



## Review

## Therapeutic potential of naringin in neurological disorders

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## ABSTRACT

Neurological illnesses are multifactorial incurable debilitating disorders that may cause neurodegeneration. These diseases influence approximately 30 million people around the world. Despite several therapies, effective management of such disorders remains a global challenge. Thus, natural products might offer an alternative therapy for the treatment of various neurological disorders. Polyphenols, such as curcumin, resveratrol, myricetin, mangiferin and naringin (NRG) have been shown to possess promising potential in the treatment of neurodegenerative illness. In this review, we have targeted the therapeutic potential of naringin as a neuroprotective agent. The overall neuroprotective effects and different possible underlying mechanisms related to NRG are discussed. In light of the strong evidence for the neuropharmacological efficacy of NRG in various experimental paradigms, it is concluded that this molecule should be further considered and studied as a potential candidate for neurotherapeutics, focusing on mechanistic and clinical trials to ascertain its efficacy.

## 1. Introduction

Alzheimer's malady (AD), Parkinson's ailment, Ischemic brain damage and Glioblastoma are neurodegenerative disorders that influences the central nervous system. The available medicines for these disorders ameliorate the symptoms but cannot cure the disease altogether. AD results, cerebrum shrinkage, cognitive deformities, social and mental issues because of ROS, collection of extracellular Amyloid-beta 42 plaques, intracellular hyper-phosphorylated Tau tangles. Until this point in time, there is no direct remedy for AD. FDA affirmed medicate routine of (anti-inflammatory and cholinesterase inhibitors) like atorvastatin, ibuprofen, and rosiglitazone for simply symptomatic alleviation yet don't fix the illness itself and have side-reactions. Subsequently, there is a need of drug, which has less symptoms and can treat the ailment by anticipating the neuronal cell demise. The traditional herbal medications are the only choice with less side-reactions, better efficacy and economical than the engineered medications. Natural products like peptides (Lunasin), Polyphenols (Curcumin, Resveratrol) Flavonoids (Quercetin, Catechin, Kaempferol) Alkaloids (Huperzine A, Berberine) and terpenes (Gensenoside, Ginkgolides, Platycodin D) are potential restorative possibility for the AD due to having anticholinesterase, anti-

inflammatory, antioxidant, and neuroprotective capacity (Deshpande et al., 2019).

Parkinson's illness (PD) is neurodegenerative turmoil with oxidative pressure, apoptosis, mitochondrial dysfunction and inflammation. Right now, the current pharmacological medications for PD can't improve generally the degenerative procedure of dopaminergic neurons and have various reactions. Concentrates of *Valeriana officinalis*, *Valeriana wallichii*, *Passiflora incarnata*, *Passiflora cincinnata*, *Hypericum perforatum*, *Ginkgo biloba*, Ginseng and Flavonoids (Baicalein, Luteolin, Quercetin, apigenin, Rutin, Kaempferol, hesperidin) are potential restorative possibility for the PD due to having antioxidant, hostile to apoptotic, anti-inflammatory impacts. Despite the fact that the utilization of natural compounds for the neurological issue has been considered as a sheltered methodology, they are still a long way from being standard medicines, because of the absence of controlled clinical examinations that could verify both their high adequacy and wellbeing. Subsequently, better structured and progressively thorough clinical preliminaries are required before they can be set up as remedial compounds (Corona, 2018).

Ischemic brain injury is one of the main sources of death worldwide and has pulled in a great deal of consideration in the field of medication

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disclosure. Cerebral ischemia is a complex obsessive procedure including a progression of components, including free radicals' generation, oxidative pressure, disturbance of the membrane work, release of neurotransmitters and apoptosis. Thrombolytic treatment is the best restorative technique, yet the advantages are a long way from being outright. Expanded consideration in the field of medication disclosure has been centered around utilizing natural compounds having all the earmarks of being a promising remedial choice for cerebral ischemia. Resveratrol, Ginkgo biloba, Curcumin, Epigallocatechin-3-gallate, Baicalin, Ligustilide, Tanshinone, Wogonin, Paeonol, Scutellarin are Herbal lead particles under scrutiny (Ghosh et al., 2014).

Glioblastoma is a standout amongst the most forceful dangerous tumors with a generally grim survival averaging one year in spite of multimodality helpful intercessions including medical procedure, radiotherapy and associative and adjuvant chemotherapy. Scarcely any medications are FDA affirmed for glioblastoma, and the expansion of temozolomide to standard treatment builds the middle survival by just 2.5 months. Targeted treatment seemed promising *in vitro* monolayer cultures, however disillusioned in preclinical and clinical preliminaries, halfway because of the poor infiltration of medications through blood cerebrum hindrance. Because of the disappointment of traditional chemotherapies and focused on medications, examine endeavors concentrating on the utilization of less lethal specialists have expanded. Glioblastoma, the most widely recognized threatening mind tumor in grown-ups, stays serious with a hopeless middle survival. Notwithstanding various endeavors there have been not many FDA affirmed drugs for its treatment, which are not all around effective. Strikingly, numerous compounds from natural sources to be specific resveratrol, betulinic acid, icariin, quercetin, curcumin, Withaferin A, thymoquinone, cucurbitacins, Toosendanin and diosquinone are reported to have defensive impacts in glioblastoma. An abundance of preclinical information exists to help further examination utilizing natural products in glioblastoma. Forthcoming randomized clinical preliminaries must be done to investigate the utilization of adjunctive natural treatment in better focusing on obstruction and synergistically enhancing standard medications (Vengoji et al., 2018).

Epilepsy is a standout amongst the most well-known neurological disorders around the world, with around 80 percent of cases thought to be in creating countries where it is for the most part connected to superstition. The restricted supply, low viability and side reactions of antiepileptic drugs involves significant concern. Herbal prescription has dependably been generally part of treatment of epilepsy. Animal models have been utilized since days of yore to test new medications, and are constantly winding up progressively modern as innovation and scientific getting advances. *Uncaria rhynchophylla*, *Desmodium triflorum*, *Viscum album*, *Morus alba*, *Berberis integerrima*, *Mussaenda philippica*, *Justicia pectoralis*, *Gladiolus dalenii*, *Ficus religiosa*, *Withania somnifera*, *Lobelia nicotianaeifolia*, *Marsilea quadrifolia*, *Passiflora incarnata*, *Mondia whitei*, *Gastrodia elata* are potential anti epileptic natural remedies tested in animal models (Manchishi, 2018).

Naringin (NRG) is a well-studied plant secondary metabolite. It was found first by De Vry in grapefruit blossoms in 1857 (Rangaswami and Seshadri, 1939). The name NRG is likely derived from "narangi" meaning "orange" (Sinclair, 1972). The chemical structure of NRG was originally characterized by Asahina and Inubuse in 1928 (Asahina and Inubuse, 1928), represented in Fig. 1. NRG is sparingly soluble in aqueous buffers, and has weakly basic nature (Tomasik, 2003). Pharmacokinetically, NRG is converted to naringenin upon phase-I metabolism, with subsequent metabolism to *p*-coumaric acid or *p*-hydroxy benzoic acid (Bharti et al., 2014).

NRG can be isolated from several plant families and species. When tested in various pharmacological assays, NRG has been shown to possess therapeutic efficacy against cancer, allergy, hypertension, diabetes and asthma. It is also protective in liver disorders and gastrointestinal tract ailments. In recent time, we already have explored the therapeutic potential plant flavonoids Nabavi et al. (2018a); Nabavi

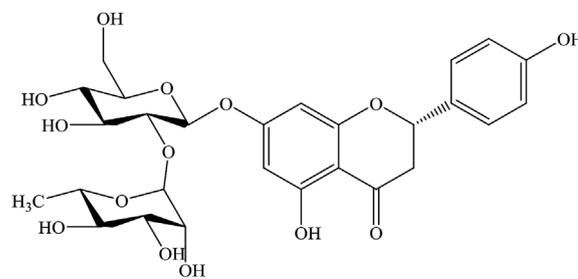
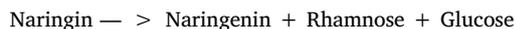


Fig - 1. Naringin structure.

et al. (2018b); Khan et al. (2019); (Rengasamy et al., 2019). Similarly, it has shown efficacy in several neurological disorders. The movement of neuroprotective drugs is constrained by the blood-cerebrum boundary. The revelation and advancement of medications for neurological sicknesses, restricted significantly because of medication selectivity presented by the BBB, prompting the neglect of most medication particles in spite of their intensity *in vitro*. NRG showed the capacity to cross the BBB which is accounted for to tie to CRMP - 2 (Collapsin Response Mediator Protein - 2), modifies structure of CRMP - 2 and decreases phosphorylation. The extensive binding capability of NRG is bolstered by the ideal negative binding energy. Furthermore, dynamic site deposits, for example, Glu 343, Thr 349, and Arg 75 were seen to contribute for the same purpose. NRG-CRMP-2 communication, combined with physicochemical properties (molecular weight, lipophilicity, polar surface zone, charge, sub-atomic flexibility, number of rotatable bond and hydrogen bonding) utilizing for an appropriate CNS medicate. So, NRG can enter the BBB and achieve the cerebrum by means of passive diffusion and applies its neuroprotective exercises (Lawal et al., 2018). This review is aimed at evaluating the available literature on the neuroprotective efficacy of this compound with underlying possible mechanism(s).

## 2. Naringin sources and structure

NRG has been isolated from several plant families. A summary of these plant species is shown in Table 1. Naringin is a disaccharide derivative that is (S)-naringenin substituted by a 2-O-( $\alpha$ -L-rhamnopyranosyl)- $\beta$ -D-glucopyranosyl moiety at position 7 via a glycosidic linkage. It is a dihydroxyflavanone, a member of 4'-hydroxyflavanones, a (2S)-flavan-4-one and a neohesperidoside (National Center for Biotechnology Information, 2019). Naringin is 4',5,7- trihydroxyflavanone- 7-rhamnoglucoside, a combination of naringenin (flavanone glycoside) and neohesperidose appended to the OH group at C-7 with bitter taste, having 208–251 °C melting point and easily dissolvable in di methyl formamide, di methyl sulfoxide and ethanol. Be that as it may, Naringin is sparingly soluble in aqueous buffers, and has weakly basic nature (Tomasik, 2003). Naringin contains the sugar moiety rutinose (L-rhamnose-D-glucose), which can be removed by hydrolysis with boiling mineral acid. The aglucose is referred to as naringenin, and it lacks the bitterness of naringin. Since naringin is only slightly soluble in water (0.05% at 20 °C), it may crystallize out when grapefruit is subjected to below-freezing temperatures (deMan et al., 2018). Removal of the bitter taste of Naringin is possible by enzymatic cleavage of the sugar moiety using a mixture of  $\alpha$ -rhamnosidase and P-glucosidase. These enzymes are isolated from microorganisms such as *Phomopsis cirri*, *Cochliobolus miyabeanus* or *Rhizoctonia solanii*:



Several neutral or bitter flavanone glycosides can be converted through ring opening to sweet chalcones, which upon additional hydrogenation, can be stabilized as sweet dihydrochalcones. Conversion of naringin to highly sweet neohesperidin dihydrochalcone is possible by alkali fragmentation to a methylketone, condensation with

**Table 1**  
The occurrence of Naringin in different plant families and part use (Haytowitz et al., 2018)

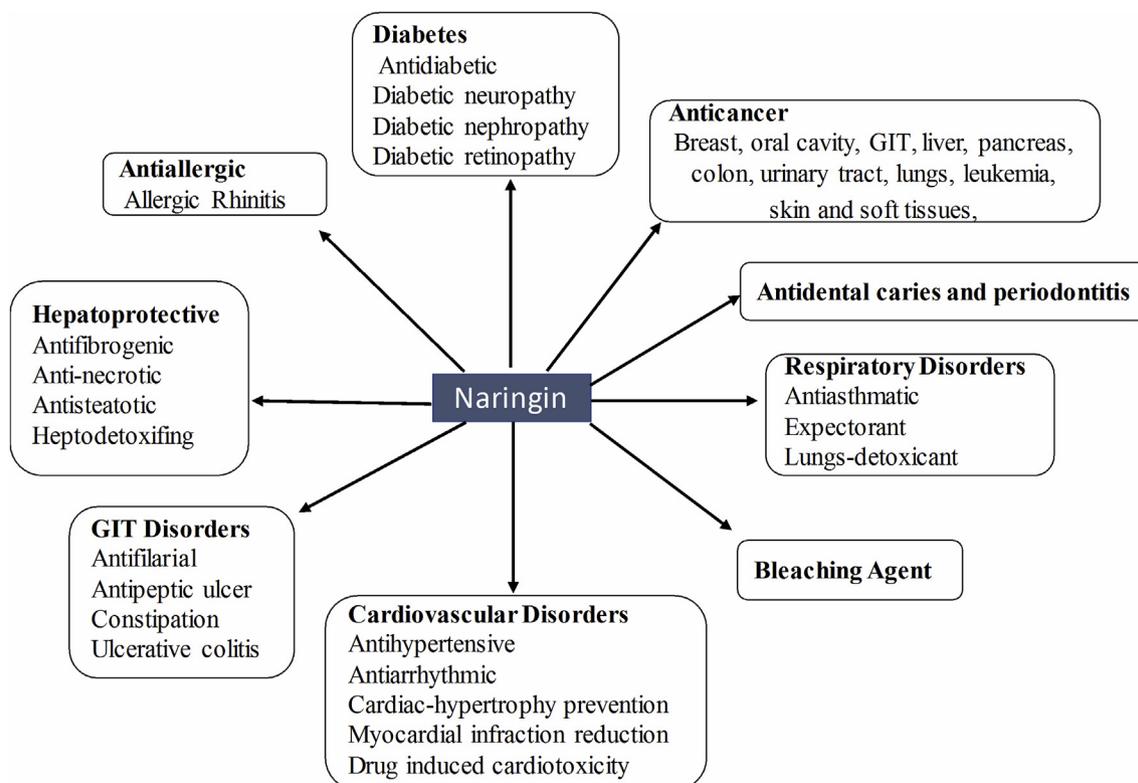
Family	Scientific name	Common name	Parts of the plant	Levels (mg/100 g)
Asteraceae	<i>Cynara scolymus</i> L.	Artichokes	Fruits	22.93
Brassicaceae	<i>Brassica oleracea</i> L.	Brussels sprouts	Raw	0.63–4.07
Poaceae	<i>Sorghum bicolor</i> (L.) Moench	Sorghum	Grains (red)	4.84
Rosaceae	<i>Fragaria × ananassa</i> (Duchesne ex Weston) Duchesne ex Rozier	Strawberries	Fruits	1.81
	<i>Prunus dulcis</i> (Mill.) D.A.Webb	Sweet almonds	Nuts	1.05
Rutaceae	<i>Citrus aurantium</i> L.	Sour Orange	Fruits	18.64–3.08
	<i>Citrus aurantiifolia</i> (Christm.) Swingle.	Lime		4.62
	<i>Citrus japonica</i> Thunb.	Kumquats		57.39
	<i>Citrus junos</i> Siebold ex Tanaka.	Yuzu		22.80–6.12
	<i>Citrus × latifolia</i> (Yu.Tanaka) Yu.Tanaka	Persian lime		3.40
	<i>Citrus limon</i> (L.) Osbeck.	Lemon		18.22
	<i>Citrus maxima</i> (Burm.) Merr.	Pummelo		1.94–32.86
	<i>Citrus paradisi</i> Macfad.	Grapefruit		16.28–62.58
	<i>Citrus reticulata</i> Blanco.	Mandarin Orange		1.74–29.15
	<i>Citrus reticulata × sinensis</i>	Tangor		3.77–11.03
	<i>Citrus sinensis</i> (L.) Osbeck.	Sweet Orange		0.11–45.42
	<i>Citrus × tangelo</i> J.W.Ingram & H.E.Moore	Tangelo		42.51
Lamiaceae	<i>Origanum vulgare</i> L.	Oregano	Aerial parts (dried)	335–418
	<i>Rosmarinus officinalis</i> L.	Rosemary	Fruits	24.86
Solanaceae	<i>Solanum lycopersicum</i> L.	Tomatoes		1.5–3.19

isovanillin to the corresponding chalcone then hydrogenation (Belitz et al., 2013). The solubility of naringin is methanol > ethyl acetate > n-butanol > isopropanol > petroleum ether > hexane, and the solubility of naringenin in these solvents follows the order ethyl acetate > isopropanol > methanol > n-butanol > petroleum ether > hexane (Zhang et al., 2015).

### 3. Therapeutic potential of naringin

NRG has shown therapeutic potential in various human disorders (Fig. 2). The hypocholesterolemic effects of NRG are characterized as antiadipogenic and antiatherogenic (Richard et al., 2013), decreasing

the esterification of cholesterol and the bioavailability of lipids to assemble lipoprotein (Cho et al., 2011) via inhibition of hepatic HMG-Coenzyme A reductase and sterol O-acyltransferase (Sui et al., 2018). NRG has been also shown to decrease infarct size of myocardium Rani et al. (2013) (Testai et al., 2013); via modulation of Na<sup>+</sup> + -K<sup>+</sup> -ATPase (Rajadurai and Prince, 2007). The beneficial role of NRG in type-2 diabetes mellitus is associated with blockage of hepatic gluconeogenesis (Constantin et al., 2014). These *in vivo* effects were identical to those inherent to gliclazide (Annadurai et al., 2012) and metformin Pu et al. (2012); (Constantin et al., 2014). *In vivo* hepatoprotective effects of NRG are expressed as regulation in hepatic lipid metabolism (Goldwasser et al., 2010). NRG has antiasthmatic effects by reducing



**Fig. 2.** Pharmacological effects of Naringin in various in-vivo and in-vitro experiments. The different reported effects are in cardiovascular, liver, cancers, allergic, GIT disorders, respiratory disorders, diabetes, dental and bleaching.

mucous production and inflammation of bronchus by lessening reactive oxygen species (ROS) production, minimizing NF- $\kappa$ B activity, cytokine and chemokine secretions Shi et al. (2014); (Yu et al., 2015). It has also shown clinical efficacy in different gastrointestinal diseases, such as an antipeptic ulcer by decreasing ulcer index and promoting gastric mucosal morphology (Galati et al., 1998). Its antifilarial activity against *Brugia malayi* further expands its use against round worm infections (Kawaguchi et al., 2004). Associated with the anti-osteoporosis effect of NRG are improved osteoblastic behaviour by HMG-CoA reductase inhibition (Wong and Rabie, 2006), increased osteogenic proliferation and differentiation and against oxidative stress (Wang et al., 2015b). NRG also impedes collagen accumulation in arthritic joints (Kawaguchi et al., 2004), diminishing PGE<sub>2</sub>, NO and TNF- $\alpha$  production as well as tissue damage in osteoarthritis (Xu et al., 2017). The anticancer effects of NRG (Kapoor, 2014), are associated with increased apoptosis in leukemia, liver Park et al. (2008); (Yen et al., 2015), colon, cervical and ovarian cancer Schindler and Mentlein (2006); Ramesh and Alshatwi (2013); (Cai et al., 2018).

#### 4. Neuroprotective effects of naringin

##### 4.1. Effects in neurodegenerative disorders

###### 4.1.1. Alzheimer's disease

Alzheimer's disease (AD) is widely recognized neurodegenerative illness characterized by memory loss and neuroinflammation (Yang et al., 2018). NRG has shown therapeutic potential against AD (Fig. 3). Aluminium chloride has been commonly used to experimentally produce AD-like symptoms. Chronic administration of NRG in aluminum-treated rats enhanced cognitive execution and reduced mitochondrial oxidative damage (Prakash et al., 2013). In another study in mice, D-galactose administration (100 mg/kg for 6 weeks) impaired memory, locomotion, oxidative defenses and the activities of mitochondria enzymes. NRG, at 40 and 80 mg/kg improved intellectual execution and redox status, and reestablished mitochondrial enzyme activities (Kumar et al., 2010b). Intracerebroventricularly administration in colchicine Alzheimer type dementia in mice, NRG treatment (40 and 80 mg/kg p. o. for 25 days) enhanced cognitive execution, lessened oxidative damage, reducing the levels MDA and nitrite levels, restored SOD and CAT

activities and decreased AchE activity. These findings establish the remedial efficacy of NRG against colchicine-induced psychological disability and related oxidative damage (Kumar et al., 2010a). NRG treatment prevented cognitive abnormalities following ICV-STZ by means of attenuating insulin signaling. NRG increased insulin expression, which, in turn, increased cholinergic activity promoting memory and learning. Furthermore, NRG increased PPAR $\gamma$  gene expression resulting in neuroprotective effects (Yang et al., 2014).

Increased apoptosis is inherent to a number of neurodegenerative disorders. Lipopolysaccharide (LPS) induced apoptosis via the generation of intracellular ROS and inflammatory mediators. NRG has been shown to enhance cell survival in a LPS-induced apoptosis in PC12 cells. It reduced oxidative stress as well as downregulated inflammatory mediators including TNF- $\alpha$ , IL-1 $\beta$ , IL-6, HMGB1, COX-2 and TRAF6 (Y Wang et al., 2017). Amyloid  $\beta$  protein (A $\beta$ ) by lipid peroxidation and free-radical generation and in nerve cells, bringing about apoptosis and cell demise and considered as a main reason for AD. NRG prevented the generation of the A $\beta$ -instigated ROS (Heo et al., 2004a). Recently, an NRG derivative, NRG dihydrochalcone, has been shown to possess enhanced cognitive capacity in transgenic AD mice by hindrance of A $\beta$  level and neuroinflammation (Yang et al., 2018).

###### 4.1.2. Parkinson's disease (PD)

Parkinson's disease (PD) is characterized by dopaminergic neuron degeneration and decreased dopamine (DA) level. NRG is considered beneficial as a natural compound for mitigating DA neurodegeneration in the adult brain (Jung et al., 2014). Oxidative stress produces apoptosis and damage to mesencephalic dopaminergic neurons in PD (Fig. 4). NRG protects DA neurons from oxidative stress and apoptosis Mercer et al. (2005); (Zbarsky et al., 2005). Activation of Nrf2/ARE signaling by NRG is unequivocally associated with neuroprotection against 6-hydroxydopamine (6-OHDA) neurotoxicity. NRG mitigates against 6-OHDA-induced neurotoxicity by activation of the Nrf2/ARE signaling pathway (Lou et al., 2014). The impacts of pre and post-treatment with NRG were seen in a PD mouse model. The outcomes demonstrated that NRG protected DA neurons from 6-OHDA-induced neurotoxicity by increasing mTORC1 expression and repressing microglial activation. Rotenone produces PD like symptoms. NRG has shown protection against rotenone-induced cell demise in human

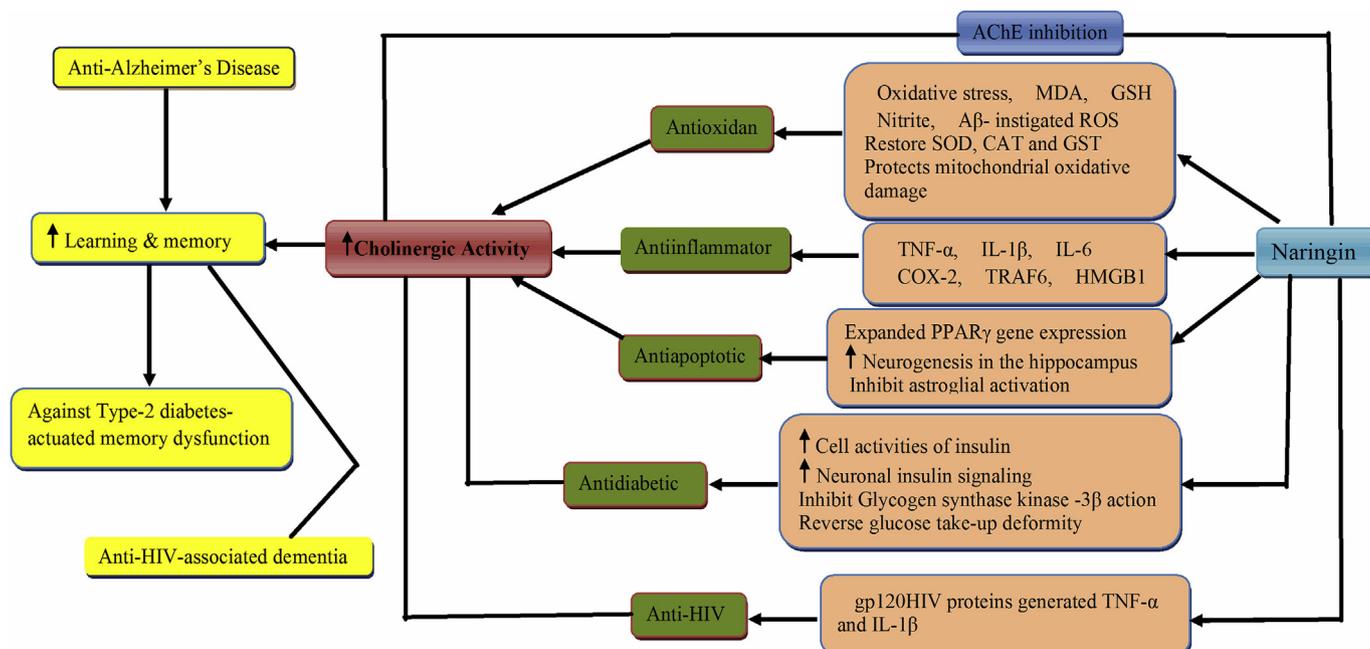
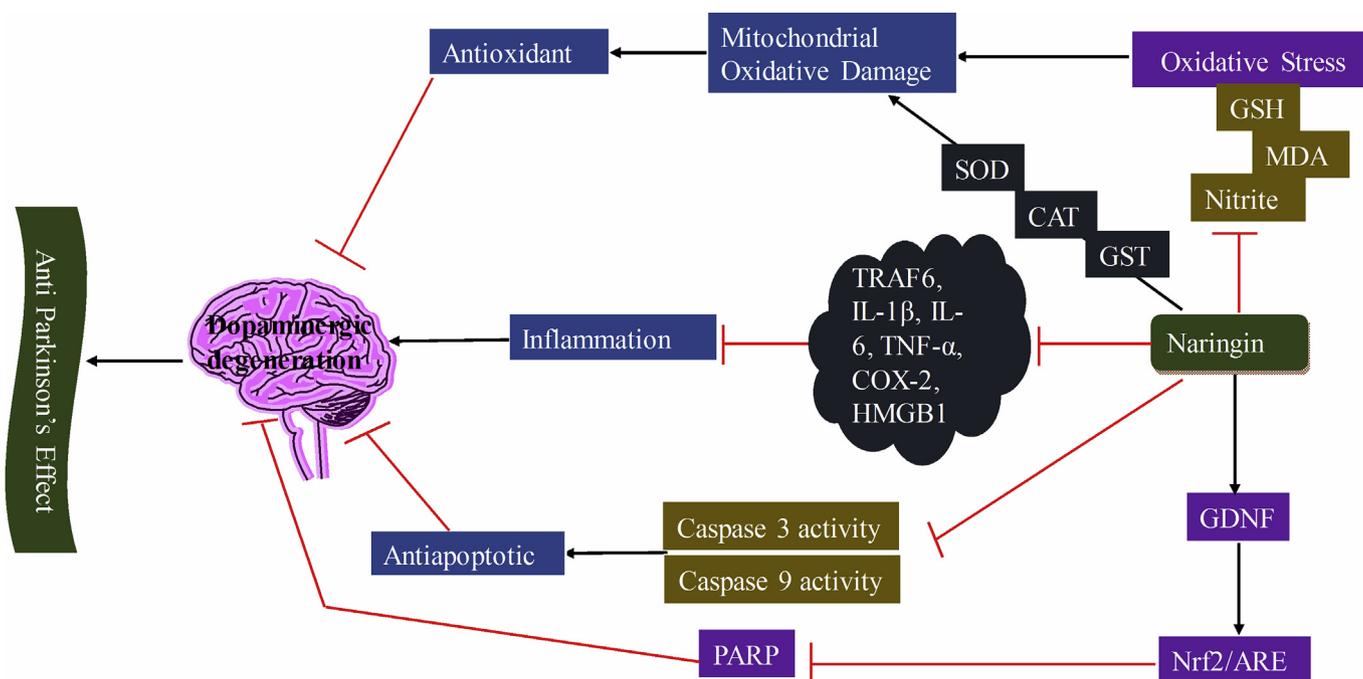


Fig. 3. Anti-Alzheimer effects of Naringin. Different mechanisms including antioxidant, antiinflammatory, antiapoptotic, antidiabetic and antiHIV causes upregulation of cholinergic activity that improve learning and memory effects and anti-Alzheimer activity.



**Fig. 4.** Anti-Parkinson's effects of Naringin. The different underlying mechanisms in the anti-Parkinson's effects involved modulation of mitochondrial oxidative damage, attenuation of various inflammatory mediators, intervention through inhibition of caspase activity and thereby antiapoptotic effects.

neuroblastoma SH-SY5Y cells, by blocking JNK phosphorylation, and BAX expression. Furthermore, NRG diminished caspase 3 activity and PARP cleavage. These outcomes suggest that NRG neuroprotective affects rotenone-induced cell demise (Kim et al., 2009). Treatment with NRG increased GDNF production in Daergic neurons, consistent with decreased neurodegeneration (Kim, 2017). Furthermore, NRG down-regulated microglial iNOS, and COX-2 production (Wu et al., 2016).

#### 4.1.3. Polyglutamine (polyQ) diseases

Polyglutamine diseases such as Huntington's disease (HD) and ataxias are neurodegenerative ailments portrayed by the protein conglomeration extended in polyQ tract. NRG (Table 2) smothered the protein conglomeration in mammalian cells and appeared to be another inducer of GRP78 expression (which is down regulated in Poly Q diseases) and might be a potential remedial agent for polyQ diseases (Cohen-Carmon and Meshorer (2012); Yamagishi et al., 2012). 3-NP essentially incites striatal oxidative pressure and caused hindrance in locomotor action, grasp quality and mitochondrial functions recommending HD like side effects in rats. NRG pretreatment secures pheochromocytoma cells from 3-NP instigated neurotoxicity through NO mechanism, improving antioxidant enzymes activity, lessened lipid peroxidation, increased Nrf2 levels, and diminished the expressions of pro-inflammatory mediators (TNF- $\alpha$ , COX-2, iNOS, NF-kB) and glial fibrillary acidic protein (Kumar and Kumar, 2010; Gopinath and Sudhandiran (2012); Kulasekaran and Ganapasam (2015); (Gopinath and Sudhandiran, 2016). NRG additionally attenuated quinolic acid (QA)-induced neurotoxicity by means of balancing striatal oxido-nitrosative pressure (SOD, glutathione, MDA and NO), neuroinflammatory markers (TNF- $\alpha$ , IL's and NF-kB mRNA) and apoptotic markers (Bax-Bcl-2, Caspase-3, and PPAR- $\gamma$  mRNA), ameliorating the deficits seen in locomotor activity, rearing, grooming, neurological score, footprint analysis and grip strength (Cui et al., 2018).

#### 4.2. Naringin efficacy in memory dysfunction

##### 4.2.1. Naringin efficacy against type-2 diabetes-induced memory dysfunction

Hyperglycemia causes neuronal damage by peroxidation and

inflammation. NRG elicited memory enhancing effects in type-2 diabetes-prompted memory dysfunction in mice by causing antioxidant and cholinergic inhibitory actions. It mediated this effect through modulation of lipid peroxide, NO, glutathione levels and cholinergic activity in experimental animals (Rahigude et al., 2012). The ameliorative impacts of NRG on diabetes-associated dementia have been studied utilizing a STZ-infused rodent model. NRG enhanced learning and memory performances by significantly expanding SOD, decreasing TNF- $\alpha$ , MDA and IL-1 $\beta$ , IL-6 level with expanded PPAR $\gamma$  articulation. Based on these outcomes it might be inferred that NRG might be a promising remedial agent for enhancing memory in diabetic associated dementia (Liu et al., 2016). In streptozotocin-initiated hyperglycemic mice, NRG additionally recuperated the concealment of neurogenesis (Okuyama et al., 2018a). Obesity actuated by high-fat diet regimen causes neuronal insulin obstruction, as well as initiated brain mitochondrial dysfunction and in addition learning disability in mice. NRG attenuates obesity and reestablishes glucose and fat metabolism at near normal levels. It likewise attenuates mitochondrial dysfunction, attenuates impaired insulin signaling, increases AMPK activity and improves memory in mice (Wang et al., 2015a). Glycogen synthase kinase (GSK)-3 $\beta$  decreases glucose metabolism in Alzheimer disease. NRG improved cognitive deficits by inhibition of GSK-3 $\beta$  action and reversal of a glucose take-up deformity (Wang et al., 2012). Recently, a meta-investigation uncovered that, NRG could reestablish oxidative stress markers in various parts of rodent brain. Be that as it may, further examinations including human subjects are prescribed to build up the safety and efficacy (Viswanatha et al., 2017).

Diabetic neuropathy is secondary to complications related to diabetes mellitus and is characterized by attenuated nerve conduction speed, elevated pain, sensory loss and nerve fiber degeneration. NRG-insulin combination has been shown to improve the diabetic condition neuropathic damage, while insulin or NRG when administered alone were potent in pain relieving response in diabetic rats. NRG has shown efficacy in hindering diabetes prompted neuropathic pain by decreasing the levels of free radicals and cytokines, including TNF- $\alpha$ , a critical mediator of neuropathic pain (Kandhare et al., 2012).

**Table 2**  
Neuroprotective effects of Naringin.

Neuroprotective effects	Outcomes of these effects
Alzheimer's Disease Acetylcholinesterase inhibitor (Heo et al., 2004b) Antioxidant effects	Increment in cholinergic activity to encourage learning and memory Lessened oxidative stress, by bringing down of MDA level and NO concentration and restoration of SOD and CAT levels (Kumar et al., 2010a) Prevented the generation of the Amyloid $\beta$ protein- instigated reactive oxygen species (Yang et al., 2018)
i) Protects mitochondrial oxidative damage (Prakash et al., 2013) ii) Reestablished mitochondria complex enzyme activities (Kumar et al., 2010b)	Improve mitochondrial function and moderate cytokine discharge (Sachdeva et al., 2014)
i) Enhances the cell activities of insulin ii) Advanced insulin expression	Prompted increment in cholinergic activity to encourage learning and memory (Yang et al., 2014)
Anti-inflammatory effects	Decrease TNF - $\alpha$ , IL - 1 $\beta$ , & - 6 (Liu et al., 2016) Downregulated TNF- $\alpha$ , IL-1 $\beta$ & - 6, HMGB1, COX-2, TRAF6 (H. Wang et al., 2017) Expanded PPAR $\gamma$ gene expression (Yang et al., 2014)
Antiapoptotic effect <b>Against type-2 diabetes- actuated memory dysfunction</b> Antioxidant and cholinergic activity.	Depletion of raised lipid peroxides and nitric oxides and restraint of hoisted cholinergic activity mutually participate in this impact (Rahigude et al., 2012) Prompted increment in cholinergic activity to encourage learning and memory
i) Improves neuronal insulin signaling (Wang et al., 2015a) ii) Inhibition of Glycogen synthase kinase -3 $\beta$ action (Wang et al., 2012) iii) Reversal of a glucose take-up deformity (Wang et al., 2012) i) Activates neurogenesis in the hippocampus (Okuyama et al., 2018a) ii) Inhibition of astroglial activation (Okuyama et al., 2018a) iii) Improves brain mitochondrial function (Wang et al., 2015a) iv) Increases AMPK activity (Wang et al., 2015a)	Neuroprotective effects in the hippocampus
<b>Human immunodeficiency virus (HIV)-associated dementia</b> Decreases the level of gp120HIV proteins generated TNF- $\alpha$ and IL-1 $\beta$ (Qin et al., 2016)	Neuroprotective effects in the hippocampus
<b>Parkinson's Disease</b> Inhibit dopaminergic degeneration	Shielding DA neurons from peroxidation and apoptosis (Jung et al., 2014) By diminishing the enzyme activity of caspase 3 (Kim et al., 2009) By diminishing the caspase 9 cleavage (Kim et al., 2009) By diminishing PARP (Kim et al., 2009) Activation of the Nrf2/ARE signaling (Lou et al., 2014) Enabling DA neurons to produce GDNF (Kim, 2017)
<b>Epilepsy</b> Antioxidant effects	Diminishing MDA, and expanding SOD and CAT in the hippocampus (Kola et al., 2018) Alleviated TNF- $\alpha$ (Golechha et al., 2014) Decreases epileptic jerks by neuroprotection
Anti-inflammatory effects Against autophagic stress and microglia-derived neuroinflammation (Jeong et al., 2015), control of granule cell dispersion (Kim, 2016) balancing the GABAA receptor (Kola et al., 2017) and diminishing dimensions of glutamate (Kola et al., 2018)	
<b>Ischemic brain injury</b> Antioxidant effects	Strong NO scavenging and furthermore hindered the superoxide, nitric oxide, NADPH oxidase and iNOS (Feng et al., 2018) Suppressing NF- $\kappa$ B-intervened neuroinflammation (Raza et al., 2013) Decrease VEGF and caspase 3 activation (Sarkar et al., 2012) Repressing the enactment of MAPK pathway (Han et al., 2017)
Anti-inflammatory effects	
constricting subarachnoid hemorrhage (SAH)-incited oxidative pressure and apoptosis	
<b>Polyglutamine (polyQ) diseases</b> Induction of endoplasmic reticulum chaperone GRP78	Inhibits polyglutamine tract-containing protein aggregation (Cohen-Carmon and Meshorer, 2012; Yamagishi et al., 2012) Expanding antioxidants enzyme activities (Kulasekaran and Ganapasam, 2015) Balancing SOD, MDA and NO (Cui et al., 2018) balance in expressions of BCL2, BAX, caspase-3, and PPAR- $\gamma$ (Kulasekaran and Ganapasam, 2015; Cui et al., 2018)
Antioxidant effects	Activation of Nrf-2 signaling pathway and decrease TNF- $\alpha$ and NF-kB (Gopinath and Sudhandiran, 2012) decreasing NF-kB, glial fibrillary acidic protein and matrix metalloproteinases (Gopinath and Sudhandiran, 2016) Balancing TNF- $\alpha$ , IL's and NF-kB (Cui et al., 2018)
Antiapoptotic properties	
Anti-inflammatory effects	
<b>Spinal cord injury</b> Improves functional recovery of spinal cord after injury	i) inhibiting neuronal apoptosis (Rong et al., 2012) ii) enhancing remyelination (Rong et al., 2017) iii) increasing BDNF and VEGF expression (Rong et al., 2012)
<b>Neuropathic pain</b> Inhibiting neuroinflammation	Suppression of TNF- $\alpha$ , IL-1 $\beta$ , MCP-1
<b>Diabetic neuropathy</b> Hinder diabetes prompted neuropathic torment	Down direction of free radical, cytokineTNF- $\alpha$ (Kandhare et al., 2012).
<b>Osteoprotective role in sciatic-neurectomy-induced bone loss</b> Osteoprotective role in sciatic-neurectomy-induced bone loss	Wnt/ $\beta$ -catenin signaling activation (Lv et al., 2015) Periostin up-regulation and sclerostin down-regulation (Lv et al., 2015)
<b>Neuroblastoma/glioblastoma</b> Suppresses the development of glioblastoma	suppress the Focal Adhesion Kinase (FAK) and its downstream pathway in glioblastoma cells (Li et al., 2017)
<b>Hyperammonemic encephalopathy</b>	

(continued on next page)

Table 2 (continued)

Neuroprotective effects	Outcomes of these effects
Protect from hyperammonemic encephalopathy	Regulates glutamate-nitric oxide cGMP pathway (Ramakrishnan et al., 2016) and upregulate the urea cycle enzymes expression (Ramakrishnan and Vijayakumar, 2017)
Antioxidant effects	upgrading antioxidant enzymes activities and hindering the lipid peroxidation (Ramakrishnan et al., 2016)
Anti-inflammatory effects	down regulate TNF- $\alpha$ , NF- $\kappa$ B, IL-6, iNOS (Ramakrishnan and Vijayakumar, 2017)
Post-stroke depression	Protective against post stroke depression
i) Nitric oxide modulation in brain (Aggarwal et al., 2010)	
ii) Reestablished mitochondrial catalyst complex activities (Viswanatha et al., 2011)	
iii) Antioxidant effects	
Anxiety and depression (Mood Disorders)	
Anxiolytic and antidepressant	monoamine oxidase inhibition (Olsen et al., 2008) increment 5-HT, NE and glucocorticoid receptor, and lessened serum corticosterone (Yi et al., 2012) Activation of hippocampal BDNF (Yi et al., 2014) Upgrade of antioxidant defense system, cholinergic transmission and lipid peroxidation inhibition (Ben-Azu et al., 2018a)

#### 4.2.2. Human immunodeficiency virus (HIV)-associated dementia

Memory and learning dysfunction are major indications of HIV associated dementia, caused by neuroinflammation triggered by gp120HIV proteins (Lucas and Nelson, 2015). In this regard, TNF- $\alpha$  and IL-1 $\beta$  expanded generation play an important role (Skaper et al., 2010). NRG at a dose of 30/mg/kg may enhance the learning and memory dysfunction caused by LV infusion of gp120 or repressing the declaration of P65 protein to diminish NF- $\kappa$ B levels in hippocampus of experimental rat (Qin et al., 2016). Similarly, the compound caused downstream regulation of P2X<sub>7</sub>-mRNA. This finding proclaims the ameliorative impact of NRG on HIV-1 envelope glycoprotein gp120-prompted memory and learning deficiencies. Subsequently, Chen et al. (2017) showed that the neurotoxicity caused by gp120 treatment was significantly attenuated by NRG administration via antiinflammatory effects through P2X<sub>7</sub> receptor intervention. The microglia injury was recovered through downregulation of eATP, TNF $\alpha$  and IL-1 $\beta$  (Chen et al., 2017).

#### 4.3. Effects of NRG in epilepsy

Oxidative stress and cognitive weakness are related with pentylenetetrazol (PTZ)-prompted seizures. NRG have ability to drag out the enlistment of myoclonic jerks portion conditionally by balancing the GABAA receptor, lessening MDA and TNF- $\alpha$  levels, and increasing glutathione, SOD and CAT levels (Fig. 5).

Phenytoin is broadly utilized anticonvulsant drug. Treatment with NRG and phenytoin on pentylenetetrazole-induced kindling in rats enhance neurochemical balance by increasing the levels of GABA and DA, decreasing glutamate and MDA levels, and stabilizing the redox status (GSH, SOD, CAT) in the hippocampus. This co-administration also offers a potential treatment for medication - resistant epilepsy (Kola et al., 2018). NRG showed efficacy against autophagic stress and neuroinflammation by retarding the onset of kainic acid -instigated seizures (Jeong et al., 2015). NRG treatment further decreased kainic acid-induced granular cell dispersion (GCD) and rapamycin complex 1 (mTORC1) activation, and neuroinflammation (Kim, 2016).

#### 4.4. Therapeutic potential in neurological injuries

##### 4.4.1. Effect of naringin in ischemic brain injury

Oxidative pressure and inflammation assume a fundamental job in the pathogenesis of cerebral ischemia that prompts the demise of neurons. The strong antioxidant and antiinflammatory impacts of NRG are responsible for neuroprotective impact against cerebral ischemia/reperfusion damage (Okuyama et al., 2018b). Oxidative stress-initiated neuroinflammation and neuronal cell demise contribute to

intracerebral hemorrhage (ICH). NRG has shown efficacy against ICH-induced neurocognitive deficiencies, alleviating oxido-nitrosative and inflammatory stress (Singh et al., 2017). NRG also attenuated the histopathological modifications in cortex, striatum and secondary to ischemia reperfusion (Gaur et al., 2009). Autophagy/mitophagy assumes imperative roles in cerebral-ischemia-reperfusion (I/R) damage. Peroxynitrite (ONOO<sup>-</sup>), comes under ROS category, intercedes unnecessary mitophagy actuation and worsens I/R damage. NRG repress ONOO<sup>-</sup> interceded mitophagy actuation, constrict cerebral I/R damage and furthermore hindered superoxide and NO production in ischemia reperfused rat brains (Feng et al., 2018). Prophylactic treatment with NRG enhanced utilitarian results and repealed the ischemic brain damage by smothering NF- $\kappa$ B-intervened neuroinflammation (Raza et al., 2013), and furthermore by downregulating the outflow of nucleotide oligomerization area like receptors 2 (NOD2), receptor-interfacing protein 2 (RIP2) and framework metalloproteinase-9 (MMP-9) (Bai et al., 2014). NRG improved early brain damage following subarachnoid hemorrhage (SAH), neurologic deficiencies by constricting SAH-incited oxidative pressure and apoptosis and by repressing the enactment of MAPK signaling pathway. It is recommended the remedial capability of NRG in giving neuroprotection after SAH (Han et al., 2017). Hypoxic injuries related to exposure to high elevation prompt high-height cerebral edema, high elevation pneumonic edema and hypoxic muscle weakness. Hypoxic injuries can be forestalled by either preconditioning with cobalt chloride or treatment with medications. The impact of NRG in neuronal damage in hypoxia prompted murine model was watched. An oral administration of NRG before each hypoxic treatment altogether decreased hypoxia inducible factor 1 $\alpha$  (HIF1 $\alpha$ ), vascular endothelial development factor (VEGF), caspase 3 enactment which propose its neuroprotective nature supportive in enhancement of hypoxia initiated brain dysfunction (Sarkar et al., 2012).

##### 4.4.2. Effect of naringin spinal cord injury

Spinal cord damage was secondary to weight-drop injury in Sprague–Dawley rodents and overall accounts for high disability rate in human (Li et al., 2018). NRG (Table 2) treatment showed neural anti-apoptotic behaviour and enhance locomotor recuperation by upregulation of BDNF and VEGF just after spinal cord injury (Rong et al., 2012). NRG treatment at a dose of 20 and mg/kg diminished demyelination of the white matter and increased the thickness of the myelin sheath (Rong et al., 2017) which is commonly observed in CNS injury (Alizadeh et al., 2015). NRG treatment therefore appears to modulate oligodendrocyte precursor cell differentiation and advances remyelination after spinal cord damage through the  $\beta$ -catenin/GSK-3 $\beta$  signaling pathway (Rong et al., 2017), a known mechanistic pathway for the prevention of neuroprotection by expression of AKT

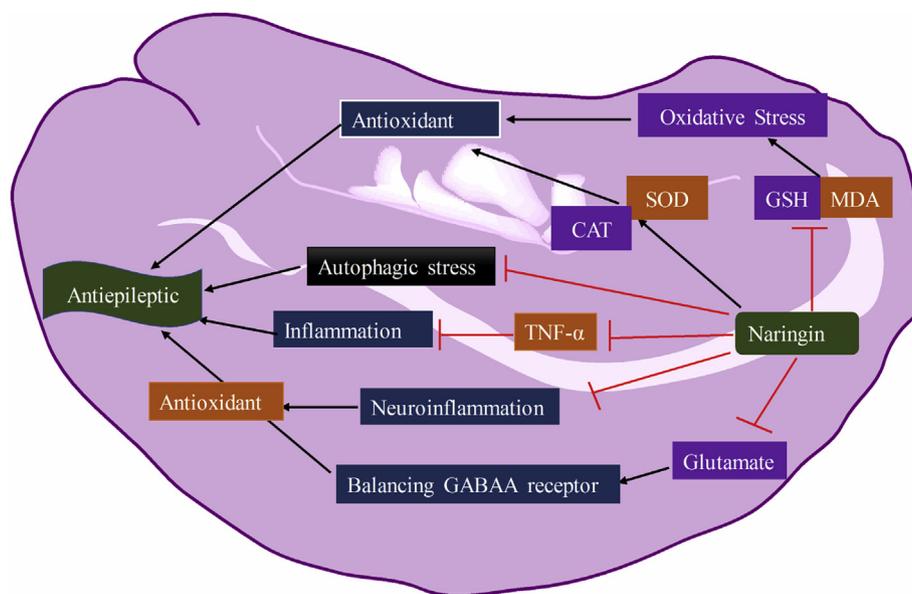


Fig. 5. Anti-epileptic effects of Naringin. The effects produced through modulation of oxidative stress, inhibition of autophagic stress, attenuation of neuroinflammation that lead to antioxidant action, balancing GABA<sub>A</sub> receptor effect through glutamate inhibition.

phosphorylation (Li et al., 2018).

#### 4.5. Effect of naringin on neuropathic pain

NRG showed pain relieving impact in sciatic nerve damage model of rats (Hu and Zhao, 2014). Repeated administration of NRG at various doses attenuated neuropathic pain, mechanical allodynia and thermal hyperalgesia possibly through inhibiting neuroinflammation which has been characterized as a primary factor of neuropathic pain (Kiguchi et al., 2012). Pretreatment of NRG at 50, 100 and 200 mg/kg caused significant pain relieving effects in neuropathic pain (Hu and Zhao, 2014). The treatment inhibited astrocytes and microglia expression through repeated injection of the compound by antagonizing the neuroinflammatory mediators (Hu and Zhao, 2014). Associated with these effects are suppression of spinal TNF- $\alpha$ , IL-1 $\beta$  and monocyte chemoattractant protein-1 (MCP-1) levels was involved. This characteristic indicates that NRG may be suitable for the long-term treatment of chronic pain. In addition, NRG infiltrates the blood brain barrier effectively. Along these lines, NRG might be a helpful medication in the treatment of neuropathic torment Kaulaskar et al. (2012); (Hu and Zhao, 2014).

#### 4.6. Osteo-protective role of naringin in sciatic-neurectomy-induced bone loss

The protective effects of NRG has been observed in various condition of osteoporosis (Wei et al., 2007 (Li et al., 2014a); which proceed through different mechanistic pathways modulation (Ang et al., 2011). Down-regulation of periostin, and up-regulation of its downstream sclerostin and inactivation of Wnt/ $\beta$ -catenin signaling are involved in neurectomy-induced bone loss (Lv et al., 2015). 4 week treatment NRG expanded periostin articulation, hence restraint of sclerostin, actuation of Wnt/ $\beta$ -catenin signaling pathways and could counteract advancement of neglect osteoporosis in rodents at a concentrations of 30 and 100 mg/kg (Lv et al., 2015), as these actions are supposed to be osteo-protective (Kramer et al., 2010). Ma et al. (2016) studied the effects on NRG in unilateral sciatic neurectomy in male adult rats (Ma et al., 2016). The result illustrated that it produced positive action on the overall bone structure and strength at various test doses. The treatment recovered the lost semaphorin 3A protein (sema3A). Experiments haven that the sema3A expression played an important in overall development of human skeleton and bone mass (Gomez et al., 2005) and NRG

expressed sema3A secretion and thus displayed its modulatory potential role in disuse osteoporosis.

#### 4.7. Effect of naringin on neuroblastoma/glioblastoma

Glioblastoma is the most aggressive malignancy that starts inside the brain is difficult to convenient analyze. NRG can explicitly suppress the Focal Adhesion Kinase (FAK) in glioblastoma cells and thus applies the counter tumor impacts (Li et al., 2017). Furthermore, the experiments of Aroui et al. (2016) showed various significant effects of NRG in glioblastoma via downstream regulations of matrix metalloproteinases and proteinase activity (Aroui et al., 2016). Similarly, it caused inhibitory effects on p38 expression in U251 glioma cell.

#### 4.8. Effect of naringin in hyperammonemic encephalopathy

Hyperammonemia is a metabolic condition portrayed by elevated levels of ammonia in the blood. Expanded passage of ammonia to the brain is an essential cause of neurologic disorders, for example, congenital inadequacies of urea cycle enzymes, hepatic encephalopathies and Reye disorder (Ramakrishnan and Vijayakumar, 2017). Neuro-protective impact of NRG (Table 2) on ammonium chloride (NH<sub>4</sub>Cl) prompted hyperammonemic rodents were examined. NRG administration radically reestablished the levels of blood ammonia, plasma urea, NO, glutamate, glutamine, lipid peroxidation, lipid profile, activities of liver marker enzymes, antioxidant status and Na<sup>+</sup>/K<sup>+</sup>-ATPase. Furthermore, NRG supplementation returned the pathological changes of liver, brain and kidney tissues, the expressions of Glutamine synthetase (GS), Na<sup>+</sup>/K<sup>+</sup>-ATPase, neuronal nitric oxide (nNOS) and soluble guanylate cyclase (sGC) in hyperammonemic rats. Henceforth, NRG successfully decreased NH<sub>4</sub>Cl prompted neurotoxicity by means of up-grading antioxidant enzymes activities and hindering lipid peroxidation and can be acts as a restorative agent to treat hyperammonemia (Ramakrishnan et al., 2016). NRG additionally upregulated the expression of urea cycle enzymes for example, carbamoyl phosphate synthase I (CPS I) and ornithine transcarbamylase (OTC), arininosuccinate synthase (ASS), argininosuccinate lyase (ASL) and arginase I (ARG) and metabotropic glutamate receptors (mGluRs) such as mGluRs I and mGluRs V and down regulate the expression of inflammatory markers like TNF- $\alpha$ , NF- $\kappa$ B, IL-6 and iNOS (Ramakrishnan and Vijayakumar, 2017).

#### 4.9. Effect of naringin on post-stroke depression

Post-stroke depression is commonly observed in those patients who survived from strokes and about one out of three patients suffered from depression (Berg et al., 2009). NRG (Table 2) influences NO homeostasis to secure against post-stroke depression model in mice. Post-stroke depression (PSD) is characterized by expanded distress, disability, poor restoration, dismalness, mortality, and self-destructive thoughts. Cerebral ischemia and reperfusion damage (Ischemia reperfusion damage) causes huge decline in locomotor activity, increment lipid peroxidation and nitrite concentration and exhausted diminished glutathione, glutathione-S-transferase, SOD and CAT) and altered mitochondrial enzyme complex activities. NO has been accounted for to improve the dangerous impact of cerebral ischemia reperfusion damage which can be additionally related with associated behavioral weaknesses. NRG (50 and 100 mg/kg) treatment in mice fundamentally attenuated neuro-behavioral alterations, oxidative harm and reestablished mitochondrial catalyst complex activities Aggarwal et al. (2010); Viswanatha et al. (2011); (Cichoń et al., 2015).

#### 4.10. Anxiety and depression

Serotonergic and noradrenergic dysfunctions are related to anxiety and depression (Hale et al., 2012). The serotonergic system controls mood, hunger and cognition (Timotijević et al., 2012). The noradrenergic system controls memory and attention (Borodovitsyna et al., 2017). NRG (Table 2) has been shown to possess antidepressant-like effects accounting for increment in 5-HT, NE and glucocorticoid receptor levels, brain-derived neurotrophic factor (BDNF) activation and decreased serum corticosterone Yi et al. (2010); Yi et al. (2012); (Yi et al., 2014). Its monoamine oxidase inhibitory effects likewise help in mitigating depression (Olsen et al., 2008). Intraperitoneal NRG administration in mice (2.5, 5 and 10 mg/kg) caused significant increment in rearing conduct, decrease immobility duration and increased the % social communication, which besides fortify its suggesting anti-depressant-like and anxiolytic-like effects. increased cholinergic transmission, antioxidant defense system, restraint of lipid peroxidation and nitrosative effects were associated with these effects Ben-Azu et al. (2018a); (Ben-Azu et al., 2018b).

### 5. Side effects of naringin

NRG 1250 mg/kg/day orally following each day to Sprague–Dawley rats for a half year did not cause any lethality or dangerous clinical signs and changes in the two sexes of rats aside from slight body weight decline and reversible male pattern baldness, which recovered after a month. Utilizing the body surface region standardization strategy, 1250 mg/kg NRG in rat thinks about to 200 mg/kg in individuals, or 12 g for a 60 kg human (Li et al., 2014b). NRG has a LD50 estimation of 2000 mg/kg and have a place with poisonous quality class 4, as per the internationally harmonized system of labeling chemical compounds (Lawal et al., 2018). Thusly, the utilization of NRG is viewed as safe for the consumer. Just couple of clinical examinations for cardiovascular illnesses and hostile to hepatitis C infection have been done (Salehi et al., 2019). No clinical preliminary performed for NRG for neurological disorders that is the reason no suggested remedial portions in various neurological disorders are made accessible.

#### 5.1. Conclusion and future directions

A wide range of experimentally documented useful impacts has been ascribed to NRG including antiatherogenic, antiadiposity, anticancer, anti-peptic ulcer, antiallergic, antiasthmatic, antidiabetic, antiosteoporosis, hepatodetoxifying; against constipation ulcerative colitis and myocardial infarction. This article features the way that NRG has the possibility to be utilized as a remedy against numerous of

neurodegenerative disorders. Referenced neuroprotective impacts significantly dependent on its antioxidant, antiapoptotic and anti-inflammatory activities. In the meantime, unwanted effects with commonly used medicines may urge to investigate more secure alternative and complementary medicines, accordingly, provoking the investigations of NRG for neuroprotective purpose. Nevertheless, NRG seem to represent a promising tool to treat different neurodegenerative diseases with lesser adverse effects. Side by side, its lower dissolution rate, low bioavailability and fast elimination are principle hindrances to develop NRG as a medicine (Rani et al., 2016). A few procedures, for example, structural modification, complexation, liposomal and nanoparticles formulations might be couple of zones to improve NRG delivery. The C-4 and C-7 structural modification in NRG expanded anti-cancer adequacy. It is additionally proposed to apply these NRG changes in neuroprotective therapeutics (Yoon H et al., 2013). NRG phospholipid complex has more half-life with improved antioxidant potential than NRG alone (Maiti K et al., 2006). NRG-cyclodextrin complex has high dissolution rate and water dissolvability with thermal stability to developed more acceptable dosage form (Shulman M et al., 2011); (Yang et al., 2013; (Xin-Rong Xu et al., 2014). Liposomes fundamentally improve the dissolvability and bioavailability of NRG (Wang Y et al., 2017). The change into amorphous form from crystalline form by solid dispersion method also improved its absorption and dissolution rate (Khan et al., 2015).

Nano-dispersions containing NRG with polyvinylpyrrolidone have shown gastric stability and improved dissolution rate for NRG drug delivery (Kanaze et al., 2010). Further, cellulose based amorphous solid dispersion might be helpful to improved bioavailability of NRG (Li B et al., 2013). Nanoparticles of NRG has exhibited higher antitumor, anti-inflammatory and hepatoprotective by enhancing the dissolvability and release of NRG in experimental models (Yen et al., 2009; (Wang K et al., 2014). In addition, the nanoemulsifying form of NRG brought about the fastest and most complete drug release with enhanced bioavailability (Khan et al., 2015). Given the scares number of studies with NRG in humans, this survey centers around the different established neuroprotective effects in preclinical experimental models. Accordingly, further clinical investigations are required to determine significant mechanistic neuroprotective insights with safety and efficacy in humans.

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### Abbreviations

3-NP	3-Nitropropionic acid
AChE	Acetylcholinesterase
ARE	Antioxidant response element
BCL 2	B-cell CLL/lymphoma 2
BAX	BCL2-related X protein
CAT	Catalase
COX-2	Cyclooxygenase-2
DA	Dopamine or dopaminergic
GABA	Gamma amino butyric acid
G D N F	Glial cell line-inferred neurotrophic factor
GSS	Glutathione synthetase
GSK-3 $\beta$	Glycogen synthase kinase-3 $\beta$
HMGB1	High mobility group box 1 protein
iNOS	Inducible nitric oxide synthase
IL	Interleukin
JNK	Jun NH2-terminal protein kinase
MDA	Malondialdehyde
mTORC1	mammalian concentration of rapamycin complex 1

MCP-1	Monocyte chemoattractant protein-1
NRG	Naringin
NO	Nitric oxide
NE	Norepinephrine
Nrf2	Nuclear factor erythroid 2-related factor 2
NF - κB	Nuclear factor kappa B
PARP	Poly (ADP-ribose) polymerase
ROS	Reactive oxygen species
5-HT	Serotonin
SOD	superoxide dismutase
TRAF6	TNF receptor-associated factor 6

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