Journal of Biological Engineering Research and Review, 2017; 4(2): 13-17
ISSN: 2349-3232 Online
DOI: 10.5281/zenodo.15341701

Mini Review

Therapeutic benefits of Ursolic acid in Parkinson's, Alzheimer's and Psychiatric diseases

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ARTICLE INFO:

Article History:
Received: 02/12/2017
Revised: 15/02/2018
Accepted: 20/02/2018
Available Online: 22/02/2018

Keywords:
Parkinson's disease;
Alzheimer's disease;
Psychiatric disorder;
Ursolic acid;
Neuroinflammation

Abstract: Ursolic acid (UA) is present in many medicinal plant plants such as Mirabilis Jalapa, Mucuna pruriens and in many fruits like apple, blueberries consumed in daily life. UA present in large quantities in apple peels. Neurodegenerative disorders are characterized by progressive degeneration of specific neurons in the central nervous system. In Parkinson's disease (PD), dopamine synthesis is impaired in the nigrostriatal region of basal ganglia, causing symptomatic movement abnormalities. Alzheimer's disease (AD) is characterized by abnormal accumulation of extracellular milieus like β-amyloid fiber and intracellular milieu like tau protein accumulation in the specific area of the brain. Psychiatric disorder (SD) also called mental disorder or mental illness is a behavioral or mental pattern that causes the noteworthy destruction of individual functioning. Oxidative stress and inflammation play an important role in the neurodegeneration of these disorders. Ursolic Acid (UA: 3β-hydroxy-urs-12-en-28-oic acid) is a natural pentacyclic triterpenoid having both anti-inflammatory and antioxidant activity which is well-established in other diseases with a relatively fewer side effect. In this review article, we have summarized the potential role and pathway of UA in PD, AD, and SD.

Citation: Rai SN, Zahra W, Birla H, Singh SS, Singh SP. Therapeutic benefits of Ursolic acid in Parkinson's, Alzheimer's and Psychiatric diseases. Journal of Biological Engineering Research and Review. 2017, 4(2), 13-17.

INTRODUCTION

Neurodegenerative disorders like Parkinson's disease (PD), Alzheimer's disease (AD), and Psychiatric disorder (SD) are the biggest burden in old ages of the whole world population. From the last few decades, researchers have tried to identify and test a novel compound that has minimal side effect and have multi-target activity in these neurodegenerative disorders. In the light of this, several compounds are identified and tested, but none have any significant impact on these neurodegenerative disorders. In recent years, Ursolic acid (UA) has shown potential impact on these disorders and having a minimal side effect. This inspires me to write a review article on this novel compound and summarizes their multi-target activity in these neurodegenerative disorders. However, epigenetics play a prominent role in the pathogenesis of this neurodegenerative disorders. Further research work is needed to test the role of UA in the epigenetics of these disorders to find a final conclusion.

Ursolic acid:

A naturally occurring pentacyclic triterpenoid Ursolic acid (UA) is found as a component in certain traditional medicinal herbs and ornamental species and is also generally common in fruits like apples, prunes, cranberries, and blueberries [1,2]. A study by Ali et al., in 2007 have focussed to study about the anti-PD potential of UA to show its protective effects based on its strong antioxidative properties [3]. UA has been widely reported to possess various biological activities such as antitumor, antioxidant and anti-inflammatory properties [4]. The biological effects of UA have been evaluated in different cell types (*in vitro*) against numerous toxic insults such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), amyloid-β (Aβ) peptides, kainic acid and others. Also, in different brain-related disorders (Alzheimer's disease (AD), Parkinson's disease (PD), depression, traumatic brain injury) based animal models, in ageing and also in clinical studies of patients with cancer and muscle atrophy, the biological effects of UA was assessed. UA shows its protective effects by preventing the oxidative damage and excessive inflammation, the major key mediators associated with multiple brain disorders. Moreover, its beneficial effect has been seen in modulating the monoaminergic system, an effect which in the cases of neurodegenerative and psychiatric conditions, might be involved to prevent mood and cognitive dysfunctions [5].

Ursolic acid and Parkinson's disease:

After the AD, PD is considered as the second most common and complex neurological disorder. PD was first of all

explained comprehensively of almost two centuries ago, but still the progress is ongoing to have the better concept of the disease. The neurodegenerative disorder, PD is basically characterized by early prominent death of dopaminergic neurons within the substantia nigra pars compacta (SNpc) in basal ganglia of the mid brain region [6]. The loss of these dopaminergic neurons causes the deficiency of dopamine (neurotransmitter) that leads to movement disorder characterised by classical parkinsonian motor symptoms. Several non- motor symptoms are also involved in the characterization of PD, some of which occurs previously to the motor dysfunction by about more than a decade. The management of PD these days involve symptomatic treatments with drugs which either focuses to increase the concentration of dopamine directly or to stimulate the dopamine receptors so as to get better results. Neurotransmitters other than dopamine such as acetylcholine are also involved in the regions of the nervous system outside the basal ganglia [6]. Earlier, primarily environmental factors were thought to be responsible for occurrence of PD, but the researchers have found that the complex interplay between genetics and environment forms the basis of PD pathogenesis. Therefore, it can be said that the neurodegenerative disorder PD is a slowly progressive disease which begins years before it can be diagnosis can be done. It is associated with various neuroanatomical areas and involves a broad range of symptoms. Clinical challenges at different steps are thus arises due to the complexities in the pathogenesis of PD are accompanied by clinical challenges at multiple steps. Principally, diagnosis of the disease at early stages is not permittable due to the lack of diagnostic tests. The post-mortem pathological examination indicating the presence of SNpc degeneration and Lewy pathology acts as the gold standard for PD diagnosis [7]. The irregular aggregation of α-synuclein protein is indicated by the presence of a pathological structure known as Lewy bodies and Lewy neurites. Still the association in between the Lewy pathology and pathogenesis of the disease is not well known. Strategies used for the management of this disease at its late stages are quite substandard. These strategies comprises of motor impairments due to dopamine depletion which do not respond to dopaminergic therapies or those that develop as complications due to long-term dopaminergic use of this drug and also due to the non-motor symptoms that appears as side-effects. So, the treatments involved in modification of the disease or to reduce the rate of neurodegeneration are still needed to be well-investigated as till now the drugs available for the management of PD are unable to match the therapeutic necessitate to stop its progression. It can only be possible by understanding the pathogenesis of PD at different stages [7].
Researchers have shown in the common form of familial PD that Ursocholanic acid helps in rescuing mitochondrial function. This rescue effect in a Parkin-deficient neuronal model system is mediated through the activation of glucocorticoid receptors and by increasing the phosphorylation of Akt by both ursocholanic acid and ursodeoxycholic acid. Ursodeoxycholic acid is a licenced drug that can be used in future for neuroprotective trials in the case of PD, while UA is a well-known naturally occurring compound [8]. Significant inhibition of dopamine-b hydroxylase (214 mmol/L), weak inhibition of MAO-B (780 mmol/L), and no inhibition against MAO-A has been seen by using UA [9]. Rai et al., in 2016 has proved the anti-oxidative activity of UA by showing that it helps in attenuating the oxidative stress in nigrostriatal tissue and by improving neurobehavioral activity in MPTP-induced Parkinsonian mouse model [6]. The authors have first standardized the dose of UA and then further shown that 25 mg/kg bwt UA is significant from that of 5mg/kg bwt. 25 mg/kgbwt of UA has shown significant increase in rotarod and hanging time while the time to cross the narrow beam by the mice was significantly reduced as compared to MPTP treated mice [6]. Different doses of UA has significantly reduced the MDA levels suggesting decreased lipid peroxidation in MPTP treated mice and 25mg/kg bwt of UA has shown the most significant result. Also, the level of catalase was found to be reduced on UA treatment as compared to MPTP mice in SN.UA treatment has also inhibited the NO radical production resulting in lower levels of ONOO– radicals in the brain and also lowered the production of reactive OH. Dopamine and its metabolites like DOPAC and HVA were also found to be significantly reduced by UA treatment [6].

Thus, the overall study done by Rai et al has helped in suggesting the neuroprotective role of UA against MPTP intoxication in mice. As oxidative stress plays an important role in PD, so the authors in this study have suggested that if the oxidative stress gets lowered, then PD can also be managed. There results have shown the reduced oxidative stress in UA treated MPTP-mice, thus suggesting the anti-oxidative property of UA. UA treatment has improved the motor impairments and the expression of TH in SN of PD mice by protecting the dopaminergic neurons. Levodopa therapy is the foremost medical treatment for the symptoms of PD. It helps in improving the motor dysfunction in the patients with PD and enhances their life by helping them in participating in day to day activities. But, on prolonged treatment Levodopa has been found to be associated with side effects like nausea, vomiting, low blood pressure, involuntary movements, and, at higher doses it may cause frail and confusion in elderlies. Evidently, this study successfully proves that UA has strong anti-oxidative activity and partial MAO-B inhibitor activity. Altogether, this study demonstrates that UA could be used as a potential drug for the prevention/treatment of PD by both reversing the symptoms and correcting the underlying cause [6].

Ursolic acid and Alzheimer's disease:

AD is the most commonly known progressive neurodegenerative disorder associated with global mental dysfunction and cognitive deterioration. Accumulation of intraneuronal tau and extracellular Aβ peptide are the common pathological features associated with AD [10]. A pathological cascade resulting in synaptic dysfunction, synaptic loss, neuronal death, and cognitive impairments occurs due to the accumulation of Aβ leaded by the deposition of insoluble neuritic or senile plaques [11]. Moreover, AD progresses due to increased oxidative stress and inflammation leading to Aβ-induced neuronal death and neurotransmitter deficits worsening the progression of AD [12]. The biological activity and toxicity of the full-length Aβ monomer is possessed by$A\beta_{25-35}$ peptide which is the core

fragment of the full-length Aβ [13]. By the intrahippocampal or intracerebroventricular (i.c.v.) injections of $A\beta_{25-35}$ the histological changes, biochemical alterations, oxidative damage, inflammatory responses, and cognitive dysfunction have been induced [14,15]. Animal model thus can be used to learn about the pathogenesis and progression of AD and this can help the researchers to screen new candidates that can be used for AD therapy [14].

In a study done by Liang et al, it was found that UA produced has protected the neurons against $A\beta_{25-35}$-induced neurotoxicity and memory impairment in mice. They have demonstrated through moris water maize (MWM) task that UA treatment has helped in attenuating $A\beta_{25-35}$-induced impairment of memory [16]. Moreover, they have seen the UA mediated reduction of MDA levels by suppressing lipid peroxidation and reduced the level of GSH in the hippocampus induced by $A\beta_{25-35}$. UA treatment has significantly suppressed the $A\beta_{25-35}$-induced upregulation of TNF-α and IL-β levels in the hippocampus. They have shown that repeated administration of UA has helped in attenuating cognitive deficits by regulating oxidative stress and inflammation in the brain [16]. In this study, $A\beta_{25-35}$ administration was seen to increase the lipid peroxidation, thus the level of MDA in the hippocampus. UA treatment has helped in reducing the level of MDA induced by $A\beta_{25-35}$, hence suggesting the beneficial effect of UA. These findings suggested that protection from lipid peroxidation is involved in the improving the effects of UA on cognitive deficits [16].

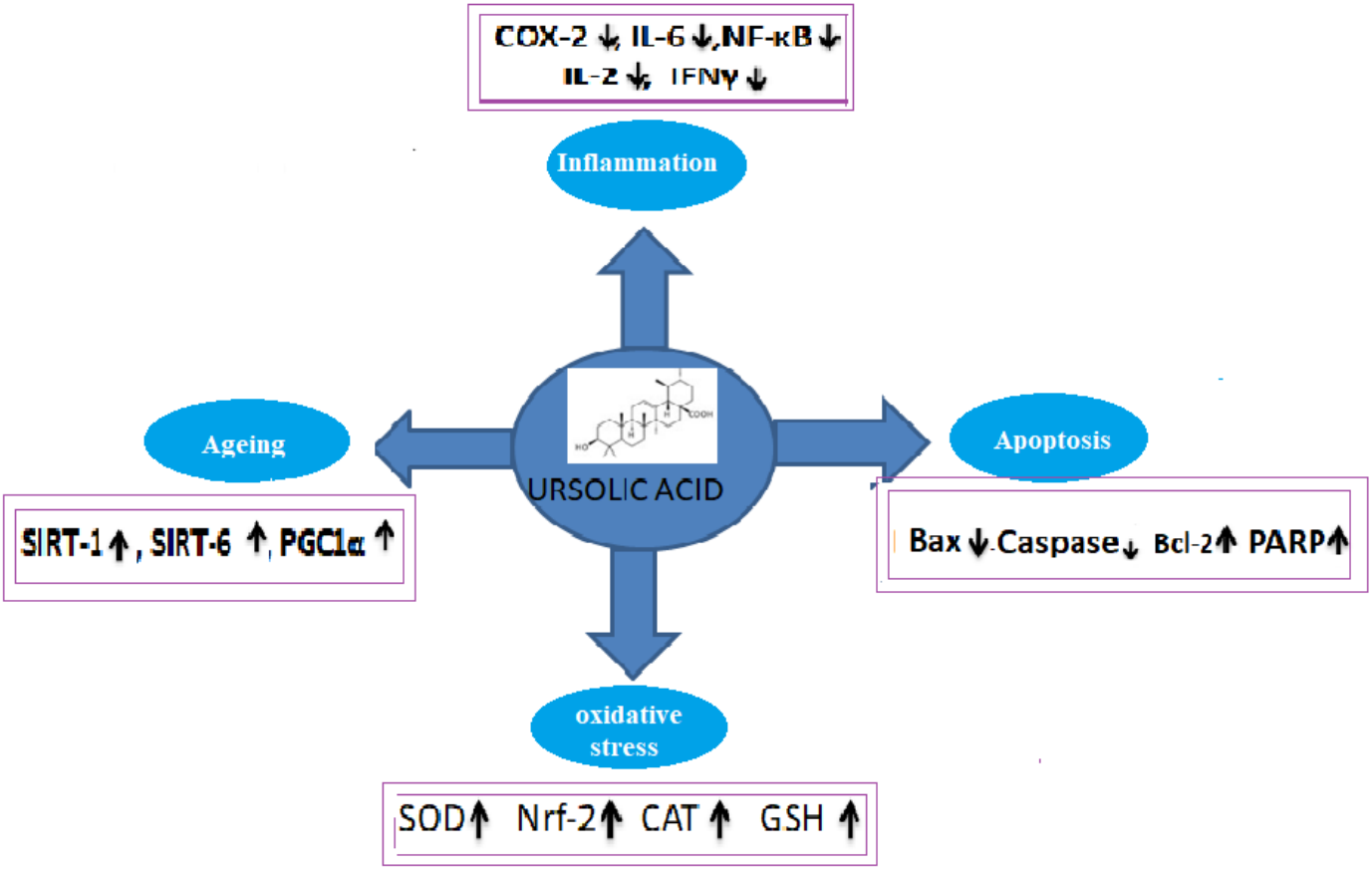

Fig. 1: Schematic representation of UA in neurodegenerative diseases like Parkinson's, Alzheimer, Psychiatric disorders through different pathway. UA controls several genes of different pathway like apoptosis, inflammation, oxidative stress and cell proliferation. Lined up arrow indicates the increased gene levels (upregulation) whereas lined down arrow indicates the decreased gene levels (down regulation) after treatment of UA.

In summary, Liang et al have demonstrated that UA can alleviate the memory impairments induced by $A\beta_{25-35}$ in mice. This beneficial effect of UA may be because of its ability to prevent oxidative stress and the inflammatory response induced by $A\beta_{25-35}$ in the hippocampus (Liang et al., 2016). In PC12 neurons, it has been seen that Aβ protein increases free radical production and lipid peroxidation leading to apoptosis and cell death. UA from *Origanum majorana* L. has helped in reducing Aβ-induced neurotoxicity in PC12 cells. UA and Vitamin E pretreatment has helped in preventing the PC12 cell from reactive oxygen species (ROS) induced by Aβ. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), lactate dehydrogenase (LDH), and trypan blue assay were used to assess decreased Aβ toxicity mediated by UA.

Thus, treatment with these antioxidants, i.e.; UA and Vitamin E has helped in inhibiting the Aβ-induced neurotoxic effect. Therefore, UA from *Origanum majorana* L. has reduced the micromolar Aβ-induced oxidative cell death [17]. In addition, the activity of caspase 3 was inhibited and the number of apoptotic cells in PC12 cells have got diminished on the administration of UA (isolated from *Cornifructus*), which is related to its effect against cell death induced by $A\beta_{25-35}$ [18].

Recent study has tried to investigate about the possible neuroprotective effect of UA in an animal model of AD. As AD is characterised by the extracellular accumulation of Aβ peptides, it can further lead to start a pathological cascade involving synaptic and neuronal loss, oxidative damage and inflammatory response associated with cognitive impairments [19]. Rodents, the widely used animal model to screen different neuroprotective agents can be induced to show this biochemical, histological and behavioural alterations by the i.c.v. administration of Aβ [20,21]. The administration of UA has lead to alleviate the learning and memory impairments in $A\beta_{25-35}$-treated mice [16] in the OFT and Morris water maze [22.23]. Additionally, UA has also helped in attenuating the level of oxidative stress and inflammatory markers in the hippocampus of mice [16].

Ursolic acid and Psychiatric disorders

In addition to the protective actions of UA against the neurodegenerative processes associated with diseases characterised by cognitive deficits and motor impairments, several studies have also suggested the probable role of UA in psychiatric disorders. Studies in this context have revealed that UA can have antidepressant effects because of its presence in some plants that have been previously reported to produce antidepressant-like effects in rodents. For example, the leaf methanolic extract of an endemic plant in India, *Mallotus peltatus* has UA as one of its main component. The local onge tribe use the leaf decocts of this plant widely as an antidepressant agent [24]. One of the first studies to show the antidepressant-like effect of UA in mice was performed by Machado et al. [25]. In this study, through the two well-recognised predictive tests of antidepressant- like action: tail suspension test (TST) and the forced swimming test, it was demonstrated that the short-term administration of UA derived from *Rosmarinus officinalis* was able to reduce the immobility time of mice [25,26]. Moreover, the effect of UA was observed at low doses and compared with that of an active doses of fluoxetine, a classical antidepressant drug [25].They have shown through pharmacological protocols that the activation of both dopamine D1 and D2 receptors are involved in the antidepressant-like effect of UA [25]. Further investigation conducted by the same group has confirmed a synergic antidepressant-like effect in the TST when the combination of sub-effective doses of UA with sub-effective doses of fluoxetine, bupropion or reboxetine was seen [25,27]. These results suggest that UA treatment may improve the efficacy of antidepressants of clinical use.

Additionally, the antidepressant-like effect of UA was found to be completely prevented by the depletion of endogenous brain serotonin levels, and by the inhibition of dopamine and norepinephrine synthesis [27]**,** reinforcing the hypothesis that the serotonergic andnoradrenergic systems are involved in its effect. Also, in TST the anti-depressant effect of UA was not affected by the administration of N-methyl-D-aspartate or the opioid receptor antagonist naloxone suggesting that neither glutamatergic nor opioid systems are involved in the behavioural effect of UA [27].

Altogether, these studies suggest that the anti-immobility effects of UA in the TST might be associated with monoaminergic neurotransmission. Of note, this mechanism of action is a feature of triple reuptake antidepressant compounds [28], which act by inhibiting the reuptake of5-hydroxytryptamine, NE and DA. So, this class of drugs help in affording a more rapid response profile, fewer side effects and better efficacy thus constituting a novel antidepressant strategy when compared with single or dual monoamine reuptake inhibitors in clinical trials [29]. Thus, UA administration may be a promising antidepressant strategy. In addition, a more recent study reported that the antidepressant-like effects of UA in the TST may depend on protein kinase A, protein kinase C, calmodulin dependent protein kinase II and mitogen-activated protein kinase (MEK 1/2) activation [29]**,** which may unite in the expression of several neurotrophins such as brain derived neurotrophic factor [30], in the same study, the authors showed thatphosphatidylinositol-3-kinase activation was not linked to the anti-immobility effect of UA [29].

CONCLUSION AND FUTURE PROSPECTIVE

In conclusion we can say that UA potentially exhibits Anti-Parkinsonian, Anti-Alzheimer's and Anti-psychiatric activity in several animal models along with *in vitro* studies (Fig. 1). Still, further research work is needed to demonstrate its therapeutic efficiency in genetic model, along with its epigenetic activity in these and some other diseases.

ABBREVIATIONS

COX-2: Cyclooxygenase-2, IL-6: Interleukin-6, NF-kB: Nuclear Factor- kB, IL-2: Interleukin 2, IFN- γ: Interferon gamma, PARP: Poly (ADP-ribose) polymerase, SOD: Superoxide Dismutase, GSH: Reduced Glutathione, CAT: Catalase, PGC1α: Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1alpha, SIRT: Sirtuin

ACKNOWLEDGMENT

The authors SNR, HB, SSS, and WZ were sincerely thankful to ICMR, DBT, ICMR, BHU India for their respective fellowship. Authors would also like to acknowledge Mallikarjuna R. Gedda for their support.

CONFLICTS OF INTEREST

The authors have reported no conflict of interest.

REFERENCES

1. Liu J. Pharmacology of oleanolic acid and ursolic acid. J Ethnopharmacol 1995; 49:57–68.
2. Neto CC, Amoroso JW, Liberty AM. Anticancer activities of cranberry phytochemicals: an update. Mol Nutr Food Res 2008; 52(1):S18–S27.

3. Ali MS, Ibrahim SA, Jalil S, Choudhary MI. Ursolic acid: a potent inhibitor of superoxides produced in the cellular system. Phytother Res 2007; 21(6):558-61.
4. Wu Dong-mei, Lu Jun, Zhang Yan-qiu, Zheng Yuan-lin, Hu Bin, Cheng Wei, Zhang Zi-feng, Li Meng-qiu. Ursolic acid improves domoic acidinduced cognitive deficits in mice. Toxicol Appl Pharmacol 2013; 271 (2):127-136.
5. Ramos-Hryb AB, Pazini FL, Kaster MP et al. Therapeutic Potential of Ursolic Acid to Manage Neurodegenerative and Psychiatric Diseases. CNS Drugs 2017; 31:1029.
6. Rai SN, Yadav SK, Singh D, Singh SP. Ursolic acid attenuates oxidative stress in nigrostriatal tissue and improves neurobehavioral activity in MPTP- induced Parkinsonian mouse model. Journal of Chemical Neuroanatomy 2016; 71(2016):41-49.
7. Rai SN, Birla H, Zahra W, Singh SN, Singh SP. Immunomodulation of Parkinson's disease using *Mucuna pruriens* (Mp). Journal of Chemical Neuroanatomy 2017; 85(2017): 27–35.
8. Mortiboys H, Aasly J, Bandmann O. Ursocholanic acid rescues mitochondrial function in common forms of familial Parkinson's disease. Brain 2013; 136:3038-50.
9. Kim Ji Ho, Kim Gun Hee, Hwang Keum Hee, Monoamine oxidase and dopamine b-hydroxylase inhibitors from the fruits of gardenia jasminoides. Biomole Ther 2012; 20(2): 214–219.
10. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006; 368(9533): 387-403.
11. Walsh DM, Selkoe DJ. Deciphering the molecular basis of memory failure in Alzheimer's disease. Neuron 2004; 44(1):181-93.
12. Massoud F, Gauthier S. Update on the pharmacological treatment of Alzheimer's disease. Curr Neurophamarcol 2010; 8(1):69-80.
13. Yankner BA, Duffy LK, Kirschner DA. Neurotrophic and neurotoxic effects of amyloid beta protein: reversal by tachykinin neuropeptides. Science 1990; 250(4978):279-82.
14. Maurice T, Lockhart BP, Privat A. Amnesia induced in mice by centrally administered β-amyloid peptides involves cholinergic dysfunction. Brain Res 1996; 706(2):181-93.
15. Lu P, Mamiya T, Lu LL, Mouri A, Zou L, Nagai T et al. Silibinin prevents amyloid β peptide-induced memory impairment and oxidative stress in mice. Br J Pharmacol 2009; 157(7):1270-7.
16. Liang W, Zhao X, Feng J, Song F, Pan Y. Ursolic acid attenuates beta-amyloid-induced memory impairment in mice. Arq Neuropsiquiatr 2016; 74(6):482-8.
17. Heo HJ, Cho HY, Hong B, Kim HK. Heo TR, Kim EK, Kim SK, Kim CJ, Shin DH. Ursolic acid of Origanum majorana L. reduces Abeta-induced oxidative injury. Mol Cells 2002; 13(1):5-11.
18. Hong SY, Jeong WS, Jun M. Protective effects of the key compounds isolated from Corni fructus against b-amyloid-induced neurotoxicity in PC12 cells. Molecules 2012; 17(9):10831–45.
19. Takahashi RH, Nagao T, Gouras GK. Plaque formation and the intraneuronal accumulation of b-amyloid in Alzheimer's disease. Pathol Int 2017; 67(4):185–93.
20. Nitta A, Itoh A, Hasegawa T, Nabeshima T. beta-Amyloid protein-induced Alzheimer's disease animal model. Neurosci Lett 1994; 170(1):63–6.
21. Takeda S, Sato N, Niisato K, Takeuchi D, Kurinami H, Shinohara M, et al. Validation of Abeta1-40 administration into mouse cerebroventricles as an animal model for Alzheimer disease. Brain Res 2009; 1280:137–47.
22. Ennaceur A. Tests of unconditioned anxiety: pitfalls and disappointments. Physiol Behav 2014; 135:55–71.
23. Vorhees CV, Williams MT. Assessing spatial learning and memory in rodents. ILAR J 2014; 55(2):310–32.
24. Chattopadhyay D, Arunachalam G, Mandal SC, Bhadra R, Mandal AB. CNS activity of the methanol extract of Mallotus peltatus (Geist) Muell Arg. leaf: an ethnomedicine of Onge. J Ethnopharmacol 2003; 85(1):99–105.
25. Machado DG, Neis VB, Balen GO, Colla A, Cunha MP, Dalmarco JB, et al. Antidepressant-like effect of ursolic acid isolated from Rosmarinus officinalis L. in mice: evidence for the involvement of the dopaminergic system. Pharmacol Biochem Behav 2012; 103(2):204–11.
26. Krishnan V, Nestler EJ. Animal models of depression: molecular perspectives. Curr Top Behav Neurosci 2011; 7:121–47.
27. Colla AR, Oliveira A, Pazini FL, Rosa JM, Manosso LM, Cunha MP, et al. Serotonergic and noradrenergic systems are implicated in the antidepressant-like effect of ursolic acid in mice. Pharmacol Biochem Behav 2014; 124:108–16.
28. Marks DM, Pae CU, Patkar AA. Triple reuptake inhibitors: the next generation of antidepressants. Curr Neuropharmacol 2008; 6(4):338–43.
29. Sharma H, Santra S, Dutta A. Triple reuptake inhibitors as potential next-generation antidepressants: a new hope? Future Med Chem 2015; 7(17):2385–406.
30. Popoli M, Brunello N, Perez J, Racagni G. Second messengerregulated protein kinases in the brain: their functional role and the action of antidepressant drugs. J Neurochem 2000; 74(1):21–33.

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