Biomedicine & Pharmacotherapy 102 (2018) 689–698

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

Antioxidant effects and mechanism of silymarin in oxidative stress induced cardiovascular diseases

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ARTICLE INFO

Keywords:
Antioxidants
CVDs
Oxidative stress
ROS
Silymarin

ABSTRACT

Cardiovascular diseases (CVDs) are considered as the major reason for mortality and morbidity worldwide. Substantial evidence suggests that increased oxidative stress plays a significant role in the pathogenesis of CVDs, including atherosclerosis, hypertension, vascular endothelial dysfunction and ischemic heart disease. Cellular oxidative stress results in the release of toxic free radicals by endothelial cells and vascular smooth muscle cells that interact with cell components such as protein, DNA or lipid resulting in cardiovascular pathology. Silymarin has antioxidant activities against CVDs and offers protection against oxidative stress-induced hypertension, atherosclerosis and cardiac toxicity. We present a comprehensive review regarding the oxidative stress and protective effects of silymarin in CVDs management. We also aim to provide mechanistic insight of the mechanisms of silymarin action in oxidative stress-induced CVDs.

1. Introduction

Cardiovascular diseases (CVDs) are the diseases of heart and blood vessels that include the blood vessel diseases, rheumatic heart, and congenital heart diseases. Patients with heart diseases are more susceptible to the development of diabetes and renal diseases. CVDs stay the leading cause of death globally accounting for 17.3 million deaths per year. The estimated cost of CVDs is more than $316.1 billion. Thus novel therapies are required to limit the burden of CVDs [1]. Risk factors for CVDs include imbalance diet, physical inactivity, age, gender, tobacco use, total cholesterol, and high-density lipoprotein cholesterol [2–5]. These factors are monitored in the primary care centres to limit the risk of developing heart diseases [6]. Different strategies such as lifestyle modifications and nutritional habits are considered for management of CVDs risk factors [7]. The primary step in the pathogenesis of CVDs is the endothelial damage in which the underlying cell layers expose to harmful inflammatory process that ultimately leads to the formation of lesions [8].

Cellular oxidative stress is the prime pathogenic factor for CVDs due to the release of toxic free radicals by endothelial cells and vascular smooth muscle cells [9,10]. Free radicals are reactive oxygen species (ROS) with an unpaired free electron in their outer most orbital. They interact with cell components such as protein, DNA or lipid and strip their electrons to become stabilize [11]. For example, Superoxide and nitric oxide are prime oxidants that play an important role in cardiovascular pathology [12,13].

Antioxidants are substances that quench reactive oxygen species and reduce the oxidative stress damage [14]. Flavonoids are widespread polyphenolic antioxidants, available in a variety of fruits and vegetables. Silymarin is one of the polyphenolic antioxidants [15] and belongs to family Asteraceae. It is an annual herb with large leaves, hard spikes and tubular flowers [16] and native to the Mediterranean region of Europe but naturalized in California and the eastern United States [17]. Silymarin is used by herbalists and physicians for the treatment of different types of liver diseases, tumors, cardiovascular and neurodegenerative diseases [18,19]. It is extracted from the seeds of milk thistle plant as a mixture of three structural isomers (i) silybin & isosilybin (ii) silydianin & isosilydianin and (iii) silychristin &isosilychristin and minor components of quercetin and taxifolin [15,20]. Silybin or Silibinin being the main component in the silymarin mixture has antioxidant and anti-inflammatory activities [21]. Absorption of silymarin after oral administration is rather low and peak plasma concentrations are achieved in 6 hours, in animal and humans. However, some authors reported plasma level of 500 mg/L (as silibinin) 90 minutes after oral administration of 200 mg/kg of silymarin in mice [22,23]. It is quickly metabolized via phase II enzymes, and elimination

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https://doi.org/10.1016/j.biopha.2018.03.140
Received 11 January 2018; Received in revised form 22 March 2018; Accepted 22 March 2018

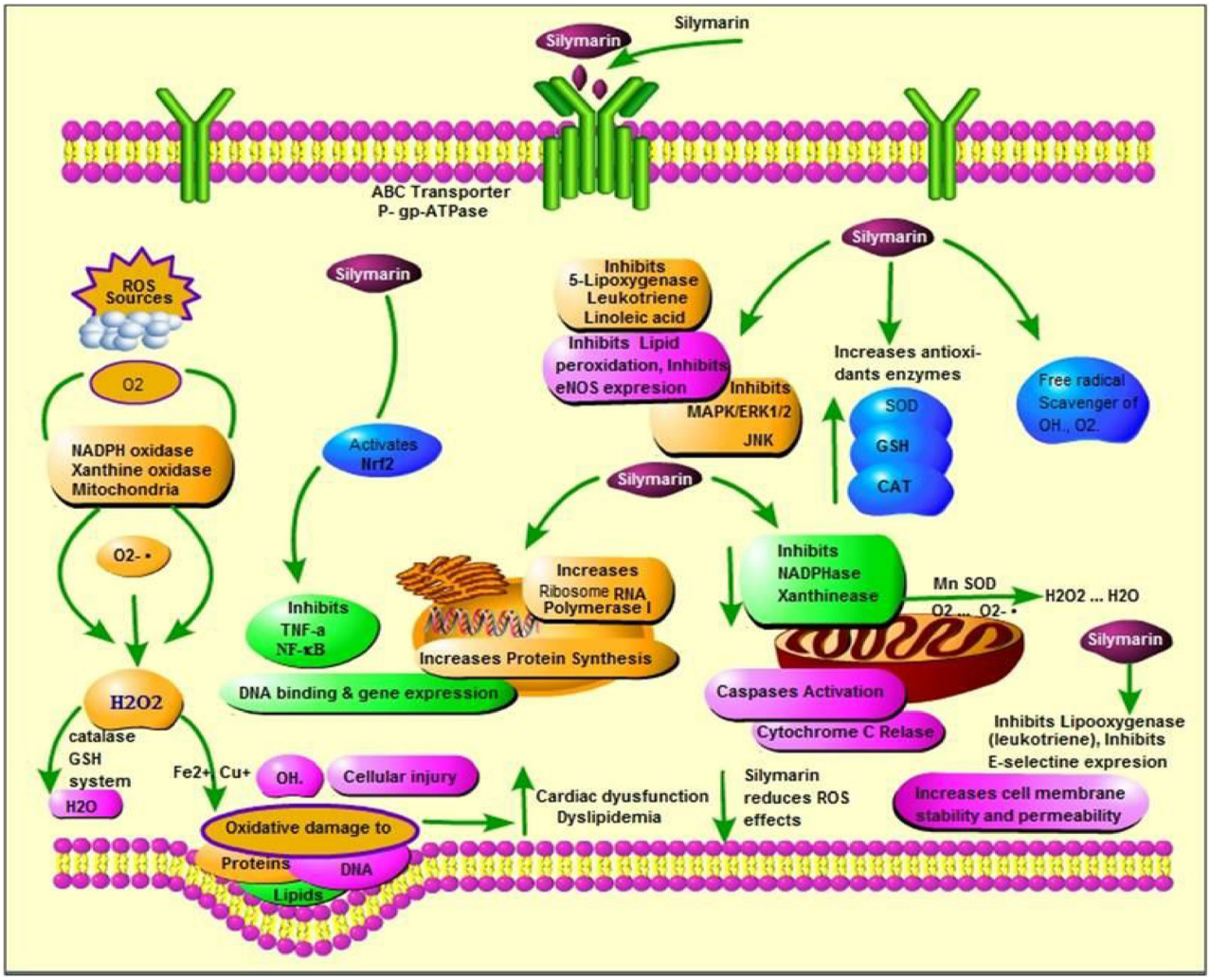

Fig. 1. Schematic presentation of the sources of ROS (NADPH oxidase, Xanthine, Mitochondria) and the resulting oxidative damage to cellular Protein, DNA and Lipids [11,51]. Silymarin shows mechanisms of actions as a scavenger of free radicals (OH·, $O_2\cdot^-$), enhances antioxidant enzymes (CAT, SOD, GPx) thereby increasing the antioxidant cell defense and increases mitochondrial enzymes activity. It also inhibits expression of eNOS and MAPK (ERK1, 2, JNK), activates Nrf2 and inhibits NF-kB, thereby regulates gene expressions [189]. Silymarin increases the regenerative ability of cardiovascular tissues by activating ribosomes and increases protein synthesis. It has been shown to stabilize the cellular membrane through modifying the transporters and receptors of cell membranes such as ABC transporters and organic anion uptake transporter peptides [193]. Silymarin has protective and cell-regenerating actions in a cell membrane, scavenges free radicals in the cytoplasm, and promotes ribosomal RNA synthesis, consequently improving the cardiovascular dysfunction and dyslipidemia [23].

half-life ranges from 6 to 8 hours. Silibinin and other components of silymarin are rapidly conjugated with sulfate and glucuronic acid in the liver. The conjugates pass into the plasma and into the bile, where they are found in amounts corresponding to 80% of the total dose administered [23]. Poor bioavailability of silymarin extract is mainly due to accompanying substances or the concentration of the extract itself. Thus solubilizing agents are added to the extract to achieve therapeutic plasma level [24,25]. Silymarin is commercially available as capsules and caplets in doses of 120 mg, 160 mg, 250 mg, and 300 mg under the brand name legalon. Its dose ranges from 280 to 800 mg/kg of body weight, and usual dosage is 1-2 tablets twice daily with a meal [26]. Consumption of acute doses of silymarin has been reported as safe and non-toxic to animals and humans. Rare side effects include mild gastrointestinal disturbance, nausea, and headache in clinical trials [27,28]. Silymarin has antioxidant activities against CVDs and offers protection against oxidative stress-induced hypertension, atherosclerosis, and cardiac toxicity. The purpose of this review is to highlight the current knowledge regarding the role of reactive oxygen species in inducing CVDs and antioxidant effects and mechanism of silymarin in preventing oxidative stress-induced CVDs (Fig. 1).

2. Reactive oxygen species and CVDs

Oxidative stress is defined as an imbalance between the formation of reactive oxygen species (ROS) and the capacity of the body to detoxify them [29,30]. They are signaling molecules produced in cells as by-products of normal cellular oxidation-reduction reaction[31,32]. ROS include superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\cdot}$) and lipid peroxy radical ($LOO^{\cdot}$) [31]. Besides, it also includes reactive nitrogen species such as nitric oxide (NO), nitrogen dioxide radical (NO_2), nitrosonium cation (NO^+) and peroxynitrite ($ONOO^-$). These reactive species can modify and alter the function of lipids and proteins by reacting with cellular components [33,34]. Peroxidation of membrane lipids is toxic and alters the biological properties of the cell membrane leading to inactivation of membrane-bound receptors or enzymes and impairing normal cellular function [35]. Reduction in Na + /K+ -ATPase activity in cell membrane correlates with elevation of lipid peroxidation products in pre-hypertensive patients, suggesting that ROS underlie some of the pathophysiological aspects linked to this condition [36].

Cardiac and vascular tissues are rich sources of ROS that play an