Life Sciences 208 (2018) 111–122

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Combating oxidative stress disorders with citrus flavonoid: Naringenin

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ARTICLE INFO

Keywords:
Naringenin
Antioxidants
Oxidative stress disorders
Alternative medicine

ABSTRACT

The incidence of diseases related to oxidative stress disorders have been increased dramatically. Alternatives medicine or the active compound extracted from the natural products received great attention among researches at the present era. Naringenin (NG), a common dietary flavanone, found in the citrus fruits such as oranges, bergamots, lemons and grapefruit. It is used in the several oxidative stress disorders as the nutraceutical value of the compound emerges. Functionally, the antioxidants effect of NG is primarily attributed by reducing the free radical like reactive oxygen species (ROS) and enhancing the antioxidants activity such as superoxide dismutase (SOD), catalase, glutathione (GSH) in chronic diseases such as cardiovascular, neurodegenerative, diabetes, pulmonary, cancer and nephropathy. The present review article summarised the antioxidant property of NG and its molecular mechanism towards such diseases. Pubmed, Science Direct, Scopus, Web of Science and Google scholar were searched using the terms 'naringenin', 'oxidative stress disorders', 'naringenin and cardiovascular diseases', 'naringenin and diabetes mellitus', 'naringenin and neurodegenerative diseases', 'naringenin and pulmonary diseases', 'naringenin and cancer' and 'naringenin and nephropathy'. There has been special attention on evaluating anti-oxidative effect of NG on neurodegenerative diseases. Although some mechanisms of action remain vague, the current review highlighted the potential use of NG as a oxidative stress reliever which can be used as next prophylaxis compound in the treatment of the various oxidative stress disorders.

1. Introduction

Oxidative stress a condition of over production of free radicals and oxidants in the body leading to counteract the homeostasis and subsequently causing serious imbalance [1, 2]. It arises from various sources of disease state or lifestyle such as episodes of ketosis or chronic hyperglycaemia, sleep restriction, and excessive nutrient intake [3]. The imbalance between oxidants and antioxidants damage the proteins, lipids and DNA which in turn cause physiological dysfunction of the cells and cell death [4].

Oxidative stress is considered as the biggest contributor in the pathogenesis of diabetes mellitus, cardiovascular disease, neurodegenerative disease like Parkinsonism and Alzheimer [5–8], and obstructive lungs disease [9]. Being the co-factor to multiple diseases, oxidative stress is an attractive candidate target for therapy. According to the literatures, different race shows different levels of oxidative stress. It was observed that Japanese in US have high level of oxidative stress markers than Caucasian [8]. In term of the trend of the dietary intake, vegetarians have low risk of developing oxidative stress diseases. On the other hand, non-vegetarians have high risk of having oxidative stress diseases. Therefore, modern researches have recommended to alter the diet in order to prevent such diseases [9]. In Malaysia, disease related to oxidative stress like diabetes mellitus are increasing up to 20.8% from 2006 to 2011 [10]. Diseases related to neurodegeneration are increasing alarmingly and expected to have 39,000 new cases in 2020 [11].

Over the decades, several alternative medicines or herbs from natural products were studied to observe the therapeutic effects. The potential effect of certain crude extracts, such as *Momordica charantia*, *Piper sarmentosum*, *Piper betel*, etc. were observed in few clinical studies [10, 11]. Several positive effects of the extracts or active compound on the oxidative stress disorders were also proved [10–12]. Lately, the studies on active compounds against several diseases have attracted the researchers as the therapeutic effect of the definite compound from the extract is gradually revealed from the findings [12]. Many compounds from the folk medicines were isolated and investigated to observe their potential effects. Several experimental and clinical studies on polyphenols, flavanones, flavonoids and isoflavones were also conducted in recent years. Among them, Naringenin is a potential flavone to be emphasized. Naringenin, is an active compound from flavonoids family, present in many citrus based fruits especially grapefruits. Its anti-oxidative property was widely studied and proven to be beneficial in

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https://doi.org/10.1016/j.lfs.2018.07.017
Received 6 June 2018; Received in revised form 5 July 2018; Accepted 10 July 2018

oxidative stress diseases [12–15]. However, the overall antioxidant effect of Naringenin on various oxidative stress disorders was not summarised in detail.

In the present article, we reviewed and summarised the available literatures on the anti-oxidative effect of Naringenin and on how it acts as oxidative reliever in numerous oxidative stress diseases.

2. Oxidative stress disease

When cell uses oxygen to create energy in term of ATP, free radicals are generated consequently. These by-products are generally known as reactive oxygen species (ROS) or reactive nitrogen species (RNS) that result from the cellular redox (reduction-oxidation) process [1]. When there are more free radicals and oxidants being produced in the body due to some on-going pathology, the excess free radicals disturb the normal body process which results in oxidant and antioxidant imbalance and eventually cause oxidative stress. Free radicals are produced endogenously or exogenously. Endogenous free radicals, ROS and RNS, come from many sources such as during irradiation by UV light, X-rays, and gamma-rays. It can be produced in the metal-catalyzed reactions, by neutrophils and macrophages during the inflammatory process. Exogenous free radicals represent as pollutants in the atmosphere. It is noted that ROS and RNS are the by-products of mitochondria-catalyzed electron transport reactions and other mechanisms [16]. The mechanism on how the oxidants causes damage is by stimulation of the cell proliferation in which rise in free calcium and proteins increased the transition metal ions that used to catalyse the free radicals, bind the protein DNA and destroy them. Eventually, it triggers the apoptosis and cause oxidative damage [2]. Endogenous oxidative enzymes such as NADPH oxidase, xanthine oxidase, or the mitochondrial respiratory chain is opposed by its anti-oxidative enzymes like superoxide dismutase, glutathione peroxidase, heme oxygenase, thioredoxin peroxidase/peroxiredoxin, catalase, and paraoxonase [17]. Mitochondria are the major site responsible for more than 90% of the ROS generation [18]. During imbalance redox reaction, interleukins and inflammatory mediators are produced. Therefore, inflammation is one of the manifestations of oxidative stress and the common factor for condition like type 2 diabetes mellitus and cardiovascular disease. The pro-inflammatory state is caused by over generation of free radicals in oxidative stress related diseases such as atherosclerosis and cancer [19]. This hypothesis was agreed upon by the other group of researchers who showed that inflammation following the oxidative stress is induced by the glucose and free fatty acid (FFA). This type of inflammation have cumulative and independent effects which can be reversed by antioxidants [19].Oxidative stress is important from a biomedical point of view because it is related to a wide variety of human diseases, such as neurodegenerative disease (e.g., Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis), inflammatory disease (e.g., rheumatoid arthritis), cardiovascular disease (e.g., muscular dystrophy), allergies, immune system dysfunctions, diabetes, aging and cancer [20]. The overall information on the mechanism of oxidative stress and its related diseases were summarised as schematic diagram in Fig. 1.

3. Naringenin

Naringenin is an active compound which was first discovered by Power and Tutin as chalcone in 1907. Its formulation was then improvised by Dean in 1963 [21]. It is a flavanone glycoside which has a molecular formula of C27H32O14 and molecular weight of 580.4 g/mol (Fig. 2). It highly enriched in citrus fruits such as grapefruits and lemon. Even though the recommended daily intake of Naringenin or flavonoids is not available at this present time, the estimated daily intake of flavonoid among US population is 1 g/day according to a study done by Kuhnau [22]. However, the latest finding on flavonoids intake showed that the daily intake of flavonoids including Naringenin depends on the ethnicity and habitation [23]. Naringenin is rich in Mediterranean diet as their diet mainly relies on fruits and vegetables based food [24].

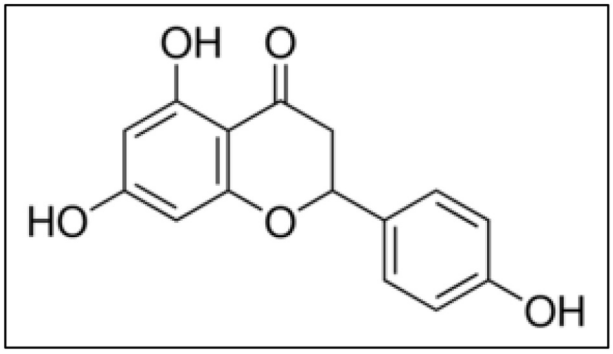

Fig. 1. Chemical structure of Naringenin [21, 22].

In an experimental animal study, Naringenin is proven to have multiple therapeutics properties. It is believed to have antithrombotic [25], anti-atherosclerosis [26], antidiabetic [27], antihypertension [28], anti-inflammatory [29] and anti-hyperlipidaemic [30] properties. However, one of the properties that is well studied is its anti-oxidative effect [13–15]. The benefits of Naringenin are attributed to its antioxidant, radical scavenging and metal chelation, enzyme activity regulation and gene expression regulation [31, 32].

Naringenin is introduced into the body as Naringin, the glycoside form of the Naringenin. It is usually bound to a glucose moiety which affecting its bioavailability [33, 34]. Once absorbed, Naringin is deglycosylated by gastrointestinal bacteria forming Naringenin. It then metabolized to form phenolic acids, *p*-hydroxyphenylpropionic acid (PHPP) and p-hydroxybenzoic acid (PHB) [14]. Naringenin can be found in the plasma, urine faeces and bile via different mechanism. The major content of Naringenin glucuronide in urine indicates that the conjugation is either from the liver or intestine. The compound is metabolized by the bile as enterohepatic recycling of the compound. In the plasma, Naringenin has been detected but not more than 4 μmol. Because of its lipophilic nature, Naringenin concentration is thought to be higher in the tissue than plasma [12]. Therefore, the bioavailability of Naringenin is less than it is anticipated. A study reported that only 4% bioavailability is achieved in an experiment on rabbit via oral administration [35]. It is suggested that NG is better to be in capsular form where the effective volume can be achieved [36]. Apart from being highly anti-oxidative, Naringenin has broad window of toxicity. It has LD50 values of 600 mg/kg body weight where 0% mortality was found at doses 100 mg/kg body weight and 100% mortality was found in the dose of 2000 mg/kg body weight [13].

Data on Naringenin intake being used as single therapeutic agent is not widely available. However, flavonoids as a whole, has long been used non-specifically in traditional medicine in Asian countries. According to the reports on the meta-analysis study in Asian population, the people who take flavonoids frequently in their diet has less number of breast and prostate cancers cases compared to the Western countries [37]. There is also an evident that Hawaiian population who takes apples and white grapefruits to form large part of their diet, has less number of lung cancer cases [36]. Other epidemiological studies also observed an inverse association between consumption of some nutritional flavonoids and the risk of human cancers at many sites [24].

Epidemiologically it was reported that Western-style diet is the major key driver to the development of cardiovascular event, hypercholesterolemia and hyperglycaemia. Consumption of fruits and vegetable enriched with citrus flavonoids showed positive impact on the metabolic syndrome including hypertension, atherosclerosis, obesity and diabetes mellitus. Generally, the active compound in the dietary sources is beneficial for the treatment of such chronic oxidative stress diseases [32]. The anti-oxidative effect of NG was summarised in Table 1.