Structure activity relationship of tautomers of curcumin: a review

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Abstract

Introduction. The aim of this review is to focus on the unique chemistry of curcumin to explain its dissimilar behaviour in different mediums.

Materials and methods. The papers regarding structure-activity relationship studies of curcumin as antioxidant or pro-oxidant were examined. This review summarizes the achievements made in this field since 1980.

Results and discussion. Curcumin is the principal curcuminoid found in turmeric and is generally considered as the most active constituent of turmeric compared to other curcuminoids. Enormous research has been carried out to explain the beneficial activities of curcumin. It has been the centre of attraction for potential treatment of an array of diseases such as cancer, Alzheimer, diabetes, allergies, arthritis and other chronic illnesses. It also possesses antioxidant activity at lower concentration. In contrast, the pro-oxidant effect has also been reported.

The behaviour of curcumin to act as antioxidant or pro-oxidant depends on its structural form. Curcumin exists in two tautomeric forms, keto and enol. In keto form, curcumin exerts antioxidant activity. The enol form is prone to degradation. Hence, it is essential to maintain curcumin in keto form. In polar and acidic medium, curcumin exists in keto form whereas in non-polar and basic medium, it undergoes degradation. The mechanisms of degradation of curcumin under different mediums are discussed. Under basic conditions, nucleophilic attack of hydroxyl group is involved and under non-polar conditions, free radical mechanism is involved. Degradation under basic conditions leads to complete breaking of the molecule while under non-polar conditions, it proceeds via peroxide intermediate formation, clarifying the pro-oxidant effect of curcumin. In either of the cases, vanillin is the degradation product besides other degradation products.

The discussion is further extended for the other two curcuminoids, viz. demethoxycurcumin and bisdemethoxycurcumin as well. The antioxidant activity of curcumin is the highest whereas bisdemethoxycurcumin exhibits least antioxidant activity amongst curcuminoids. However, the rate of degradation of curcumin is also maximum amongst curcuminoids followed by demethoxycurcumin and bisdemethoxycurcumin. This reveals that the electron donating methoxy group influences the activity of curcuminoids.

Thus, structure of a constituent is responsible for its activity.

Conclusion. The importance of a particular medium to achieve the beneficial activities of curcumin is confirmed.

Introduction

Curcuminoids are the major polyphenolic compounds found in turmeric rhizome. The curcuminoids include curcumin (the main bioactive component), demethoxycurcumin and bisdemethoxycurcumin [1, 2, 3]. The unique structure of curcumin, which has the phenolic hydroxyl groups, heptadiene chain and diketone moiety [4, 5, 6], is responsible for all the therapeutic activities of curcumin such as anti-inflammatory, antitumor, anticancer, anti-HIV, antibacterial, antidiabetic [7, 8, 9, 10, 11, 12, 13]. It is used as an antioxidant [9], a wound healing agent [14, 15, 16] and to prevent Alzheimer disease [17, 18]. Recently, it has also been reported as an antidepressant agent [19]. However, the pro-oxidant effect of curcumin is also observed [20]. This review emphasizes the fundamental of the stabilization and degradation of curcumin with the help of existing theories [21, 22], explaining its dissimilar behaviour.

Materials and methods

Review is constructed on the basis of previously available research articles.

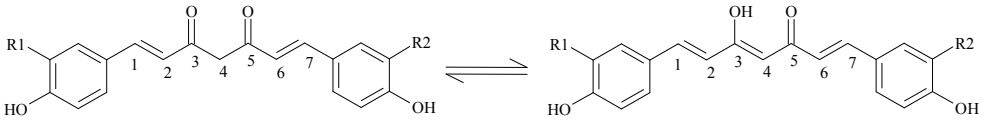
Result and discussion

Structure of keto and enol tautomers

The keto enol tautomerism in curcumin is because of the presence of carbonyl groups on the carbon number 3 and 5 in heptadiene ring [23, 24, 25, 26] (Figure 1). The stabilization of enol tautomer with respect to the keto tautomer is due to the conjugation of the carbonyl double bond with the enol double bond and a pi orbital system, i.e., phenyl group in conjugation with the conjugated C=C double bonds [27]. The enol tautomer is characterized by the formation of strong intramolecular hydrogen bonding compared to intermolecular hydrogen bonding which exists in the keto form [28]. The enolisation of curcumin brings about a fundamental change, i.e., the polar keto tautomer is converted to the non-polar enol tautomer. The dependency of the structure of curcumin on solvent has already been proved as it exhibits different λ_{max} in different solvents [29, 30]. Depending upon the polarity of the medium, curcumin exists in different proportion as a tautomeric mixture of keto and enol forms in the medium. Both the tautomers get solubilized in the medium through different forces. Polar-polar solubilization takes place by means of dipole-dipole forces, while non-polar–non-polar and polar–non-polar solubilization takes place by means of dispersion forces. Like prefers like. Hence, in the polar medium, the activity of keto form predominates while in the non-polar medium, the activity of enol form predominates [31].

Role of methylene group in curcumin

In the keto form of curcumin (1-i), the heptadienone linkage between the two methoxyphenol rings contains an active methylene group. Jovanovic et al. [32] proved that curcumin acts as an antioxidant only in the keto form by donating H-atom from the methylene group, i.e., $-CH_2$ group which is between two electron withdrawing carbonyl groups. The resulting carbon radical formed after abstraction of H-atom (3) is stabilized by resonance (4 and 5) (Figure 2). The active methylene group takes up the reaction site only in acidic or polar medium.



1 Keto form **2** Enol form

Figure 1. Tautomerism of curcuminoids

where,
(i) R1 = R2 = -OCH_3; Curcumin (Diferuloylmethane)
(ii) R1 = -OCH_3, R2 = -H; Demethoxycurcumin (*p*-Hydroxycinnamoyl feruloylmethane)
(iii) R1 = R2 = -H; Bisdemethoxycurcumin (*p,p'*-Dihydroxydicinnamoylmethane)

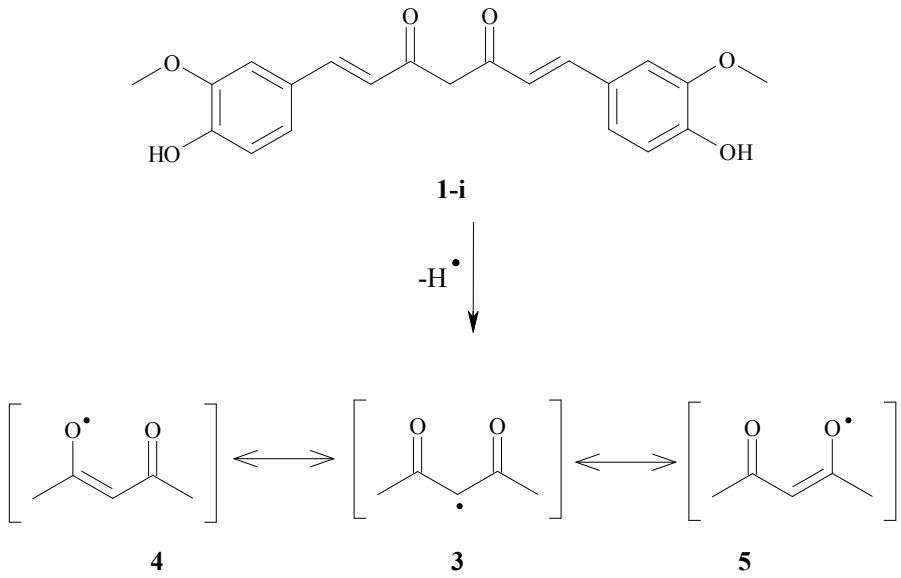


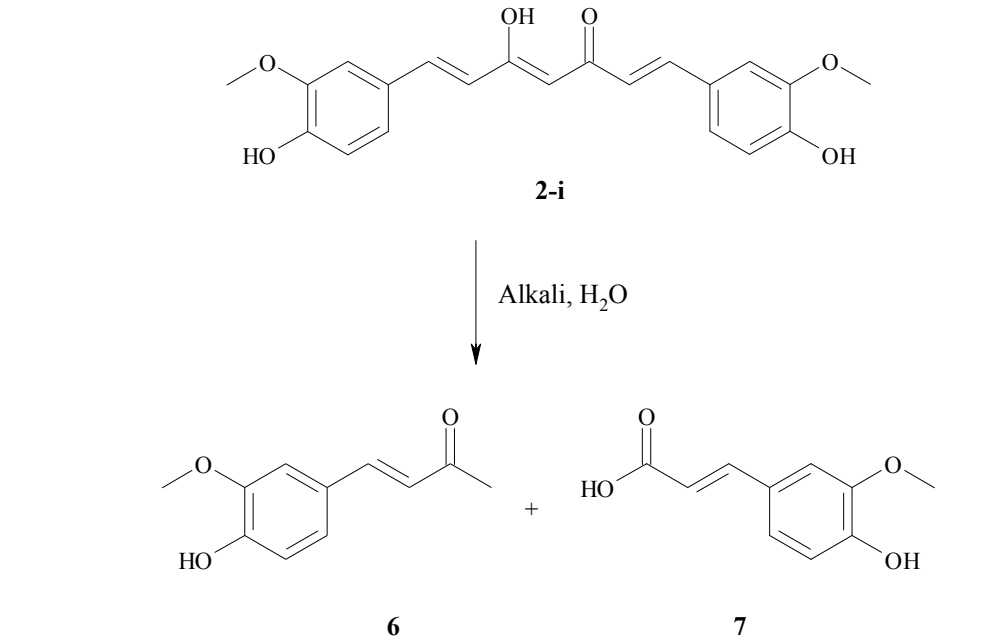
Figure 2. Donation of H-atom from active methylene group

In basic or non-polar medium, the phenolic moiety of curcumin primarily gets involved in the reaction and -CH_2 group involves in enolic form (2-i) [33]. Curcumin is prone to degradation in alkaline [34] and non-polar medium [31].

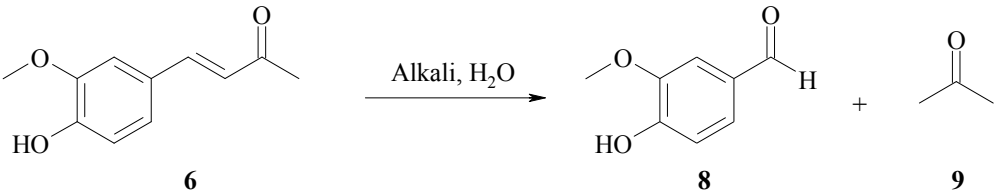
Degradation of curcumin

Various studies have been carried out to study the degradation of curcumin. Depending upon the medium, whether it is alkaline or non-polar, degradation of curcumin takes place through different pathways.

In basic medium, the degradation occurs by nucleophilic attack of basic -OH (hydroxyl) ion. Feruloylmethane (6) and ferulic acid (7) are formed by the alkaline hydrolysis of curcumin. The feruloylmethane further undergoes hydrolysis to form vanillin (8) and acetone (9) [35] (Figure 3). Thus, the degradation pathway under basic medium involves breaking of heptadienone moiety, leading to disappearance of active methylene group that mainly imparts antioxidant activity to curcumin. Hence, curcumin cannot act as an antioxidant.



(i) Formation of primary products

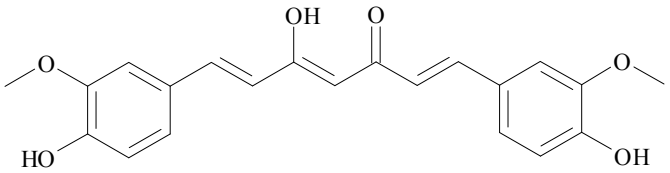


(ii) Formation of secondary products

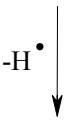
Figure 3. Degradation of curcumin under alkaline medium

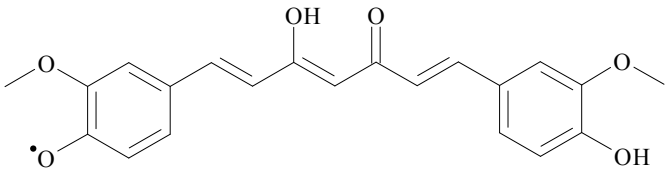
In non-polar medium, Masuda et al. [36] postulated the degradation of curcumin through radical formation to form vanillin and ferulic acid [37, 38, 39]. The enol form of curcumin degrades to form oxy radical I (10) initially, which further gets converted to carbon radical I (11) and carbon radical II (12). Because of conjugation, carbon radical II is more stable than carbon radical I. Both the radicals independently react with molecular oxygen to produce two types of peroxy radicals (13, 16), which get cyclized at adjacent positions. The

cyclic intermediates (14, 17) get decomposed to form stable products through an abstraction of the hydrogen atom from hydrogen atom donor compounds. The enol form of trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal (15-i) and vanillin are formed by the carbon radical I [40] whereas ferulic acid is formed by the carbon radical II. The enol form of trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal can tautomerize to keto form (15-ii) (Figure 4). Thus, the degradation pathway under non-polar medium involves autoxidation of curcumin. Hence, curcumin acts as a pro-oxidant.

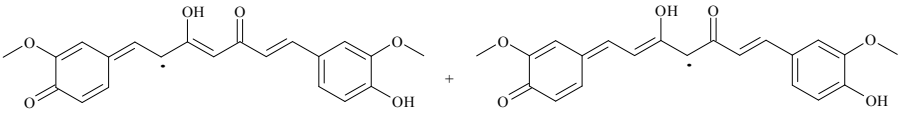


2-i





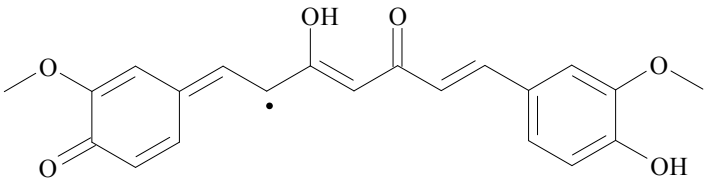
10
Oxy radical I (Highly unstable)



11
Carbon radical I (Minor)

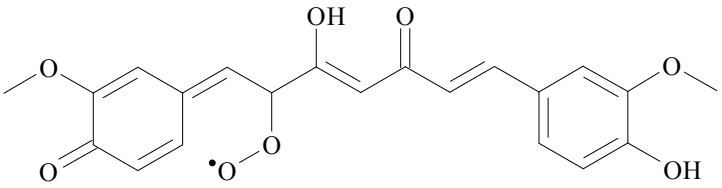
12
Carbon radical II (Major)

(i) Radicals generated by curcumin



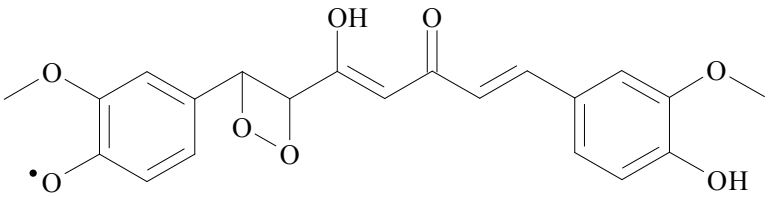
11

O_2



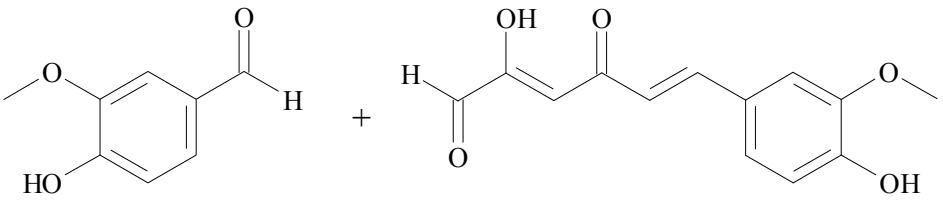
13

Cyclization

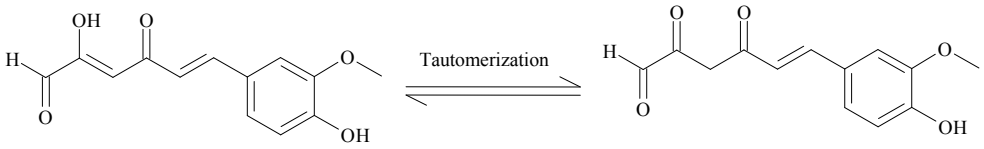


14

$+ H^{\bullet}$



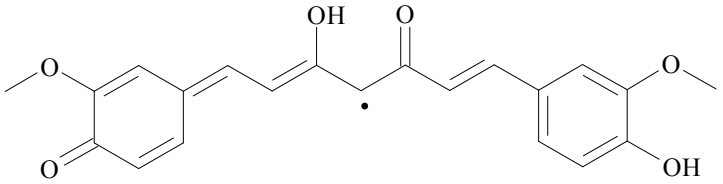
8 + **15-i**



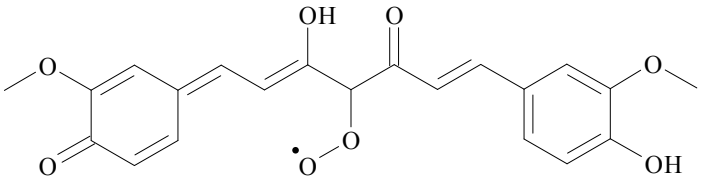
15-i
enol form

15-ii
keto form

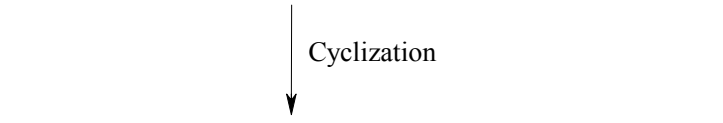
(ii) Reaction of radical I with O_2

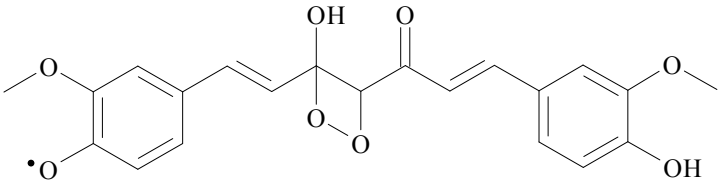


12

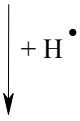


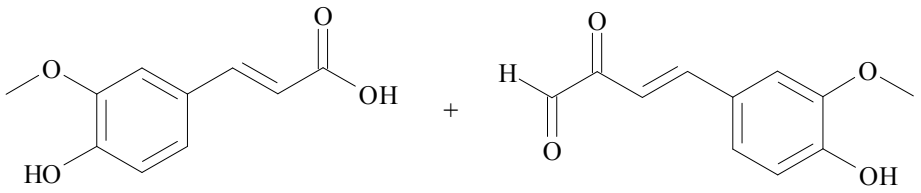
16





17





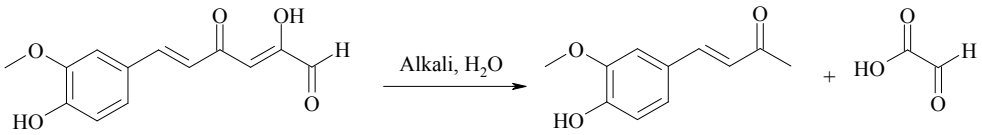
7 **18**

(iii) Reaction of radical II with O_2

Figure 4. Degradation of curcumin under non-polar medium

Degradation of trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal

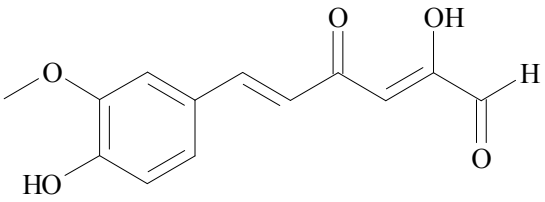
It can be envisaged [40] from the studies that similar to curcumin, the enol tautomer of trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal (15-i) may undergo degradation under alkaline medium to form feruloylmethane (Figure 5), which gets converted to vanillin and acetone on hydrolysis as mentioned previously.



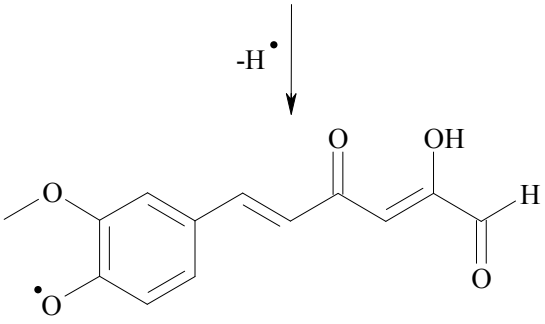
15-i **6** **19**

Figure 5. Degradation of Trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal under alkaline medium

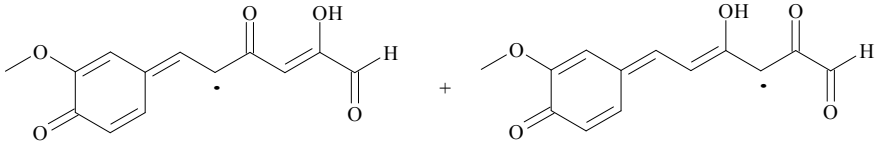
In non-polar medium, the enol tautomer of trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal undergoes degradation to form oxy radical II (20), which gets converted to carbon radical III (21) and carbon radical IV (22). Like carbon radical II, carbon radical IV is more stable than carbon radical III because of conjugation. The radicals so formed combine with molecular oxygen forming two types of peroxy radicals (23, 26), which get cyclized at adjacent positions (24, 27). As discussed previously, the stable products from these cyclic intermediates are obtained by simultaneous abstraction of the hydrogen atom from hydrogen atom donor compound and decomposition (Figure 6). Carbon radical III forms vanillin while carbon radical IV forms ferulic acid.



15-i



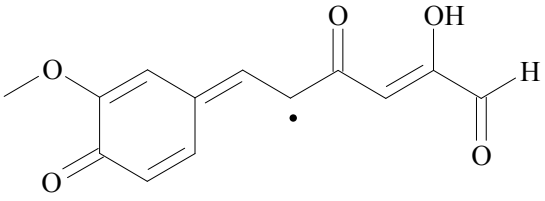
20
Oxy radical II (highly unstable)



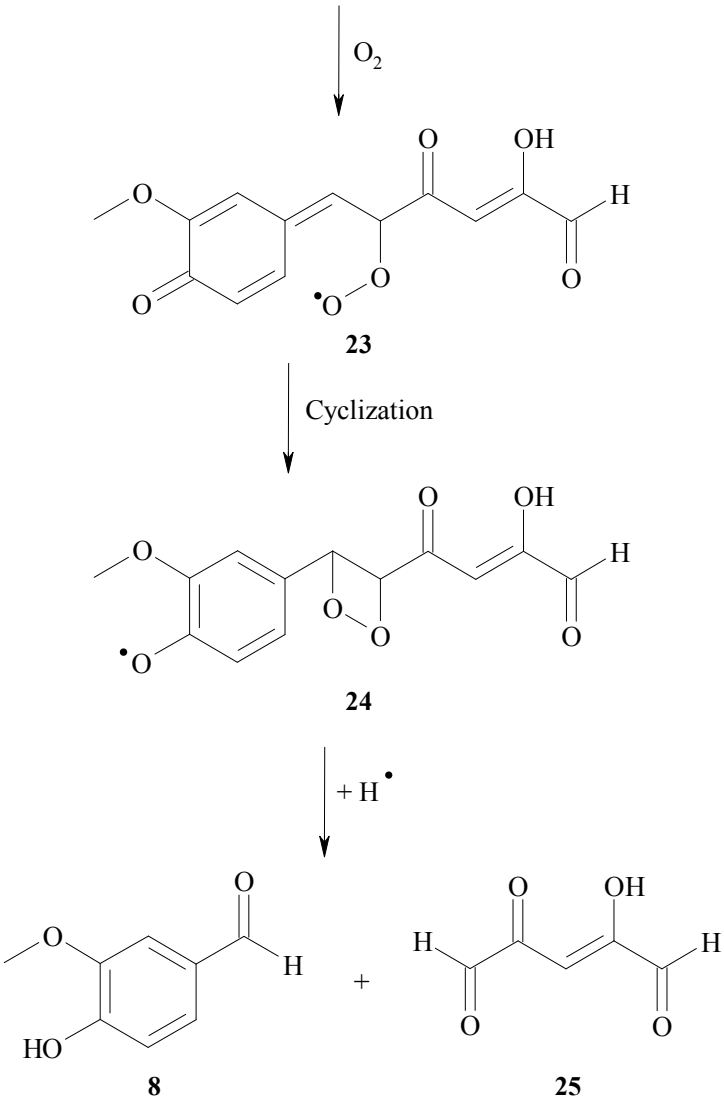
21
Carbon radical III (Minor)

22
Carbon radical IV (Major)

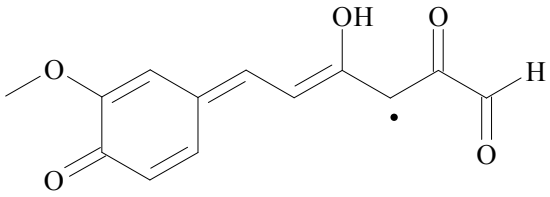
(i) Radicals generated by Trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal

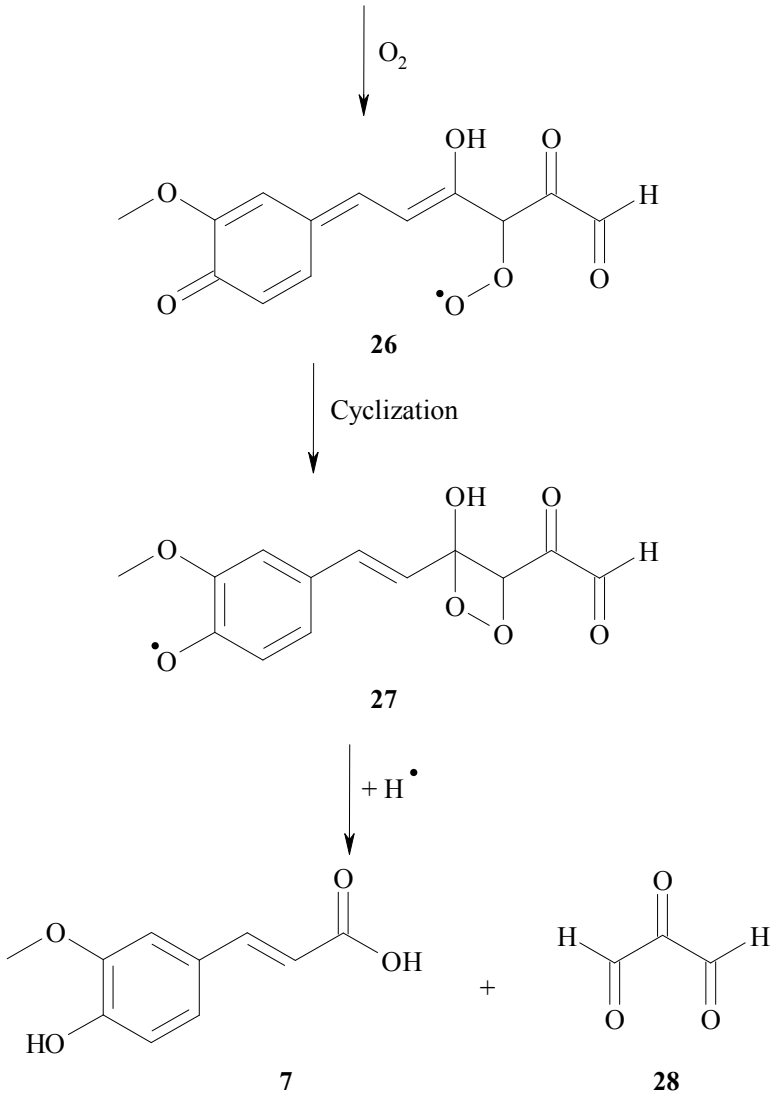


21



(ii) Reaction of radical III with O_2





(iii) Reaction of radical IV with O_2

Figure 6. Degradation of Trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal under non-polar medium

Inference about degradation products

The aforementioned mechanisms indicated that vanillin is the degradation product of curcumin in alkaline as well as non-polar medium along with other products in the respective mediums. Consequently, these mechanisms support the formation of more amount of vanillin during the degradation of curcumin.

The overall discussion is represented in Figure 7.

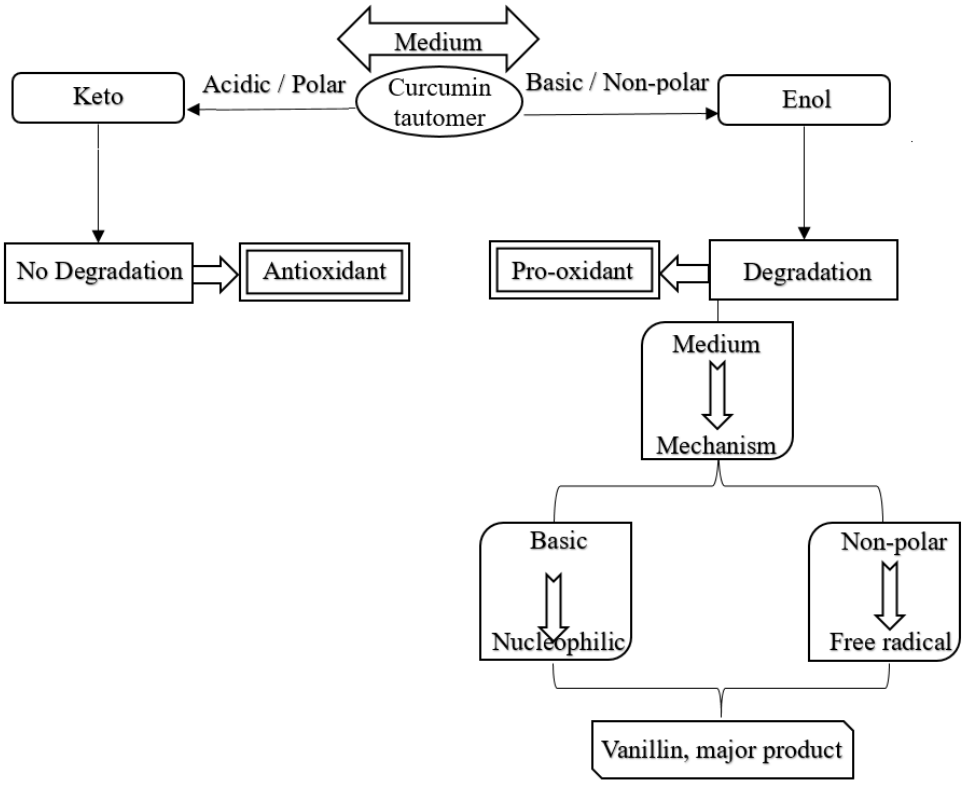


Figure 7. The activity of tautomers of curcumin in different mediums

Structure activity relationship of demethoxycurcumin and bisdemethoxy-curcumin and comparison with curcumin

General introduction about demethoxycurcumin and bisdemethoxycurcumin. Similar to curcumin, the other two curcuminoids (i.e., demethoxycurcumin and bisdemethoxycurcumin) contain phenolic hydroxyl groups, heptadiene chain and diketone moiety (Figure 1), which account for the various therapeutic activities of demethoxycurcumin and bisdemethoxycurcumin such as antioxidant, anti-inflammatory, anticancer [41, 42, 43]. Both are useful for the prevention of Alzheimer disease [44]. Since phenolic groups and heptadienone moiety are responsible for the general chemistry of curcumin as notified earlier, the theories postulated for curcumin hold good for other two curcuminoids.

Comparison of antioxidant activity of curcumin with demethoxycurcumin and bisdemethoxycurcumin. Although all the three curcuminoids exhibit identical activities, their reactivity differs. Jayaprakasha et al. [41] evaluated that the antioxidant potential of curcumin is the highest followed by demethoxycurcumin and bisdemethoxycurcumin. This finding is valid only when curcuminoids do not undergo degradation, by employing acidic or

polar medium. On the contrary, under basic or non-polar medium, bisdemethoxycurcumin is less susceptible to degradation than demethoxycurcumin, which is still less susceptible to degradation than curcumin [45]. Besides pH or nature of the medium, the structure of the phenolic compounds has an impact on the stability of the phenolic compounds [46]. The methoxy group plays an important role in determining the activity of curcuminoids.

Nevertheless, in curcuminoids the antioxidant activity is mainly due to the active methylene group; the presence of electron donating methoxy group at *ortho* to phenolic hydroxyl group also contributes to the antioxidant activity of the molecule, by increasing the electron density on the hydroxyl group by means of an inductive effect [47]. Amongst three curcuminoids, the existence of two methoxy groups in curcumin ensures the maximum antioxidant activity. By the virtue of the occurrence of one methoxy group in demethoxycurcumin, it has better antioxidant activity than bisdemethoxycurcumin, which is devoid of methoxy group [48].

The electron donating group favours enol tautomer [49]. Hence, owing to two methoxy groups, the equilibrium shifting towards formation of enol tautomer is maximum in case of curcumin and minimum in case of bisdemethoxycurcumin among three curcuminoids. Correspondingly, bisdemethoxycurcumin is less prone to degradation than demethoxycurcumin, which in turn is less prone to degradation than curcumin.

Accordingly, in acidic or polar solvent, the rate of antioxidant activity of curcuminoids and in basic or non-polar solvent, the rate of degradation of curcuminoids is same, i.e., curcumin > demethoxycurcumin > bisdemethoxycurcumin.

Conclusion

Curcumin is a specially gifted molecule provided by Mother-Nature to protect humans from chronic health problems. By looking at its chemical structure, we can presume that its chemistry is also very simple. However, with increasing scientific research, curcumin appears to be a more complex, unique and difficult structure to comprehend. It is a symmetrical molecule found abundance in turmeric with relatively high stability in its natural form. In view of the degradation study of curcumin, this review attempts to justify the formation of different degradation products under various reaction mediums. The heptadienone moiety in curcuminoids needs to be protected from degradation to avail its beneficial effects. Since the mechanisms are elucidated on the basis of reported literature, further studies need to be carried out regarding degradation of curcuminoids, which will account for the formation of unknown degradation products.

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