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Determination of Antioxidant Capacity of 2,6-Quinolinediol

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ABSTRACT: The compounds of the quinolone group have been widely used in the alive metabolism, paint and pharmaceutical industry. Therefore, various quinoline derivatives are synthesized and synthesis methods are developed. The synthesis of the quinoline compounds in the industrial field is formed in a separate area. 2,6-quinolinediol is derivative a quinoline. In this study, different bioanalytical methods such as reducing capacity by Fe^{3+}-Fe^{2+} transformation method, Fe^{3+}-TPTZ reducing capacity by FRAP method, Cu^{2+}-Cu^{+} reducing capacity by CUPRAC method, the ferric ions (Fe^{2+}) chelating activity by using bipyridyl reagent, DPPH, ABTS, DMPD radical scavenging activities, superoxide anion radicals ($O_2^{\cdot-}$) scavenging activity have been used. Also, Trolox, α-Tocopherol, BHA and BHT have been used as reference antioxidants. The IC_{50} inhibition value of the ABTS radical removal activity for this substance was calculated as 3.39 µg mL^{-1}. Reference antioxidants such as trolox, BHA, α-Tocopherol and BHT exhibited ABTS radical removal inhibitions at 2.59, 4.44, 7.07 and 32.36 µg mL^{-1}, respectively. Studies have shown that 2,6-quinolinediol is an effective antioxidant.

Keywords: 2,6-quinolinediol, Antioxidant activity, Radical scavenging

2,6- Kinolindiol Bileşiğinin Antioksidan Kapasitesinin Belirlenmesi

ÖZET: Kinolin grubu bileşikleri, canlı metabolizması, boya ve ilaç sektöründe geniş çapta kullanılmaya başlamıştır. Bu nedenle çeşitli kinolin türevleri sentezlenmekte ve sentez yöntemleri geliştirilmektedir. Endüstriel açıdan kinolin bileşiklerinin sentezi ayrı bir alan oluşturmaktadır. 2,6-kinolindiol bir kinolin türevidir. Bu çalışmada; Fe^{3+}-Fe^{2+} transformasyonu metoduna göre indirgeme kapasitesi, CUPRAK metoduna göre Cu^{2+}-Cu^{+} indirgeme kapasitesi, FRAP metoduna göre Fe^{3+}-TPTZ indirgeme kapasitesi, bipiridil reaktifi kullanarak ferröz iyonları (Fe^{2+}) şelatlama aktivitesi, DPPH, ABTS, DMPD radikal giderme aktiviteleri ile süperoksit anyon radikalleri ($O_2^{\cdot-}$) giderme aktivitesi gibi farklı biyoanalitikal metotlar kullanıldı. Ayrıca BHA, BHT, α-tokoferol ve troloks referans antioksidan olarak kullanıldı. Bu madde için ABTS radikal giderme IC_{50} inhibisyon değeri 3.39 µg mL^{-1} olarak hesaplandı. BHA, α-Tocopherol, trolox, BHT ve gibi standart antioksidanlar, sırasıyla 2.59, 4.44, 7.07 ve 32.36 µg mL^{-1} olarak ABTS radikal giderme inhibisyonları sergiledi. Çalışmalar 2,6-kinolindiolün, etkili bir antioksidana sahip olduğunu açıkça göstermiştir.

Anahtar Kelimeler: 2,6-kinolindiol; Antioksidan aktivite; Radikal giderme

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INTRODUCTION

Oxygen has a special place in aerobic life. Because oxygen is the last electron acceptor in ATP production which is an important compound for living life (Davies, 1995). During the electron flow, unconjugated electrons are formed. These electrons create free radicals, causing various damages in the organism (Gulcin, 2012). The biggest dangers of free radicals are the unstable molecules. This is because they oxidize living and non-radical molecules with uncomplicated electron pairs (Gulcin, 2012; Topal, 2018). Due to lipid peroxidation, the membrane lipids have the greatest damage (Bursal et al., 2013).

ROS is produced at a certain level in healthy cells in live metabolism. They have the capacity to damage important biomolecules such as proteins, nucleic acids, carbohydrates, polyunsaturated fatty acids and lipids. They cause mutations by damaging DNA and RNAs. If they are not removed by ROS-effective cellular components, they can cause serious metabolic damage by stimulating radical chain reactions after damaging the protein, lipid and nucleic acids, and finally cellular biomolecules (Öztaşkın et al., 2015). As a result, ROS; It has been observed to cause more than 100 diseases such as heart attack, stroke, asterosclerosis, immunodeficiency syndrome, diabetes, cancer and malaria (Alho and Leinonen, 1999; Gulcin 2012). Antioxidants are substances that inhibit or stop oxidizing molecules. An antioxidant molecule should be able to prevent oxidation even at low concentrations. In addition, they protect living organisms from the damage of ROS. On the other hand, they are also the shield against chronic diseases (Taslimi and Gulcin, 2018). The terms antioxidant activity or antioxidant capacity may be used to indicate the antioxidant capabilities of food ingredients, but they are both different. Phenol derivatives prevented metabolic cholesterol oxidation. A wide range of synthetic antioxidants are available in the pharmaceutical, food, and cosmetic industries (Hudson, 1990; Eberhardt et al., 2000). But, the use of synthetic antioxidants was restricted to legal rules due to the suspicion of being carcinogenic and toxic (Wichi, 1988; Sherwin, 1990). Therefore, the interest in safer antioxidants is increasing for food applications and the trend towards natural antioxidants in consumer preferences has led to an acceleration of attempts to explore antioxidant sources (Gulcin, 2007).

Quinoline is a hetero ringed compound wherein a benzene ring and a pyridine are fused (Fessenden et al., 2001; Hart et al., 2011). The most important examples are quinoline and isoquinoline and are similar to naphthalene. Quinoline and isoquinoline rings are found in many natural compounds like quinine and papaverine (Hart et al., 2011). Quinoline derivatives have been attracted to scientific studies and pharmaceuticals due to their carcinogenic and mutagenic properties (Ökten et al., 2015).

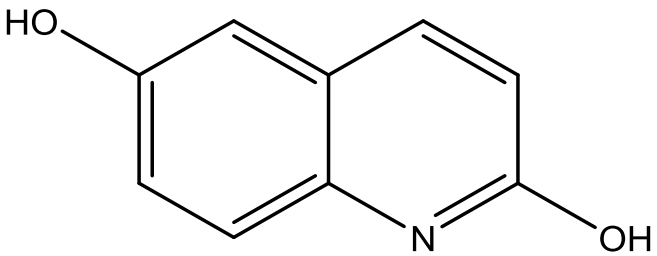

Figure 1. Chemical structure of 2,6-Quinolinediol

In our article, we investigated the antioxidant activities and capacities of 2,6-quinolinediol using 8 different antioxidant methods. Considering the results, it is thought that it is a highly effective molecule and will contribute to new literature studies.

MATERIALS AND METHODS

Ferric Ions (Fe^{2+}) Chelating Activity

Ferric ions (Fe^{2+}) binding ability of 2,6-quinolinediol was determined according to method of Dinis et al. (1994) with minor modification (Gulcin et al., 2004). This method, Fe^{2+} capacity of 2,6-quinolinediol was recorded at 562 nm. 0.6 mM $FeCl_2$ were added 2,6-quinolinediol 10 and 20μg mL^{-1}concentrations in methanol. 5 mM of ferrozine solution were added this mixed. At 25 ^oC for 10 min, the solution was mixed and incubated. Finally; absorbance values were measured spectrophotometrically at 562 nm (Gulcin, 2010).

Cupric Ions (Cu^{2+}) Reducing-CUPRAC Assay

Cupric ions (Cu^{2+}) reducing ability was used as a second reducing method for 2,6-quinolinediol. Cu^{2+} reducing capability was done according to the method described by Apak et al. (2004) with slight modification (Gulcin et al., 2011). Cupric ions reducing ability was used as a second reducing method for 2,6-quinolinediol. For this purpose, 0.01 M, 0.5 mL of $CuCl_2$ solution, 0.5 mL, $7.5x10^{-3}$ M neocuproine solution and 1 M, 0.5 mL of NH_4Ac buffer solution were put in to experimental environment, which contains 2,6-quinolinediol at 10 and 20 μg mL^{-1} concentrations. Finally, the volume was completed to 4 mL with pure water. Absorbance of samples was recorded at 450 nm after 35 min (Gulcin et al., 2010).

Fe^{3+} Reducing Power Assay

For this method, 10 and 20 μg mL^{-1} concentrations of 2,6-quinolinediol in 1.5 mL of pure water were added with 2.5 mL of 0.2 M, pH 6.6 phosphate buffer and 2.5 mL of potassium ferricyanide(III) (1%). This mixture incubated at 50^oC, 20 min. Then, in test tube, 2.5 mL of TCA was added. 1 mL of $FeCl_3$ (0.1%) was added to this mixture and the absorbance values were measured at 700 nm (Topal et al., 2016).

Superoxide Anion Rradical Scavenging Activity

Superoxide radicals ($O_2^{\bullet-}$) scavenging activity of 2,6-quinolinediol was performed in accordance with the method of Zhishen et al. (1999) with slightly modification (Gulcin et al., 2005). 20 W of fluorescent lamp was stimulated in this experiment. All of this assay was prepared in 0.05 M, pH 7.8 phosphate buffer. This test medium was applied using a 20 W fluorescent lamp. To the buffer solution containing 2,6-quinolediol was added at certain concentrations from methionine, NBT and riboflavin. The test tubes were incubated for 45 minutes at 25°C in 20 W light environment. The absorbances were measured at 560 nm (Aksu et al., 2015).

DPPH Scavenging Activity

This radical removal method was performed according to Gulcin et al. (2010). Briefly, fresh solution of DPPH· (0.1 mM) was prepared in ethanol, and 0.5 mL of this solution was added to 1.5 mL of 2,6- quinolinediol solution in ethanol at different concentrations (10-20 μg mL^{-1}). These solutions were mixed vigorously and incubated in dark for 30 min. Then, the absorbance value was recorded at 517 nm in a spectrophotometer (Gulcin, 2005; Gulcin et al., 2005).

$ABTS^{\bullet+}$ Scavenging Activity

$ABTS^{\bullet+}$ scavenging activity of 2,6-quinolediol was done using the spectrophotometric method of Re et al. (1999). The $ABTS^{\bullet+}$ was acquired by reacting 7 mM solution of ABTS with 2.45 mM $K_2S_2O_8$, stored in the dark at room temperature for 6 h. The

ABTS radical cation solution was diluted with ethanol to an absorbance of 0.750±0.05 at 734 nm. Then, 1 mL of $ABTS^{\bullet+}$ solution was added to 3 mL of 2,6-quinolinediol in ethanol at different concentrations (10-20 μg mL^{-1}). The extent of decolorization is calculated as percentage reduction of absorbance (Gulcin et al., 2010).

$DMPD^{\bullet+}$ Scavenging Activity

DMPD radical scavenging ability of 2,6-quinolinediol was done according to the method described by Fogliano et al. (1999). 0.1 M DMPD was prepared in acetate buffer (0.1 M, 200 mL and pH 5.3). DMPD radical was obtained. 0.05 M $FeCl_3$ solution was added to this radical. The sample was added to the mixture from different concentrations of the solution. The final volume was added up to 500 μL of pure water. After a 10 minute wait, the absorbances were evaluated at 505 nm (Gulcin et al., 2012).

Bipyridyl Chelating Activity

Fe^{2+} chelating activity was performed according to the method determined by Re et al. (Re et al., 1999). For this purpose, the test tubes were transferred 0.125 mL of $FeSO_4$ solution (2 mM). This solution was added 2,6-quinolediol or standard solutions (10 and 20 μg mL^{-1}). Then 0.5 mL of Tris-HCl buffer (pH: 7.4) was added and in the dark incubated in for half-hour. Later, 0.5 mL of a 0.2% biphiryl solution dissolved in HCl (0.2 M) was added. The absorbance of the sample containing 1.25 mL of ethanol and 0.625 mL of pure water was measured at 522 nm.

RESULTS AND DISCUSSION

The reduction capacity of the 2,6-quinolinediol can be calculated by direct reduction of Fe^{+3} to Fe^{+2} (Gulcin et al., 2010). In this bioanalytical method used in antioxidant studies, the yellow color of the prepared solution turns into different green tones due to the reduction activities of the antioxidants in the environment (Çakmakçı et al., 2015). The 2,6-quinolinediol reduction capacity used in the study increases in direct proportion with increasing concentration. The reduction potential of 2,6-quinolinediol was determined by measuring the absorbance of the solutions at different concentrations (10 and 20 μg mL^{-1}) at 700 nm. The capacity of reducing 2,6-quinolinediol ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}) was plotted (Table 1). For each standard antioxidant and 2,6-quinolinediol, the absorbance values corresponding to 20 μg mL^{-1} were compared. Comparison of the reduction forces of ferric ions (Fe^{3+}) with 2,6-quinolinediol and standard antioxidants at this concentration: BHA (2.433) > 2,6-Quinolinediol (1.432) > BHT (1.364) > Trolox (1.328) > α-Tocopherol (0.876) was determined to be. In addition, the high absorbance values shown in Table 1 indicate the high reduction capacity. The results proved that 2,6-quinolinediol had marked Fe^{3+} reducing ability.

Reduction capacity of 2,6-quinolinediol cupric ions (Cu^{2+}) was determined by measuring the absorbance at 450 nm of solutions of different concentrations (10 and 20 μg mL^{-1}). The reduction capacity of 2,6-quinolinediol cupric ions (Cu^{2+}) was found to increase in direct proportion to concentration. After the graph of reduction of 2,6-quinolinediol solutions and cupric ions (Cu^{2+}) of standard antioxidants the absorbance values corresponding to 20 μg mL^{-1} for each standard antioxidant and 2,6-quinolinediol were compared (Table 1). The results of 2,6-quinolinediol and standard antioxidants (20 μg mL^{-1}), respectively. BHA (1.993) > 2,6-Quinolinediol (1.633) > BHT (1.626) > Trolox (0.456) > α-Tocopherol (0.374).

Table 1. Determining the reducing power of 2,6-Quinolinediol

Antioxidants	Fe^{3+}-Fe^{2+} reducing[a]		Cu^{2+}-Cu^{+} reducing[a]		Fe^{3+}-TPTZ reducing[a]	
	Absorbans (20 μg mL^{-1})	**R^2**	**Absorbans** (20 μg mL^{-1})	**R^2**	**Absorbans** (20 μg mL^{-1})	**R^2**
BHA	2.433	0.998	1.993	0.991	2.209	0.842
BHT	1.364	0.980	1.626	0.999	1.483	0.781
α-Tocopherol	0.876	0.998	0.374	0.996	1.779	0.925
Trolox	1.328	0.989	0.456	0.999	2.092	0.887
2,6-Quinolinediol	1.432	0.948	1.633	0.979	1.645	0.845

[a] expressed as absorbance values.

The FRAP method is an electron-free method that shows antioxidant activity. In this method, ferric ions (Fe^{3+}) are reduced to ferrous ions (Fe^{2+}). The resulting ferrous (Fe^{2+}) ions form a blue complex with TPTZ. This blue colored complex shows maximum absorbance at 593 nm. According to the 2,6-quinolinediol FRAP method; the capacity to reduce ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}) was found to increase in direct proportion to the concentration (Table 1). In addition, comparison of reducing activity according to FRAP method with standard antioxidants of 2,6-quinolinediol was performed: BHA (2.209) > Trolox (2.092) > α-Tocopherol (1.779) > 2,6-Quinolinediol (1.645) > BHT (1.483).

DPPH free radical removal activity of 2,6-quinolinediol solutions increases in direct proportion to the concentration (Table 2). The 2,6-quinolinediol and the standard antioxidant molecules used exhibited DPPH free radical removal activity, respectively. Trolox > BHA > α-tocopherol > BHT > 2,6-quinolinediol. IC_{50} values were found as 57.75 μg mL^{-1} for 2,6-quinolinediol, 5.33 μg mL^{-1} for trolox, 9.36 μg mL^{-1} for α-tocopherol, 31.45 μg mL^{-1} for BHT and 8.45 μg mL^{-1} for BHA. A high $DPPH^{\cdot}$ removal activity indicates a low IC_{50}.

$ABTS^{\cdot+}$ removal activity, such as DPPH free radical removal activity, is also frequently used in the radical removal activities of aqueous mixtures, beverages, extracts or pure substances (Miller, 1996; Gulcin et al., 2007b). For this purpose, $ABTS^{\cdot+}$ must be created from ABTS. After plating the 2,6-quinolinediol $ABTS^{\cdot+}$ radical removal activity for standards and 2,6-quinolinediol were calculated IC_{50} values (Table 2). $ABTS^{\cdot+}$ removal activities of 2,6-quinolinediol and used standard antioxidant molecules were observed as: BHA > BHT > 2,6-quinolinediol > α-tocopherol > trolox. The IC_{50} value for 2,6-quinolinediol in this analysis was 3.39 μg mL^{-1}. The concentration of $ABTS^{\bullet+}$ appears to be significantly reduced due to the cleavage ability at different concentrations of 2,6-quinolinediol. Moreover, IC_{50} values for BHT, BHA, α-tocopherol and trolox were found to be 3.36 μg mL^{-1}, 2.59 μg mL^{-1}, 4.44 μg mL^{-1} and 7.07 μg mL^{-1}, respectively.

If the principle of $DMPD^{\bullet+}$ operation is used at acidic pH and appropriate oxidant solution, DMPD may form a stable and colored radical cation. $DMPD^{\bullet+}$ indicates the maximum absorbance value at 505 nm (Garibov et al., 2016). The $DMPD^{\bullet+}$ method provides a very constant end point according to the $ABTS^{\bullet+}$ scavenging method. The main disadvantage of $DMPD^{\bullet+}$ was reported to be significantly reduced in terms of sensitivity and renewability if standard antioxidants such as α-tocopherol or BHT were used. Therefore, these compounds are not suitable for use in the $DMPD^{\bullet+}$ sweep assay. (Gulcin, 2012; Halliwell, 1997; Göçer and Gulcin, 2011).

In $DMPD^{\bullet+}$ scavenging assay of 2,6-quinolinediol was as effective as in other methods. IC_{50} value for 2,6-quinolinediol was found as 15.50 μg mL^{-1}. This value was found as

15.40 μg mL^{-1} for BHA, and 10.04 μg mL^{-1} for trolox (Table 2). BHT and α-tocopherol didn't show activity in this assay (Köksal et al., 2009, Gulcin et al., 2012). There was a significant decrease in $DMPD^{\bullet+}$ concentration owing to the scavenging ability of 2,6-quinolinediol concentrations.

Table 2. Determination of IC_{50} (μg mL^{-1}) of 2,6-Quinolinediol and standard radical scavenging activities

Antioxidants	Bipyridyl Fe^{2+} chelating	DPPH· scavenging	$ABTS^{\bullet+}$ scavenging	$DMPD^{\bullet+}$ scavenging	$O_2^{\cdot-}$ scavenging
BHA	36.47	08.45	02.59	15.40	14.74
BHT	05.25	31.45	32.36	-*	43.31
α-Tocopherol	25.67	09.36	04.44	-*	28.88
Trolox	63.00	05.33	07.07	10.04	40.76
2,6-Quinolinediol	04.10	57.75	03.39	16.50	08.06

*: BHT or α-Tocopherol didn't show activity in this assay.

In this context, 2,6-quinolinediol was also effective in the bipyridyl chelating method (Table 2). EDTA is used as a metal chelator. Accordingly, the IC_{50} values are calculated and listed as follows: EDTA (2.78 μg mL^{-1}) < 2,6-quinolinediol (4.10 μg mL^{-1}) < BHT (5.25 μg mL^{-1}) < α-Tocopherol (25.67 μg mL^{-1}) < BHA (36.47 μg mL^{-1}) < Trolox (63.00 μg mL^{-1}). According to the results, it was observed that the bipyridyl metal chelating effect of 2,6-quinolinediol was higher than the standard antioxidants.

The 2,6-quinolinediol $O_2^{\cdot-}$ removal activity was based on the riboflavin / methionine / light method (Gulcin et al., 2004c). The 2,6-quinolinediol and standard antioxidant molecules used for superoxide anion radical removal activities were found to be 2,6-quinolinediol > BHA > α-tocopherol > trolox > BHT, respectively. When we seem $O_2^{\cdot-}$ radical scavenging activity results, it was determined that $O_2^{\cdot-}$ cleaning activity of 2,6-quinolinediol was higher than standard compounds. As shown in Table 2, the IC_{50} value of 2,6-quinolinediol was 8.06 μg mL^{-1}. According to these results, the IC_{50} values of antioxidants, which are preferred as synthetic antioxidants, are much higher than the substances in our study. In comparison with a natural antioxidant α-tocopherol, its IC_{50} value was 28.88 μg mL^{-1} and the 2,6-quinolinediol was found to be 8.06 μg mL^{-1}. A substance must be effective at low concentration to be an antioxidant. 2,6-quinolinediol was manifest by the results obtained in this regard.

CONCLUSION

When the results were evaluated, in the 8 different antioxidant methods, 2,6 quinolindiol showed antioxidant effect which was more effective or closer than the standard antioxidants. The positive results of both reductions and reduction capacities showed that 2,6-quinolindiol compound could be preferred as antioxidant. In this case, it is thought that our material may shed light on the works in the field.

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