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Technical Note

Bioinformatic investigation of dietary natural compounds for prevention of onset of pre-symptomatic Alzheimer's disease by inhibiting caspase-1

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Abstract: Caspase-1 (CASP1) is a cysteine protease which is an integral part of the inflammasome and is involved in the proteolytic cleavage of inflammatory cytokines and regulating cell apoptosis. Inhibition of CASP1 deters neurodegeneration and can delay the onset of pre-symptomatic Alzheimer's disease (AD). Various clinical trials have highlighted the significance of dietary natural compounds (DNCs) in the prevention of AD. However, these trials focused on exploring the efficacy of these compounds in already established disease pathology. This research article evaluates the efficacy of DNCs against CASP1 in the prevention of pre-symptomatic AD disease. To determine the interactive potential of DNCs, an elaborate literature review was performed to look for those compounds involved in the prevention of AD. Twenty-six compounds were obtained and these are commonly found in fruits and vegetables. These compounds were further analysed with iGEMDOCK to determine their affinity with the reported active site of CASP1. Among 26 compounds, apigenin, chlorogenic acid, caffeic acid, epigallocatechin gallate, quercetin, petunidin and syringic acid successfully interacted with the reported active site of CASP1. From this study, we provide an insilico justification that these DNCs may prevent the onset of pre-symptomatic AD and rescue neuronal integrity and synaptic plasticity from CASP1.

Keywords: pre-symptomatic neurodegeneration, caspase-1, dietary natural compounds, Alzheimer's disease, molecular docking

INTRODUCTION

Alzheimer's disease (AD) is a reticent neurodegenerative disorder that inflicts the memory and causes cognitive impairment, which is the principal cause of dementia worldwide [1, 2]. AD is

progressive and requires decades before the onset of memory and cognitive dysfunction. This disease happens to affect mainly the elderly and individuals aged approximately 40 years [3]. Over the years, the global prevalence of AD has risen 60% and it is predicted to increase to 71% by 2040 [4]. The major contributing factor in the rise of dementia associated with AD is population aging [5, 6]. The pathophysiology of AD is complex but the appearance of amyloid plaques and neurofibrillary tangles in the brain are the principal hallmarks of the advanced AD stage. Many research groups have dedicated to discovering and developing molecular biomarkers to predict the risk of AD during the prodromal phase. Diagnosing AD at an early phase and immediate therapeutic interaction might retard the activation of inflammatory pathways and the production of toxic proteins. Recently, Flores et al. [7] identified the role of caspase-1 (CASP1) in the pre-symptomatic mouse model of AD.

CASP1, also known as interleukin-1 converting enzyme, is a cysteine protease that occurs in the form of zymogen [8]. It has a size of 30 KDa, which on proteolysis cleaves into p10 (10 KDa) and p20 (20 KDa). These protein subunits interact with apoptosis-associated speck-like protein containing a C-terminal caspase-recruitment domain (CARD) and nod-like receptor family CARD containing protein-4 (NLRC4) followed by NLR family pyrin domain containing protein-1 (NLRP1) and other intermediary proteins to form the inflammasome complex [9]. The basic function of the complex is to regulate the activity of CASP1 and induce cell death in response to endogenous danger signals produced by dying cells and pathogenic infiltration [10]. It has been observed that thwarting of CASP1 and the associated inflammasome protein reverses cognitive and memory deficits and ameliorates synaptic functioning and inflammation [7, 11-13]. Knockout mouse studies showed that the disruption of the apoptosis-associated speck-like protein reduces the deposition of amyloid-beta and increases cognitive recovery [14].

Recently, scientists have finally recognised the importance of the NLR family pyrin domain containing protein-1, CASP1 and CASP6 (NLRP1-CASP1-CASP6) pathway in the pre-symptomatic development of AD. This offers hope for robust therapeutic development for this disease [15]. Drug discovery and development is a long and strenuous process and to prepare therapeutic drugs and take them through the clinical trials and approval process may take years or even decades. On the other hand, dietary natural compounds (DNCs) are extensively explored in different diseases [16]. These compounds possess both pharmacological and biological effects and are commonly reported in different fruits, vegetables and spices. Many of these compounds are under investigation in various AD clinical trials. In the present study we hypothesise that these DNCs have anti-inflammatory and anti-CASP1 activities, We search for commonly exploited DNCs from the literature and determined their interactions with CASP1 using molecular docking method to put forward promising candidates for the prevention of pre-symptomatic AD.

METHODS

Literature Review

A literature survey of dietary compounds that are naturally found in fruits and vegetables was carried out in this study. Publications published between 2012-2021 were searched using specific keywords. Plant extracts and extract-based studies were omitted.

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Docking Method

Molecular interactions of CASP1 with each bioactive dietary compound were sought using iGEMDOCK drug screening algorithm [17]. This software determines molecular interactions between receptors and ligands using a computer-aided molecular docking method. The protein database code of CASP1 selected as the receptor is 1RWX. This protein is in complex with 4-oxo-3-{6-[4-(quinoxalin-2-yloxy)-benzoylamino]-2-thiophen-2-yl-hexanoylamino}butyric acid (YBH), which uses ARG179, HIS237, GLN283, SER339, TRP340, ARG341, HIS342, VAL348, PHE377 and ARG383 amino acids to interact with CASP1. In our study we used these same amino acid residues to find the interaction of these ligands with CASP1. The iGEMDOCK software was utilised and a standard docking algorithm was used for molecular docking [17, 18]. All docking procedures were performed thrice.

RESULTS

Results of Literature Review

An extensive literature review results in a total of 73 articles, which were analysed to extract information on DNCs and their therapeutic roles in pre- and post-clinical studies. An inclusion criterion for selecting a compound was: 1) it should be naturally occurring in fruits, vegetables and spices, and 2) it should be already identified and available in the PubChem database. Excluded were plant extracts, extract-based studies and insilico and network pharmacological studies. From our analysis, we obtained information on 26 DNCs, listed in Table 1. They have shown superior anti-Alzheimer's activity by reducing oxidative stress, neuronal apoptosis, amyloid toxicity and plaque formation while ameliorating memory and cognitive deficits in cell and animal-based models. Some of these compounds, e.g. chlorogenic acid, curcumin, epigallocatechin gallate, genistein, quercetin, and resveratrol, have been explored in clinical trials. Some compounds did not show any promising activity in clinical trials while others have results pending (Table 1). We used these compounds listed in Table 1 to check the activity of interactions with CASP1 protein using the molecular docking method.

Molecular Interaction between CASP1 and DNCs

To investigate the chemical interactions of DNCs with CASP1, we used the drug screening software iGEMDOCK as the method of molecular docking. The dietary compounds were used as ligands and the CASP1 as receptor, which was then added to the software. The binding residues in CASP1 were specified by selecting YBH as a target binding site in the software for site specific docking. The docking accuracy setting was calibrated by keeping default settings for the drug screening, keeping a number of docked solutions at 3 and population and generation size at 200/70. The docking studies were carried out thrice to obtain reproducible results and increase confidence in the results. Out of a total 26 ligands competing for interactions with the CASP1 defined active sites, 7 ligands, namely apigenin, caffeic acid, chlorogenic acid, epigallocatechin gallate, petunidin, quercetin and syringic acid, efficiently interact with the defined active site residues. These compounds form hydrogen bonding with the residues and also form hydrophobic interactions with nearby residues to stabilise the docked complexes. The results of docked interactions are listed in Table 2.

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Table 1. List of selected DNCs in in vitro and clinical studies

Compound name	Source	In vitro/In vivo study	Clinical trial	Reference
Apigenin	Plants, fruits, vegetables	β-Secretase inhibitor, anti-inflammatory and antioxidant	-	[26]
Caffeic acid	Fruits, vegetables	Reverses cognitive impairment, counteracts with amyloid toxicity, prevents tau phosphorylation	-	[27]
Chlorogenic acid	Fruits, vegetables	Reduces Aβ induced toxicity and apoptosis, restricts production of amyloid plaques and cognitive dysfunction	Pilot study in healthy individuals: improves cognitive and memory functions, mildly improves cognitive functions.	[28-30]
Curcumin	Vegetables	Reduces amyloid neurotoxicity, reverses cognitive and memory deficits	No therapeutic effect observed	[31-33]
Cyanidin	Fruits	Suppresses amyloid-beta-induced neurodegeneration, reverses cognitive impairment	-	[34, 35]
Daidzein	Vegetables	Antioxidant, improves cognitive recovery	-	[36]
Delphinidin	Fruits, vegetables	Antioxidant, reduces amyloid plaques formation, prevents action of acetylcholinesterase and amyloid fibril formation, improves cognitive recovery	-	[37, 38]
Epigallocatechin gallate	Green tea	Reduces amyloid plaques formation, improves cognitive recovery	Ongoing (Clinical trial identifier code: NCT00951834)	[39]
Eriodictyol	Fruit	Reduces amyloid plaques formation, improves cognitive recovery	-	[40]
Genistein	Vegetables	Reduces amyloid plaques formation, improves cognitive recovery	Results not posted yet (Clinical trial identifier code: NCT01982578)	[41]
Hesperetin	Fruits	Antioxidant, improves cognitive recovery	-	[42]
Inuline	Cooking spice	Reduces neuroinflammation	-	[43]
Kaempferol	Fruits, vegetables	Antioxidant, reduces neuroinflammation	-	[44]
Luteolin	Fruits, vegetables	Reduces neuroinflammation	-	[45]
Malvidin	Fruits	Antioxidant	-	[46]
Myricetin	Fruits, vegetables	Increases hippocampal CA3 pyramidal neurons population, improves cognitive recovery	-	[47]
Naringenin	Fruits, vegetables	Reduces amyloid plaques formation, improves cognitive recovery	-	[48]
Pelargonidin	Fruits, vegetables	Reduces amyloid plaques formation, improves cognitive recovery	-	[49]
Peonidin	Fruits, vegetables	Reduces amyloid plaques formation, improves cognitive recovery	-	[50]
Petunidin	Fruits, vegetables	Antioxidant	-	[46]

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Table 1 (Continued).

Compound name	Source	In vitro/in vivo study	Clinical trial	Reference
Quercetin	Fruits, vegetables	Inhibition of Aβ aggregation and tau phosphorylation	Ongoing (Clinical trial identifier code: NCT04685590)	[51]
Resveratrol	Fruits	Reduces amyloid plaques formation, improves cognitive recovery	No effect observed (Clinical trial identifier code: NCT01504854)	[52]
Silibinin	Fruits, vegetables	Inhibits acetylcholinesterase activity and amyloid aggregation	-	[53]
Silymarin	Fruits, vegetables	Reduces amyloid neurotoxicity, reverses cognitive and memory deficits	-	[54]
Sulforaphane	Vegetables	Reduces amyloid plaques formation, improves cognitive recovery	Ongoing (Clinical trial identifier code: NCT04213391)	[55]
Syringic acid	Vegetables	Reduces neuroinflammation	-	[56]

Table 2. Profile of interactions of DNCs with CASP1

Compound	Binding energy (kJ/mol)	CASP1 active site residues	Interactions observed
Apigenin	-105.7	ARG179, HIS237, GLN283, SER339, TRP340, ARG341, HIS342, VAL348, PHE377, ARG383	Hydrogen Bonding: ARG352, GLN385, PHE377; Pi-Sigma: VAL348; Pi-Anion: ASP381; Pi-Alkyl: ARG383, ALA384
Chlorogenic acid	-116.2		Hydrogen Bonding: ARG179, SER339, CYS285, GLN283, ARG341; Pi-Sigma: ILE176, HIS237; Pi-Alkyl: PRO177
Caffeic acid	-84.3		Hydrogen Bonding: ARG179, GLN283, SER347, SER236; Pi-Alkyl: ARG341, CYS285
Epigallocatechin gallate	-128.1		Hydrogen Bonding: MET235, SER236, ALA284, GLN283, ILE282, ARG286; Pi-Sulfur: MET211
Petunidin	-105.6		Hydrogen Bonding: ARG179, SER236, GLN283, ASP288; Pi-Pi Interaction: HIS237; Pi-Alkyl: ARG341
Quercetin	-108.7		Hydrogen Bonding: ARG179, GLN283, GLY238, HIS237, CYS285; Pi-Cation: ARG341
Syringic acid	-85.1		Hydrogen Bonding: HIS237, CYS285, SER236, ARG179, ARG341

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DISCUSSION

Human primary neurons express NLRP1, which is a vital component of the inflammasome complex [19]. The release of endogenous damage-associated molecular patterns from neurons activates NLRP1, which stimulates the activity of CASP1. This protein then regulates the expression of CASP6 and interleukin-1β [10]. All these proteins together direct the proteolytic processing of amyloid plaques, neurofibrillary tangles, axonal and synaptic degeneration, cytoskeletal disorganisation, and neuronal degeneration in addition to neuroinflammation [15]. Therefore, the NLRP1-CASP1-CASP6 pathway is considered an attractive target for designing and repurposing drugs in the treatment of pre-symptomatic AD [10]. These targets are exploited by various non-steroidal anti-inflammatory drugs (NSAIDs) to block the NLRP1-CASP1-CASP6 signalling pathway to alleviate inflammation [20], reduce the accumulation of amyloid plaques and improve cognitive and synaptic functioning [21, 22]. However, all these NSAIDs fail to show any desired results in the clinical trials [23].

Diet plays an important role in regulating and influencing various metabolic and physiological processes of our body. A diet comprising various phytochemicals is highly efficacious in preventing inflammation and amyloid plaque build-up and has a wide range of neuroprotective and anti-inflammatory activities [24, 25]. In this study we selected DNCs and predicted their interactions with CASP1, which is a critical element of inflammasome and NLRP1-CASP1-CASP6 signalling pathway and implicated in pre-symptomatic AD. We searched these DNCs reported in the literature and investigated their inhibitory interactions with CASP1 using insilico method. Our literature review provided a list of 26 efficient DNCs, which were explored in our study. Among these ligands, seven compounds, namely apigenin, caffeic acid, chlorogenic acid, epigallocatechin gallate, petunidin, quercetin and syringic acid, successfully established hydrogen bonding with the active pocket of CASP1. It is reported in the literature that hydrogen bonding of ligands with the receptor's active site brings functional changes within the receptor, which often results in inhibition [18]. This means these ligands might disrupt the enzymatic activity of CASP1 upon interaction in vitro, indicating a possibility of stunting the progression of AD.

CONCLUSIONS

The results of this insilico study provide preliminary findings about the role of DNCs in the possibility of preventing of pre-symptomatic AD by inhibiting CASP1. An in vitro validation in both animal and cell-based models will be fully addressed in future studies.

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