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A Mini-Review: Comparison between curcumin and tetrahydrocurcumin based on their activities

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ABSTRACT

Curcumin, a natural ingredient present in turmeric rhizome is known for its various therapeutic activities such as antioxidant, anti-inflammatory, anticancer, antidiabetic, NF-kB activation suppresser. The hydrogenated derivative of curcumin, i.e., tetrahydrocurcumin, is also found to reveal the same activities. Moreover, the pro-oxidant effect of curcumin is reported, whereas tetrahydrocurcumin does not show any pro-oxidant effects. This contrasting behaviour of the two is attributed to their structures, because conjugation is involved only in curcumin, not in the tetrahydrocurcumin. It can be evidently concluded that double bonds affect the keto-enol ratio of the molecules and are therefore responsible for the degradation of curcumin, whereas tetrahydrocurcumin remains stable. Nevertheless, these double bonds are liable to affect the kinetics of beneficial activities of curcumin and tetrahydrocurcumin.

Introduction

Tetrahydrocurcumin, hexahydrocurcumin and octahydrocurcumin are the metabolites of curcumin. Synthetically, they are obtained by the reduction of curcumin (Somparn et al., 2007; Ishida et al., 2002). These hydrogenated derivatives of curcumin display the same beneficial activities as shown by curcumin (Anand et al., 2008). Amongst these, tetrahydrocurcumin has the same reactive sites as that of curcumin viz. two ortho-methoxy phenolic groups and a reactive methylene group (Sugiyama et al., 1996). However, the rate of beneficial activities of tetrahydrocurcumin and curcumin is different. In some cases, tetrahydrocurcumin is superior to curcumin (Osawa et al., 1995; Somparn et al., 2007; Murugan et al., 2008; Hoehle et al., 2006). On the other hand, in some studies, curcumin is found to be better than tetrahydrocurcumin (Nakamura et al., 1998; Pan et al., 2000).
Also, it is observed that curcumin undergoes autoxidation and reveals pro-oxidant effects (Semwal et al., 1997; Rege et al., 2012), whereas tetrahydrocurcumin is devoid of pro-oxidant potential (Prabhu et al., 2011; Aggeli et al., 2013; Aggarwal et al., 2015). This remarkable discrepancy is mainly because of the variation in their structures and the effect of the medium. In this review paper, the difference in the chemistry of curcumin and tetrahydrocurcumin has been discussed. Also, the effect of medium on the activities of the two is studied.

Structure-activity relationship of curcumin and tetrahydrocurcumin

Role of diene moiety in tetrahydrocurcumin

Tetrahydrocurcumin is obtained from curcumin by selective reduction of double bonds in the heptane linkage (Wagner et al., 2013). Structurally, curcumin (1) contains double bonds present in the heptane chain, while tetrahydrocurcumin (2) is devoid of double bonds present in the heptane chain (Fig. 1).

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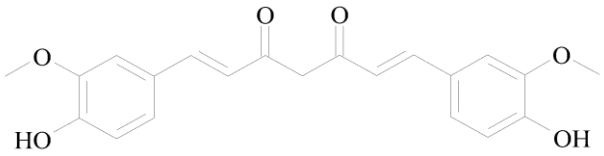

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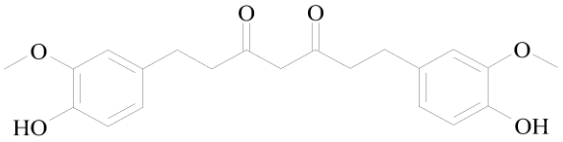

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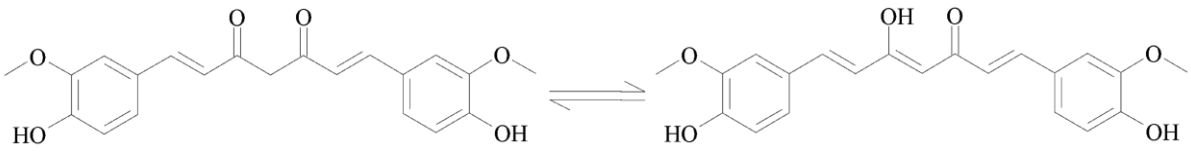
Fig. 1. Structures of curcumin and tetrahydrocurcumin

However, these double bonds, i.e., diene moiety plays a crucial role in making tetrahydrocurcumin chemically different than curcumin. Curcumin is yellow in colour, whereas tetrahydrocurcumin is colourless (Nakamura et al., 1998). Thus, the diene moiety acts as a chromophore imparting colour to the curcumin. Regarding the solubility, curcumin is more lyophilic than tetrahydrocurcumin, while tetrahydrocurcumin is more lyophobic than curcumin (Khopde et al., 2000). Curcumin acts as a Michael acceptor due to diene moiety (Anand et al., 2008). Tetrahydrocurcumin is incapable to form Michael adducts (Trivedi et al., 2020).

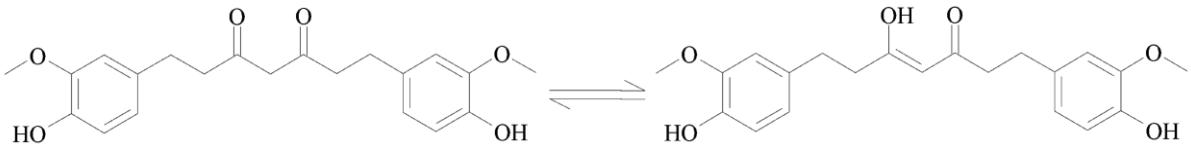
The beneficial activities of curcumin take place by the chelating effect of the diketone moiety with metal ions (Tomeh et al., 2019) or by hydrogen atom donation from active methylene group (Jovanovic et al., 1999; Priyadarsini et al., 2003). The former mechanism is enhanced due to the presence of the electron-donating ability of diene moiety and the later mechanism is enhanced due to the presence of the diene moiety, which is responsible for the interconnectivity between the ortho-methoxy phenolic groups and the diketo moiety. Consequently, the radical formed due to hydrogen atom donation is stabilized (Sandur et al., 2007). Moreover, the diene moiety affects the polarity of the molecules. Curcumin is more polar than tetrahydrocurcumin (Somparn et al., 2007). It has been observed that the polar constituents can offer better hydrogen atom donation than non-polar constituents (Oboh et al., 2008). Accordingly, the chelating effect and the rate of stabilization of radical must be less for tetrahydrocurcumin than curcumin.

Owing to the presence of β-dicarbonyl moiety, tetrahydrocurcumin exhibits keto-enol tautomerism similar to curcumin (Wagner et al., 2013; Girija et al., 2004) (Fig. 2). The enol tautomers of curcumin and tetrahydrocurcumin are shown by structures (3) and (4), respectively.

The other resonating structures of curcumin stabilized due to diene moiety (Rege et al., 2019) are shown in Fig. 3.



1 Keto form **3** Enol form



2 Keto form **4** Enol form

Fig. 2. Keto-enol tautomerism of curcumin and tetrahydrocurcumin

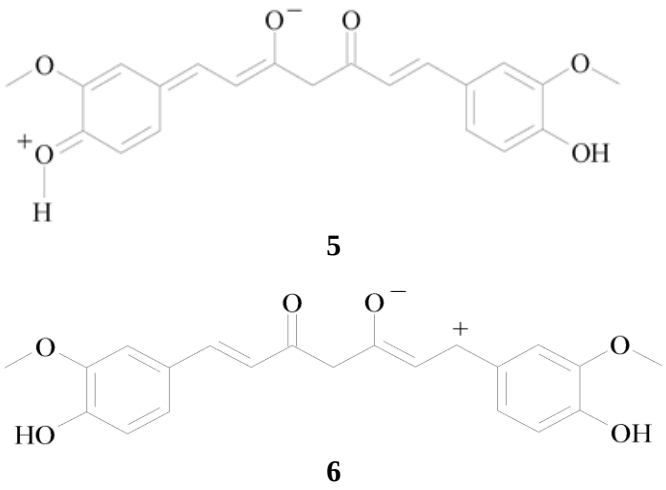
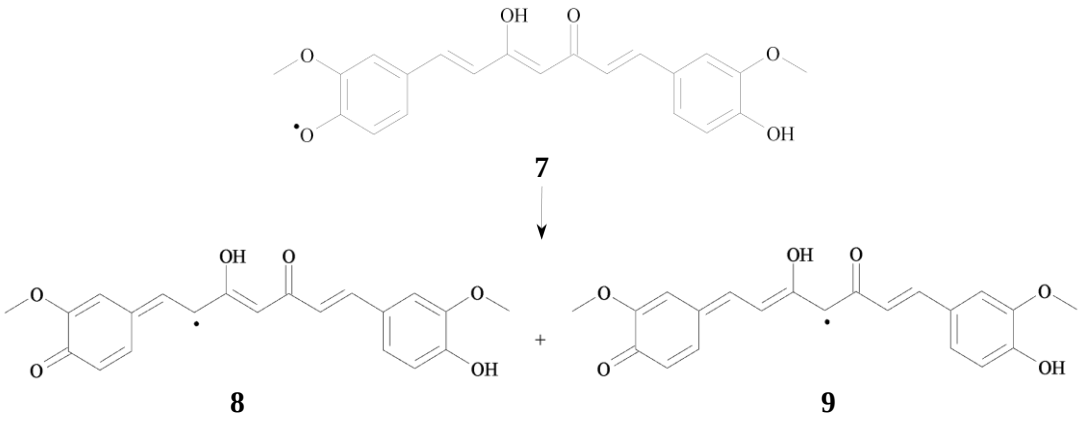


Fig. 3. Zwitterions formed by curcumin

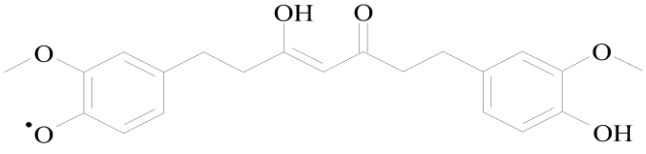
Structures (5) and (6) resemble enolic form. Since tetrahydrocurcumin is devoid of diene moiety, the formation of zwitterions similar to (5) and (6) is ruled out. As a result, the equilibrium shift towards enol tautomer is lower in tetrahydrocurcumin than that of curcumin. Consequently, the enol proportion of tetrahydrocurcumin is less than that of curcumin (Sandur et al., 2007).

Effects of medium on the activity

Curcumin imparts beneficial activities in the acidic or polar medium when the activity of keto tautomer predominates, i.e., when curcumin gets stabilized, whereas it is susceptible to degradation in the basic or non-polar medium when the activity of enol tautomer predominates (Rege et al., 2019). Hence, under stabilizing conditions, viz. acidic or polar medium, the rate of activity of curcumin is more than that of tetrahydrocurcumin. Furthermore, tetrahydrocurcumin is chemically more stable than curcumin (Hoehle et al., 2006). It is stable at neutral and basic pH (Aggarwal et al., 2015).



(a) Radicals formed by curcumin



(b) Radical formed by tetrahydrocurcumin

Fig. 4. Radicals formed by curcumin and tetrahydrocurcumin

Basic medium brings about the degradation of curcumin, making it inactive (Tonnesen and Karlsen, 1985). Now, in non-polar medium, the ortho-methoxy phenolic groups take up the reaction site and hydrogen atom donation occur through phenolic moiety to form an oxy radical (Jovanovic et al., 1999). Curcumin as well as tetrahydrocurcumin form oxy radical. The oxy radical formed in curcumin (7) gets converted to more stable carbon radicals (8) and (9), which take up oxygen accounting for the autoxidation (Rege et al., 2019) (Fig. 4). The oxy radical formed by tetrahydrocurcumin (10), unlike curcumin, does not get converted to carbon radicals due to absence of conjugation and hence, tetrahydrocurcumin does not undergo autoxidation.

Thus, α, β-unsaturated carbonyl moiety of curcumin is responsible for the production of reactive carbon species (Malik and Mukherjee, 2014; Das and Das, 2002). Hence, in the non-polar medium, curcumin displays a pro-oxidant effect whereas tetrahydrocurcumin does not. Consequently, under basic or non-polar medium, the rate of beneficial activities of tetrahydrocurcumin is more than that of curcumin.

Conclusion

Tetrahydrocurcumin varies structurally from curcumin in lacking the double bond. However, these double bonds perform the key role in determining the keto-enol ratio as well as the rate of activities. It can be concluded that under polar or acidic conditions, the rate of beneficial activities of curcumin is more than that of tetrahydrocurcumin. Under basic or non-polar conditions, double bonds promote the degradation of curcumin. However, in basic medium, curcumin cannot impart beneficial activities as it undergoes degradation. Under non-polar conditions, curcumin exhibits pro-oxidant effect as initially formed oxy radical gets converted to carbon radicals whereas tetrahydrocurcumin forms oxy radical which does not get converted to carbon radicals. It is confirmed that, besides the main reactive sites, the other functional groups also contribute to determine the rate of activity of the molecule. Thus, the structure-activity relationship makes an important reflection for evaluating the rate of activities of curcumin and tetrahydrocurucmin. Further research needs to be done to determine the role of diene moiety, on which the entire chemistry is based.

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