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Research Paper

Silymarin As A Promising Natural Agent for Alzheimer's Disease

Bio-medical

KEYWORDS : Alzheimer's disease, silymarin, silibinin, amyloid β peptide plaque

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ABSTRACT

Alzheimer's disease (AD) is the most common cause of dementia and has increasing prevalence worldwide, while there is no effective agent to combat this disorder so far. In this review, we discussed the current evidence supporting the great potential of the natural agent silymarin to treat AD, including antioxidation, inhibiting amyloid β peptide (Aβ) aggregation, decreasing Aβ plaque, suppressing amyloid protein precursor expression, and inhibiting acetylcholinesterase. More studies are warranted to examine the therapeutic effects of silymarin on AD.

1. Introduction

As an aging-related progressive neurodegenerative condition, Alzheimer's disease (AD) clinically manifests as progressive impairments in memory, cognition and behavior [1-3]. The steadily rising incidence of AD imposes a heavy socioeconomic burden for human society. In the past decades, we have gained deeper understanding of the pathogenesis of AD, which provided opportunity to develop therapeutic approaches to novel pathogenic targets. Despite several approved agents for AD treatment can delay onset or slow progression of this disorder, unfortunately so far there is no agent exhibiting profound disease-modifying effects.

In recent years, numerous studies suggest phytochemicals from traditional herbs represent a type of novel and promising agents to combat AD and other neurodegenerative diseases [4-7]. Silymarin is a natural extract isolated from the herb milk thistle (*Silybum marianum*) and contain a unique mixture of polyphenolic compounds, including silibinin, isosilibinin, silicristin, silidianin and *etc.*. Silibinin is considered as the major active constituent of silymarin (Figure 1). Silymarin has attracted much interest in the past decades due to their wide range of biological and pharmacological activities [8]. Silymarin is widely used in the clinical treatment of various liver diseases such as chronic cirrhosis and hepatitis [9-12]. Silymarin is also indicated to be a potential anti-cancer agent against a broad range of cancer types [13,14]. In recent years, increasing studies support that silymarin may be a novel therapeutic agent for AD. In the present review, we reviewed the current *in vitro* and *in vivo* evidence supporting the therapeutic potentials of silymarin for AD to impel future therapeutic applications of this promising agent for AD.

2. Antioxidation

Oxidative stress has been widely accepted to be a key pathogenic factor for AD [15-17]. The interests on the therapeutic potential of silymarin against AD are firstly stimulated by its antioxidant activity. Silymarin can exert antioxidant effects through scavenging free radicals directly or modulating the expression of antioxidant enzymes including glutathione and superoxide dismutase [18-20]. Lu *et al.* found that silibinin exhibited protective effects against amyloid β peptide (Aβ)(25-35)-induced neurotoxicity by preventing memory impairment and amelioration of oxidative stress and inflammatory response [21]. Tsai *et al.* investigated the activities of silymarin on oxidative stress and lipopolysaccharide stimulation in primary neuronal/glial cell cultures and found that silymarin exhibited protective effects on glial cells against peroxide-induced reactive oxygen species (ROS) formation and cell damage. In mixed neuronal/glial cell cultures from cerebral cortex or spinal cord, silymarin was found to be more effective than silibinin to decrease peroxide-induced ROS formation [22]. In addition, Kumar *et al.* reported that silymarin administration can increase the lifespan of CL4176 C. elegans model for AD and delay paralysis through enhancing resistance to oxidative stress [23].

3. Inhibiting Aβ aggregation

The abnormal aggregation of Aβ into amyloid plaque has been considered to be a central pathogenic event for AD [24-26]. Many *in vitro* and *in vivo* studies indicated that silymarin can target Aβ through several mechanisms.

First, silibinin acts as a novel inhibitor of Aβ aggregation. Yin *et al.* investigated Aβ aggregation-inhibitory activity of silibinin employing a ThT assay and electron microscopic imaging methods and found that silibinin can inhibit Aβ aggregation dose-dependently [27]. A recent study by Duan *et al.* found that silibinin possessed inhibitory effect on Aβ aggregation [28]. In addition, Duan *et al.* also found that silibinin can inhibit acetylcholinesterase (AChE) activity, and thus, they proposed that silibinin may be a promising dual-target therapeutic agent for AD [28].

4. Attenuating Aβ plaque

Second, several animal studies indicated that silymarin administration can attenuate the Aβ plaque burden. For instance, Murata *et al.* and Yaghmaei *et al.* found that silymarin can decrease the Aβ plaque burden and improve behavioral abnormalities in AD mouse model [29,30].

5. Suppressing APP expression

Third, various forms of Aβ are derived from amyloid protein precursor (APP) and overexpression of APP is associated with AD pathophysiology [31,32]. The study of Yaghmaei *et al.* indicated that silymarin administration can suppress the gene expression of APP in rat's brain [30].

6. Conclusions

In summary, a series of current evidence suggests that silymarin is a promising agent to combat AD. More future animal and human studies are strongly encouraged to investigate the effects of silymarin for AD.

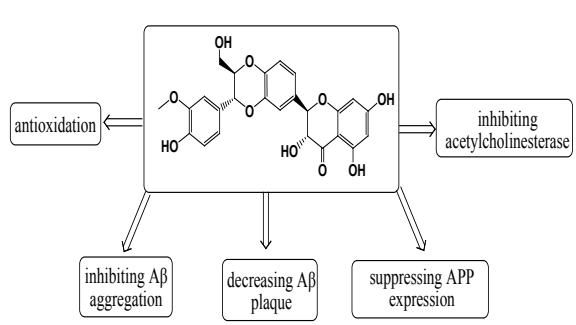


Figure 1. Chemical structure of silibinin and multiple activities supporting silymarin as a promising agent to treat AD.

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