Biomedicine & Pharmacotherapy 101 (2018) 579–584

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Review

Potential of resveratrol in mitigating metabolic disturbances induced by ethanol

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ARTICLE INFO

Keywords:
Resveratrol
Alcohol
Metabolism
Liver damage

ABSTRACT

Alcohol abuse is associated with numerous health problems, including metabolic disturbances and liver damage. Therefore, different compounds are continuously being tested to evaluate their potential effectiveness in reducing these harmful changes. Animal studies clearly show that resveratrol is capable of ameliorating some consequences of ethanol ingestion. Resveratrol is a naturally occurring diphenolic compound having pleiotropic, health-promoting properties. Its beneficial action have been also demonstrated in animal models with ethanol-induced metabolic disturbances and liver injury. In ethanol treated animals, resveratrol effectively reduced liver lipid accumulation. Moreover, this compound diminished necrosis of hepatocytes, and also reduced liver fibrosis. The hepatoprotective action of resveratrol is largely associated with its ant-oxidant and anti-inflammatory properties, and also covers changes in activities of some enzymes. It is known that this compound upregulates the adiponectin-SIRT1-AMPK signaling pathway in the liver. Resveratrol was also found to positively affect blood lipids in animals exposed to ethanol. Moreover, administration of resveratrol to animals with ethanol-induced hypoinsulinemia and insulin resistance was shown to alleviate these disturbances.

These outcomes clearly indicate that resveratrol holds great potential to reduce some consequences of ethanol ingestion. However, human studies are required to fully assess its therapeutic value.

1. Introduction

Alcohol abuse is a serious global problem associated with risk of many diseases, and also with increased morbidity and mortality. The number of alcohol-attributable diseases is very big and includes, among others, cancer, liver cirrhosis, pancreatitis, cardiovascular diseases, metabolic disorders, diabetes, infections, stroke, mental disorders and more [1]. Therefore, new synthetic drugs, and also naturally occurring compounds are continually being tested to prevent and better treat consequences of alcohol abuse [2]. Recently, there is a growing body of evidence that resveratrol, one of the naturally occurring agents, has a great potential in mitigating metabolic consequences of ethanol ingestion.

Resveratrol (3,5,4′-trihydroxystilbene, Fig. 1) is a polyphenol found in different plant species, among others in grapes, berries and peanuts. The richest natural source of resveratrol is *Polygonium cuspidatum*, a plant that has been used in oriental folk medicine. This compound is also present in red wine and has been proposed to be responsible for the "French paradox", *i.e.* low mortality due to cardiovascular disease as a result of moderate consumption of red wine [3,4]. Resveratrol belongs to the biologically active agents, and its ingestion is associated with several benefits in the organism. Resveratrol rises great interest, in particular due to its health-promoting properties. Numerous favorable effects of this compound have been shown not only in animal studies, but also in humans. Its action is pleiotropic and involves, among others, anti-cancer [5], cardio-protective [6], anti-inflammatory [7], anti-diabetic [8,9], neuro-protective [10], anti-obesity [11] and anti-oxidative [12] effects. Moreover, experiments with mice on a high-calorie diet revealed the capacity of resveratrol to increase the survival and motor function. These effects were also accompanied by changes in expression of some genes and by reduction in fat depots [13,14].

At the cellular level, resveratrol is known to positively affect energy expenditure, mitochondrial biogenesis and cell survival. Its molecular targets involve many intracellular signaling molecules and regulatory proteins, including AMP-activated protein kinase (AMPK) and silent information regulator 1 (SIRT1) [15].

In the light of numerous benefits of resveratrol ingestion that have been documented under various pathological conditions, data from the literature showing the capability of this compound in ameliorating consequences of ethanol exposure seem to be very intriguing and create new perspectives for its use. This review summarizes results of studies addressing to the action of resveratrol in rodents exposed to ethanol

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https://doi.org/10.1016/j.biopha.2018.02.063
Received 21 November 2017; Received in revised form 6 February 2018; Accepted 15 February 2018

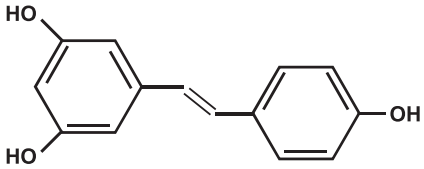

Fig. 1. Chemical structure of *trans*-resveratrol.

(Fig. 2).

2. Hepatoprotective action of resveratrol

In mammals, liver is the main organ in which ethanol undergoes degradation and thereby hepatocytes are subjected to damage by ethanol, and also by products of its metabolism. Oxidative metabolism of ethanol to acetate involves two steps. The first one is conversion to acetaldehyde. This reaction is catalyzed largely by alcohol dehydrogenase (EC 1.1.1.1), and also by catalase and microsomal enzymes. The second step is conversion of acetaldehyde to acetate in the presence of aldehyde dehydrogenase (EC 1.2.1.3). The mechanism underlying the hepatotoxic action of ethanol is complex and is attributed to many factors, including increased formation of NADH, generation of reactive oxygen species, induction of inflammation and more [16,17]. The degree of liver injury strongly depends on doses of ethanol and term of its ingestion.

2.1. Effects of resveratrol on liver lipids

Increased accumulation of fat in hepatocytes is the earliest response

Table 1
Effects of resveratrol on blood and liver lipids in ethanol-treated animals.

Parameter		Ethanol		Resveratrol	Animal	Ref
Blood						
Triglycerides	↑	10%, drinking water, 2 w	↓	10 mg, ig., 2 w	Rat	[23]
		2.4 g/kg bw, liquid diet		100 mg, 22 w	Rat	[24]
		liquid diet, 4 w		30 or 100 mg	Mouse	[20]
		200 mg, oral, 4 w		100 mg, oral, 4 w	Mouse	[19]
		liquid diet		200 or 400 mg, 2 w	Mouse	[18]
Free fatty acids	↑	10%, drinking water, 2 w	↓	10 mg, ig., 2 w	Rat	[23]
Total cholesterol	↑	2.4 g/kg bw, liquid diet	↓	100 mg, 22 w	Rat	[24]
LDL-cholesterol		liquid diet		30 or 100 mg	Mouse	[20]
Liver lipids	↑	10%, drinking water, 2w	↓	10 mg, ig., 2 w	Rat	[23]
		liquid diet, 4w		200 or 400 mg, 2 w	Mouse	[18]
		3 g/kg bw, ip, 6w		5 g/kg diet	Rat	[21]
		liquid diet		30 or 100 mg	Mouse	[20]
		200 mg, oral, 4w		100 mg, oral 4 w	Mouse	[19]
		6.5 g/kg bw, ig 4 w		250 mg, ig, 4 w	Rat	[22]

mg – mg/kg body weight, bw – body weight, w – weeks, ip – intraperitoneal, ig – intragastric.
LDL – low density lipoproteins.
↑ - increase, ↓- decrease.

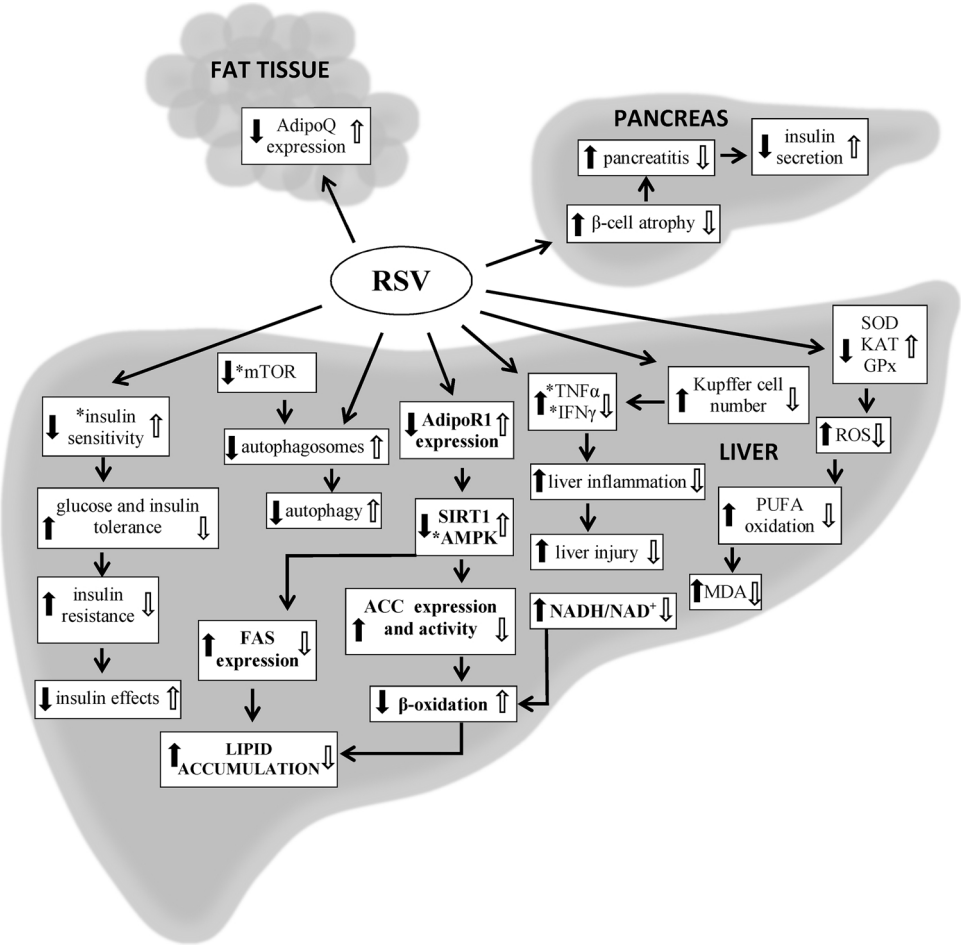

Fig. 2. Proposed mechanisms of resveratrol action in ethanol-treated animals. Black arrows - effects of ethanol; open arrows - effects of resveratrol. * - chronic ethanol ingestion.