

NARINGIN REVEALS AMELIORATIVE PROPERTY OVER ELEVATED OXIDATIVE STRESS LEVELS IN ANIMAL MODELS

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ABSTRACT

Oxidative stress (OxiS) has been implicated in the pathogenesis of many diseases. Free radicals interact with different cell components including DNA, proteins, and lipids to become stable. In this process, these free radicals damage the integrity of these biological moieties and result in various health implications. Naringin (NG), a naturally occurring phytochemical commonly found in grapefruit juice has been explored for its protective role against OxiS. In this short review paper, an attempt has been made to compile the study reports revealing the antioxidative nature of NG in different animal models. Studies have reported NG as a potential antioxidant in various health ailments including diabetes, cardiac fibrosis, cognitive dysfunction, and neurodegeneration.

Keywords: Phytocompounds, Naringin, Oxidative stress, Free radicals, Antioxidant.

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INTRODUCTION

Oxidative stress (OxiS) is defined as a state in biological systems in which oxidation exceeds the antioxidant systems of the body secondary to a loss of the balance between them [1]. It also causes hazardous events such as lipid peroxidation and oxidative DNA damage. Development of OxiS as a result of free oxygen radical generation has been implicated in the pathogenesis of many diseases including Parkinson's disease, Alzheimer's disease, atherosclerosis, heart failure, myocardial infarction, and even cancer [1]. A free radical is oxygen-containing a molecule that has one or more unpaired electrons, making it highly reactive with other molecules. Free radicals can chemically interact with cell components such as DNA, proteins or lipids, and steal their electrons to become stabilized. The reactive oxygen metabolites produced are more reactive than the original oxygen molecule and are called active oxygen species. Many daily habits are closely associated with OxiS which includes smoking [2-5], drinking [6-9], and an irregular diet [10-13]. The superoxide radical ($\cdot O_2^-$), one of the reactive oxygen species (ROS), is known to be generated in brain and is involved in the reduction of certain iron complexes including cytochrome C. Superoxide dismutase is a metalloenzyme catalytically eliminating superoxide radical as a first-line defense mechanism against OxiS [14]. In the same way, nitric oxide ($NO\cdot$) [15-18] and Peroxyl ($RO_2\cdot$) radicals [19] are highly unstable moieties also. These are formed in the human body and disrupt proteins and promote DNA damage [20-23]. ROS are also engaged in disruption of the integrity of polyunsaturated fatty acids. Hypochlorous acid, peroxyxynitrite, hydrogen peroxide, and ozone are the non-radical forms of ROS that can easily enter free radical reactions.

OxiS leads to many pathophysiological conditions in the body. Some of these are neurodegenerative diseases, gene mutations, atherosclerosis, and cancers [24,25]. Thus, various antioxidant defense mechanisms have developed in the process of evolution to cope up with the increasing OxiS levels. Different compounds have been identified which play a key role in minimizing the levels of OxiS. Flavonoid is the group of chemicals which possess different reported broad-spectrum therapeutic and pharmacological properties including free radical scavenging and antioxidant capacity. Naringin (NG) is a flavonoid which is widely distributed in plant foods. In its pure form, it exists as a yellow colored powder. NG has similar structure to hesperidin. It is mainly extracted from grapefruit and some other related citrus species. Its metabolite naringenin is ubiquitously distributed in plant foods and

traditional Chinese medicines. Both NG and its metabolite naringenin have been reported to show broad spectrum of therapeutic and pharmacological properties including anti-inflammatory [26-30], free radical-scavenging [31-33], lipid-lowering [34,35], antioxidant [36-39], anti-fibrosis, and anti-obesity effects [34,35,40]. Recently, NG has been extensively checked for its antioxidant property in different animal models. In this particular paper, we have reviewed the latest research works highlighting the ameliorative property of NG on biological oxidative status (Table 1).

Table 1: Diseases associated with OxiS with respect to different organs

Body Part	Disease
Brain	Alzheimer's disease
	Parkinson's disease
	Multiple Sclerosis
	Amyotrophic lateral sclerosis
	Obsessive compulsive disorder
	Attention deficit hyperactivity disorder
	Autism
	Migraine
	Insomnia
	Depression
	Dementia
	Bi-polar disorder
	Cancer
	Heart
Stroke	
High blood pressure	
Atherosclerosis	
Kidney	Angina
	Chronic kidney disease
Skin	Renal Nephritis
	Wrinkles
	Acne
	Eczema
	Psoriasis
	Dermatitis
	Cancer

(Contd...)

Table 1: Diseases associated with OxiS with respect to different organs (Continued)

Body Part	Disease
Multi-Organ	Diabetes
	Chronic fatigue
	Fibromyalgia
	Heavy metal toxicity
	Lyme disease
Joints	Rheumatoid arthritis
	Osteoarthritis
	Psoriatic arthritis
Immune System	Chronic inflammation
	Auto-immune disorders
	HIV
	Herpes
	Lupus
Blood Vessels	Cancer
	Atherosclerosis
	Hypertension
	Varicose veins
	Elevated Cholesterol and triglycerides
Lung	Asthma
	COPD
	Allergies
	Chronic bronchitis
	Cancer
Eyes	Macular degeneration
	Retinal degeneration
	Cataract

HIV: Human immunodeficiency virus, COPD: Chronic bronchitis, COPD: Chronic obstructive pulmonary disease. OxiS: Oxidative stress

STUDIES ON AMELIORATIVE NATURE OF NG AGAINST OXIS

NG is a naturally occurring phytochemical commonly found in grapefruit juice with a number of health benefits [41]. It has been much explored by different research groups for its capability to ameliorate hazardous effects of various metals [42] as well as in different pathological conditions [43-45]. NG has been reported to mitigate cisplatin-induced OxiS and inflammatory response. Administration of NG (25, 50, and 100 mg/kg) was able to attenuate deterioration in striatum tissue, abrogate antioxidant enzyme activities and suppressed the increase in malondialdehyde in rats [46]. NG has shown preventive effects against lipid peroxides and antioxidants [47]. Oral administration of NG (10, 20, and 40 mg/kg) to isoproterenol exposed Wistar rats showed a considerable decrease in the levels of lipid peroxidation products and improved the antioxidant status [47]. NG is known for its anti-inflammatory [46,48-50] and antioxidative nature [43,45,51,52]. Arsenic-induced hepatic and renal toxicity are reported to be reduced by anti-inflammatory and antioxidative nature of NG [53]. Different from other studies involving the ameliorative action of NG on oxidative status have also been summarized in Table 2.

Effect of NG on OXIS in diabetic models

NG alleviated diabetic retinopathy symptoms as evidenced by the increased retinal ganglion cells and decreased GFAP level in rat retina. NG exhibited anti-inflammatory and antioxidative effects as revealed by the down-regulated pro-inflammatory cytokines, tumor necrosis factor-alpha, interleukin-1beta, and interleukin-6. Glutathione, superoxide dismutase, and catalase were reported to be upregulated [43]. Hyperglycemia promotes myocardial fibrotic lesions through upregulation of PKC and p38 in response to redox changes. NG was also shown to reduce hyperglycemia-induced cardiac fibrosis by relieving OxiS. Adebisi *et al.* [57] investigated the effects of NG on

Table 2: Studies focused on ameliorative property of NG over OxiS

S.no	Author name	Year	Model	Inference	Reference no.
1.	Oluwafeyisetan <i>et al.</i>	2016	Wistar rats	NG ameliorated OxiS and NRTI-induced mitochondrial damage	[54]
2.	Adil <i>et al.</i>	2015	Rats	NG ameliorates sodium arsenite-induced renal and hepatic toxicity and OxiS	[53]
3.	Jain and Parmar	2011	Rats	NG showed anti-inflammatory and antioxidative in nature	[55]
4.	Rajadurai and Stanely Mainzen Prince	2006	Wistar rats	NG possess anti-lipoperoxidative and antioxidant activity in experimentally ISO-induced cardiac toxicity	[47]
5.	Liu <i>et al.</i>	2017	Diabetic rats	NG attenuated inflammation and OxiS, reducing diabetic retinopathy	[43]
6.	Viswanatha <i>et al.</i>	2017	Rodents	NG play a beneficial role against OxiS-induced neurobehavioral disorders and cognitive dysfunction	[44]
7.	Han <i>et al.</i>	2017	Rats	NG attenuated early brain injury after experimental subarachnoid hemorrhage by reducing OxiS and inhibiting apoptosis	[56]
8.	Liu <i>et al.</i>	2016	Mice	NG revealed protective role against ankylosing spondylitis exerted through induction of ossification, suppression of inflammation, and OxiS.	[45]
9.	Adebisi <i>et al.</i>	2016	Sprague Dawley rats	NG reduces hyperglycemia-induced cardiac fibrosis by relieving OxiS	[57]
10.	Adebisi <i>et al.</i>	2015	Wistar rats	NG reverses metabolic complications associated with NRTIs by ameliorating OxiS and apoptosis	[58]
11.	Chen <i>et al.</i>	2015	Rats	NG alleviates diabetic kidney disease through inhibiting OxiS and inflammatory reaction	[48]
12.	Adebisi <i>et al.</i>	2016	Sprague Dawley rats	NG mitigates cardiac hypertrophy by reducing OxiS and Inactivating c-Jun Nuclear Kinase-1 protein in type 1 diabetes	[59]
13.	Qi <i>et al.</i>	2015	Rats	NG ameliorates cognitive deficits through reducing OxiS and pro-inflammatory in a type 2 diabetes	[52]
14.	Dhanya <i>et al.</i>	2015	L6 Rat cell line	NG activated GSH synthesis through a novel antioxidant defense mechanism preventing oxidative damage in addition to its effect on glycemic control	[60]

(Contd...)

Table 2: Studies focused on ameliorative property of NG over OxiS (Continued)

S.no	Author name	Year	Model	Inference	Reference no.
15.	Chtourou <i>et al.</i>	2015	Rats	NG revealed protective role against cisplatin-induced OxiS, inflammatory response and apoptosis	[46]
16.	Golechha <i>et al.</i>	2014	Rats	NG ameliorated pentylenetetrazol-induced seizures and associated OxiS, inflammation and cognitive impairment	[49]
17.	Gopinath and Sudhandiran	2012	Rats	NG modulates OxiS and inflammation in 3-nitropropionic acid-induced neurodegeneration	[50]
18.	Mahmoud <i>et al.</i>	2012	Rats	NG attenuated hyperglycemia-mediated OxiS and pro-inflammatory response	[51]
19.	Akondi <i>et al.</i>	2011	Rats	NG revealed suppressive effects on testicular ischemia-reperfusion induced OxiS	[61]
20.	Jagetia and Reddy	2011	Mouse liver mitochondria	NG alleviated iron-induced OxiS	[42]
21.	Kumar <i>et al.</i>	2010	Mice	NG alleviated cognitive impairment, mitochondrial dysfunction, and OxiS induced by D-galactose	[62]

NG: Naringin, RT-PCR: Reverse transcription polymerase chain reaction, DPPH: 1,1-diphenyl-2-picrylhydrazyl, MAPK: Mitogen-activated protein kinase pathway, OxiS: Oxidative stress, LSD: Least significant difference, DNPH: 2,4-dinitrophenylhydrazine, GSH: Glutathione, NRTI: Nucleoside reverse transcriptase inhibitor, HUVECs: Human umbilical vein endothelial cells, ISO: Isoproterenol

hyperglycemia-induced myocardial fibrotic changes and its putative effects on PKC-beta and p38 protein expression in Type 1 rat model of diabetes. NG was described as to reduce OxiS, NADPH oxidase activity, cardiac fibrosis, PKC-beta, and p38 mitogen-activated protein kinase expression. Similarly, another study investigated the protective effect of NG against diabetic kidney disease elucidating its possible molecular mechanism. NG relieved the kidney injury, improved renal function, inhibited collagen formation and renal interstitial fibrosis and restrained OxiS by activating Nuclear factor-erythroid 2-related factor-2 (Nrf2) antioxidant pathway [48]. A study also reported the effect of NG on the regulation of diabetes-associated cognitive decline and its underlying mechanisms. An experimental diabetes mellitus rat model was induced by streptozotocin (50 mg/kg) and NG treatment (100 and 200 mg/kg) for 16 weeks was given. A Morris water maze test was used to analyze the effects of NG on the cognitive deficit, and the results demonstrated that NG ameliorated cognitive deficits through OxiS, pro-inflammatory factors, and the peroxisome proliferator-activated receptor gamma signaling pathway in the Type 2 diabetic rat model [52].

Effect of NG on OxiS in neurodegenerative models

Role of OxiS has been well documented in aging and related disorders such as Alzheimer's disease [62]. Bioflavonoids have been used in many researches used as neuroprotectants in the treatment of neurological disorders. NG has been reported to modulate OxiS and inflammation in 3-nitropropionic acid-induced neurodegeneration [50]. It also alleviated cognitive impairment and OxiS induced by D-galactose in mice [62]. Nrf2 mediated regulation of cellular antioxidant production play an important role in neuroprotection. Rats were injected with 3-nitropropionic acid (10mg/kg body weight/day, i.p.) for 2 weeks to develop neurodegeneration. Treatment with NG amended the reduced glutathione/oxidized glutathione ratio with an associated decrease in the levels of hydroxyl radical, hydro-peroxide, and nitrite [50]. OxiS and cognitive impairment are associated with PTZ-induced convulsions. The administration of PTZ induced myoclonic jerks and generalized tonic-clonic seizures. The study reported that NG significantly prolonged the induction of myoclonic jerks in a dose-dependent manner and NG (80 mg/kg, i.p.) pretreatment protected all rats. NG reduced brain MDA and TNF-alpha levels and conserved GSH [49]. 6-week NG (40 and 80 mg/kg) treatment has also been reported to improve oxidative defense, and cognitive performance in D-galactose induced cognitive dysfunctional mice [62]. NG has been reported to be a potential anti-inflammatory agent as it showed a highest binding affinity (8.6 Kcal/mol) and satisfied the Lipinski's rule of five [63]. Like NG, Naringenin coadministration has also been reported to play a protective role against arsenic-induced toxicity in liver tissues of male rats [64].

CONCLUSION

OxiS is a biological state which is associated with the pathogenesis of many diseases. Free radicals damage the integrity of biological molecules including DNA, proteins, and lipids resulting in various health implications. A number of phytochemicals have been checked for their protective role against OxiS. In this short review paper, we have compiled the study reports revealing the antioxidative nature of NG. After review of studies, it has been found that NG is a natural potential antioxidant and its supplements can be used in various health disorders including diabetes, diabetic retinopathy, neurodegeneration, early brain injury, subarachnoid hemorrhage, cognitive dysfunction, cardiac fibrosis, cardiac hypertrophy, diabetic kidney, and ankylosing spondylitis.

AUTHOR'S CONTRIBUTION

All the authors contributed equally to the paper.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest..

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