Ageing Research Reviews 21 (2015) 1–15

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

Resveratrol supplementation: Where are we now and where should we go?

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ARTICLE INFO

Article history:
Received 13 August 2014
Received in revised form 9 January 2015
Accepted 15 January 2015
Available online 24 January 2015

Keywords:
Resveratrol
Bioavailability
Metabolism
Clinical trials
Translational research

ABSTRACT

Pre-clinical findings have provided mounting evidence that resveratrol, a dietary polyphenol, may confer health benefits and protect against a variety of medical conditions and age-related complications. However, there is no consistent evidence of an increased protection against metabolic disorders and other ailments when comparing studies in laboratory animals and humans. A number of extraneous and potential confounding variables can affect the outcome of clinical research. To date, most of the studies that have investigated the effect of resveratrol administration on patient outcomes have been limited by their sample sizes. In this review, we will survey the latest advances regarding the timing, dosage, formulation, bioavailability, toxicity of resveratrol, and resveratrol–drug interactions in human studies. Moreover, the present report focuses on the actions of resveratrol treatment in combating diseases, such as cancer, diabetes, neurodegeneration, cardiovascular disease, and other age-related ailments.

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Contents

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http://dx.doi.org/10.1016/j.arr.2015.01.002
1568-1637/Published by Elsevier B.V.

"Let food be your medicine and medicine be your food"
Hippocrates

Since the beginning of the 1990s, various reports began to emerge that resveratrol, a compound present in red wine, might contribute in part to the "French paradox", a phenomenon that refers to the relative low rate of cardiovascular disease (CVD) in France despite high intake of dietary saturated fat (Renaud and de Lorgeril, 1992). Resveratrol (3,4′,5-trihydroxystilbene, RSV) is a small polyphenol compound found in various berries, nuts, grapes, and other plants sources, including traditional Asian medicines. Although this polyphenol exists as *cis* and *trans* isomers, *trans*-RSV is the predominant form found in dietary sources and supplements. The growing interest in the use RSV is due to its pleiotropic action as a molecule that affords protection against inflammation, oxidative stress and cancer, and as a caloric restriction mimetic (Baur and Sinclair, 2006; Cottart et al., 2014). RSV has gained considerable interest in the medical community as possible treatment to combat several human chronic diseases (Baur and Sinclair, 2006).

This review will focus on recent insights into the metabolism of RSV and its biological effects in humans (Fig. 1). We considered only studies that tested known quantities of RSV and not formulations that may contain other potentially efficacious compounds (*e.g.*, quercetin) (Tables 1 and 2). In addition, mechanistic insights into RSV signaling in *in vitro* and animal models were limited to a minimum as to not detract the readers from the main objective of this review. In that regard, a general overview of the pleiotropic effects of RSV in animal studies precedes the presentation of clinical trials that were mostly conducted with small sample sizes. We will discuss the beneficial and adverse responses to RSV supplementation, and the challenges of translating these preliminary findings in humans to thorough and stringent clinical trials.

1. Introduction

Animal models and clinical studies have established that RSV is generally well tolerated, although some adverse effects were reported. These effects were observed among a wide range of doses (from 0.5 to 5 g per day), but according to the authors not all adverse effects were deemed possibly associated with RSV intake (Brown et al., 2010). Adverse reactions to RSV in animals included nephrotoxicity (Crowell et al., 2004), while the gastrointestinal tract was the most affected in humans (Brown et al., 2010; Chow et al., 2010; Howells et al., 2011; La Porte et al., 2010; Poulsen et al., 2013). Other side effects ranging in intensity from low to mild were fully resolved (Almeida et al., 2009; Vaz-da-Silva et al., 2008). Daily consumption of 450 mg of RSV has been deemed safe for a 60-kg individual (Smoliga et al., 2012). The potency of RSV may be influenced by its interaction with other drugs, vitamins, and dietary components. Although no negative drug–drug interactions have been reported to date, high doses of RSV have been found to inhibit cytochrome P450 isoenzymes and, consequently, can influence the pharmacokinetic profile of many drugs (Detampel et al., 2012; Smoliga et al., 2012).

The clinical trials presented here report a wide range of RSV concentrations, ranging from 5 mg to 5 g, and comprise various treatment durations. The specifics about the dosage, duration and mode of administration of RSV for subjects with health problems are found in Table 1, whereas Table 2 encompasses clinical trials with healthy and/or obese participants that do not take medication, unless indicated otherwise. From these studies, it is clear that a consensus must be found by determining the minimum effective concentration of RSV that confers health benefits with minimal side effects.

2. General overview of the pleiotropic effects of RSV in *in vitro* and animal studies

It is now well recognized that RSV extends the lifespan of numerous lower organisms, including *Saccharomyces cerevisiae* (Howitz et al., 2003), *Caenorhabditis elegans* and *Drosophila melanogaster*, without reducing fecundity (Wood et al., 2004). Although RSV exerts significant beneficial effects in the treatment of age-related pathologies, such as cancer, type 2 diabetes (T2DM), and cardiovascular and neurodegenerative diseases, no extension of lifespan was reported in animals fed a standard diet *ad libitum* supplemented with RSV (Miller et al., 2011; Pearson et al., 2008; Strong et al., 2013). This contrasts with a significant increase in lifespan and changes associated with longer life when mice were fed a high-fat

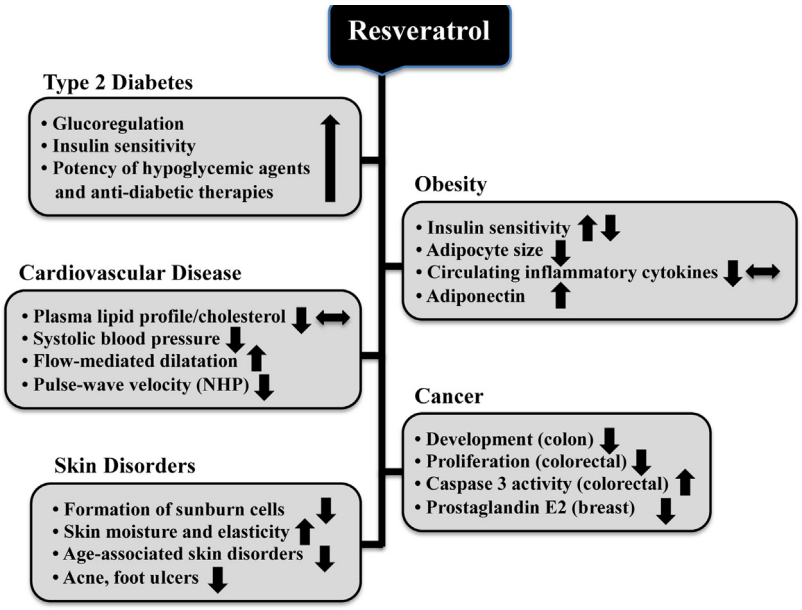

Fig. 1. Summary of the effects of resveratrol in human clinical trials when conducted in patients with type 2 diabetes, obesity, cardiovascular disease, cancer or skin disorders. The symbol ↔ denotes lack of effect, and ↑↓ opposite action in some trials.