Journal of Translational Science

Research Article ISSN: 2059-268X

Vascular dementia and aliamides: A new approach for the future

Cordaro M[1], Cuzzocrea S[1,2]* and Di Paola R[1]

[1]Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Viale Ferdinando Stagno D'Alcontres 31, 98166 Messina, Italy

[2]Department of Pharmacological and Physiological Science, Saint Louis University School of Medicine, 1402 South Grand Blvd, St Louis, MO 63104, USA

Abstract

Vascular dementia (VaD) is the first usual cases of dementia after Alzheimer's disease, causing approximately 15% of instances. Yet, unlike Alzheimer's disease, there are no treatments to diminish the inflammatory process correlated to vascular dementia.

Palmitoylethanolamide (PEA) was discovered more than five decenniums ago and has been proved to counteract peripheral inflammation and mast-cell degranulation, as good as to exert neuroprotective and antinociceptive effects in rats and mice experimental model.

Luteolin (Lut) is an important flavone that has advantageous neuroprotective impacts both *in vitro* and *in vivo*.

This mini-review gives a little outline of current information of PEA and Luteolin impact on various experimental model and the novel possible PEA-Lut use for the treatment of VaD.

Background

Vascular dementia (VaD) is a dynamic disorder that influences psychological capacities that were caused by lessened blood stream to the cerebrum [1]. VaD patients may suffer both distinctive subjective impedance, for example, discouragement and tension and additionally the loss of executive capacities [1]. Until today, no other medication, excluding cholinesterase inhibitors and memantine, has demonstrated a particular advantage in the treatment of VaD, anyway they are dubious clinical criticalness; likewise Cerebrolysin has indicated advantageous impacts on VaD patients, notwithstanding, an ongoing meta-examination presumed that there is as yet lacking confirmation to prescribe it as a normal treatment for VaD [2,3]. Therefore is required to test constantly new particles, in order to find a treatment that is able to stop the progression of this pathology.

Neuroinflammation and oxidative stress (OS) has been widely correlated to be involved in the pathogenesis of both Alzheimer's disease (AD) and VaD.

Experimental evidence suggests that after stroke, the microglia acquires a M2 phenotype, which step by step changes into a pro-inflammatory M1 phenotype in the peri-infarct area [4]. The pathologic mechanism, for example, oxidative/nitrosative stress and apoptosis can stimulate the release of a proinflammatory mediators by receptive glial cells (microglia and astrocytes), and this impact can be exacerbated by an enlargement in BBB permeability, in this manner empowering the penetration of proinflammatory factors, for example, interleukins (IL-1, IL-6) and TNF-α and prompt neurodegeneration and cell passing in various cerebral locales, including those associated with psychological capacities, for example, the hippocampus [1,5-7].

Developing confirmation exhibited that OS isn't just connected to VaD, yet additionally to all its hazard factors, for example, diabetes, hypercholesterolemia and hyperhomocysteinemia [8-10]. The importance of OS in such a significant number of neurodegenerative issue the brain is highly susceptible to reactive oxygen species (ROS), since it is wealthy in unsaturated fats, which are sensible to peroxidation, moreover it has not a powerful antioxidant activity, and considering that it expends a ton of oxygen it is presented to a vital free-radicals amassing [11,12].

Several researches have been directed with a specific end goal to explore whether antioxidant and neuroprotective exerts a role in the prevention and treatment of VaD. In fact, in the last year, more than fifteen author all over the world, have focused their attention on the link between vascular dementia and neuroinflammation/oxidative stress relationship (Table 1).

One of the most widely studied families of molecules in recent years in the field of neuroinflammation is the family of ALIAmides.

ALIAmides stands for Autacoid Local Injury Antagonist amides (ALIAmides) and rapresent a group of endogenous bioactive acyl ethanolamides that include the renowned palmitoyl ethanolamide (PEA), stearoyl ethanolamide (SEA), and oleoyl ethanolamide (OEA) and that are involved in several biologic processes such as nociception, lipid metabolism and inflammations [13]. Several mechanisms describe the anti-inflammatory, anti-hyperalgesic and neuroprotective effects of PEA. In particular, PEA down-regulates mast cell activation and prevent

Correspondence to: Salvatore Cuzzocrea, Department of chemical, biological, pharmaceutical and environmental sciences, University of Messina, Viale Ferdinando Stagno D'Alcontres n°31 98166 Messina, Italy, Tel: (39) 090-6765208; E-mail: salvator@unime.it

Received: July 09, 2018; **Accepted:** July 16, 2018; **Published:** July 18, 2018

Table 1. Last year publications on vascular dementia an oxidative stress

Author(s)	Title	References
Du et al.	Molecular Mechanisms of Vascular Dementia: What Can Be Learned from Animal Models of Chronic Cerebral Hypoperfusion?	[6]
El-Dessouki et al.	Neuroprotective Effects of Simvastatin and Cilostazol in L-Methionine-Induced Vascular Dementia in Rats.	[69]
Ye et al.	Mechanisms of acupuncture on vascular dementia-A review of animal studies	[70]
Singh et al.	Possible role of endothelin receptor against hyperhomocysteinemia and β-amyloid induced AD type of vascular dementia in rats.	[71]
Siracusa et al.	Anti-Inflammatory and Neuroprotective Effects of Co-UltraPEALut in a Mouse Model of Vascular Dementia.	[25]
Yadav et al.	Resveratrol loaded solid lipid nanoparticles attenuate mitochondrial oxidative stress in vascular dementia by activating Nrf2/HO-1 pathway.	[72]
Wang et al.	Calmodulin inhibitor ameliorates cognitive dysfunction via inhibiting nitrosative stress and NLRP3 signaling in mice with bilateral carotid artery stenosis	[73]
Tanaka et al.	Thioredoxin-albumin fusion protein prevents copper enhanced zinc-induced neurotoxicity via its antioxidative activity.	[74]
Zangh et al.	Edaravone attenuates oxidative stress induced by chronic cerebral hypoperfusion injury: role of ERK/Nrf2/HO-1 signaling pathway.	[75]
Hu et al.	Postoperative intermittent fasting prevents hippocampal oxidative stress and memory deficits in a rat model of chronic cerebral hypoperfusion.	[76]
Zhu et al.	Anti-oxidative and Anti-apoptotic Effects of Acupuncture: Role of Thioredoxin-1 in the Hippocampus of Vascular Dementia Rats.	[77]
Bin-Jaliah and Sakr.	Melatonin ameliorates brain oxidative stress and upregulates senescence marker protein-30 and osteopontin in a rat model of vascular dementia.	[78]
Tiwari et al.	Potential of carnosine, a histamine precursor in rat model of bilateral common carotid artery occlusion-induced vascular dementia.	[79]
Kaundal et al.	Betulinic acid, a natural PDE inhibitor restores hippocampal cAMP/cGMP and BDNF, improve cerebral blood flow and recover memory deficits in permanent BCCAO induced vascular dementia in rats.	[80]
Zhao et al.	Ling-Yang-Gou-Teng-decoction prevents vascular dementia through inhibiting oxidative stress induced neurovascular coupling dysfunction.	[81]
Du et al.	Acupuncture inhibits TXNIP-associated oxidative stress and inflammation to attenuate cognitive impairment in vascular dementia rats.	[82]

their degranulation, modulates the activation of nuclear factor kB (NF-kB) and the synthesis of pro-inflammatory enzymes and promotes the activation of a cell surface cannabinoid CB2-like receptor, or a nuclear receptor of the peroxisome proliferator-activated receptors (PPARs) family [14]. However, the PEA does not have direct antioxidant action to prevent oxidative stress and counteract injury to proteins and DNA.

For this reason during the years, PEA was associated with different antioxidant molecules such as a (trans)resveratrol glucoside(s), polydatin [15-18] and (trans)polydatin [19-23] as well as a flavonoid luteolin [24-38].

Luteolin (Lut), like PEA, exerts a variety of pharmacological activities and anti-oxidant properties releated with its great ability to scavenge oxygen and nitrogen species. Luteolin has been appeared to constrain cytokine expression and modulates NF-kB and TLR4 signalling at micromolar concentrations in immune cells, including mast cells [39-41]. Moreover, luteolin has been shown to attenuate microglial activation and mediate BDNF-like behavior both in-vitro and in-vivo [42,43]. Until today, luteolin has been shown a protective effect on several experimental model such as epilepsy [44-48], autism spectrum disorders [26,49-60], AD [61-65] and Parkinson Disease [63,66-68].

Until now, the only work that has analyzed the antioxidant, neuroprotective and anti-inflammatory of the PEA and luteolin in an experimental model of vascular dementia was made by Siracusa et colleagues [25].

In this work co-ultraPEALut, a compound based on the association of PEA an Luteolin in a ratio of 10:1, was able to improving the behavior and histopathological features in mice after VaD-induction ameliorating cognitive and social function VaD-reduced, modulating the NF-kB and apoptotic pathway, decreasing iNOS and COX-2 expression VaD-induced and increasing BDNF and NT-3 expression.

Conclusion

Growing evidence has indicated that oxidative stress and neuroinflammation plays a key role in the progression of VaD. Disparity between antioxidant enzyme activities and ROS generation will cause lipid peroxidation, protein oxidation and nuclear and mitochondrial DNA damage, resulting in brain damage. PEA possess a very important capacity to counteract inflammation but intriguingly, has no antioxidant property per se, however its co-ultramicronization with luteolin is more efficacious than both molecule alone. This could be represents a complementary therapeutic treatment to manage VaD-associated neuroinflammation.

References

1. Venkat P, Chopp M, Chen J (2015) Models and mechanisms of vascular dementia. *Exp Neurol* 272: 97-108. [Crossref]
2. Kavirajan H, Schneider LS (2007) Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. *Lancet Neurol* 6: 782-792. [Crossref]
3. Chen N, Yang M, Guo J, Zhou M, Zhu C, et al. (2013) Cerebrolysin for vascular dementia. *Cochrane Database Syst Rev* : CD008900. [Crossref]
4. Hu X, Li P, Guo Y, Wang H, Leak RK, et al. (2012) Microglia/macrophage polarization dynamics reveal novel mechanism of injury expansion after focal cerebral ischemia. *Stroke* 43: 3063-3070.
5. Iadecola C (2013) The pathobiology of vascular dementia. *Neuron* 80: 844-866. [Crossref]
6. Du SQ, Wang XR, Xiao LY, Tu JF, Zhu W, et al. (2017) Liu, molecular mechanisms of vascular dementia: what can be learned from animal models of chronic cerebral hypoperfusion? *Mol Neurobiol* 54: 3670-3682. [Crossref]
7. López-Valdés HE, Martínez-Coria H (2016) The role of neuroinflammation in age-related dementias. *Rev Invest Clin* 68: 40-48. [Crossref]
8. Maritim AC, Sanders RA, Watkins JB 3rd (2003) Diabetes, oxidative stress, and antioxidants: a review. *J Biochem Mol Toxicol* 17: 24-38. [Crossref]
9. Dias IH, Polidori MC, Griffiths HR, Hypercholesterolaemia-induced oxidative stress at the blood-brain barrier. *Biochem Soc Trans* 42: 1001-1005. [Crossref]
10. Derouiche F, Bôle-Feysot C, Naïmi D, Coëffier M. (2014) Hyperhomocysteinemia-induced oxidative stress differentially alters proteasome composition and activities in heart and aorta. *Biochem Biophys Res Commun* 452 740-745.
11. Uttara B, Singh AV, Zamboni P, Mahajan RT (2009) Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol* 7: 65-74. [Crossref]
12. Luca M, Luca A, Calandra C (2015) The role of oxidative damage in the pathogenesis and progression of alzheimer's disease and vascular dementia. *Oxid Med Cell Longev* 504678. [Crossref]

13. Chiurchiù V, Leuti A, Smoum R, Mechoulam R, Maccarrone M (2018) Bioactive lipids ALIAmides differentially modulate inflammatory responses of distinct subsets of primary human T lymphocytes. *FASEB J* fj201800107R. [Crossref]

14. Farquhar-Smith WP, Jaggar SI, Rice AS (2002) Attenuation of nerve growth factor-induced visceral hyperalgesia via cannabinoid CB(1) and CB(2)-like receptors. *Pain* 97: 11-21. [Crossref]

15. Gugliandolo E, Fusco R, Biundo F, D'Amico R, Benedetto F, et al. (2017) Palmitoylethanolamide and Polydatin combination reduces inflammation and oxidative stress in vascular injury. *Pharmacol Res* 123: 83-92.

16. Cordaro M, Impellizzeri D, Siracusa R, Gugliandolo E, Fusco R, et al. (2017) Effects of a co-micronized composite containing palmitoylethanolamide and polydatin in an experimental model of benign prostatic hyperplasia. *Toxicol Appl Pharmacol* 329: 231-240. [Crossref]

17. Di Paola R, Fusco R, Gugliandolo E, Crupi R, EvangelistaM, (2016) Co-micronized Palmitoylethanolamide/Polydatin Treatment Causes Endometriotic Lesion Regression in a Rodent Model of Surgically Induced Endometriosis. *Front Pharmacol* 7: 382. [Crossref]

18. Esposito E, D I, G B, M C, R S (2016) A new co-micronized composite containing palmitoylethanolamide and polydatin shows superior oral efficacy compared to their association in a rat paw model of carrageenan-induced inflammation. *Eur J Pharmacol* 782: 107-118.

19. Cobellis L, Castaldi MA, Giordano V, Trabucco E, De Franciscis P, et al. (2011) Effectiveness of the association micronized N-Palmitoylethanolamine (PEA)-transpolydatin in the treatment of chronic pelvic pain related to endometriosis after laparoscopic assessment: a pilot study. *Eur J Obstet Gynecol Reprod Biol* 158: 82-6.

20. Murina F, Graziottin A, Felice R, Radici G, Tognocchi C (2013) Vestibulodynia: synergy between palmitoylethanolamide + transpolydatin and transcutaneous electrical nerve stimulation. *J Low Genit Tract Dis* 17: 111-6.

21. Lo Monte G, Soave I, Marci R (2013) Administration of MICRONIZED PALMITOYLETHANOLAMIDE (PEA)-transpolydatin in the treatment of chronic pelvic pain in women affected by endometriosis: preliminary results. *Minerva Ginecol* 65: 453-463. [Crossref]

22. Lo Monte G, Soave I, Marci R (2013) [Administration of micronized palmitoylethanolamide (PEA)-transpolydatin in the treatment of chronic pelvic pain in women affected by endometriosis: preliminary results]. *Minerva Ginecol* 65: 453-63.

23. Tartaglia E, Armentano M, Giugliano B, Sena T, Giuliano P, et al. (2015) Effectiveness of the association N-Palmitoylethanolamine and transpolydatin in the treatment of primary dysmenorrhea. *J Pediatr Adolesc Gynecol* 28: 447-50.

24. Skaper SD, Barbierato M, Facci L, Borri M, Contarini G (2018) Co-Ultramicronized Palmitoylethanolamide/Luteolin facilitates the development of differentiating and undifferentiated rat oligodendrocyte progenitor cells. *Mol Neurobiol* 55: 103-114. [Crossref]

25. Siracusa R, Impellizzeri D, Cordaro M, Crupi R, Esposito E (2017) Anti-Inflammatory and neuroprotective effects of co-ultrapealut in a mouse model of vascular dementia. *Front Neurol* 8: 233. [Crossref]

26. Bertolino B, Crupi R, Impellizzeri D, Bruschetta G, Cordaro M (2017) Beneficial effects of co-ultramicronized palmitoylethanolamide/luteolin in a mouse model of autism and in a case report of autism. *CNS Neurosci Ther* 23: 87-98. [Crossref]

27. Petrosino S, Di Marzo V (2017) The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations. *Br J Pharmacol* 174: 1349-1365. [Crossref]

28. Parrella E, Porrini V, Iorio R, Benarese M, Lanzillotta A (2016) PEA and luteolin synergistically reduce mast cell-mediated toxicity and elicit neuroprotection in cell-based models of brain ischemia. *Brain Res* 1648: 409-417. [Crossref]

29. Caltagirone C, Cisari C, Schievano C, Di Paola R, Cordaro M, et al. (2016) Stroke Study, co-ultramicronized palmitoylethanolamide/luteolin in the treatment of cerebral ischemia: from rodent to man. *Transl Stroke Res* 7: 54-69. [Crossref]

30. Barbierato M, Facci L, Marinelli C, Zusso M, Argentini C, et al. (2015) Co-ultramicronized palmitoylethanolamide/luteolin promotes the maturation of oligodendrocyte precursor cells. *Sci Rep* 5: 16676.

31. Siracusa R, Paterniti I, Impellizzeri D, Cordaro M, Crupi R, et al. (2015) The Association of palmitoylethanolamide with luteolin decreases neuroinflammation and stimulates autophagy in parkinson's disease model. *CNS Neurol Disord Drug Targets* 14: 1350-1365. [Crossref]

32. Siracusa R, Paterniti I, Bruschetta G, Cordaro M, Impellizzeri D, et al. (2016) The Association of palmitoylethanolamide with luteolin decreases autophagy in spinal cord injury. *Mol Neurobiol* 53: 3783-3792. [Crossref]

33. Skaper SD, Facci L, Barbierato M, Zusso M, Bruschetta G, et al. (2015) N-Palmitoylethanolamine and neuroinflammation: a novel therapeutic strategy of resolution. *Mol Neurobiol* 52: 1034-1042. [Crossref]

34. Paterniti I, Cordaro M, Campolo M, Siracusa R, Cornelius C, et al. (2014) Neuroprotection by association of palmitoylethanolamide with luteolin in experimental Alzheimer's disease models: the control of neuroinflammation. *CNS Neurol Disord Drug Targets*13: 1530-1541.

35. Cordaro M, Impellizzeri D, Paterniti I, Bruschetta G, Siracusa R, (2016) Neuroprotective effects of co-ultrapealut on secondary inflammatory process and autophagy involved in traumatic brain injury. *J Neurotrauma* 33: 132-146. [Crossref]

36. Impellizzeri D, Esposito E, Di Paola R, Ahmad A, Campolo M, et al. (2013) Palmitoylethanolamide and luteolin ameliorate development of arthritis caused by injection of collagen type II in mice. *Arthritis Res Ther* 15: R192. [Crossref]

37. Paterniti I, Impellizzeri D, Di Paola R, Navarra M, Cuzzocrea S (2013) A new co-ultramicronized composite including palmitoylethanolamide and luteolin to prevent neuroinflammation in spinal cord injury. *J Neuroinflammation* 10: 91. [Crossref]

38. Crupi R, Paterniti I, Ahmad A, Campolo M, Esposito E, et al. (2013) Effects of palmitoylethanolamide and luteolin in an animal model of anxiety/depression. *CNS Neurol Disord Drug Targets* 12: 989-1001. [Crossref]

39. Kim JS, Jobin C (2005) The flavonoid luteolin prevents lipopolysaccharide-induced NF-kappaB signalling and gene expression by blocking IkappaB kinase activity in intestinal epithelial cells and bone-marrow derived dendritic cells. *Immunology* 115: 375-87.

40. Lee JK, Kim SY, Kim YS, Lee WH, Hwang DH, et al. (2009) Suppression of the TRIF-dependent signalling pathway of Toll-like receptors by luteolin. *Biochem Pharmacol* 77: 1391-1400. [Crossref]

41. Weng Z, Patel AB, Panagiotidou S, Theoharides TC4 (2015) The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. *J Allergy Clin Immunol* 135: 1044-1052. [Crossref]

42. Lin CW, Wu MJ, Liu IY, Su JD, Yen JH (2010) Neurotrophic and cytoprotective action of luteolin in PC12 cells through ERK-dependent induction of Nrf2-driven HO-1 expression. *J Agric Food Chem* 58: 4477-4486. [Crossref]

43. Patil SP, Jain PD, Sancheti JS, Ghumatkar PJ, Tambe R, et al. (2014) Neuroprotective and neurotrophic effects of Apigenin and Luteolin in MPTP induced parkinsonism in mice. *Neuropharmacology* 86: 192-202.

44. Ayoobi F, Shamsizadeh A, Fatemi I, et al. (2017) Bio-effectiveness of the main flavonoids of Achillea millefolium in the pathophysiology of neurodegenerative disorders- a review. *Iran J Basic Med Sci* 20: 604-612. [Crossref]

45. Tambe R, Patil A, Jain P, Sancheti J, Somani G, et al. (2017) Assessment of luteolin isolated from Eclipta alba leaves in animal models of epilepsy. *Pharm Biol* 55: 264-268. [Crossref]

46. Lodhi, Jain A, Jain AP, Pawar RS, Singhai AK (2016) Effects of flavonoids from martynia annua and Tephrosia purpurea on cutaneous wound healing. *Avicenna J Phytomed* 6: 578-591.

47. Emran TB, Rahman MA, Uddin MM, Dash R, Hossen MF, et al. (2015) Molecular docking and inhibition studies on the interactions of Bacopa monnieri's potent phytochemicals against pathogenic Staphylococcus aureus. *Daru* 23: 26.

48. Shaikh MF, Sancheti J, Sathaye S (2013) Effect of eclipta alba on acute seizure models: a GABAA-mediated Effect. *Indian J Pharm Sci* 75: 380-384.

49. Zuiki M, Chiyonobu T, Yoshida M, Maeda H, Yamashita S, et al. (2017) Luteolin attenuates interleukin-6-mediated astrogliosis in human iPSC-derived neural aggregates: A candidate preventive substance for maternal immune activation-induced abnormalities. *Neurosci Lett* 653: 296-301. [Crossref]

50. Theoharides TC, Tsilioni I, Patel AB, Doyle R (2016) Atopic diseases and inflammation of the brain in the pathogenesis of autism spectrum disorders. *Transl Psychiatry* 6: 844.

51. Tsilioni I, Taliou A, Francis K, Theoharides TC (2015) Children with autism spectrum disorders, who improved with a luteolin-containing dietary formulation, show reduced serum levels of TNF and IL-6. *Transl Psychiatry* 5: 647. [Crossref]

52. Theoharides TC, Stewart JM, Hatziagelaki E, Kolaitis G (2015) Brain "fog," inflammation and obesity: key aspects of neuropsychiatric disorders improved by luteolin. *Front Neurosci* 9: 225. [Crossref]

53. Theoharides TC, Athanassiou M, Panagiotidou S, Doyle R (2015) Dysregulated brain immunity and neurotrophin signaling in Rett syndrome and autism spectrum disorders. *J Neuroimmunol* 279: 33-38.

54. Theoharides TC, Asadi S, Panagiotidou S, Weng Z, (2013) The "missing link" in autoimmunity and autism: extracellular mitochondrial components secreted from activated live mast cells. *Autoimmun Rev* 12: 1136-1142.

55. Taliou A, Zintzaras E, Lykouras L, Francis K (2013) An open-label pilot study of a formulation containing the anti-inflammatory flavonoid luteolin and its effects on behaviour in children with autism spectrum disorders. *Clin Ther* 35: 592-602.

56. Theoharides TC (2013) Is a subtype of autism an allergy of the brain? *Clin Ther* 35: 584-591. [Crossref]

57. Theoharides TC, Asadi S, Patel AB (2013) Focal brain inflammation and autism. *J Neuroinflammation* 10: 46. [Crossref]

58. Theoharides TC, Asadi S, Panagiotidou S (2012) A case series of a luteolin formulation (NeuroProtek(R)) in children with autism spectrum disorders. *Int J Immunopathol Pharmacol* 25: 317-323.

59. Asadi S, Theoharides TC (2012) Corticotropin-releasing hormone and extracellular mitochondria augment IgE-stimulated human mast-cell vascular endothelial growth factor release, which is inhibited by luteolin. *J Neuroinflammation* 9: 85.

60. Parker-Athill E, Luo D, Bailey A, Giunta B, Tian J, et al. (2009) Flavonoids, a prenatal prophylaxis via targeting JAK2/STAT3 signaling to oppose IL-6/MIA associated autism. *J Neuroimmunol* 217: 20-27. [Crossref]

61. Kwon Y (2017) Luteolin as a potential preventive and therapeutic candidate for Alzheimer's disease. *Exp Gerontol* 95: 39-43. [Crossref]

62. Omar SH, Scott CJ, Hamlin AS, Obied HK2 (2017) The protective role of plant biophenols in mechanisms of Alzheimer's disease. *J Nutr Biochem* 47: 1-20. [Crossref]

63. Rangarajan P, Karthikeyan A, Dheen ST (2016) Role of dietary phenols in mitigating microglia-mediated neuroinflammation. *Neuromolecular Med* 18: 453-464.

64. Leyva-Lopez N, Gutierrez-Grijalva EP, Ambriz-Perez DL, Heredia JB (2016) Flavonoids as cytokine modulators: a possible therapy for inflammation-related diseases. *Int J Mol Sci* 17. [Crossref]

65. Nabavi SF, Braidy N, Gortzi O, Sobarzo-Sanchez E, Daglia M (2015) Luteolin as an anti-inflammatory and neuroprotective agent: A brief review. *Brain Res Bull* 119: 1-11. [Crossref]

66. Wu Y, Jiang X, Yang K, Xia Y (2017) Cheng S, Inhibition of alpha-Synuclein contributes to the ameliorative effects of dietary flavonoids luteolin on arsenite-induced apoptotic cell death in the dopaminergic PC12 cells. *Toxicol Mech Methods* 27: 598-608. [Crossref]

67. Natalya A. Smirnova, Navneet Ammal Kaidery, Dmitry M. Hushpulian, Ilay I. Rakhman, Andrey A. Poloznikov (2016) Bioactive flavonoids and catechols as hif1 and nrf2 protein stabilizers - implications for parkinson's disease. *Aging Dis* 7: 745-762.

68. Hu LW, Yen JH, Shen YT, Wu KY, Wu MJ (2014) Luteolin modulates 6-hydroxydopamine-induced transcriptional changes of stress response pathways in PC12 cells. *PLoS One* 9: e97880.

69. El-Dessouki AM, Galal MA, Awad AS, Zaki HF (2017) Neuroprotective effects of simvastatin and cilostazol in l-methionine-induced vascular dementia in rats. *Mol Neurobiol* 54: 5074-5084.

70. Ye Y, Zhu W, Wang XR, Yang JW, Xiao LY, et al. (2017) Mechanisms of acupuncture on vascular dementia-A review of animal studies. *Neurochem Int* 107: 204-210. [Crossref]

71. Singh M, Prakash A (2017) Possible role of endothelin receptor against hyperhomocysteinemia and beta-amyloid induced AD type of vascular dementia in rats. *Brain Res Bull* 133: 31-41.

72. Yadav A, Sunkaria A, Singhal N, Sandhir R (2018) Resveratrol loaded solid lipid nanoparticles attenuate mitochondrial oxidative stress in vascular dementia by activating Nrf2/HO-1 pathway. *Neurochem Int* 112: 239-254.

73. Wang R, Yin YX, Mahmood Q, Wang XJ, Gao YP (2017) Calmodulin inhibitor ameliorates cognitive dysfunction via inhibiting nitrosative stress and NLRP3 signaling in mice with bilateral carotid artery stenosis. *CNS Neurosci Ther* 23: 818-826. [Crossref]

74. Tanaka KI, Shimoda M, Chuang VTG, Nishida K, Kawahara M (2018) Thioredoxin-albumin fusion protein prevents copper enhanced zinc-induced neurotoxicity via its antioxidative activity. *Int J Pharm* 535: 140-147. [Crossref]

75. Zhang D, Xiao Y, Lv P, Teng Z, Dong Y (2018) Edaravone attenuates oxidative stress induced by chronic cerebral hypoperfusion injury: role of ERK/Nrf2/HO-1 signaling pathway. *Neurol Res* 40: 1-10. [Crossref]

76. Hu Y, Zhang M, Chen Y, Yang Y, Zhang JJ (2018) Postoperative intermittent fasting prevents hippocampal oxidative stress and memory deficits in a rat model of chronic cerebral hypoperfusion. *Eur J Nutr*, 2018. [Crossref]

77. Zhu W, Wang XR, Du SQ, Yan CQ, Yang NN, et al. (2018) Anti-oxidative and anti-apoptotic effects of acupuncture: role of thioredoxin-1 in the hippocampus of vascular dementia rats. *Neuroscience* 379: 281-291. [Crossref]

78. Bin-Jaliah I, Sakr HF (2018) Melatonin ameliorates brain oxidative stress and upregulates senescence marker protein-30 and osteopontin in a rat model of vascular dementia. *Physiol Int* 105: 38-52. [Crossref]

79. Tiwari N, Bhatia P, Kumar A, Jaggi AS, Singh N (2018) Potential of carnosine, a histamine precursor in rat model of bilateral common carotid artery occlusion-induced vascular dementia. *Fundam Clin Pharmacol* [Crossref]

80. Kaundal M, Zameer S, Najmi AK, Parvez S, Akhtar M (2018) Betulinic acid, a natural PDE inhibitor restores hippocampal cAMP/cGMP and BDNF, improve cerebral blood flow and recover memory deficits in permanent BCCAO induced vascular dementia in rats. *Eur J Pharmacol* 832: 56-66. [Crossref]

81. Zhao X, Liu J, Yang S, Song D, Wang C, et al. (2018) Ling-Yang-Gou-Teng-decoction prevents vascular dementia through inhibiting oxidative stress induced neurovascular coupling dysfunction. *J Ethnopharmacol* 222: 229-238. [Crossref]

82. Du SQ, Wang XR, Zhu W, Ye Y, Yang JW, et al. (2018) Acupuncture inhibits TXNIP-associated oxidative stress and inflammation to attenuate cognitive impairment in vascular dementia rats. *CNS Neurosci Ther* 24: 39-46. [Crossref]