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Chemistry

EFFECT OF TWEEN 80 ON THE STABILITY AND CONFORMATION OF TELOMERIC G-QUADRUPLEX DNA

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Abstract. G-quadruplex DNA is formed in telomer. It inhibits telomerase enzyme which is found active in more than 85 % of cancer cells. In this work, the effect of Tween 80 on telomeric G-quadruplex DNA, $AGGG(TTAGGG)_3$ was studied using circular dichroism spectroscopic technique. The obtained results showed that using Tween 80 with telomeric quadruplex is safe up to less than 1.0 %.

Keywords: telomere; quadruplex; Tween 80; circular dichroism; conformation.

1. Introduction

Telomerase enzyme is found active in more than 85 % of cancers. Telomere, the substrate (template) of telomerase, is located at the ends of DNA.[1] The major part of the telomere (5-15 kilobases) consists of double-stranded DNA while the minor part at 3' end (100-200 bases) consists of single-stranded DNA, both are non-coding DNA.[2] It has been found that the telomeric single stranded part (3'-end) under physiological conditions (*in vitro*) can fold and form a four-stranded structure called G-quadruplex or tetraplex DNA.[2-4] Telomerase enzyme is inhibited indirectly by the formation of G-quadruplex structure. This structure prevents telomerase enzyme from replicating DNA during cell division. If a drug can selectively target and stabilize telomeric quadruplex structure, indirect inhibition of telomerase enzyme will be achieved.[5] Several chemical compounds have been reported as G-quadruplex stabilizers including anthraquinones,[6,7] acridines,[8,9] porphyrins,[10,11] porphyrazines,[12] phthalocyanines,[13] thymoquinone,[4] carbazole, GW2974,[14] and telomestatin.[15,16]

G-quadruplex structure can be formed under physiological conditions at two different places: the ends of human chromosomes (telomeres) and close or in many promoters of human genes. Many sequences are enriched by guanine repeats in the human genome. It is thought that there are *ca.* 300,000-400,000 guanine-rich sequences that can potentially form quadruplex DNA structures.[17-20] Formation of G-quadruplex structures has been confirmed in telomere, thrombin binding aptamer (TBA), immunoglobulin switch regions, gene transcriptional regulatory regions such as the insulin gene, and also the promoter of certain oncogenes, such as c-MYC and BCL2. Formation of G-quadruplex *in vitro* is confirmed by NMR spectroscopy, X-ray crystallography, and CD spectroscopy.[21]

G-quadruplexes under physiological conditions are highly polymorphic and form different conformations *in vitro*.[20] The conformation of G-quadruplex depends mainly on DNA sequence, number of strands forming quadruplex structure (uni-, bi-, and tetramolecular), syn/anti conformation of guanine residues (glycosidic bond angle), strands direction, type and size of linking loops, environmental conditions such as existence, type of associated monovalent ions, the molecular crowding as well as the presence of binding ligands.[22,23] Telomeric quadruplex (TelQ) with the following sequence $AGGG(TTAGGG)_3$ has shown several conformations in Na^+ and K^+ solutions. In Na^+ solution, it forms an anti-parallel structure known as basket-type where two opposing parallel strands across the diagonal are directing anti-parallel to the other two strands with two lateral and one diagonal TTA loops as shown in Fig. 1.[24] In K^+ solution, it forms one of the following structures; anti-parallel basket-type, anti-parallel chair-type, parallel propeller-type and anti-parallel mixed-type (hybrid) with one propeller and two lateral loops (Figure 1) which is the most common one.[25,26] It has been found that the variation of $AGGG(TTAGGG)_3$ structures in K^+ solution depends on its concentration.[27,28]

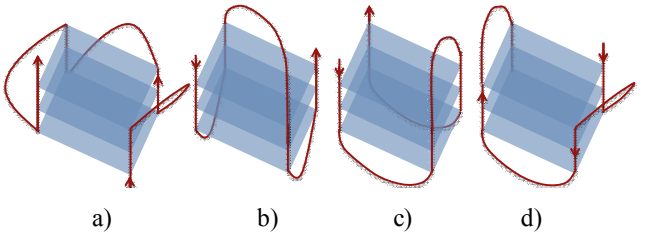

Fig. 1. G-quadruplex intramolecular conformations; parallel propeller type (a), anti-parallel basket-type (b), anti-parallel chair-type (c) and anti-parallel mixed-type (hybrid) (d)

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One of the major problems during the formulation of a new drug is water solubility.[29] A reported study has shown that 40 % of the currently marketed drugs consist of poorly water-soluble molecules.[30] This information was used to forecast future development at that time. The study showed that 90 % of the drugs that will be prepared may be poorly soluble in water therefore the biopharmaceutical properties of these drugs will be negatively affected. Although, some researchers have succeeded to synthesize drugs with high selectivity and affinity towards telomeric quadruplex, some of these drugs are poorly soluble in water.[31,32] To increase the solubility of these compounds *in vitro*, the buffer solutions were mixed with proportions of organic solvents (cosolvent) or the drugs were dissolved in a pure organic solvent or mixed with water or a buffer solution.[29,33] Some of the reported organic solvents include ethanol[34,35] and DMSO.[36] Moreover, some surfactants are used to increase the solubility of the drugs and prevent their aggregation such as Tween 20-80.[35,37]

Surfactants are chemical compounds that lower the surface tension between a substance (gas, liquid, or solid) and a liquid solvent.[38] Surfactant's molecule is amphiphilic which means it consists of hydrophilic moiety (head) and hydrophobic moiety (tail) and is classified based on the head into cationic, anionic, zwitterionic, and non-ionic. In general, the main acts of these surfactants are cleaning, wetting, emulsifying, foaming, anti-foaming, and dispersing.[39,40] One of these surfactants is Tween 80 which is chemically known as Polyoxyethylene (20) Sorbitan monooleate (Fig. 2). Tween 80 is a water-soluble non-ionic surfactant. It is widely used in the pharmaceutical and biotechnology industries because of its characteristics such as high effectiveness at low concentrations, relatively low toxicity, and weak or no interaction with the active ingredients.[41,42] Tween 80 is used to enhance the solubility of the insoluble or partially soluble substances in aqueous solutions.[4] In aqueous media, Tween 80 molecules aggregate and form micelles with a nonpolar inner core which allows for the nonpolar substances to engulf inside the core.[41,44]

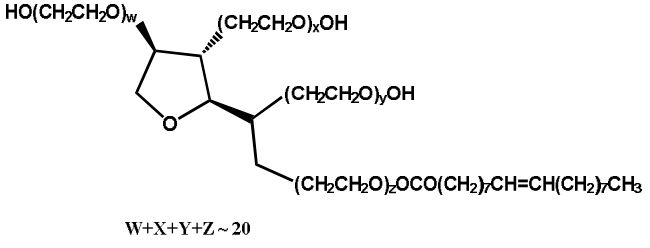

Fig. 2. Chemical structure of Tween 80

In this work, since some surfactants are used in the study of the interaction between the drugs and G-quadruplex DNA therefore the effect of Tween 80 on the conformation and stability of telomeric G-quadruplex DNA 5'-AGGG(TTAGGG)$_3$-3' (TelQ) was studied using circular dichroism spectroscopic technique. The melting temperature of the telomeric quadruplex with and without Tween 80 was studied as well.

2. Experimental

2.1. Materials and Reagents

All chemicals and reagents were used without further purification. Ethylenediaminetetraacetic acid (EDTA), potassium chloride, and tris(hydroxymethyl) aminomethane hydrochloride (Tris-KCl) were purchased from Sigma-Aldrich, USA. HPLC purified telomeric DNA sequences 5'-AGGGTTAGGGTTAGGGTTAGGG-3' was purchased from AlphaDNA, Canada. All experiments were conducted using Millipore deionized water.

2.2. Instrumentation

Absorption measurements were made on Agilent 8453 UV-Vis spectrophotometer, Austria matched with 1 cm quartz cells. Circular dichroism measurements were carried out using Jasco J-815 spectrometer (Jasco, USA) matched with a 1.00 cm path length quartz cell. pH measurements were conducted using Orion-401-Plus pH meter supported with Orion glass electrode.

2.3. Preparation of Standard Solutions

2.3.1. Buffer Solution

A Tris–KCl buffer solution, (pH 7.4, 0.01 M, 1.00 L) was prepared using tris–hydroxymethylaminomethane hydrochloride (10.00 mM, 1.576 g), EDTA (1.00 mM, 0.3077 g), and KCl (100. mM, 7.455 g) in deionized water. pH of the prepared buffer solution was adjusted using the glass electrode.

2.3.2. G-Quadruplex DNA (TelQ)

G-quadruplex structure was prepared by gentle heating of a 2000 μL of the stock single-stranded 5'-AGGGTTAGGGTTAGGGTTAGGG-3' primer up to 95.0°C and incubated for 10.00 minutes. Resultant solution was left to gently cool to room temperature then kept in fridge at 4.0°C overnight.

The concentrations of DNA stock solutions were determined in Tris-KCl buffer solution (pH 7.4) using absorbance spectroscopy at 260 and 280 nm. Concentrations in μg/ml were calculated using the following equation:

$$C_{(\mu g/mL)} = A_{260} \times \text{weight per OD} \times \text{dilution factor}$$

where OD is the optical density at 260 nm. The estimated purity of the purchased oligonucleotide was calculated based on the ratio A_{260}/A_{280}. Ratios ≥1.8 indicate high purity for the synthetic and calf thymus DNAs.[45] Since single-stranded DNA is folded to form G-quadruplex structure so G-quadruplex's concentration will be similar to that of its single-stranded DNA.

2.4. Effect of Tween 80 on TelQ DNA

The effect of Tween 80 on the structure and conformation of TelQ was studied using CD spectroscopy. A 1000 µL solution of TelQ DNA (4.0×10^{-6} M) was prepared from the stock solution (1.18×10^{-4} M) using Tris-KCl buffer, pH 7.4. The solution was scanned in a 1500 µL cuvette (1 cm path length) at room temperature over the wavelength range of 200-400 nm with 50 nm/min, bandwidth 1 nm, and 3 accumulations. The experiment was repeated with 0.05 %, 0.1 %, and 1.0 % of Tween 80 separately. The solution was incubated before scanning. The incubation time was increased up to one hour without a change in the obtained spectrum of the solution so 3 min incubation time was used in all measurements. CD of the blank and cuvette was scanned first then auto subtracted from samples' CD.

2.5. Effect of Temperature

The effect of temperature on G-quadruplex and its mixtures with Tween 80 was studied using CD spectrophotometer equipped with Julabo open heating bath circulator. TelQ solution (1.00 mL, 4.0×10^{-6} M) in Tris-KCl-buffer, pH 7.4 was heated up in 5.0°C increments over the range 25-95°C then incubated for 5 minutes at these temperature intervals. CD spectra were recorded in the range 200-400 nm with 50 nm/min, bandwidth 1 nm, and 3 accumulations. The experiment was repeated with 0.05 %, 0.1 %, and 1.0 % of Tween 80. All CD spectra were auto baseline corrected against blank solution.

2.6. Melting Temperature Curves

The effect of Tween 80 on the melting temperature curve for G-quadruplex was studied using CD spectroscopic technique. TelQ solution (1.00 mL, 4.0×10^{-6} M) in Tris-KCl-buffer, pH 7.4 was heated up over the range 25-95°C and was allowed to incubate for 5 minutes at each temperature value. CD spectra were recorded in the range 200-400 nm with 50 nm/min, bandwidth 1 nm, and 3 accumulations. The experiment was repeated with 0.05 %, 0.1 %, and 1.0 % of Tween 80. All CD spectra were auto baseline-corrected against blank solution. Intensities of CD peaks at 293 nm for G-quadruplex and its Tween 80 solutions were recorded.

3. Results and Discussion

3.1. TelQ DNA Conformation

CD spectroscopy is an effective technique used to study the conformation of G-quadruplex and the effect of the environment such as the type and pH of the buffer solution, solvent, and temperature on such conformation. Moreover, DNA sequence plays an important role in the conformation of G-quadruplex. CD spectroscopy is also used to study the interaction between DNA and drugs. In this work, CD spectroscopy was used to study the effect of Tween 80 on the stability and the conformation of telomeric G-quadruplex $AGGG(TTAGGG)_3$ in Tris-KCl buffer, pH 7.4.

Several studies have been conducted on the conformation of the telomeric G-quadruplex sequence $AGGG(TTAGGG)_3$. In Na^+ solution, G-quadruplex $AGGG(TTAGGG)_3$ forms antiparallel structure whereas in K^+ solution, it forms a mixture of parallel and antiparallel conformations known as hybrid conformations.[24,26] Fig. 3 shows CD spectrum of TelQ in Tris-KCl, pH 7.4. It shows a maximum positive band at 293 nm, a shoulder at 253 nm and a negative band at 235 nm. These bands indicated that the quadruplex structure was formed with a mixture of parallel and antiparallel structures (hybrid conformation). These results are in agreement with the previously reported conformation of TelQ in K^+ solution.[46]

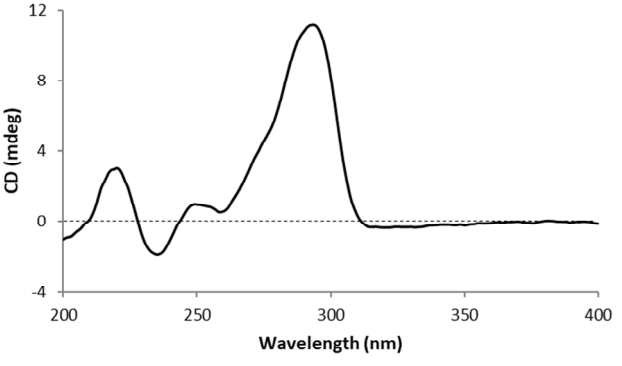

Fig. 3. CD spectrum of telomeric quadruplex (4×10^{-6} M) in Tris-KCl buffer, pH 7.4

Addition of 0.05 % Tween 80 to TelQ solution has shown no change of the peaks' position of TelQ with a very slight increase at 293 nm as shown in Fig. 4. These results indicated that 0.05 % Tween 80 did not affect the conformation of TelQ DNA. TelQ solution with 0.1 % Tween 80 has shown a CD spectrum very close to that obtained with 0.05 % Tween 80 (Fig. 4) indicating that 0.1 % Tween 80 did not affect the conformation of TelQ DNA as well. In contrast, addition of Tween 80 1.0 %

induced an increase in the absorbance of TelQ and the disappearance of the shoulder at 253 and the negative band at 235 nm, and the appearance of a new negative band at 250 nm as shown in Fig. 4. Therefore, Tween 80, 1.0 % induced a conformational change from one hybrid to another one or to antiparallel quadruplex structure. Lannan *et al.*[47] found that the addition of 40 % of polyethylene glycol (PEG 200) to TelQ DNA d[$TAG_3(TTAG_3)_3$] in potassium phosphate buffer, pH 7 changed the conformation of DNA from hybrid to parallel.[47] It was concluded that the viscosity of the solution affected the folding of quadruplex DNA and consequently its conformation. As the viscosity increases (water activity decreases) TelQ DNA favors the parallel structure. Heddi and Phan[48] found that the conformation of telomeric quadruplex (5'-d($GGG(TTAGGG)_3$)) changed from hybrid to propeller in high concentrations of polyethylene glycol. They suggested that the change from hybrid to propeller conformation was due to the molecular crowding because DNA in the crowded solution will be converted to a more compact structure, however, propeller is less compact than hybrid structure. Therefore, the change in the conformation of telomeric quadruplex at 1.0 % Tween 80 may be attributed to the solution viscosity or/and the crowding in the solution.

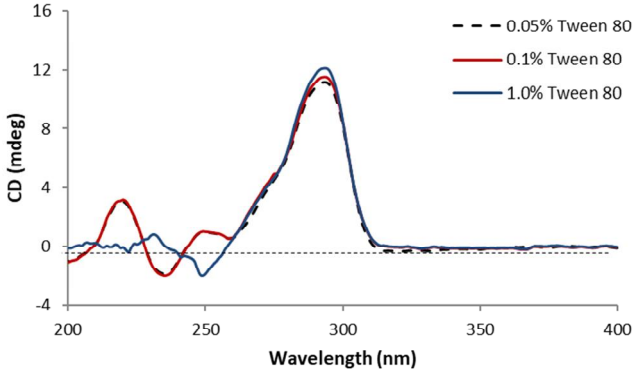

Fig. 4. CD spectrum of telomeric quadruplex ($4x10^{-6}$ M) in Tris-KCl buffer, pH 7.4 with 0.05 % Tween 80 (black-dash), 0.1 % Tween 80 (red-solid), and 1.0 % Tween 80 (blue-solid)

3.2. Effect of Temperature

The effect of temperature on TelQ with 0.0 %, 0.05 %, 0.1 %, and 1.0 % Tween 80 was studied using CD spectroscopy. The temperature was increased from 25 to 95°C and the resulted CD was recorded as shown in Fig. 5. When the temperature increases, CD intensity decreases. In case of TelQ - 0.0 %, 0.05 %, and 0.1 % Tween 80 (0.05 % and 0.1 % are not shown), CD intensity decreases with the increase of temperature without a change in the peaks' positions. CD spectra of TelQ - 0.05 % and 0.1 % Tween 80 are very close to that of TelQ. These findings may confirm the obtained results (section 3.1) that 0.05 % and 0.1 % of Tween 80 did not affect the conformation of TelQ DNA. When Tween 80 was increased to 1.0 %, an evident shift in CD spectra of TelQ into a higher wavelength at a temperature more than 80°C was observed as shown in Fig. 5 (down).

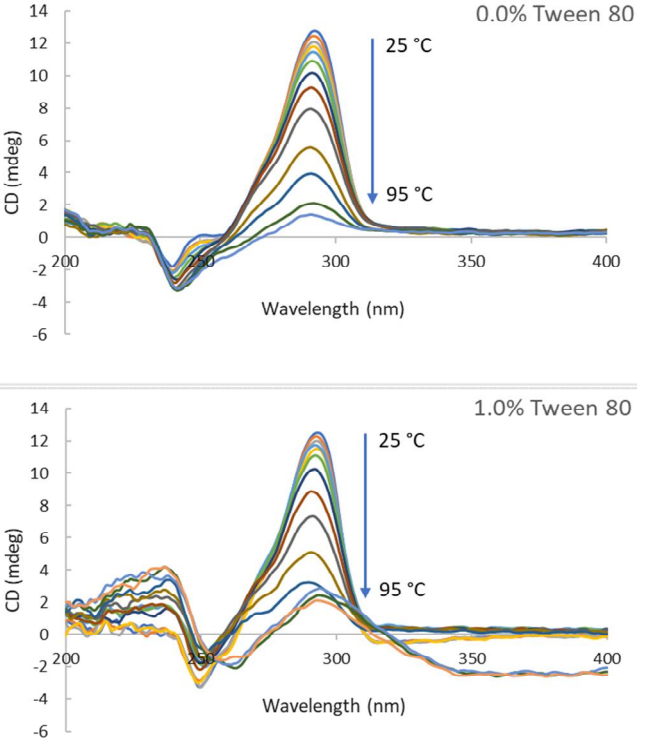

Fig. 5. Effect of temperature (25-95°C) on CD spectrum of TelQ (4×10^{-6}M) in Tris-KCl buffer, pH 7.4 without (above) and with 1.0 % Tween 80 (below)

3.3. Melting Temperature

In this work, effect of Tween 80 on the melting temperature of telomeric quadruplex DNA was studied using CD spectrophotometry and that indicates the stability of DNA quadruplex as well. Melting temperature (T_m), is the temperature at which 50 % of duplex, triplex, or quadruplex DNA is converted to a single-stranded DNA.[49] Melting temperature indicates the stability of DNA conformation, as well as the stability of DNA-ligand complex compared with its DNA molecule.[49] It is also used to indicate the selectivity of a ligand towards quadruplex over double-stranded DNA through the comparison between ΔT_m of TelQ-drug and that of duplex DNA-drug complexes. In this experiment, T_m of TelQ DNA, TelQ-0.05 % Tween 80, TelQ-0.1 % Tween 80, TelQ-1.0 % Tween 80 was determined separately. In the melting curve, CD intensity at 293 nm is plotted against the corresponding temperature.

The resulted melting curve of TelQ DNA (Fig. 6) showed a melting temperature of 68.5°C which is consistent with the reported melting temperature of the telomeric quadruplex DNA in KCl-buffer, pH 7.4. During the melting temperature experiment, as the temperatures increases the quadruplex structure denatures gradually into the single-stranded structure. As a result, CD intensity decreases without a change in the peaks' positions. Addition of 0.05 % of Tween 80 slightly changed the melting temperature of TelQ into 70.5°C with ΔT_m = 2°C as shown in Table. When Tween 80 was increased to 0.1 %, the melting temperature of TelQ increased to 73.5°C and the difference with that of TelQ increased to 5.0°C. Increasing Tween 80 to 1.0 % has increased the melting temperature of TelQ to 76°C and ΔT_m increased to 7.5°C as shown in Table. The obtained results showed that as the amount of Tween 80 increases the melting temperature increases which may indicate that the conformation may be changed, and the stability of this conformation increased. Lannan *et al.*[47] found that the presence of 40 % of polyethylene glycol (PEG 200) with TelQ DNA in potassium phosphate buffer, pH 7 increased the melting temperature of TelQ from 63 to 91°C.

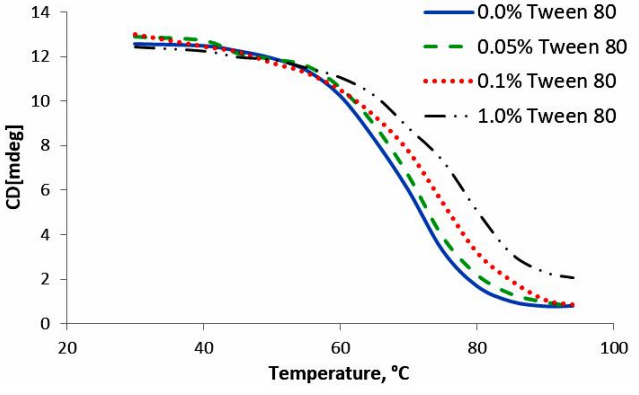

Fig. 6. Melting curves of TelQ ($4x10^{-6}$ M) in Tris-KCl buffer, pH 7.4 with 0.0 % Tween 80 (blue-solid), 0.05 % Tween 80 (green-dash), 0.1 % Tween 80 (red-dash), and 1.0 % Tween 80 (black-dash)

Table. Melting temperature (T_m) and melting temperature change (ΔT_m) of TelQ ($4x10^{-6}$ M) in Tris-KCl buffer, pH 7.4 with 0.0 %, 0.05 %, 0.1 %, and 1.0 % Tween 80

TelQ - Tween 80	Melting temperature, T_m (°C)	ΔT_m (°C)
0.0 %	68.5	0
0.05 %	70.5	2.0
0.1 %	73.5	5.0
1.0 %	76.0	7.5

Since the obtained results showed that the conformation and the melting temperature of telomeric quadruplex DNA were slightly changed it can be indicated that using Tween 80 with telomeric quadruplex is safe up to less than 1.0 %.

4. Conclusions

Many of the currently marketed drugs consist of poorly water-soluble molecules. Buffer solutions are mixed with organic solvents or organic cosolvents to increase the solubility of these compounds *in vitro* such as ethanol and DMSO. Tween 20 - 80 are used as well to increase the solubility of the drugs and prevent their aggregation. In this work, the effect of Tween 80 (0.05, 0.1, and 1.0 %) on telomeric quadruplex DNA $AG_3(TTAGGG)_3$ in Tris-KCl buffer, pH 7.4 was studied using CD spectroscopic technique. Addition of 0.05 and 0.1 % Tween 80 to TelQ has shown no or weak effects on the conformation and melting temperature of the telomeric quadruplex. In contrast, addition of 1.0 % has shown a change in the conformation of TelQ from hybrid to another hybrid or antiparallel structure. In addition, the melting temperature of TelQ has increased from 68.5 to 76.0°C with the addition of 1.0 % Tween 80. These findings indicated that using Tween 80 with telomeric quadruplex is safe up to less than 1.0 %.

Declarations of interest

The author declares no competing interests.

Acknowledgement

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ВПЛИВ ТВІН 80 НА СТАБІЛЬНІСТЬ І КОНФОРМАЦІЮ ТЕЛОМЕРНОЇ G-КВАДРУПЛЕКСНОЇ ДНК

Анотація. *G-квадруплексна ДНК утворюється в теломері. Вона пригнічує фермент теломеразу, активний у більш ніж 85 % ракових клітин. У цій роботі було вивчено вплив Твін 80 на теломерну G-квадруплексну ДНК AGGG(TTAGGG)$_3$ за допомогою спектроскопічної методики циркулярного дихроїзму. Отримані результати показали, що використання Твін 80 з теломерним квадруплексом є безпечним за концентрації до 1,0 %.*

Ключові слова: *теломер; квадруплекс; Твін 80; циркулярний дихроїзм; конформація.*