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Review

The beneficial role of Naringin- a citrus bioflavonoid, against oxidative stress-induced neurobehavioral disorders and cognitive dysfunction in rodents: A systematic review and meta-analysis

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ABSTRACT

Objectives: Naringin is a bioflavonoid, very abundantly found in citrus species. In literature, naringin has been scientifically well documented for its beneficial effects in various neurological disorders. In this systematic review and meta-analysis, we have made an attempt to correlate the protective role of naringin against oxidative stress-induced neurological disorders in rodents.
Methods: The systematic search was performed using electronic databases; the search was mainly focused on the role of naringin in oxidative stress-induced neuropathological conditions in rodents. While, the meta-analysis was performed on the effect of naringin on oxidative stress markers [superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), reduced glutathione (GSH), lipid peroxidation (LPO)], nitrite, mitochondrial complexes (I to IV) and enzymes (acetylcholinesterase, Na^+-K^+-ATPase, Ca^{2+}-ATPase, and Mg^{2+}-ATPase) in the rodent brain. The data was analyzed using Review Manager Software.
The results: Based on the inclusion and exclusion criteria, twenty studies were selected. The meta-analysis revealed that, naringin could significantly inhibit various physical and chemical stimuli- induced neurological perturbances in the rodent brain, mediated through oxidative stress. Further, naringin also significantly restored the levels of all the oxidative stress markers (oxidative, nitrosative, enzymes, and mitochondrial complexes) in different parts of the rodent brain.
Summary: This systematic review and meta-analysis supports the available scientific evidence on the beneficial role of naringin in the management of various neurological ailments. However, further studies involving human subjects is recommended to establish the safety and therapeutic efficacy in humans.

Abbreviations: ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GSH, reduced glutathione; LPO, lipid peroxidation; GPX, glutathione peroxidase; GST, glutathione-s-transferase; PD, parkinson disease; HD, huntington disease; AD, alzheimer's disease; MDA, malondialdehyde; SEM, standard error of mean; SD, standard deviation; MPP^+, 1-Methyl-4-phenylpyridinium; DA, dopamine; MFB, medial forebrain bundle; GDNF, glia-derived neurotrophic factor; mTORC1, mammalian target of rapamycin complex 1; TNF-α, tumor necrosis factor-α; 6-OHDA, 6-hydroxydopamine; SN, substantia niagra; BDNF, brain-derived neurotrophic factor; Bcl-2, b-cell lymphoma 2; Bad, bcl-2-associated agonist of cell death; Bax, bcl-2-associated X protein; COX-2, cyclo-oxygenase-2; iNOS, inducible nitric oxide synthase; Nrf2, nuclear factor-erythroid 2-related factor-2; GST-P1, glutathione S-transferase P1; BBB, blood-brain barrier; MMP-2, matrix metalloproteases-2; MMP-9, matrix metalloproteases-9; TIMP-1, tissue inhibitors of matrix metalloproteases-1; TIMP-2, Tissue inhibitors of matrix metalloproteases-2; NF-κB, nuclear factor-kappa-B; GFAP, glial fibrillary acidic protein; STZ, streptozotocin; PPAR-γ, peroxisome proliferation activated receptor -gamma; IL-6, interleukin-6; IL-1β, interleukin-1β; HFD, high fat diet; AchE, acetylcholinesterase; DOX, doxorubicin; EPM, elevated plus maze; HWM, hebbs Williams Maze; 3-NP, 3-Nitropropanoic acid; $AlCl_3$, aluminum chloride; OKA, okadaic acid; ICV, intracerebroventricular; TGF-β, tissue growth factor; NORT, novel object recognition task; KA, kaininc acid; DG, dentate gyrus; PTZ, pentylenetetrazole; GABA, gamma amino butyric acid; I/R, ischemia-reperfusion; TBI, traumatic brain injury; SCI, spinal cord injury; VEGF, vasculae endothelial growth factor; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; OC, osteocalcin; ALP, alkaline phosphatase; TG, triglyceride; AS, ankylosing spondylitis; STAT3, signal transducer and activator of transcription 3; JAK2, janus kinase 2; IV, inverse variance; CI, class intraval; H_2O_2, hydrogen peroxide; OH, hydroxyl radicals; DNA, deoxyribonucleic acid; RNA, ribonucleic acid; CNS, central nervous system; ATP, adenosine triphosphate.

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Contents

1. Introduction

Reactive oxygen species (ROS) are the most detrimental and free radicals are generated by diverse metabolic processes in a living system, which have the potential to cause oxidative stress [1]. The living system is known to have an intrinsic antioxidant defense system to counteract the ROS generated in the metabolic process [2], when this intrinsic antioxidant defense falls short, the antioxidants should be supplemented from an external source by means of supplements. In this context, flavonoids are well known and scientifically proved to possess potent antioxidant property, and in some instance flavonoids are proved to be even more potent than Vitamin C and E; the rich of source of flavonoids are seeds, nuts, fruits, vegetables and bark of the plants [3].

In the above context, Naringin is a well-known bioflavonoid, chemically known as 4′, 5, 7-trihydroxy flavonone 7-rhamnoglucoside (Fig. 1), and citrus species are identified as one of the rich source of naringin [4]. In literature, naringin has been scientifically

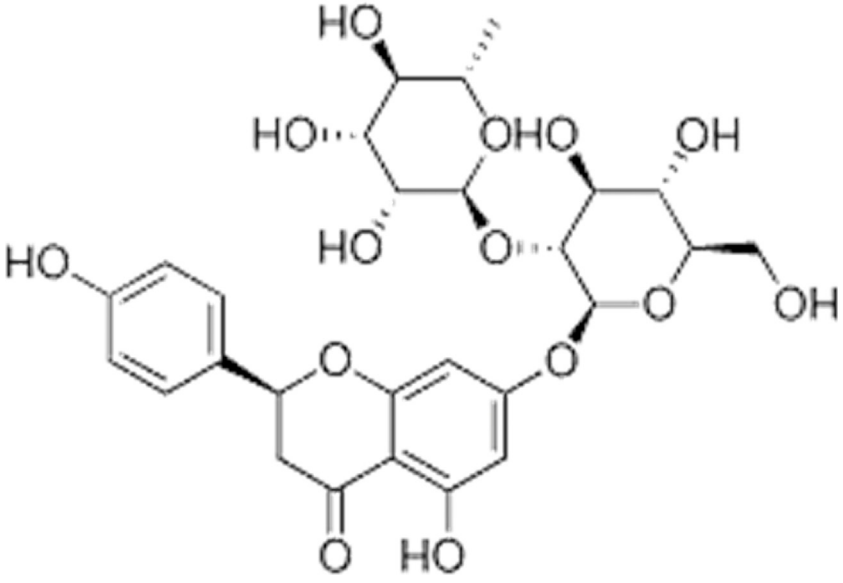

Fig. 1. Chemical structure of Naringin.