



## A Short Review on Effect of Curcumin and its Derivatives against Alzheimer's

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Received: 03-01-2020; Revised: 18-03-2020; Accepted: 25-03-2020.

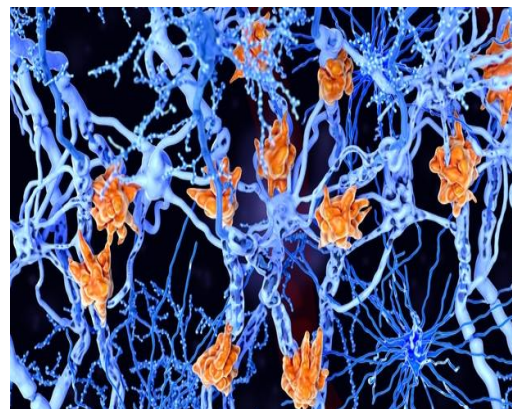
### ABSTRACT

Curcumin is a polyphenol, and it has been shown to multiple signaling molecules with demonstrating activity at the level of cells, will support its for multiple health benefits. It has been shown to the metabolic syndrome and to help in the management of inflammatory, Alzheimer, degenerative eye conditions, In addition, it has been shown to benefit the kidneys, most of these benefits are due to its anti-inflammatory and antioxidant effects. The growing body of evidence indicates the free radicals, oxidative stress, beta amyloid, cerebral deregulation caused by bio-metal toxicity and abnormal reactions is responsible for event in Alzheimer's disease. The various pharmacological benefits such as decreased, metal-chelation, delayed degradation of neurons, Beta-amyloid plaques, anti-inflammatory and antioxidant and decreased microglia formation, so the overall memory in patients with AD has improved due to curcumin. The review of curcumin and its derivatives discusses the pharmacological importance of curcumin and its derivatives provides new perspectives on its therapeutic potential and limitations. Especially actions in treating neurodegenerative diseases such as Alzheimer's.

**Keywords:** Curcumin, Alzheimer's, Neuroprotective,  $\beta$ -amyloid.

### INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease. It is characterized by progressive cognitive deterioration alongside declining activities of daily living and behavioral changes shown in fig 1. It is the foremost common sort of pre-senile and Alzheimer's. According to world Health Organization (WHO), 5% of men and 6% of woman of above the age of 60 years are affected with Alzheimer's type dementia worldwide. In India, the overall prevalence of Alzheimer's is of 33.6% per 1000 people, of which AD constitutes approximately 54% and vascular dementia constitutes approximately 39%. AD affects approximately 4.5 million people within the or approximately 10% of the population over the age of 65, and this number is projected to succeed in four times by 2050.

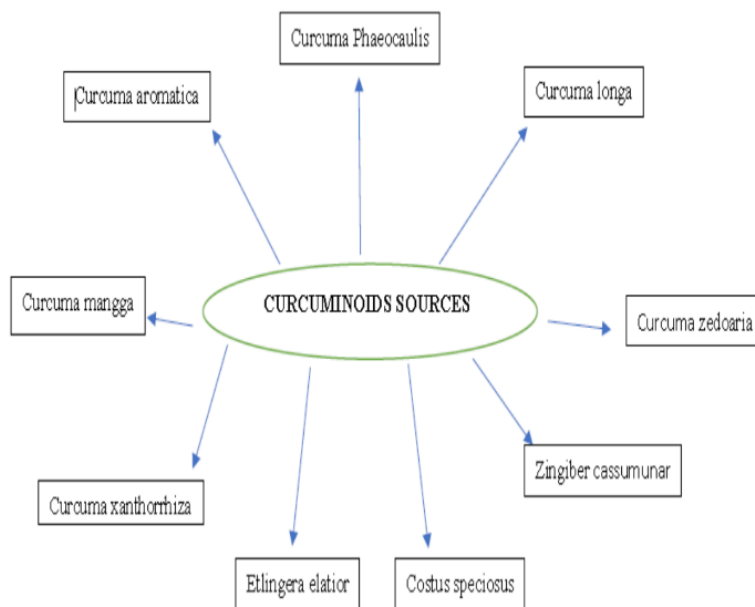


**Figure 1:** Progressive neurodegenerative disease

Since from earlier lifestyles natural source are playing important role in maintaining the normal physiology. Through advancement in research it was identified that the chemical constituents present in those natural sources are responsible for producing activity. Curcumin a polyphenol active constituent along with Curcuminoids which is present in the Turmeric belonging to family Zingiberaceae, which is said as gold solid responsible for many purposes. It was estimated that curcumin was first isolated in the year 1851 and later in the year 1910 its structure was traced as diferuloylmethane, which is freely soluble in acetone, ethanol, oils and dimethyl sulfoxide. Curcumin is present in two tautomeric forms referred to as keto and enol. The enol form is that the more stable in both solid and solution phases. Curcumin also can be used for the quantification of boron since it

reacts with boric acid to make a red colored compound called rosocyanine. The color of turmeric/curcumin was converted to deep red from yellow color when exposed to acidic conditions since it was used for many religious ceremonies. Metabolic activities of curcumin were found that when it is orally administered it metabolized to curcumin glucuronide and

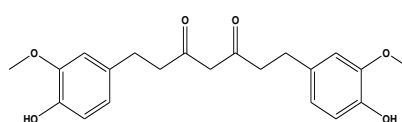
curcumin sulfonate, it is metabolized into hexahydrocurcuminol, hexahydrocurcumin and tetrahydrocurcumin when administered IP. Tetrahydrocurcumin was found to be more active than other metabolites<sup>4</sup>. The sources of Curcuminoids was shown in fig 2.



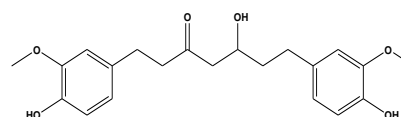
**Figure 2:** Source of curcumin

Through inhibition of glial scar formation, it suggests the therapeutic role of curcumin by repairing spinal cord injury and reduces inflammation<sup>2</sup>. Inflammation is linked with the cancer formation through inhibition of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and lipoxygenase (LOX) curcumin plays role in preventing inflammation<sup>3</sup>. It also possesses biological activities including anti-microbial, anti-angiogenesis, HIV therapies and Alzheimer's disease<sup>4</sup>. Curcumin it also plays active attention in treating in neurodegenerative disease, cardiovascular disease, diabetes, cell-apoptosis, anti-cell adhesion and motility, anti-angiogenesis<sup>5</sup> shown in figure 3. Alzheimer's is one of the most unwelcome condition where the patients suffer from dementia followed by unable to do their simple tasks. According to the survey it mainly occurs in the mid-60 aged people, curcumin is the major investigating agent used in the early detection<sup>6</sup>, the antimicrobial studies of curcumin and its derivatives (Curcumin diglucoside) revealed that, those are active even on penicillin resistant bacterial strains<sup>7</sup>.

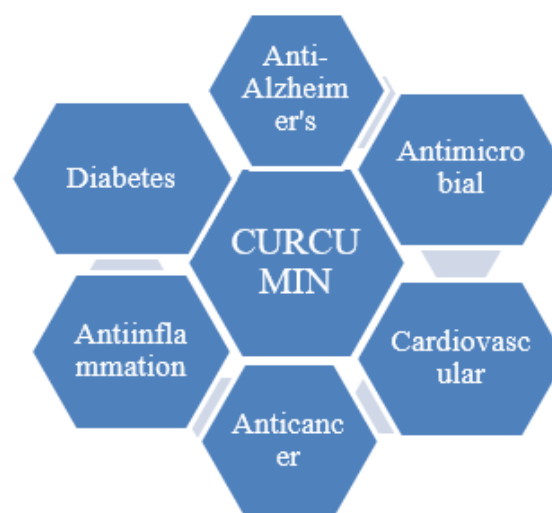
#### Structure of Curcumin



**Keto form**



**Enol form**



**Figure 3:** Pharmacological activities of Curcumin.

#### Synthesis of Curcumin

Pabon HJ reported synthesis of curcumin by using vanillin, Tributyl borate which is reacted with acetylacetone boric anhydride in the presence of Butylamine later 45% yield obtained after adding HCl and extracting with ethyl

acetate at elevated temperature. Were yield is increased to 68% under room temperature<sup>8</sup>.

Later by slight modification by adding AADFB E. Venkata Rao and P. Sudheer Curcumin was prepared by dissolving aromatic aldehyde in EtOAc and AADFB under stirring conditions, n-Butylamine which acts as a catalyst was added with microsyringe, again stirring was continued and solvent was distilled off for further isolation<sup>9</sup>.

Erika F et al., the interaction studies of therapeutic/diagnostic in neurodegenerative disease by Curcumin derivatives against A $\beta$ - fibrillar aggregates, here curcumin scaffold with some structural modifications were investigated for its ability to interfere against  $\beta$ -amyloid fibrils, among all synthesized compounds, compound1 (K2F21) shows the best activity, and the pharmacokinetic stability at physiological parameters and acid-base reactivity of the derived curcumin derivatives were studied through molecular docking and dynamic simulations<sup>10</sup>.

Gamal AE et al., Novel synthetic steroidal curcumin derivatives against Alzheimer's based on in vivo studies, which involves the synthesis of combined curcumin molecule with steroidal moiety and curcumin moiety with heterocyclic nucleus. All the synthesized molecules were exposed to the female adult albino rats so which extends the study of anti-Alzheimer's disease. Among the tested compounds (2, 3, 8C) with various intensities showed anti-Alzheimer's activity<sup>11</sup>.

Manuel SG et al., (2013) Aiming for identifying the features of chemical moiety against Ache (acetylcholinesterase) of Electricus, Table-1. The set of 9 derivatives of curcumin were synthesized in that 7 derivatives shown inhibitory activity. Through computational approach molecules were docked to active site of Ache, by generation of pharmacophore model the distance between two aromatic rings allows curcumin and its derivatives to bind with the active site of Ache was concluded, the synthesized compounds were compared with standard drugs (Tacrine & Galanthamine) among all structure 5&6 did not gave any activity. The activity against Ache was enhanced by the hydrogen bond donors and acceptors in keto-enol moiety and in aromatic ring of curcumin, structures and values are mentioned in the table 2<sup>12</sup>.

Ricardo BM et al., (2017) Curcumin which exerts neuroprotective effect, considering that effect of curcumin was investigated in neuronal cell culture which is previously exposed to prooxidant conditions in presence and absence of curcumin, results revealed that presence of curcumin will prevent toxicity of oxidative agents H<sub>2</sub>O<sub>2</sub> & Fe<sup>+3</sup> and relieving neuronal cells from loss of neuritogenic process through prooxidants. In addition, it also disassembles tau and slow down the tau aggregation curve. Thus, curcumin concluded as a potential compound in the prevention of cognitive disorders<sup>13</sup>.

Ikuo T et al., (2014) through modulating the A $\beta$  aggregation it is considered as a target for AD. Accordingly, Curcumin shown a good effects in modulating those aggregation, the derivatives of curcumin i.e. FMeC1 and FMeC2 were synthesized through condensation and hydrolysis, upon synthesizing these derivatives were exposed to mice which is measured through Morris water Maze test, Y-Maze test and immunohistochemistry. Here FMeC1 plays important role in the therapeutic effect towards A $\beta$  aggregation, however the amount of FMeC1 crossed BBB is low due to conversion of FMeC1 to FMeC2 in plasma which is having very low permeability towards BBB. Curcumin due to its high metabolism through GIT, and in the liver its bioavailability is very less<sup>14</sup>.

Hassan R et al., (2015) Due to poor bioavailability and instability clinical application of curcumin against AD is minimized. Through modification of curcumin by cyclohexanone in the place of diketone ring 3 derivatives of curcumin were synthesized and optimized linker length, among the synthesized derivatives 2,6-bis(3,4-dimethoxybenzylidene)-1- cyclohexanone is more stable than 2, 6-bis (3, 4-methylenedioxybenzylidene)1-cyclohexanone and 2,6-divanillylidencyclohexanone. Here the inhibitory effect of the compounds was measured by (HEWL) hen egg white lysozyme fibrillation using MTT, Thioflavin T, AFM assay. Among all the synthesized compounds, all compounds shows inhibitory activity against HEWL and through docking results were demonstrated as the compounds will bind and occupy whole active site of lysozyme<sup>15</sup>.

Lei F et al., (2014) Derivatives of curcumin showed that free radical scavenging activity, anti-Alzheimer activity rather than curcumin. Eight dimethyl amino methyl-substituted derivatives of curcumin were designed, synthesized among these compound 3a showed inhibitory activity against A $\beta$  fibrils, which is investigated through phosphate-buffered solution in presence and absence of FBS and suggesting through the logP = 3.48 it is actively crosses BBB because of its high lipophilicity. While curcumin alone did not possess the above mentioned properties<sup>16</sup>.

Michiaki Okuda et al., have been synthesized a series of curcumin derivatives to develop a new moiety for AD, among the derivatives synthesized 3-[(1E)-2-(1H-indol-6-yl) ethenyl]-5-[(1E)-2-[2-methoxy-4-(2-pyridylmethoxy) phenyl] ethenyl]-1H-pyrazol has been shown effective pharmacological activity in vivo and desirable pharmacokinetic effect when compared with curcumin. Derivative of curcumin is synthesized by using acetyl acetone as a starting material and aromatic aldehyde to obtain derivative, thus stating a better drug for AD<sup>17</sup>.

Shuangsheng Z et al., have been reported that Alzheimer's which is caused by amyloid beta which leads to incurable disease, curcumin and its derivatives plays important role in diagnosing, treating. Here the author has been synthesized the derivative of curcumin which is



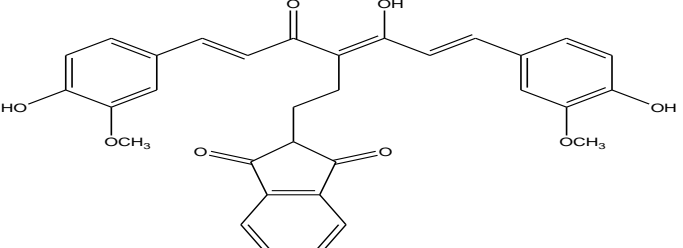
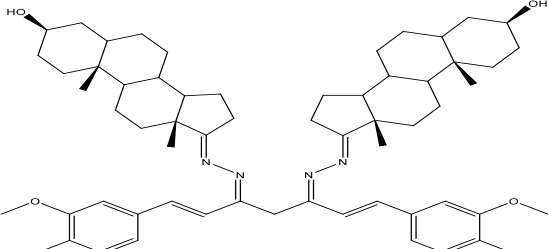
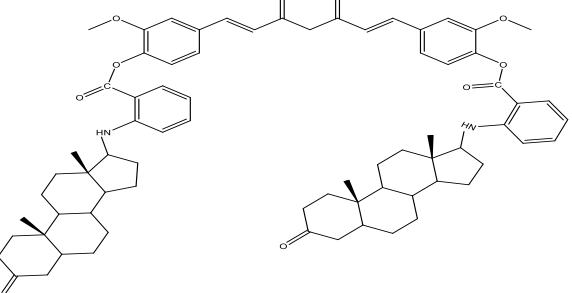
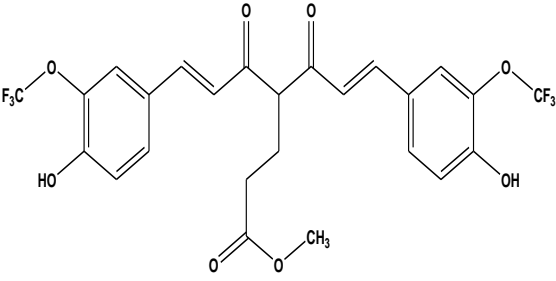
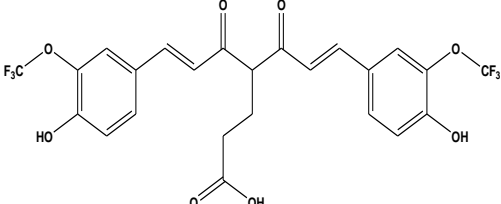
used as near-infrared (NIR) fluorescence imaging, those probes are used for the detection of A $\beta$ , dye2 has been shown very good probe for the detection of A $\beta$ <sup>18</sup>.

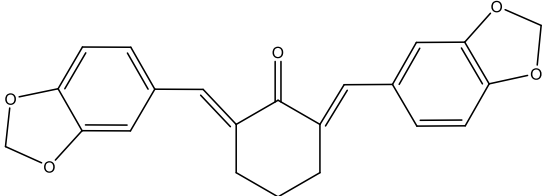
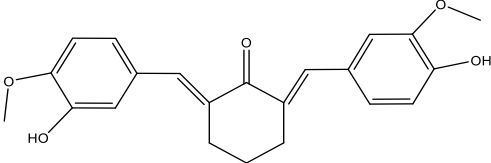
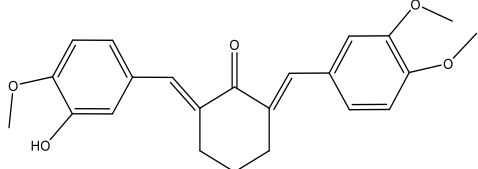
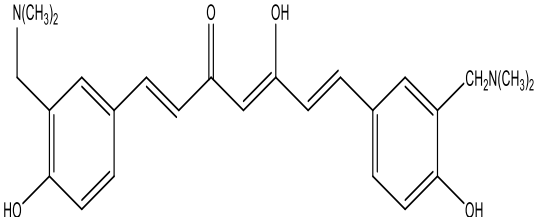
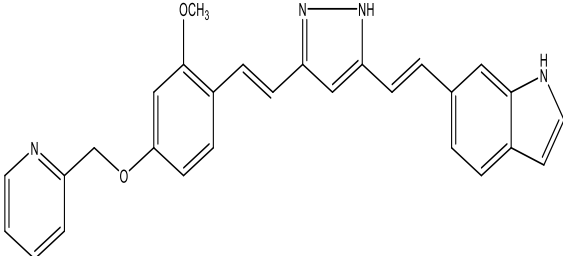
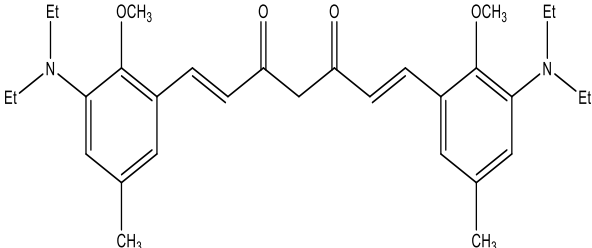
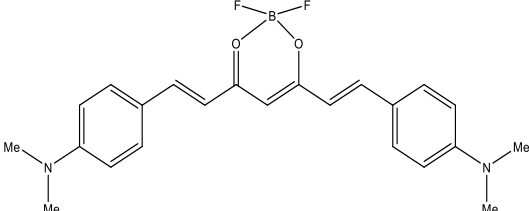
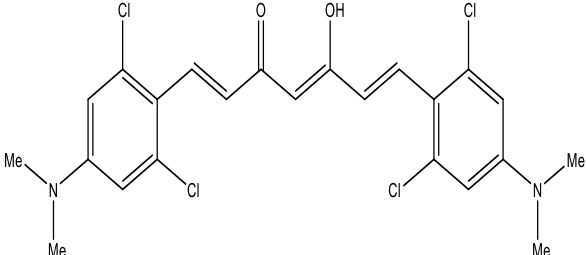
Hyunah Choo and Youhoon Chong, have been reported the detection of tau fibrils by curcumin derivative were derivative has been synthesized by using CRANAD-2 a scaffold of curcumin which is reported previously by Anna Met al<sup>19</sup> with modification of the difluoroboron chelate of the diketone author has been synthesized derivatives among them (4-dimethylamino-2, 6-dimethoxy) phenyl derivative has been shown very good fluorescent

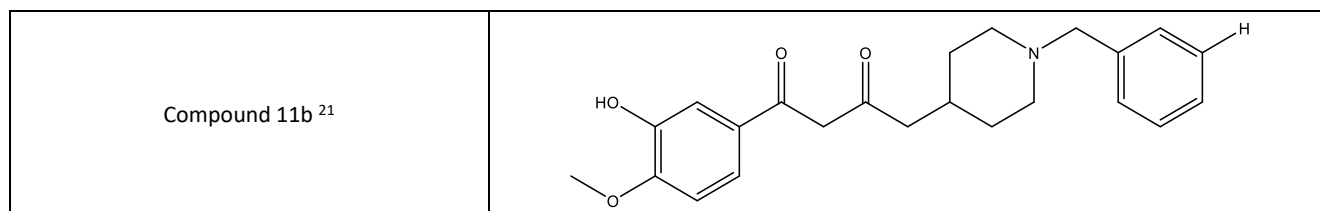
property when it binds to tau fibrils for the detection of AD<sup>20</sup>.

Hui W and Xingshu L, have been synthesized a series of novel compounds through fusing donepezil and curcumin. Among the synthesized compounds were subjected to acetylcholinesterase inhibition activity, among them compound 11b having highest acetylcholinesterase inhibition and it also exhibits excellent blood brain barrier permeability indicating that compound is having high potential while penetrating CNS and showing acetylcholinesterase inhibition activity<sup>21</sup>.

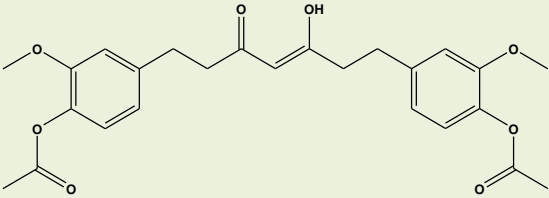
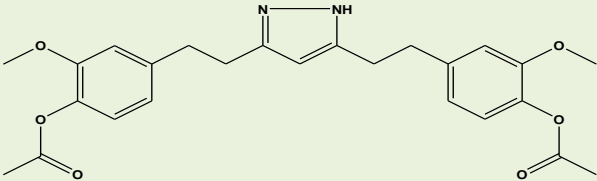
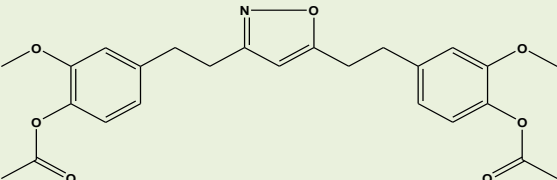
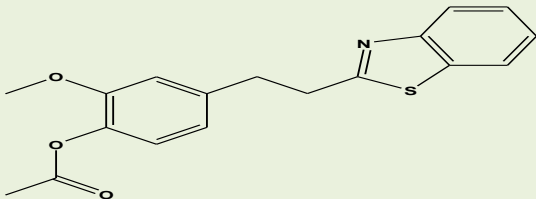
**Table 1:** Curcumin Derivatives

Compound 1 <sup>10</sup>	
Compound 2 <sup>11</sup>	
Compound 3 <sup>11</sup>	
Compound 4 <sup>14</sup> FMeC1	
Compound 5 <sup>14</sup> FMeC2	

2,6-bis(3,4-dimethoxybenzylidene)-1-cyclohexanone <sup>15</sup>	
2,6-divanillylidene Cyclohexanone <sup>15</sup>	
2,6-bis(3,4-methylenedioxy benzylidene)-1-cyclohexanone <sup>15</sup>	
Compound 3a <sup>16</sup>	
3-[(1E)-2-(1H-indol-6-yl) ethenyl]-5-[(1E)-2-[2-methoxy-4-(2-pyridylmethoxy) phenyl] ethenyl]-1H-pyrazol <sup>17</sup>	
Dye 2 <sup>18</sup>	
CRANAD-2 <sup>19</sup>	
(4-dimethylamino-2, 6-dimethoxy) phenyl <sup>20</sup>	

**Table 2:** IC value of Curcumin Derivatives <sup>12</sup>

Compounds	IC <sub>25</sub> (μM) <sup>a</sup>	95%CI <sup>b</sup> (μM)
Tacrine	55pM	7.8-533pM
Galanthamine	0.167	0.113-0.227
 Structure.1	13.2	4.4-39
 Structure.2	103	85-126
 Structure.3	52	42-64
 Structure.4	158	107-234
 Structure.5	NO <sup>c</sup>	

 <p style="text-align: center;">Structure.6</p>	NO <sup>c</sup>	
 <p style="text-align: center;">Structure.7</p>	151	116-195
 <p style="text-align: center;">Structure.8</p>	131	104-163
 <p style="text-align: center;">Structure.9</p>	303	278-328

## CONCLUSION

Based on the main findings detailed above, curcumin will lead to a promising treatment for Alzheimer's disease. The clinically studied chemical properties of curcumin and its various effects on AD shows the possibility to do further research and develop better drugs based on curcumin for treating AD. The recent review paper of John Ringman also supports some of the abovementioned properties of curcumin in AD however, large-scale human studies are required to identify the prophylactic and therapeutic effect of curcumin.

Several unanswered questions remain: What is the one main chemical property of curcumin that can be exploited in treating AD? What is the role of curcumin in other neurological disorders such as Parkinson's, Huntington's and other dementias? How does curcumin interact with neuronal plaques? Is it effective only as a food additive? Would it be effective when used alone or with other anti-inflammatory drugs? Overall, it is clear from the studies described that curcuminoids are highly promiscuous and can be used as a novel drug in future.

The complete inhibition of a target molecule by a high affinity ligand within a disease associated pathway may not work in chronic diseases such as AD because essentially all enzymes and signaling molecules have multiple roles within the body, some of which are necessary to maintain viability. Perhaps a recent example of this problem is the toxicity of secretase inhibitors. It is also likely that a ligand that dissociates A $\beta$  with high affinity will also be toxic, for the assumption that the molecular interactions stabilizing amyloid fibrils are unique to amyloid is certainly not valid; similar protein-protein interactions necessary for survival will also be affected. Therefore, the identification of drugs with more modest affinity for multiple targets may be the most effective against complex neurological diseases. Finally, while the majority of the drug development work for AD has been focused upon well-defined targets such as the secretases and A $\beta$  aggregation, much less work has been directed toward the ultimate problem, nerve cell death. The synthesis of a small molecule that is protective in a variety of neurotoxicity assays is a small step in this direction.

**ABBREVIATIONS****FBS:** Fetal Bovine Serum**AD:** Alzheimer's disease**BBB:** Blood Brain Barrier

**Acknowledgement:** I am very thankful to Principal and HOD, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B. G. Nagar, Mandya, Karnataka for providing all the facilities to carry out this work.

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**Source of Support: Nil, Conflict of Interest: None.**

