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Research Article

Resveratrol Functionalized Carboxymethyl-β-Cyclodextrin: Synthesis, Characterization, and Photostability

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The resveratrol functionalized carboxymethyl-β-cyclodextrin conjugate was synthesized by two simple steps. The conjugate was successfully demonstrated by ^{1}H NMR, ^{13}C NMR, UV, and FTIR. The photostability of the conjugate was studied by ultraviolet absorption spectrum. After 360 min of UV light irradiation, the conjugate showed a total loss in absorbance of only 12.54%, while the resveratrol and its CM-β-CD inclusion complex showed a total loss in absorbance of 32.15% and 24.05%, respectively. The results indicate that the conjugate was more stable than resveratrol and its CM-β-CD inclusion complex.

1. Introduction

Resveratrol, 3,4′,5-trihydroxystilbene (Figure 1), is a type of naturally existing phenol and is widely used as food additive [1]. Resveratrol was found in many plants such as grapes, olives, blackberries, pines, and peanuts [2–6]. And the modern pharmacology experiments demonstrated that resveratrol is much beneficial to human health, mainly reducing blood fat and cholesterol [7], inhibiting the platelet activity [8, 9], having protecting effect on atherosclerosis and coronary heart disease [10–12], and preventing the cancer [13, 14]. The recent results indicated that *trans*-resveratrol can become *cis*-resveratrol in the light condition, but the *trans*-resveratrol appears to be more active [15, 16]. However, clinical applications of *trans*-resveratrol are strongly limited due to its poor solubility, instability, and rapid metabolism in the body. Nowadays, researchers pay great attention to studying the stability of resveratrol [17, 18]. For example, a new approach to the stabilization of resveratrol is its O-glycosylation technology. Recently, Marié's group demonstrated the authentically successful O-glycosylation of *trans*-resveratrol to overcome its low water solubility and stability by enzymatic synthesis of resveratrol α-glycosides from β-cyclodextrin-resveratrol complex in water [19]. Torres's group reported the synthesis of a series of α-glucosyl derivatives of resveratrol by a *trans*-glycosylation reaction catalyzed by the enzyme cyclodextrin glucanotransferase (CGTase) using starch as glucosyl donor [20].

Cyclodextrins (CDs) are a class of macrocyclic oligosaccharides, which come from enzymatic reaction. According to the number of the linked glucose units, cyclodextrins can be divided into three classes (α-, β-, and γ-cyclodextrin) [21–23]. CD is an amphipathic molecule with secondary hydroxyl groups on the wide side and primary hydroxyl groups on the other narrow side. Besides these hydrophilic hydroxyl groups are located on the rims of each side, it has a hydrophobic cavity which could accommodate some hydrophobic guest molecules such as aromatic compounds. Because of having the proper cavity and number of hydroxyl groups, β-cyclodextrin (β-CD) is widely used in protecting the unstable small molecules from being damaged under the light irradiation [24, 25].

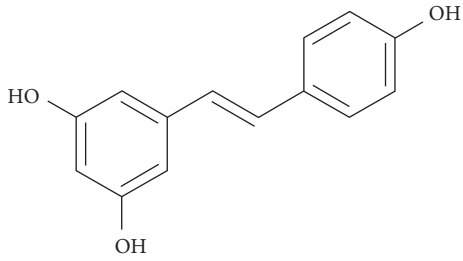
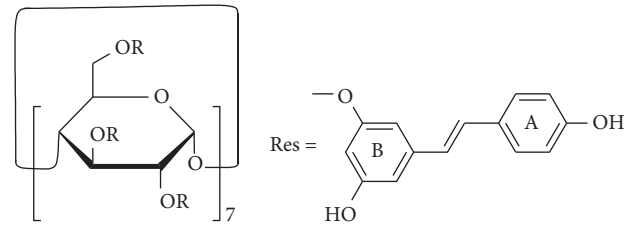


Figure 1: The structure of resveratrol.



R = -H or -CH_2COOH or -CH_2-CO-Res

Figure 2: The schematic structure of the CDRes.

Due to the low solubility of β-CD in aqueous solution [26], considerable efforts have been made on modifying the parent structure to increase its solubility. One of the modified derivatives is carboxymethyl-β-cyclodextrin (CM-β-CD), which has the carboxylmethyl groups on the sides of β-CD. Nowadays, CM-β-CD is widely used in many fields [27–30]. For instance, Furusaki groups successfully synthesized the conjugate of CM-β-CD with chitosan, which demonstrated the better inclusion ability with 6-(*p*-toluidino)-2-naphthalene-6-sulfonate [27]. Here, we reported a two-step synthetic route to prepare the conjugate of cyclodextrin with resveratrol (CDRes), which has better photostability than resveratrol and its CM-β-CD inclusion complex.

2. Experimental

2.1. Materials and Methods. CM-β-CD (DS = 6.8) and resveratrol were obtained from Chengdu Yuannuotiancheng Co., Ltd. (Sichuan, China). Oxalyl chloride was obtained from Macklin Biochemical Technology Co., Ltd. (Shanghai, China). Methanol and acetone were kindly provided by Damao Ltd. (Tianjin, China). They were of analytical grade.

NMR spectra were recorded in DMSO-d_6 (TMS) on a Bruker Avance 400 MHz (Boston, MA) NMR spectrometer.

FTIR spectra were obtained from solid samples such as KBr disks using a Perkin Elmer Spectrum GX, which is a singlebeam, Michelson interferometer-based, Fourier transform infrared spectrometer. The spectra were measured over a range of 4,000–400 cm^{-1} with a resolution of 4 cm^{-1}.

Samples for the photostability study were irradiated at 365 nm in ZF-20D which is the UV chemical reactor. Samples were always placed 10 cm from the lamp and irradiated over a range of time periods to a maximum of 360 min. Solution samples were placed in a 50 mL volumetric flask.

2.2. Resveratrol Solution. Resveratrol (0.0015 g, 6.58×10^{-6} mol) was dissolved in 50% of the methanol solution (10 mL) to give a final concentration of solution (6.58×10^{-4} mol/L).

2.3. CDRes Solution. CDRes (0.0015 g, 1.12×10^{-6} mol) was dissolved in 50% of the methanol solution (10 mL) to give a final concentration of the solution (1.12×10^{-4} mol/L).

2.4. Resveratrol CM-β-CD Inclusion Complex Solution. CM-β-CD (0.02 g, 1.32×10^{-5} mol) was dissolved in 50% of the methanol solution (10 mL) and resveratrol (0.0015 g, 6.58×10^{-6} mol) was added. The solution was stirred for 4 h in the dark to give a final concentration of solution (6.58×10^{-4} mol/L).

2.5. Synthesis Processes of CDRes Conjugate. CM-β-CD (1.000 g, 0.0006 mol) was dissolved in dimethyl formamide (DMF, 15 mL). Oxalyl chloride (0.9 mL, 0.1044 mol) was added dropwise, and the reaction mixture was stirred for 12 h at room temperature. The product in this step was the acid chloride of CM-β-CD. Afterwards, resveratrol (1.368 g, 0.006 mol) and sodium hydroxide (0.048 g, 0.0012 mol) were added in the solution. The reaction was performed for 24 h. Then the solution was diluted with acetone (400 mL), and the product was obtained by filtration. The crude residue was separated by the reversed phase column (methanol/water) to achieve pure product (0.155 g, 14.05%).

Elemental analysis: C, 47.89; H, 5.32; O, 46.48.

FTIR (cm^{-1}): 1734 (C=O), 1161 (phenyl), 849 (*p*-phenyl), 759 (*o*-phenyl).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.79, 9.21, 8.23, 8.13, 7.40, 6.99, 6.94, 6.90, 6.82, 6.78, 6.76, 6.74, 6.38, 6.37, 6.11, 5.93, 5.76, 5.08, 4.83, 4.69, 4.65, 4.49, 4.36, 4.10, 4.09, 4.07, 4.04, 4.00, 3.82–3.17, 3.74, 3.67, 3.65, 3.62, 3.59, 3.45, 3.42, 3.37, 3.36, 3.23, 3.17, 2.89, 2.76, 2.51.

^{13}C NMR (101 MHz, DMSO-d_6) δ 172.14 (s), 163.49 (s), 158.92–104.74 (m), 100.80–99.67 (m), 82.26–82.06 (m), 80.58–80.38 (m), 73.68–73.48 (m), 72.02–70.99 (m), 68.87 (s), 60.28–58.69 (m), 40.41 (*d*, J = 21.0 Hz), 40.00 (*d*, J = 18.6 Hz), 39.78 (*d*, J = 20.7 Hz), 39.68 (s), 39.57 (d, J = 21.0 Hz), 39.26 (s).

Supplementary data for ^{1}H, ^{13}C NMR spectra of CDRes are available here.

3. Results and Discussion

3.1. Synthesis and Characterization. The schematic structure of CDRes is shown in Figure 2. In this study, the resveratrol was substituted into the unmodified CM-β-CD. The synthesis of the novel CD conjugate (CDRes) from the unmodified CM-β-CD was completed by one-pot two-step reaction where the reaction intermediates were not separated out. In the first step, the carboxyls of CM-β-CD reacted with oxalyl chloride to form carboxymethyl chloride-β-cyclodextrin through nucleophilic substitution. In the second step,

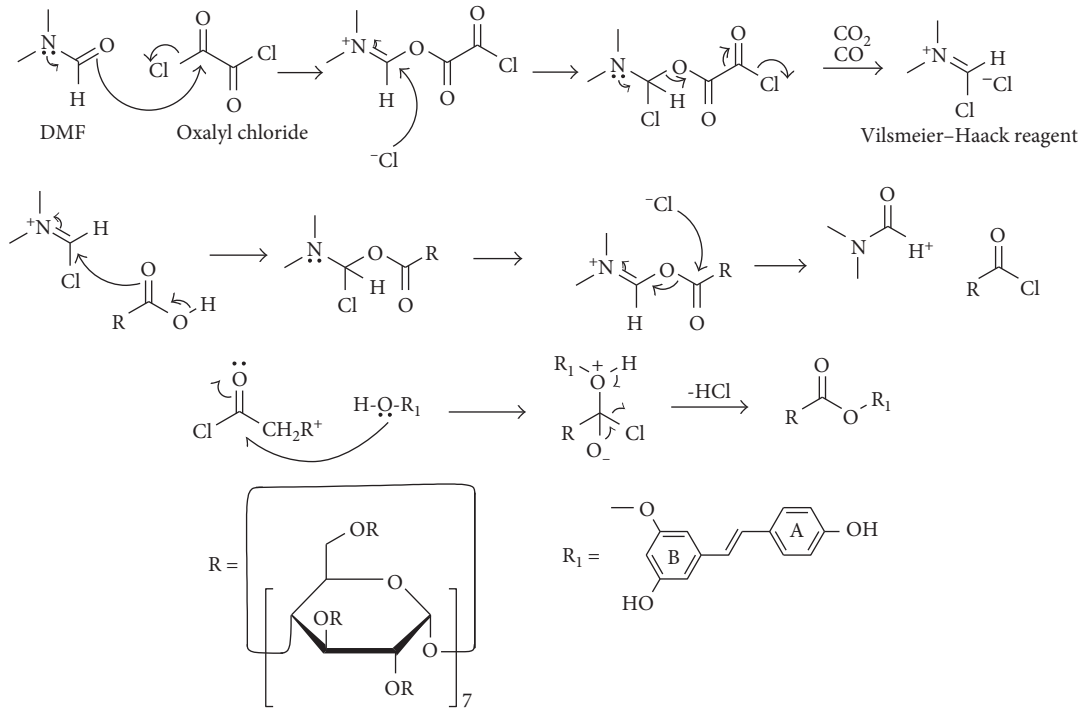


Figure 3: The reaction mechanism of the process.

carboxymethyl chloride-β-cyclodextrin reacted with resveratrol to give CDRes.

3.2. The Synthesis Mechanism of This Reaction. The synthesis of conjugate is a typical esterification process which belongs to the affinity addition-elimination reaction. In this study, it can be inferred that the reaction mechanism of the carboxylic acid ester obeys nucleophilic addition reaction mechanism. Among them, the carboxymethyl chloride-β-cyclodextrin was successfully synthesized by the reaction of CM-β-CD with oxalyl chloride under the catalysis of DMF [31]. In the next step, the acid chloride reacted with resveratrol to form the ester. Therefore, the reaction mechanism of the process is shown in Figure 3.

3.3. FTIR Analysis. FTIR has a very wide range of applications in the field of identifying compound groups. Figure 4 represents the FTIR spectra of CM-β-CD before and after modified by resveratrol. First of all, the raw material CM-β-CD was identified by FTIR which had some characteristic peaks in Figure 4(b). It was observed that there were several bands around 1605 cm^{-1}, 1419 cm^{-1}, and 1030 cm^{-1}, corresponding to stretching deformation of C=O and C-O-C, respectively, while the bands at about 2937 cm^{-1} are attributed to the asymmetric stretching and symmetric vibrations of CH_2 in these samples. The broader and stronger absorption peak at 3419 cm^{-1}, resulting from stretching vibration of the O-H bond, was the characteristic peak of hydroxyl groups. Especially, the newly formed ester bond carbonyl peak was very apparent in the 1734 cm^{-1} region (Figure 4(a)). The band at 1161 cm^{-1} in the FTIR spectrum of the final product could be assigned to =C-O of the –Ar-O- group. And the bands at 849 cm^{-1} and 750 cm^{-1} were assigned to the replacement of benzene. The other bands of conjugate were similar with the CM-β-CD. These results proved the successful conjugation of resveratrol with CM-β-CD together by ester bond.

3.4. NMR Spectroscopy. The NMR spectrum was used for the structure analysis of CM-β-CD and its conjugate. In the ^{1}H NMR spectra of CDRes, there were new peaks at $\delta = 5.76$–8.23 ppm in addition to all the peaks of CM-β-CD. The newly formed peaks at $\delta = 6.11$–8.23 ppm indicated that there were the absorption peaks of aromatic ring. In comparison, the ^{1}H NMR spectra of CM-β-CD did not include the peaks of aromatic ring. In the ^{13}C NMR spectrum of CDRes, the signal at 172.14 ppm was assigned to carbon atom of the carboxyl groups of the CM-β-CD [32]. The signal at 163.49 was assigned to the ester bond [33]. The signals at 104.74–158.92 ppm could be similarly assigned to the aromatic carbon range. These results suggested the successful conjugation of the resveratrol moiety to CM-β-CD via ester bond formation.

3.5. Photostability Study. The photostability of the compound was studied under the UV light-irradiating condition. The UV absorption spectra of resveratrol, inclusion complex of resveratrol with CM-β-CD, and conjugate of resveratrol with CM-β-CD are shown in Figure 5. UV scanning results of resveratrol showed that resveratrol had two absorption peaks assigned to the aromatic ring, which were located in 200 to 400 nm. In the inclusion complex of resveratrol with

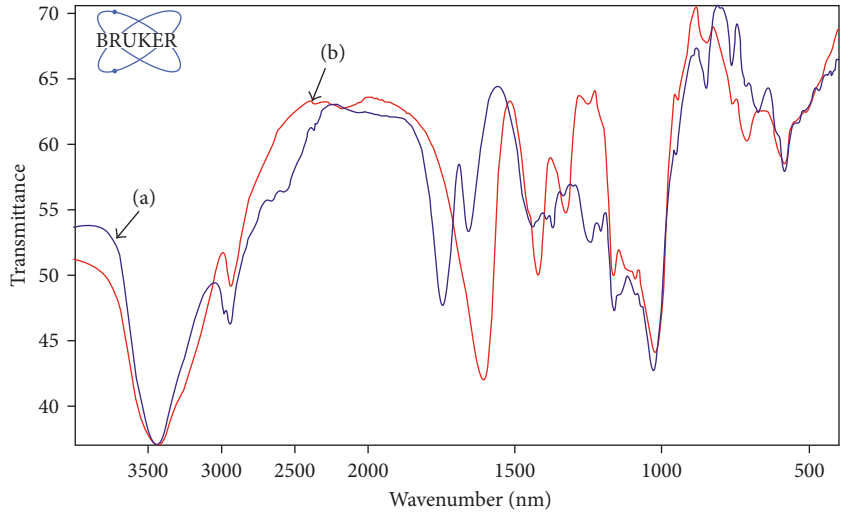


Figure 4: The absorption peaks by FTIR: (a) CDRes and (b) raw material of CM-β-CD.

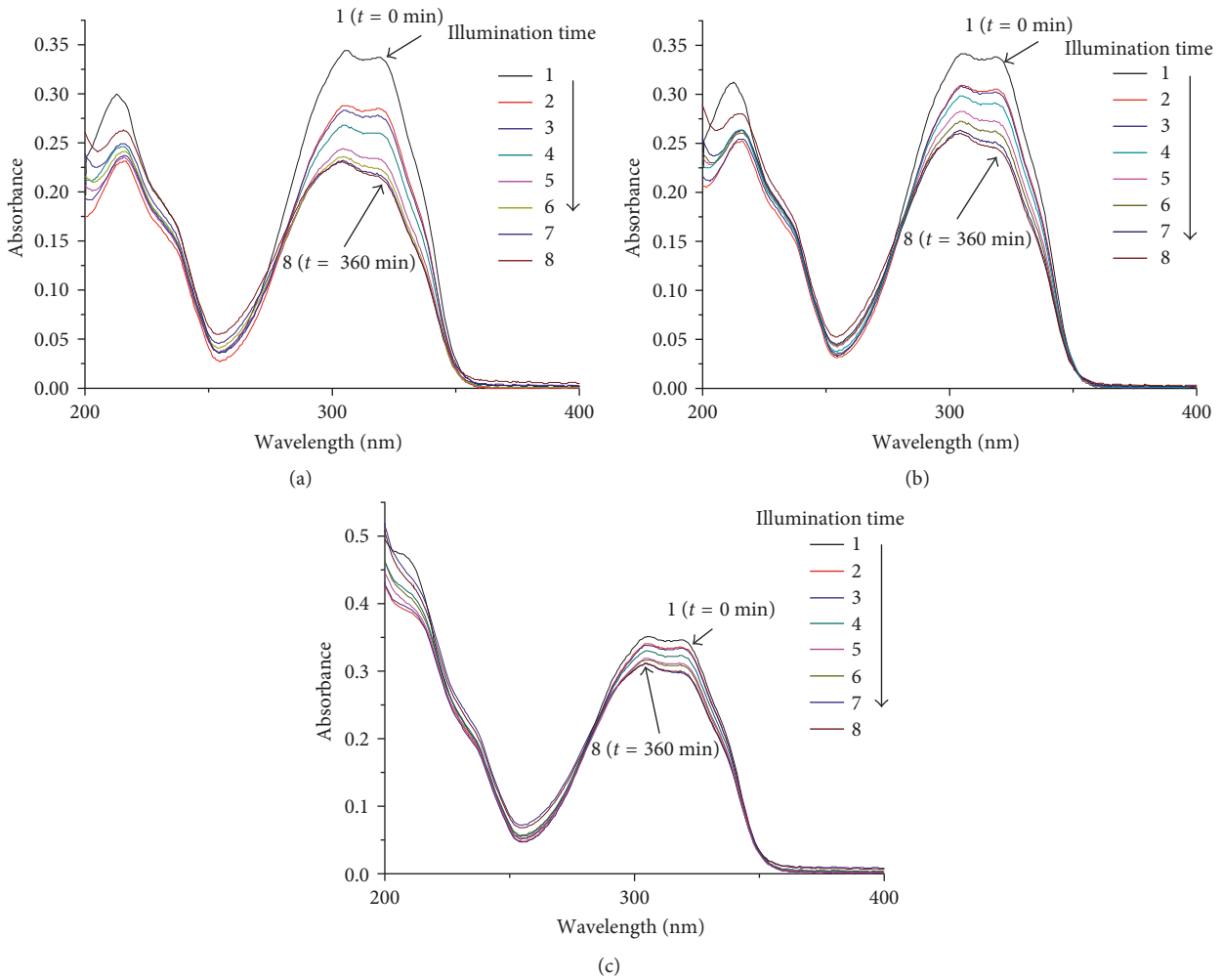


Figure 5: UV absorption spectra of aqueous solutions of three different solutions irradiated over 360 min: (a) the solution of resveratrol (Res), (b) the solution of inclusion complexes (CD + Res), and (c) the solution of conjugate (CDRes).

Table 1: Absorbance at 305 nm of resveratrol (Res), CDRes, and inclusion complex of CM-β-CD with Res after exposure to UV radiation at 365 nm.

Exposure time to λ_{365nm} (min)	A_{305nm} Res	$A_0 - A_t$ Res	A_{305nm} CDRes	$A_0 - A_t$ CDRes	A_{305nm} CD + Res	$A_0 - A_t$ CD + Res
0	0.339	0	0.351	0	0.341	0
30	0.288	0.051	0.34	0.011	0.309	0.032
60	0.283	0.056	0.338	0.013	0.308	0.033
120	0.268	0.071	0.33	0.021	0.298	0.043
180	0.243	0.096	0.319	0.032	0.282	0.059
240	0.236	0.103	0.316	0.035	0.272	0.069
300	0.231	0.108	0.311	0.04	0.262	0.079
360	0.23	0.109	0.307	0.044	0.259	0.082

CM-β-CD, the similar bands were obtained because the complex was formed by the resveratrol with CM-β-CD. However, the maximum absorption peaks of CDRes were 304 nm and 200.5 nm which made a difference from that of the resveratrol (305 nm, 215 nm) and its inclusion complex (304.5 nm, 212.5 nm). The band was seen in the UV absorption spectrum of CDRes due to the presence of the resveratrol moiety in the structure. The reason why there was a shift in the UV absorption was analyzed by their structure. When the resveratrol formed the inclusion complex with CM-β-CD, the complex could form hydrogen bonds to change its UV absorption. In addition, when the conjugate formed, the original structure of resveratrol was changed, and the other groups could affect the UV absorption of resveratrol.

The irradiation of light can affect the stability of resveratrol. It can be clearly seen from Figure 5(a) that when the solution of resveratrol was directly exposed under UV light, the absorbance at 305 nm decreased with the time of exposure increasing (Figure 5(a)). Initially, the absorbance of resveratrol decreased significantly. Although the absorbance at 305 nm also gradually decreased on further irradiation, the change tended to be stable. The previous article focused on the study of the transformation of *trans*-resveratrol into the *cis* under UV irradiation [34]. The reason of this change was that resveratrol was an unstable polyphenol which was easily damaged by UV irradiation [19, 35]. In addition, comparable results were obtained when resveratrol formed inclusion complex with CM-β-CD. The absorbance at 305 nm also decreased with increasing exposure time of UV light (Figure 5(b)). The absorbance of inclusion complex decreased rapidly and finally tended to be stable. But the absorbance change of inclusion compound was less than that of resveratrol. The results suggest that the inclusion complex was more photostable than resveratrol. The reason of this change was that the resveratrol was protected by the CM-β-CD. When CM-β-CD formed inclusion complex with resveratrol, the resveratrol formed stable hydrogen bonds with the CM-β-CD. Thus, the inclusion complex might reduce the degradation rate of resveratrol, and the association constant ($K_a = 4395$) of the complex was calculated by nuclear magnetic titration (a series of samples with the ratio of guest to host ranging from 0 to 4 were prepared ($D_2O : CD_3OD = 1 : 1$)). In addition, the concentration of free resveratrol in the solution was 2.27×10^{-4} mol/L. However, when the solution of CDRes was exposed to UV radiation under the same condition, its absorption spectrum showed the least changes in three solutions (Figure 5(c)). Absorbance at 305 nm decreased initially under the UV exposure and remained relatively unchanged. The reason of the change was that resveratrol formed conjugate with CM-β-CD. Resveratrol, as part of a conjugate, might be included into the CM-β-CD cavity. The conformation of conjugate could result in its more stable structure. Therefore, the conjugate was found to be more stable than resveratrol and its inclusion complex of CM-β-CD.

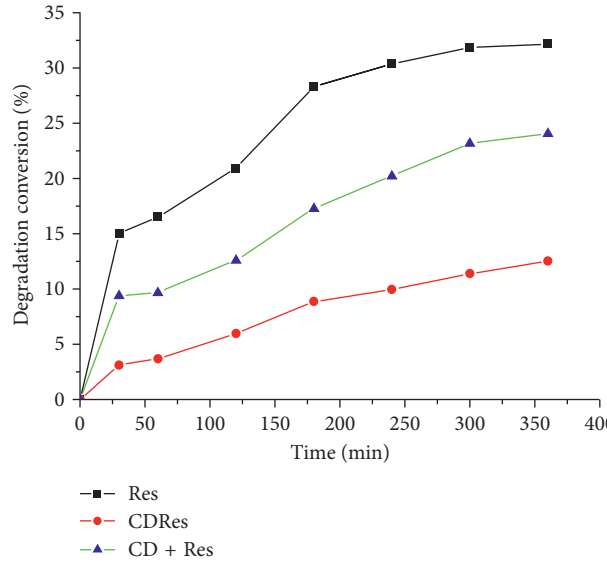


Figure 6: Difference in degradation conversion versus length of time of irradiation of 360 min for 50% of the methanol solution samples.

The results of the absorbance of three solutions at different times are shown in Table 1. A plot of the change in degradation conversion versus the time of exposure is presented in Figure 6. It was important to note that the rate of absorbance change within 30 min was quite noticeable. The absorbance of resveratrol was reduced by 15.04% at the beginning of 30 min. And the inclusion complex, by contrast, showed a loss in absorbance of 9.38% after 30 min. But the conjugate showed the results with a loss in absorbance of only 3.13% after 30 min. The trend of the rate began to gradually flatten after 180 min. And after 360 min of

Table 2: Degradation percentages at 305 nm of resveratrol (Res), CDRes, and inclusion complex of CM-β-CD with Res after exposure to UV radiation at 365 nm.

Exposure time to λ_{365nm} (min)	A_{305nm} Res (%)	A_{305nm} CDRes (%)	A_{305nm} CD + Res (%)
0	0	0	0
30	15.04	3.13	9.38
60	16.52	3.70	9.68
120	20.94	5.98	12.61
180	28.31	9.12	17.30
240	30.38	9.97	20.23
300	31.86	11.39	23.17
360	32.15	12.54	24.05

exposure to UV radiation, the decrease in absorbance of resveratrol continued with a loss of nearly 32.15%, the decrease in absorbance of the inclusion complex with a total loss of 24.05%. However, the conjugate gave the best results with a total loss of only 12.54% after 360 min. According to the experimental data, the percentage of degradation within 360 min was calculated (Table 2).

4. Conclusions

An effective method of the synthesis of cyclodextrin-resveratrol conjugate has been successfully developed. The conjugate is fully characterized by NMR, UV, and FTIR. Since cyclodextrin reacts with resveratrol to form a stable ester bond, the photostability of the conjugate is improved compared to the parent resveratrol and its inclusion complex. These results suggest that CDRes may provide a stable way of resveratrol. Furthermore, it can provide a new idea of the resveratrol formulation as a potential food additive with multifunctionalities.

Data Availability

The (NMR, FTIR, and UV) data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

The authors Jin Gui Cheng and Bing Ren Tian contributed equally to this work.

Acknowledgments

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Supplementary Materials

The supplemental material file briefly describes the ^{1}D ^{1}H, ^{1}D ^{13}C NMR spectra of the conjugates (CDRes). (*Supplementary Materials*)

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