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Research paper

Proposal for novel curcumin derivatives as potent inhibitors against Alzheimer's disease: *Ab initio* molecular simulations on the specific interactions between amyloid-beta peptide and curcumin

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ABSTRACT

Accumulation of amyloid-β (Aβ) peptides in a brain is closely related with the pathogenesis of Alzheimer's disease. To suppress the production of Aβ peptides, we propose novel curcumin derivatives and investigate their binding properties with the amyloid precursor protein (APP), using protein-ligand docking as well as *ab initio* molecular simulations. Our proposed derivative (curcumin XIV) is found to have a large binding energy with APP and interacts strongly with the cleavage site Ala19 by secretase. It is thus expected that curcumin XIV can protect APP from the secretase attack and be a potent inhibitor against the production of Aβ peptides.

1. Introduction

The pathogenesis of Alzheimer's disease (AD) is recognized as being associated with the accumulation of amyloid-β (Aβ) peptide in a brain [1]. Aβ peptide species with various lengths (37–43 residues) are produced by both the β-secretase and the γ-secretase cleavages of an amyloid precursor protein (APP), which consists of 770 amino acid residues [2]. Among the species produced, Aβ40 and Aβ42 have a large population and the amount of Aβ42 is greater than that of Aβ40 in the brains of AD patients. To suppress the production of these pathogenic Aβ peptides, it is effective to inhibit the APP cleavage process by the secretases. However, since these secretases play an important role in cleaving other important proteins [3,4], inhibitors for the secretases may have several side effects. In the previous experiments [5,6], several γ-secretase modulators (GSMs) were synthesized to inhibit only the production of Aβ peptides, however these GSMs were effective only in mild AD patients [7]. Therefore, it is necessary to develop novel compounds that specifically bind not to the γ-secretase but to the cleavage site of APP and inhibit the attack of the γ-secretase to APP [8].

Curcumin derivatives have been widely used [9,10] as a conventional drug for treating many diseases such as inflammation, carcinoma, viral disease, oxidative stress induced apoptosis, neurodegenerative disease. Curcumin is contained in the roots of *Curcumae Rhizoma* and other curcuminoids such as demethoxycurcumin (curcumin II) and bisdemethoxycurcumin (curcumin III) are also included at the root [11]. Marketed product of curcumin usually contains curcumin I (about 77%), curcumin II (about 17%) and curcumin III (about 3%) [12]. Curcumin was found to bind directly to Aβ peptide and inhibit the aggregation of Aβ40 and Aβ42 peptides [13], suggesting the efficacy of curcumin as a therapeutic agent for ADs. Furthermore, it was revealed that curcumin can bind to APP and interfere with the production of Aβ peptides [14]. However, the mechanism of inhibition processes caused by curcumin has yet to be elucidated.

In our previous studies [15,16], the specific interactions between a short APP peptide and the nine types of curcumin derivatives were investigated, using protein-ligand docking and *ab initio* molecular simulations. Based on the results simulated, we proposed some novel curcumin derivatives that can bind specifically to the γ-secretase cleavage site of APP and inhibit the attack of γ-secretase to APP. In the present study, we additionally proposed new curcumin derivatives and investigated their binding properties with APP in the same way as that in the previous molecular simulations [15,16], in order to elucidate which curcumin derivative is the most effective inhibitor against the Aβ peptide

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production. The present results will be useful for developing new type of inhibitors against ADs.

2. Details of molecular simulations

In our previous studies [15,16], the specific interactions between APP and nine types of curcumin derivatives (curcumins I to IX) were investigated. Among them, curcumins IV to IX are our proposed derivatives, which are modified compounds of natural substance curcumin I. In fact, we substituted the two hydrogen atoms of the central part of curcumin I by the other group, because these atoms of curcumin I were found to have no remarkable contribution to the binding between APP and curcumin I in our molecular simulations. It is thus expected that this substitution may enhance the interaction between the central part of curcumin and APP.

In the present study, we additionally proposed four types of new curcumin derivatives (curcumins X–XIII) and investigated their binding properties with APP. Their chemical structures are shown in Fig. 1. In curcumin X, the two hydrogen atoms of the central part of curcumin I are substituted by a hydrophobic vinylidene group, because the previous molecular simulation [16] revealed that the curcumin derivative having a hydrophobic group at this part binds strongly to APP. In curcumin XI, the methylene group of curcumin X is substituted by two methyl groups, in order to increase the interacting sites with APP. In curcumins XII and XIII, the two hydrogen atoms of curcumin I are substituted with one or two phenyl group to enhance the hydrophobic interactions between APP and curcumin derivative. Since the γ-secretase cleavage site of APP is hydrophobic Ala19, the introduction of phenyl group is expected to enhance the hydrophobic interactions between Ala19 and the curcumin derivative. The structures of these curcumin derivatives were fully optimized by using the

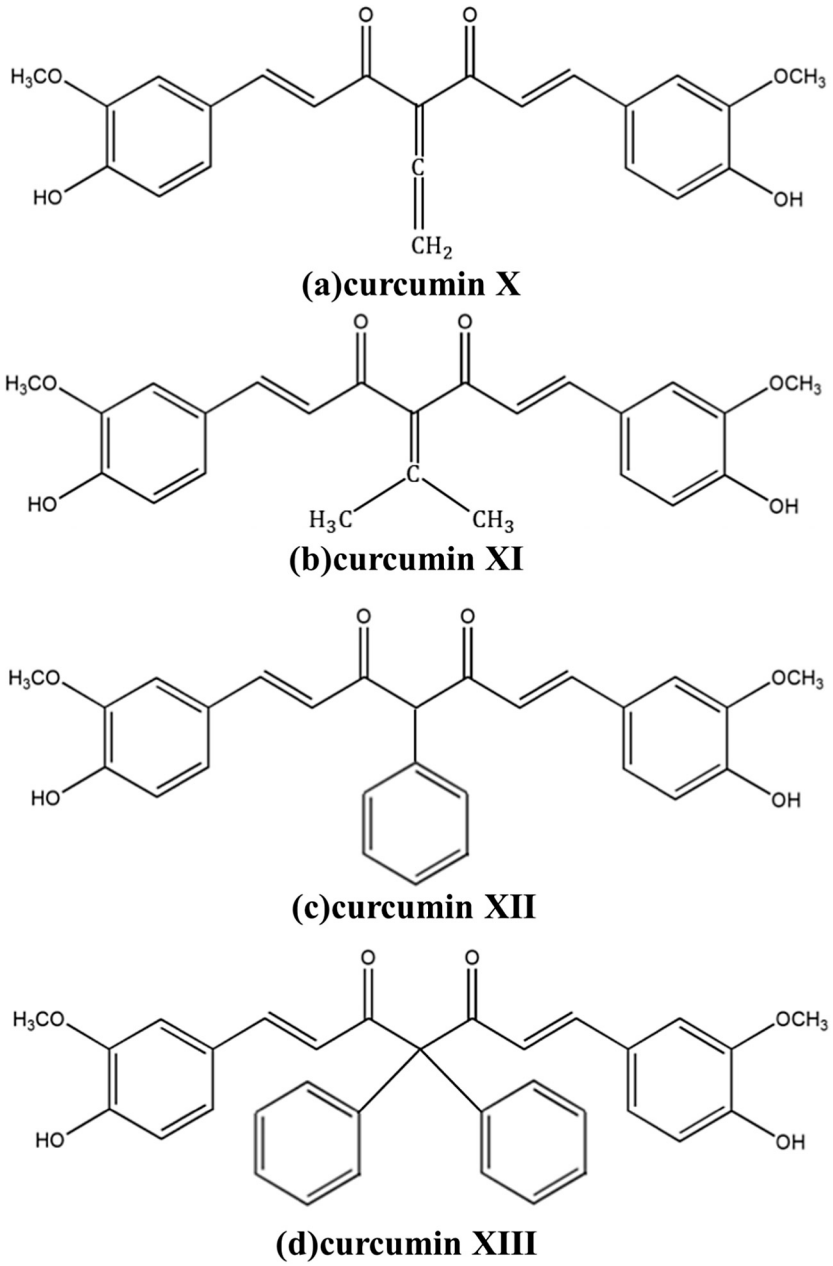

Fig. 1. Chemical structures of (a) curcumin X, (b) curcumin XI, (c) curcumin XII and (d) curcumin XIII proposed in the present study.