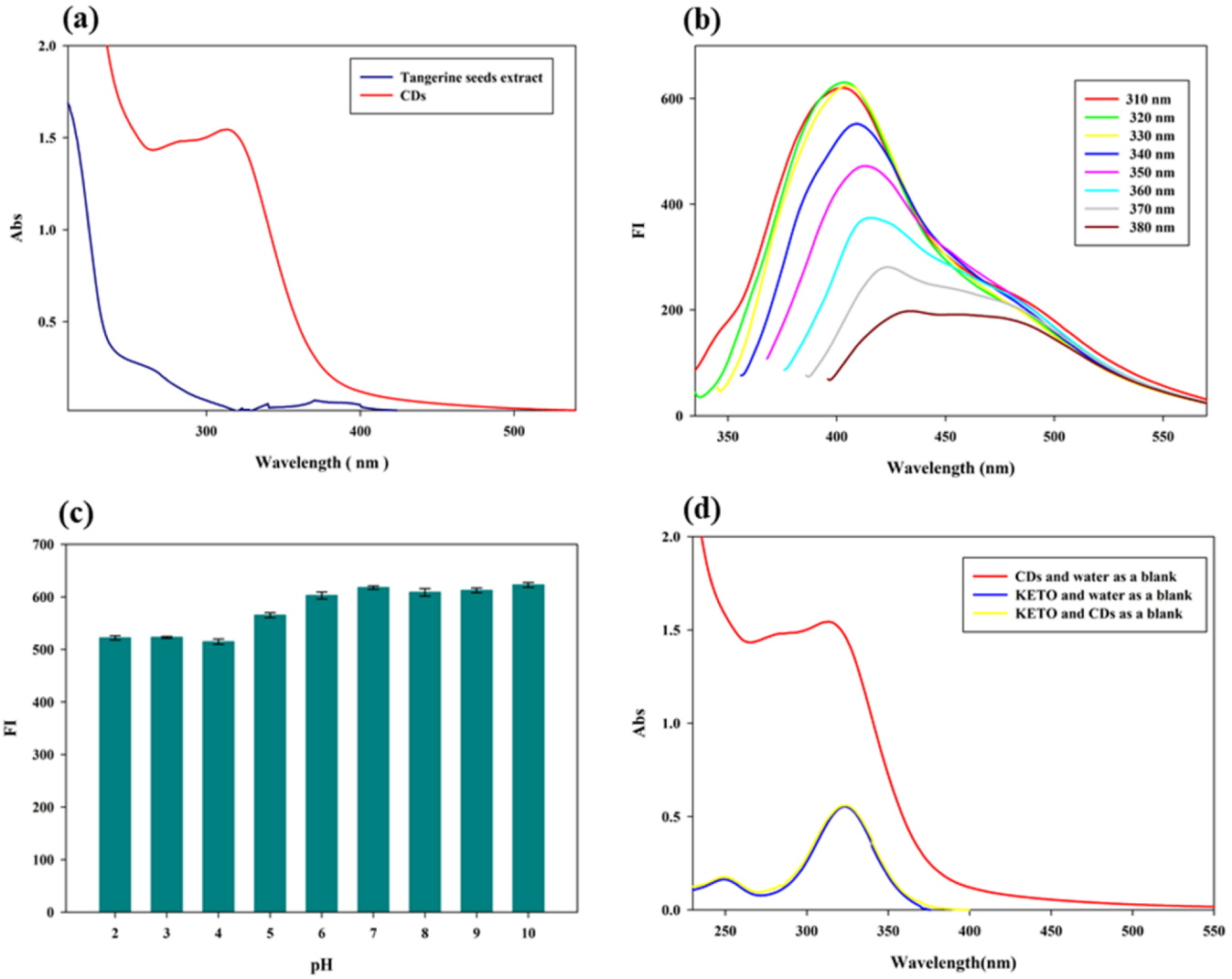

Figure 3. (a) Absorption spectra of tangerine seeds extract and CDs, (b) emission spectra of the developed biogenic CDs at various excitation wavelengths, (c) effect of different pHs on the FI of the prepared CDs, and (d) absorption spectra of the biogenic CDs (water as a blank), KETO (water as a blank), and KETO after mixing with the prepared biogenic CDs (using biogenic CDs solution as a blank).

at 1381.52/1386.08 $cm^{-1}$and 1744.33/1655.58/1660.66 cm^{-1} refer to C−O and C═O stretching, respectively. The peaks at 3282.19/3211.99 cm^{-1} and 2935/2928.21 cm^{-1} contribute to O−H and C−H aliphatic stretching, respectively. The zeta potential and polydispersity index (PDI) of the developed CDs had been investigated, and they had been found to be (−23 mv) (Figure S3) and 0.371, respectively. The high negative value of zeta potential (−23 mv)[35,36] provides stability to the prepared CDs as the repulsion between the negatively charged CDs inhibits their aggregation, in addition to the resulted value of PDI indicates the narrow particle size distribution of the prepared CDs. The FT-IR, EDX, and zeta potential results indicate that the synthesized CDs are rich in oxygen species that may be responsible for the blue shift of the maximum excitation wavelength of biogenic CDs. The absorption spectrum of the prepared biogenic CDs (Figure 3a) displayed a continuous increase in the absorbance starting from 550 nm to 230 nm, and a broad peak at 320 nm has been noticed. Furthermore, we compared the absorption spectrum of tangerine seeds extract with that of the resulting CDs, as shown in Figure 3a, a strong peak was clearly observed at 320 nm in the absorption spectrum of the prepared CDs which may be attributed to the n-π^* transition of the functional groups present on CDs, on the other hand, no observable peak could be found in the absorption spectrum of tangerine seeds extract at 320 nm. The obtained results prove the successful formation of CDs.[34,37] The FI of the prepared biogenic CDs depends on the excitation wavelength across the 310−380 nm range (Figure 3b). The developed biogenic CDs have a maximum FI centered at λ_{em} = 404 nm after their maximum excitation at λ_{ex} = 320 nm. The QY was calculated using five different batches of the developed biogenic CDs, and it was found to be (39% ± 2.89%, n = 5) without the need to use the common doping atoms such as nitrogen and sulfur.

3.3. Photostability Study of the Biogenic CDs. It is well reported in the literature that the photostability of CDs can be strongly affected by numerous parameters such as pH and ionic strength of the media, time of light exposure, and storage time. Accordingly, these important parameters should be carefully studied before applying the developed biogenic CDs as fluorescent-based probe for sensing KETO in different media. First, the effect of pH on the emission of the biogenic CDs was studied over a pH range of 2.0−10.0 using Britton Robinson buffer (BRB) (0.04 M). The FI is significantly

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Table 1. Comparison of the Performance of the Developed CDs with the Published Oxygen-Rich CDs

name	QY (%)	the utilized precursors	method and time consumed	solvent used	reference
CDs	-	chocolate	chocolate was dispersed in 10 M NaOH solution and vigorously stirred then the mixture was reacted at 200 °C for 8 h using the solvothermal method and the product was neutralized using HCl.	water	10
CDs	25.7%	discard chewing gum	the hydrothermal oxidation of discard chewing gum via H_2O_2 (3 wt %) at 180 °C for 8 h.	water	12
CS-CDs	-	coffee bean shells	the coffee bean shells were dispersed in 4% aqueous NaOH for 1.5 h then the filtrate was acidified with 0.5 M HCl.	methanol/water (1:1 v/v)	13
C-dots	9.91%	peanut shells	pyrolysis at 250 °C for 2 h.	water	11
CDs	39% ± 2.89%, (n=5)	tangerine seeds	hydrothermal treatment of tangerine seeds powder at 200 °C for 12 h.	water	this work

reduced over the pH range from 2.0 to 4.0, while the FI begins to increase at pH 5.0 with significant increase in FI at pH 6.0 followed by a negligible change in FI with increase in pH up to 10.0 (Figure 3c). The obtained results revealed that the produced biogenic CDs are pH sensitive. The non-significant variation in the FI of the developed biogenic CDs after pH 6.0 provides insight that they can be applied for monitoring along with biological applications. The pH-sensitive behavior of the synthesized biogenic CDs could be well explained via the well-reported explanation model based on the protonation/deprotonation of the attachable function groups.[38] Consequently, for the developed biogenic CDs, the strong acidic media (< pH 5.0) cause the attachable function groups to be protonated giving rise to the non-covalent molecular interaction that leads to the formation of biogenic CDs aggregates, and finally to the decrease of their FI.[39] The noteworthy enhancement of the biogenic CDs FI over the pH range of 6.0−10.0 is attributable to the deprotonation of the abundant oxygen-rich function groups that leads to boosting the negative charges located on the surface, hindering CDs aggregates, and eventually boosts their FI.[40] The effect of different diluting solvents on the FI of synthesized biogenic CDs had been studied, and the obtained results revealed that using water as a diluting solvent yielded the highest FI as illustrated in Figure S4a. Also, the prepared biogenic CDs FI stays nearly unaltered in concentrated NaCl solution (500.00 mM) (Table S2), after their exposure to xenon lamp radiation for up to 1 h (Figure S4b), and over a long storage period reached to 6 months (Figure S4c). The percentage reduction in fluorescence intensity of the CDs through the long-term storage period (after 6 months of storage at 4 °C) had been calculated, and it was found to be 2.1%. All of these above-mentioned results revealed that the developed biogenic CDs have reasonable stability that makes them suitable for real-life applications.

3.4. Comparison of the Performance of the Developed CDs with the Reported Oxygen Rich CDs. The synthesized CDs had been compared to other CDs in the literature which are rich in oxygen containing function groups. As illustrated in Table 1, the reported CDs have notable limitations, as some studies employed hazardous solvents and reagents during the preparation process.[10,12,13] Additionally, they neglected the calculation of the QY, a crucial parameter for determining the efficiency of the generated CDs.[10,13] Furthermore, the reported methods for preparing oxygen-functional group-rich CDs[11,12] suffer from low QY. In contrast, our developed method yields CDs with the highest QY. These CDs are derived from readily available and abundantly wasted tangerine seeds, making them easily obtainable. The synthesis is achieved through a simple one-step hydrothermal method using only water as a solvent.

3.5. Optimization of the Experimental Conditions. The KETO quenching effect on the biogenic CDs FI was investigated by utilizing (BRB) (0.04 M) at various pH levels extending from 6.0 to 10.0. Surprisingly, no significant variation in the FI quenching efficiency of KETO was observed across the investigated pH range (Figure S5a). Furthermore, the optimal biogenic CDs concentration for quenching the FI of the biogenic CDs was found to be 8.00 μg/mL, after studying a concentration range extending from 4.00 to 14.00 μg/mL (Figure S5b). The effect of incubation time was also assessed, revealing that the entire reaction required only 1 min, as proved by the measured FI taken over a period of 0 to 15 min (Figure S5c). Moreover, the FI was stable over 4 h.

3.6. Elucidation of the Quenching Mechanism. It is well established in the literature that there are numerous mechanisms behind the quenching of CDs FI such as static quenching, dynamic quenching, IFE, and so on. Dynamic quenching mechanism is based on the radiationless relaxation of the fluorophore due to its collision with the quencher while static quenching depends on the pre-excitation complex formation between the fluorophore and quencher molecules.[41] The temperature has great effect on both dynamic and static quenching as the quenching efficiency is enhanced upon raising the temperature for dynamic quenching, on the other hand, it is decreased for static quenching but the IFE mechanism is temperature independent.[41] As shown in Figure 3d, the absorption spectrum of KETO shows λ_{max} at 320 nm, which is completely overlapped with the maximum excitation wavelength of the biogenic CDs (320 nm), so the IFE is expected to be the principal quenching mechanism. To ignore other quenching mechanisms behind the quenching of the prepared biogenic CDs FI via KETO, the quenching efficiency was studied using the Stern−Volmer equation:

$$F^0/F = 1 + K_{SV}[Q]$$

where F^0 and F refer to the FI of the prepared biogenic CDs in the absence and presence of KETO, respectively. [Q] is KETO concentration, and K_{SV} is the Stern−Volmer quenching constant. The interaction of KETO with the synthesized biogenic CDs was investigated via Fluorescence titration at two different temperatures. As shown in Figure S6a, the quenching constant value upon increasing the temperature had not significantly varied (K_{sv} at 298 K = 0.05659× 10^6 L Mol^{-1} and K_{sv} at 313 K = 0.05668× 10^6 L Mol^{-1}, suggesting that the IFE

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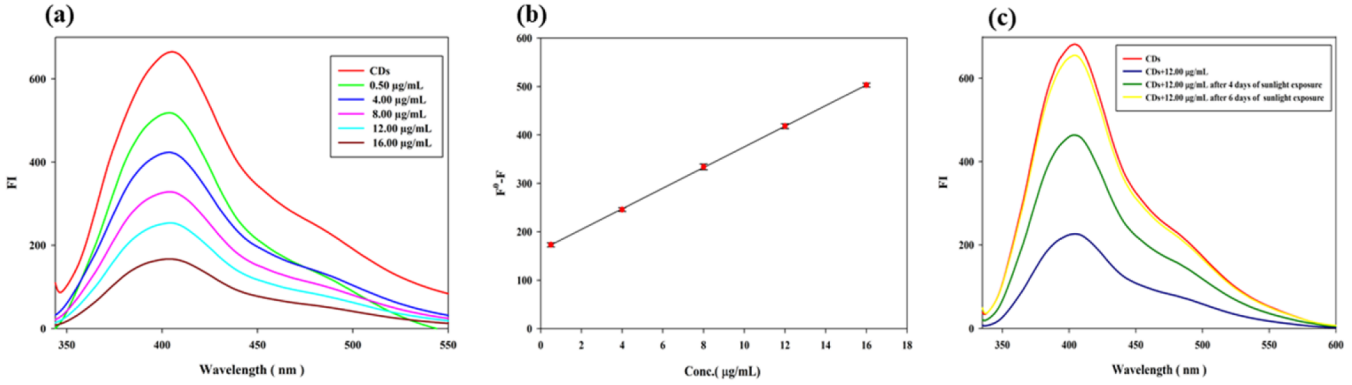

Figure 4. (a) The fluorescence emission spectra of the biogenic CDs in the presence of different concentrations of KETO, (b) calibration curve of KETO, and (c) photodegradation study of KETO.

Table 2. Assay of KETO in Ketolac 10 mg Tablets

concentration taken (μg/mL)	8.00	12.00	16.00
N	3	3	3
mean concentration found (μg/mL)	7.87	11.775	15.76
mean % recovery ± SD	98.37 ± 0.50	98.13 ± 0.43	98.50 ± 0.50

may be the principal mechanism responsible for quenching the FI of the biogenic CDs by the studied drug. The IFE is not considered a quenching process but it is rather occurred because of masking the light of excitation[42] or reabsorption of the emitted light of the fluorescent substance,[43] consequently, the absorption peaks of the biogenic CDs or KETO would not change.[41] As illustrated in Figure 3d, the mixture spectrum utilizing the identical concentration of the biogenic CDs in the mixture as a blank was the same as that of KETO alone, which further confirmed that the IFE is the principal quenching mechanism.

3.7. Determination of KETO. The FI of the developed probe was gradually switched off upon the addition of increasing concentrations of KETO (Figure 4a). The FI quenching (F^0-F) of the prepared biogenic CDs quantitatively increased upon increasing KETO concentrations within the range of 0.50−16.00 μg/mL (Figure 4b) with 0.17 μg/mL as detection limit as illustrated in Table S1. To investigate the reliability of the developed probe for practical work, possible interfering substances such as co-formulated drugs (fluorometholone), other analgesics and anti-inflammatory drugs such as diclofenac sodium and etodolac, co-prescribed drugs such as paracetamol, common excipients in dosage form, and common interfering substances and ions were used to investigate the selectivity of the developed sensor toward the studied drug. The obtained results showed that the studied interfering compounds and ions do not affect the determination of KETO as shown in Table S2 and Figure S6b.

3.8. Method Applications. *3.8.1. Assay of KETO in Its Commercial Tablets.* As this biogenic CDs-based fluorescent platform has reasonable selectivity, sensitivity, and fast response to KETO, it has been employed in its analysis in commercial tablets. The obtained high % recovery, in addition to the minor values of SD, as illustrated in Table 2 confirm the developed method's accuracy and precision. Furthermore, the results obtained from the developed method and the comparison method[21] were statistically compared utilizing the Student's *t* test and variance ratio F-test. As illustrated in Table 3, no statistically significant difference was found between the two compared methods as the assessed *t*- and F-values are lower than the tabulated values, indicating the reliability of the developed fluorescent platform for the analysis of the investigated drug in the commercial tablets.

Table 3. Comparison of the Performance of the Developed Probe and the Reported Method for the Analysis of KETO in Tablet Dosage Form

	developed method		reported method[21]
mean % recovery ± SD	98.13 ± 0.43		98.63 ± 0.57
N	3		3
Student's *t* test (2.776) at *p* = 0.05		1.226	
F-test (19) at *p* = 0.05		1.71	

3.8.2. Application of the Prepared Biogenic CDs for Studying KETO Photostability in Its Commercial Tablets. The photostability of the studied drug was investigated using the constructed biogenic CDs-based probe after KETO exposure to direct sunlight. It was found that after KETO had been exposed for 4 days to photodegradation, it was found that up to 70.83% of KETO had been degraded, and after 6 days of KETO sunlight exposure, it completely lost its ability to quench the resulting biogenic CDs FI due to its complete degradation (Figure 4c). So, the prepared biogenic CDs can be applied for tracking the stability of KETO in its tablet dosage form without any interference from the resulting photodegradation products; moreover, this highly selective fluorescent probe can be applied for testing the complete elimination of KETO in the aquatic ecosystem via photocatalytic elimination techniques, which is a great advantage of the prepared biogenic CDs that confirms its high selectivity and accuracy for the determination of KETO in environmental samples.

3.9. Evaluation of the Environmental Sustainability of the Developed Method. The proposed method was evaluated using three commonly cited metrics: Complex GAPI, AGREE, and AES.[44] Complex GAPI is particularly advantageous for assessing analytical methods, as it considers the

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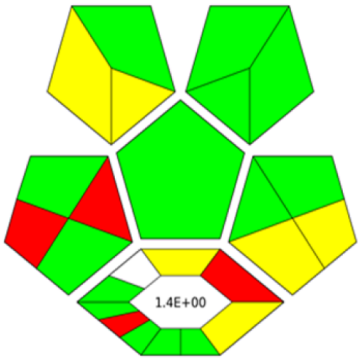
(a)



(b)

Eco-scale parameter		Penalty point
Reagents	Distilled water	0
instruments	Oven	2
	Sonicator	0
	Centrifuge	0
	Spectrofluormetry	0
Occupational hazard	No reagent	0
Waste	< 0.6 g	0
∑ penalty points		2
Total score		98

(c)

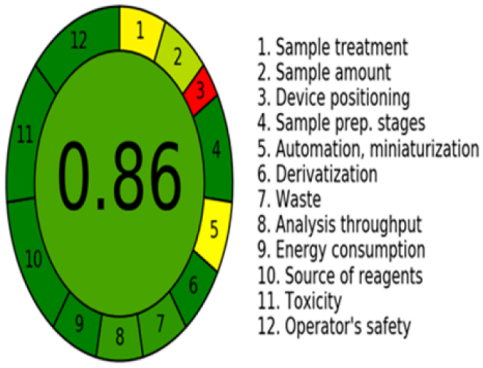


Figure 5. (a) Complex GAPI, (b) eco-scale, and (c) AGREE results for evaluating the greenness of the constructed method.

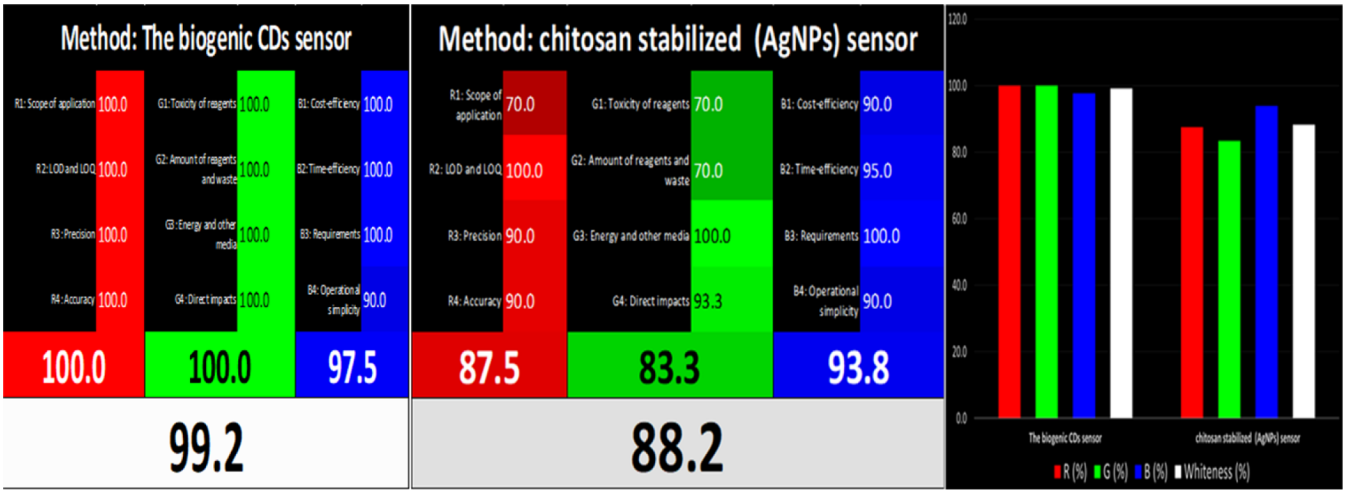


Figure 6. Comparison of the two model methods for sensing KETO in dosage form according to the 12 principles of white analytical chemistry (WAC) performed by utilizing the RGB 12 algorithm.

environmental impact of materials used before the analytical step. The lower hexagon in Complex GAPI symbolizes the "green" nature of preanalysis techniques, encompassing factors such as environmental assessment, reagents and solvents used, equipment, workup procedures, and purification of final products. The upper pentagonal fields represent the green features of the analytical method itself, taking into account various aspects, such as the amount and safety hazards of reagents and solvents, energy consumption, generation of waste, and the nature of the method (qualitative/quantitative). According to each stage of the preanalysis process, the colors green, yellow, and red represent low, medium, and high environmental impacts, respectively.[45] In Figure 5a, it can be observed that only two red zones appeared in the upper pentagonal fields owing to the offline sampling process and the need for transportation to the quality control laboratories. This situation arises owing to the division between the areas where pharmaceutical production takes place and the areas dedicated to quality control. In terms of the greenness of the preanalysis techniques, as assessed by the bottom hexagon, there were only two red zones present. These red zones corresponded to the temperature, time, and energy consumption during the preparation of the resulting bioinspired CDs. In terms of introducing quantitative evaluation of their metrics, AGREE and AES[46,47] outperform Complex GAPI. When a method violates one of the Green Analytical Chemistry (GAC) principles, the AES deducts penalty points from the total score of 100, whereas AGREE offers a numerical value between 0 and 1 for evaluation inside its central pictogram. The overall analysis results illustrated in Figure 5b,c show the AES and AGREE final scores of 98 and 0.86, respectively, indicating the excellent greenness of the developed method.

3.10. Assessing and Contrasting the Sustainability of the Developed Method with the Recently Published Spectrofluorimetric Approach. Nowak et al.[48] introduced "white analytical chemistry" (WAC) as a sustainable analytical methodology that considers multiple dimensions of sustainability. WAC evaluates the whiteness of a method using the RGB color model, integrating principles related to analytical performance, environmental impact, and functional properties. An Excel spreadsheet facilitates the assessment, providing straightforward tables with individual evaluations for each principle and an overall whiteness score. A comparison has been done between the developed biogenic CDs sensor and the recently published spectrofluorimetric method for sensing KETO[19] which is based on sensing KETO in its injection

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dosage form and river water via quenching the FI of chitosan stabilized silver nanoparticles (CT-AgNPs). The results illustrated in Figure 6 show that the biogenic CDs sensor achieved higher scores in analytical performance (100%), green character (100%), and productivity (97.5%), resulting in an overall whiteness score of 99.2%. In contrast, the reported spectrofluorimetric method achieved scores of analytical performance (87.5%), green character (83.3%), and productivity (93.8%) with an overall whiteness score of 88.2%. The lower analytical performance of the recently published spectrofluorimetric method score was attributed to the interference from Cl^- ions during the application of (CT-AgNPs) for sensing KETO in river water besides the lower achieved precision and accuracy upon its application for sensing KETO in injection dosage form. The lower green character score of the recently published spectrofluorimetric method was due to the potential toxicity and non-eco-friendly reagents used in the method. Finally, the reported (CT-AgNPs)-based fluorescent sensor has achieved a productivity score of (93.8%), which is lower than that achieved by our developed biogenic CDs sensor (97.5%) as it was reported by authors that the reported sensor takes 10 min per sample analysis which lowers the number of samples that can be analyzed using this method. This is not the case upon using the biogenic CDs sensor as its FI had been spontaneously quenched, and hence, stable results were attained upon contacting with KETO which increased the productivity of our method in comparison to the reported one (CT-AgNPs). The previous findings showed that the developed biogenic CDs sensor had received unanimous approval from various greenness and whiteness assessment tools, establishing it as an excellent environmentally friendly and efficient fluorescent-based sensor for the determination of KETO in different matrices when compared to the reported (CT-AgNPs) sensor.

4. CONCLUSION

This work introduces the synthesis of sustainable and cost-effective biogenic CDs from largely wasted tangerine seeds with somewhat high QY reached (39% ± 2.89%, n = 5) through a hydrothermal method. The resulting CDs exhibit high selectivity, sensitivity, rapid response, and eco-friendliness. The biogenic fluorescent probe was successfully applied for the determination of KETO in commercial tablets, in the presence of co-formulated drugs, co-administered drugs, different interfering ions and substances, and even KETO photocatalytic degradation products. The developed method demonstrates excellent selectivity, making it suitable for photostability study of KETO in various pharmaceuticals, and investigating its elimination from the aquatic systems. Unlike the recently published metal-based quantum dots probe, this biogenic CDs-based probe surpasses it in terms of its exceptional green and whiteness properties. The study employed various assessment tools, such as AES, AGREE metric approach, Complex GAPI, and RGB 12 algorithm to highlight the eco-friendliness of the probe, emphasizing its sustainable nature and positive environmental impact.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c02757.

The utilized instruments, chemicals, and reagents, the blue fluorescence of the synthesized CDs under the long UV radiation (365 nm), the study of different factors affecting the photoluminescence of CDs, the zeta potential distribution curve of the prepared CDs, factors affecting the quenching efficiency of KETO, the fluorescence spectra of the effect of the studied interfering substances on the FI of CDs, the quenching mechanism behind the quenching of the FI of CDs via KETO, the studied regression parameters, and the effect of different interferents on the FI of the synthesized CDs(PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ge, G.; Li, L.; Wang, D.; Chen, M.; Zeng, Z.; Xiong, W.; Wu, X.; Guo, C. Carbon Dots: Synthesis, Properties and Biomedical Applications. *J. Mater. Chem. B* **2021**, *9* (33), 6553−6575.

(2) Cui, L.; Ren, X.; Sun, M.; Liu, H.; Xia, L. Carbon Dots: Synthesis, Properties and Applications. *Nanomaterials* **2021**, *11* (12), 3419.

(3) Ng, H. S.; Kee, P. E.; Yim, H. S.; Chen, P.-T.; Wei, Y. H.; Lan, J. C.-W. Recent Advances on the Sustainable Approaches for Conversion and Reutilization of Food Wastes to Valuable Bioproducts. *Bioresour. Technol.* **2020**, *302*, 122889.
(4) Esparza, I.; Jiménez-Moreno, N.; Bimbela, F.; Ancín-Azpilicueta, C.; Gandía, L. M. Fruit and Vegetable Waste Management: Conventional and Emerging Approaches. *J. Environ. Manage.* **2020**, *265*, 110510.
(5) Sindhu, R.; Gnansounou, E.; Rebello, S.; Binod, P.; Varjani, S.; Thakur, I. S.; Nair, R. B.; Pandey, A. Conversion of Food and Kitchen Waste to Value-Added Products. *J. Environ. Manage.* **2019**, *241*, 619−630.
(6) Fang, M.; Wang, B.; Qu, X.; Li, S.; Huang, J.; Li, J.; Lu, S.; Zhou, N. State-of-the-Art of Biomass-Derived Carbon Dots: Preparation, Properties, and Applications. *Chin. Chem. Lett.* **2024**, *35*, 108423.
(7) Sharma, K.; Mahato, N.; Cho, M. H.; Lee, Y. R. Converting Citrus Wastes into Value-Added Products: Economic and Environmently Friendly Approaches. *Nutrition* **2017**, *34*, 29−46.
(8) Vollmerhausen, T. L.; Ramos, N. L.; Dzung, D. T. N.; Brauner, A. Decoctions from Citrus Reticulata Blanco Seeds Protect the Uroepithelium against *Escherichia Coli* Invasion. *J. Ethnopharmacol.* **2013**, *150* (2), 770−774.
(9) Hernández-Montoya, V.; Montes-Morán, M. A.; Elizalde-González, M. P. Study of the Thermal Degradation of Citrus Seeds. *Biomass Bioenergy* **2009**, *33* (9), 1295−1299.
(10) Liu, Y.; Zhou, Q.; Li, J.; Lei, M.; Yan, X. Selective and Sensitive Chemosensor for Lead Ions Using Fluorescent Carbon Dots Prepared from Chocolate by One-Step Hydrothermal Method. *Sensors Actuators B Chem.* **2016**, *237*, 597−604.
(11) Xue, M.; Zhan, Z.; Zou, M.; Zhang, L.; Zhao, S. Green Synthesis of Stable and Biocompatible Fluorescent Carbon Dots from Peanut Shells for Multicolor Living Cell Imaging. *New J. Chem.* **2016**, *40* (2), 1698−1703.
(12) Hu, Y.; Gao, Z. Highly Photoluminescent Carbon Dots Derived from Discarded Chewing Gum: Toward Multiple Sensing of PH, Ferric Ion, and Adenosine Triphosphate. *ChemistrySelect* **2019**, *4* (43), 12807−12814.
(13) Zhang, X.; Wang, H.; Ma, C.; Niu, N.; Chen, Z.; Liu, S.; Li, J.; Li, S. Seeking Value from Biomass Materials: Preparation of Coffee Bean Shell-Derived Fluorescent Carbon Dots via Molecular Aggregation for Antioxidation and Bioimaging Applications. *Mater. Chem. Front.* **2018**, *2* (7), 1269−1275.
(14) Nguyen, K. G.; Baragau, I. A.; Gromicova, R.; Nicolaev, A.; Thomson, S. A. J.; Rennie, A.; Power, N. P.; Sajjad, M. T.; Kellici, S. Investigating the Effect of N-Doping on Carbon Quantum Dots Structure, Optical Properties and Metal Ion Screening. *Sci. Rep.* **2022**, *12* (1), 1−12.
(15) Ding, H.; Wei, J. S.; Xiong, H. M. Nitrogen and Sulfur Co-Doped Carbon Dots with Strong Blue Luminescence. *Nanoscale* **2014**, *6* (22), 13817−13823.
(16) Zaaba, N. F.; Ismail, H.; Jaafar, M. Effect of Peanut Shell Powder Content on the Properties of Recycled Polypropylene (RPP)/Peanut Shell Powder (PSP) Composites. *BioResources* **2013**, *8* (4), 5826−5841.
(17) Vadivelu, N.; Gowda, A. M.; Urman, R. D.; Jolly, S.; Kodumudi, V.; Maria, M.; Taylor, R.; Pergolizzi, J. V. Ketorolac Tromethamine - Routes and Clinical Implications. *Pain Pract.* **2015**, *15* (2), 175−193.
(18) Mabrouk, M.; Hammad, S. F.; Abdella, A. A.; Mansour, F. R. Chitosan-Based Molecular Imprinted Polymer for Extraction and Spectrophotometric Determination of Ketorolac in Human Plasma. *Spectrochim. Acta, Part A* **2020**, *241*, 118668.
(19) Mabrouk, M.; Hammad, S. F.; Abdella, A. A.; Mansour, F. R. A Novel Strategy for Ketorolac Detection Based on Turn-on Plasmonic Enhanced FRET Synchronous Fluorometric Sensor Employing Micellized Chitosan/ AgNPs Nanocomposites: Preparation and Mechanism Investigation. *Colloids Surfaces A Physicochem. Eng. Asp.* **2021**, *614*, 126182.
(20) El Yazbi, F. A.; Hassan, E. M.; Khamis, E. F.; Ragab, M. A. A.; Hamdy, M. M. A. Stability Indicating HPLC-DAD Method for Analysis of Ketorolac Binary and Ternary Mixtures in Eye Drops: Quantitative Analysis in Rabbit Aqueous Humor. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2017**, *1068−1069*, 218−225.
(21) El Yazbi, F. A.; Hassan, E. M.; Khamis, E. F.; Ragab, M. A. A.; Hamdy, M. M. A. HPTLC Analysis of Ternary Mixture Containing Ketorolac Tromethamine, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate. *J. Liq. Chromatogr. Relat. Technol.* **2016**, *39* (19−20), 869−876.
(22) Sawkar, R. R.; Patil, V. B.; Shanbhag, M. M.; Shetti, N. P.; Tuwar, S. M.; Aminabhavi, T. M. Detection of Ketorolac Drug Using Pencil Graphite Electrode. *Biomed. Eng. Adv.* **2021**, *2*, 100009.
(23) Chaturvedi, G.; Kaur, A.; Kansal, S. K. CdS-Decorated MIL-53 (Fe) Microrods with Enhanced Visible Light Photocatalytic Performance for the Degradation of Ketorolac Tromethamine and Mechanism Insight. *J. Phys. Chem. C* **2019**, *123* (27), 16857−16867.
(24) Rizk, M.; Toubar, S.; Ramzy, E.; Helmy, M. I. Fluorescent Carbon Dots as Selective Nano Probe for Determination of Diacerein in Presence of Co-Formulated Drugs. *Spectrochim. Acta, Part A* **2022**, *278*, 121388.
(25) Vijeata, A.; Chaudhary, G. R.; Chaudhary, S.; Umar, A.; Akbar, S.; Baskoutas, S. Label Free Dual-Mode Sensing Platform for Trace Level Monitoring of Ciprofloxacin Using Bio-Derived Carbon Dots and Evaluation of Its Antioxidant and Antimicrobial Potential. *Microchim. Acta* **2023**, *190* (7), 258.
(26) Arul, V.; Sampathkumar, N.; Kotteeswaran, S.; Arul, P.; Aljuwayid, A. M.; Habila, M. A.; Govindasamy, M. Biomass Derived Nitrogen Functionalized Carbon Nanodots for Nanomolar Determination of Levofloxacin in Pharmaceutical and Water Samples. *Microchim. Acta* **2023**, *190* (6), 242.
(27) Osman, M. M.; El-Shaheny, R.; Ibrahim, F. A. Green and Fast Microwave-Driven Synthesis of Fluorescent N,S-Carbon Dots for Determination of Two 5-Nitroimidazole Antimicrobials. *Sustainable Chem. Pharm.* **2023**, *36*, 101255.
(28) Shi, X.; Wang, X.; Zhang, S.; Zhang, Z.; Meng, X.; Liu, H.; Qian, Y.; Lin, Y.; Yu, Y.; Lin, W.; Wang, H. Hydrophobic Carbon Dots Derived from Organic Pollutants and Applications in NIR Anticounterfeiting and Bioimaging. *Langmuir* **2023**, *39* (14), 5056−5064.
(29) Liu, H.; Deng, Z.; Zhang, Z.; Lin, W.; Zhang, M.; Wang, H. Graphene Quantum Dots as Metal-Free Nanozymes for Chemodynamic Therapy of Cancer. *Matter* **2024**, *7* (3), 977−990.
(30) Rurack, K. Fluorescence Quantum Yields: Methods of Determination and Standards. In *Standardization and quality assurance in fluorescence measurements I: techniques*; Springer, 2008; pp. 101145.
(31) Bressi, V.; Balu, A. M.; Iannazzo, D.; Espro, C. Recent Advances in the Synthesis of Carbon Dots from Renewable Biomass by High-Efficient Hydrothermal and Microwave Green Approaches. *Curr. Opin. Green Sustainable Chem.* **2023**, *40*, 100742.
(32) Siddique, A. B.; Pramanick, A. K.; Chatterjee, S.; Ray, M. Amorphous Carbon Dots and Their Remarkable Ability to Detect 2,4,6-Trinitrophenol. *Sci. Rep.* **2018**, *8* (1), 1−10.
(33) Zulfajri, M.; Gedda, G.; Chang, C. J.; Chang, Y. P.; Huang, G. G. Cranberry Beans Derived Carbon Dots as a Potential Fluorescence Sensor for Selective Detection of Fe3+ Ions in Aqueous Solution. *ACS Omega* **2019**, *4* (13), 15382−15392.
(34) Li, L. S.; Zhang, Y. X.; Gong, W.; Li, J. Novel β-Cyclodextrin Doped Carbon Dots for Host-Guest Recognition-Assisted Sensing of Isoniazid and Cell Imaging. *RSC Adv.* **2022**, *12* (46), 30104−30112.
(35) Qandeel, N. A.; El-Masry, A. A.; Eid, M.; Moustafa, M. A.; El-Shaheny, R. Fast One-Pot Microwave-Assisted Green Synthesis of Highly Fluorescent Plant-Inspired S, N-Self-Doped Carbon Quantum Dots as a Sensitive Probe for the Antiviral Drug Nitazoxanide and Hemoglobin. *Anal. Chim. Acta* **2023**, *1237*, 340592.
(36) Bhatt, S.; Bhatt, M.; Kumar, A.; Vyas, G.; Gajaria, T.; Paul, P. Green Route for Synthesis of Multifunctional Fluorescent Carbon Dots from Tulsi Leaves and Its Application as Cr(VI) Sensors, Bio-Imaging and Patterning Agents. *Colloids Surfaces B Biointerfaces* **2018**, *167*, 126−133.

https://doi.org/10.1021/acsomega.4c02757
ACS Omega 2024, 9, 27517−27527

(37) Sinha, R.; Bidkar, A. P.; Rajasekhar, R.; Ghosh, S. S.; Mandal, T. K. A Facile Synthesis of Nontoxic Luminescent Carbon Dots for Detection of Chromium and Iron in Real Water Sample and Bio-imaging. *Can. J. Chem. Eng.* **2020**, *98* (1), 194−204.
(38) Liu, C.; Zhang, F.; Hu, J.; Gao, W.; Zhang, M. A Mini Review on PH-Sensitive Photoluminescence in Carbon Nanodots. *Front. Chem.* **2021**, *8*, 605028.
(39) Mondal, T. K.; Mondal, S.; Ghorai, U. K.; Saha, S. K. White Light Emitting Lanthanide Based Carbon Quantum Dots as Toxic Cr (VI) and PH Sensor. *J. Colloid Interface Sci.* **2019**, *553*, 177−185.
(40) Wang, Q.; Yang, H.; Zhang, Q.; Ge, H.; Zhang, S.; Wang, Z.; Ji, X. Strong Acid-Assisted Preparation of Green-Emissive Carbon Dots for Fluorometric Imaging of PH Variation in Living Cells. *Microchim. Acta* **2019**, *186*, 468.
(41) Zu, F.; Yan, F.; Bai, Z.; Xu, J.; Wang, Y.; Huang, Y.; Zhou, X. The Quenching of the Fluorescence of Carbon Dots: A Review on Mechanisms and Applications. *Microchim. Acta* **2017**, *184*, 1899−1914.
(42) Fan, H.; Xiang, G. Q.; Wang, Y.; Zhang, H.; Ning, K.; Duan, J.; He, L.; Jiang, X.; Zhao, W. Manganese-Doped Carbon Quantum Dots-Based Fluorescent Probe for Selective and Sensitive Sensing of 2, 4, 6-Trinitrophenol via an Inner Filtering Effect. *Spectrochim. Acta, Part A* **2018**, *205*, 221−226.
(43) Su, K.; Xiang, G.; Jin, X.; Wang, X.; Jiang, X.; He, L.; Zhao, W.; Sun, Y.; Cui, C. Gram-Scale Synthesis of Nitrogen-Doped Carbon Dots from Locusts for Selective Determination of Sunset Yellow in Food Samples. *Luminescence* **2022**, *37* (1), 118−126.
(44) Hafez, H. M.; El Deeb, S.; Swaif, M. M.; Ibrahim, R. I.; Kamil, R. A.; Abdelwahed, A. S.; Ibrahim, A. E. Micellar Organic-Solvent Free HPLC Design of Experiment for the Determination of Ertapenem and Meropenem; Assessment Using GAPI, AGREE and Analytical Eco-Scale Models. *Microchem. J.* **2023**, *185*, 108262.
(45) Płotka-Wasylka, J.; Wojnowski, W. Complementary Green Analytical Procedure Index (ComplexGAPI) and Software. *Green Chem.* **2021**, *23* (21), 8657−8665.
(46) Pena-Pereira, F.; Wojnowski, W.; Tobiszewski, M. AGREE—Analytical GREEnness Metric Approach and Software. *Anal. Chem.* **2020**, *92* (14), 10076−10082.
(47) Gałuszka, A.; Migaszewski, Z. M.; Konieczka, P.; Namieśnik, J. Analytical Eco-Scale for Assessing the Greenness of Analytical Procedures. *TrAC, Trends Anal. Chem.* **2012**, *37*, 61−72.
(48) Nowak, P. M.; Wietecha-Posłuszny, R.; Pawliszyn, J. White Analytical Chemistry: An Approach to Reconcile the Principles of Green Analytical Chemistry and Functionality. *TrAC, Trends Anal. Chem.* **2021**, *138*, 116223.

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