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A comparative study on the antioxidant properties of curcuminoids and its rubrocurcumin analogues

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Abstract

The yellow colored pigment, curcumin present in turmeric is responsible for its various biological activities like antioxidant, anti-inflammatory and anticarcinogenic activity. Different functional group present in curcumin includes a β–diketone group, carbon–carbon double bond and two phenyl rings with hydroxy and methoxy substituents. A controversy exists in literature on the site and mechanism for the antioxidant activity (AOA), the keto–enol/phenolic moiety present in curcumin. In the present work AOA of curcuminoids and its boron complex with oxalic acid – rubrocurcumin analogues were conducted which differ in the substituent in the benzene ring. Since in rubrocurcumin analogue β-diketone group is blocked through bonding with boron its influence will be absent in its antioxidant activity.

Keywords: curcumin, antioxidant, rubrocurcumin, β–diketone

1. INTRODUCTION

Curcumin isolating from the rhizomes of the plant turmeric shows remarkable pharmacological activities and is widely used as a spice and food coloring agent [1–2]. The antioxidant activity of curcumin is mainly responsible for its biological activities [3–6]. However its instability in water mediated system and its low bioavailability reduces its application as an oral drug. Curcumin derivatives and analogues are better options for drug applications and many reviews are observed in literature. A closely related molecule of curcumin having enhanced AOA is the best choice. Since curcumin has different functional groups structure activity relationship study will help to find the actual antioxidant site for curcumin and the ways to enhance its activity [7–9]. Commercial curcumin contains three different curcuminoids; curcumin (C1), demethoxycurcumin (C2) and bisdemethoxycurcumin (C3) and their antioxidant nature decreases in the order C1>C2>C3 [10–11].

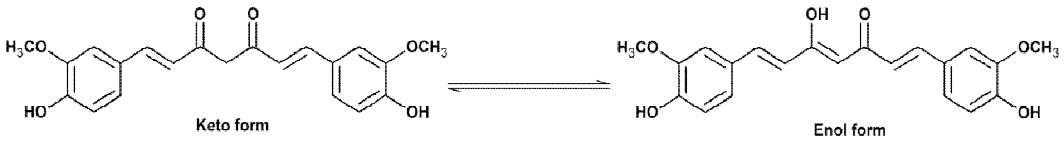

Fig. 1: Keto-enol tautomeric forms of curcumin

Curcumin exist in equilibrium with the keto enol tautomeric forms (Figure 1) and in solution it exists mainly in enol form. NMR spectroscopic studies in solvents of various polarities have shown that curcumin exists predominantly as enol tautomer [12–13]. The physical, chemical and biological activities of curcumin may be due to its unique chemical structure and the existence of keto-enol tautomeric forms. Curcumin in the enol form has better activity because of its ability to accept and donate hydrogen bonds and its ability to chelate positively charged metal ions [14].

The enol form of curcumin is excellent metal chelators and will form complexes with all metal ions and helps to prevent Alzheimer's disease caused by metal deposition in brain tissues [15–18]. The metal complexation deny the possibility of enolic group to act as the antioxidant centre and the present group demonstrated a slight decrease in the antioxidant property of transition metal complexes [19]. In the present work the antioxidant property rubrocurcumin analogues were revealed in which curcumin complexes with boric acid along with oxalic acid. Rubrocurcumin classically used for the estimation of boron in different matrices even at low concentration i.e. less than 1 ppm [20]. The less hydrolytic stability of these boron complexes is its main drawback in using them as spectrophotometric reagent for boron determination [20–21]. However the low hydrolytic stability of these complexes makes them a suitable candidate for the carrier system for the delivery of curcumin in human body.

All curcuminoids; curcumin (C1), demethoxycurcumin (C2) and bisdemethoxycurcumin (C3) form the corresponding rubrocurcumin analogues RC1, RC2 and RC3 when reacted with boric acid and oxalic acid (Figure 2) [22]. Another rubrocurcumin analogue (RC4) was prepared using a curcumin analogue which doesn't have any substituent in benzene ring (C4). AOA studies of these compounds will give clear indication regarding the structure activity relationship in the antioxidant mechanism of curcumin and the influence of methoxy group in its AOA.

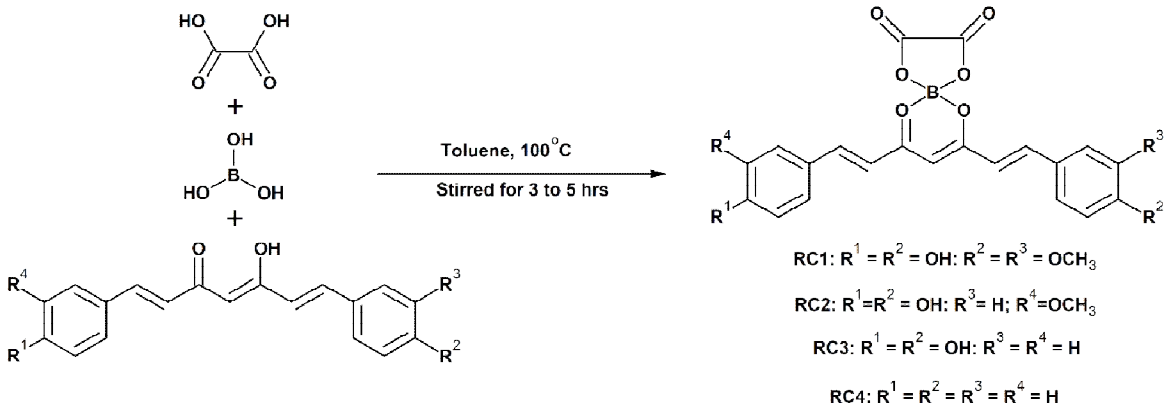

Fig. 2: Synthesis of rubrocurcumin analogues.

2. MATERIALS AND METHODS

2.1. Antioxidant activity assay

The AOA of curcuminoids and rubrocurcumin analogues were assayed as reported in literature [25]. To 0.5 mL of diluted ABTS solution having absorbance 0.8 to 0.9, 2.5 mL of sample in methanol at different concentrations ($1–9\times10^{-5}$ µg/mL) were added and the percentage of radical

scavenged was determined for each concentrations of sample relative to a blank containing no sample. The percentage inhibition was calculated using the equation

$$\% \text{ inhibition } = \left(1 - \frac{A_S}{A_C}\right) \times 100$$

Where A_s is the absorbance of the remaining ABTS radical in presence of sample and A_c is the absorbance of blank without sample. All the analyses were done in duplicate and the averaged results were used for analysis of the data. From the % inhibition vs. concentration graph, 50% fall in ABTS solution was determined as IC_{50} value in µM which determines the AOA of a compound.

3. RESULTS AND DISCUSSIONS

DPPH method was commonly employed for the study of free radical scavenging activity however not suitable for rubrocurcumin analogues since they absorb in the same region of DPPH radical. The AOA of four different curcuminoids along with all the synthesized rubrocurcumin analogues were assessed using ABTS method. The AOA values depends on the method used, the time and reaction conditions such as solvent polarity, pH, temperature and concentration of the reactive species [19, 26–29]. The radical scavenging activity of curcuminoids and its rubrocurcumin analogues are shown in Table 1 as IC_{50} values. A larger IC_{50} value indicates low AOA. The AOA of curcuminoids decreases in the order C1 > C2 > C3 and are consistent with reported antioxidant activity of curcuminoids in DPPH method [10]. C4 shows no AOA up to the concentration of 30×10^{-5} µg/mL supporting the antioxidant property of curcuminoids is due to the presence of hydroxyl group present in the phenyl rings [7–8]. The *o*-methoxy group can form an intramolecularhydrogen bond with the phenolic hydrogen making the H-atom abstraction from the *o*-methoxy phenols surprisingly easy which resulted in the enhance antioxidant activity of C2 and C1 over C3 [30]. However Somparn *et al.*, suggested that the antioxidantactivities of curcumin and its derivatives can arise both from the *o*-methoxyphenol and from central methylenic hydrogen in the central seven carbon chain and β-diketone moiety [10]. However the absence of antioxidant activity of C4 and the antioxidant activity shown by the transition metal complexes [19] of curcumin show that the enol moiety have no role in initiation [28] or the antioxidant activity of curcumin and its analogues.

Table 1: IC_{50} values in µM of curcumin and its rubrocurcumin analogues

Curcuminoids	IC_{50}(µM)	Rubrocurcumin analogues	IC_{50}(µM)
C1	11.65	RC1	11.82
C2	15.74	RC2	13.73
C3	21.50	RC3	18.02
C4	No activity	RC4	No activity

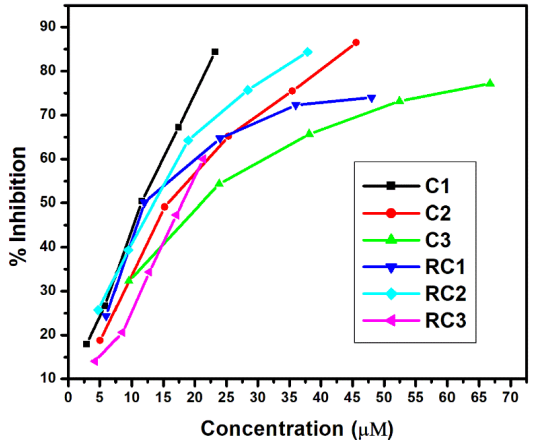

Fig. 3: ABTS scavenging activity of curcuminoids and its rubrocurcumin analogues.

The AOA order of rubrocurcumin analogues is RC1 > RC2 > RC3 indicating the influence of lactone ring of rubrocurcumin in antioxidant behaviour. Similar to C4, RC4 doesn't show any AOA up to the concentration of 30×10^{-5} µg/mL. The percentage inhibition vs. concentration graph used to calculate the IC_{50} values for the curcuminoids and its rubrocurcumin analogues are shown in Figure 3. The IC_{50} value of C1 and RC1 are comparable and is within the error percentage. However a comparatively large variation is observed for C2 and C3 with its rubrocurcumin analogues.

Antioxidant reaction mechanism for rubrocurcumin

Litwinienko *et al.,* suggested that the antioxidant activity of curcumin take place by SPLET mechanism, where the first stage is the ionization of Ar–OH into $Ar–O^-$ anion by the solvent. In the second stage electron transfer occurs from this anion to free radical [19], which is highly depended on the hydrogen bonding interaction of solvent with the phenolic moiety [28].The formation of phenoxide ion determines the AOA activity and is largely depend on the nature of diketone moiety. In polar medium the enol moiety exchange its hydrogen with the solvent and the formed anionic group displaces electrons towards the phenolic groups through the extended conjugated structure of curcumin making the conversion of phenolic OH to $Ar–O^-$ anion less susceptible. In rubrocurcumin analogues, the diketone moiety complexes with boron atom to form [BO_4^-] moiety which is less negative and will promote the formation of $Ar–O^-$ anion in faster rate than curcumin. The influence of charge delocalization is prominent in free Ar–OH rather than intramolecularly hydrogen bonded Ar–OH as in C1 and C2. In RC1 methoxy group is present in ortho position forms intramolecular hydrogen bond which retard the influence electron flow of from [BO_4^-] moiety thus its activity is similar to that of C1.

The results of AOA of rubrocurcumin analogueis a clear indication that the OH group is not independently acting as AOA group as claimed by Barclay [7]. The electron flow and the molecular dissociation via free radical rupture process may be totally different and require detailed investigation by studying in different solvent systems and rubrocurcumin analogues with changes in lactone rings.

4. CONCLUSIONS

Rubrocurcumin is an admirable molecule which can be used as the biological carriers for curcumin in human body. Not many studies were reported so far on its biological activities. In this work an attempt were made to study its AOA using ABTS method. A comparative study was also conducted between curcuminoids and their corresponding rubrocurcumin analogues to check the influence of boron complexation in its AOA. From the result it is clear that the rubrocurcumin analogues are good antioxidant agents similar to curcumin and RC2 and RC3 are more active than its corresponding curcuminoids. The increase in AOA of these compounds may due to the electronic interaction of [BO_4^-] moiety towards the antioxidant site.

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