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Ethnopharmacological aspects of resveratrol (a French paradox) – A review

Rajesh Singh Pawar*, Deepa Iyer, Sunny Sinha, Pradeep Pateriya

VNS Group of Institutions, Faculty of Pharmacy, Vidhya Vihar, Neelbud, Bhopal-- 462044, MP (India)

Abstract

The origin of the name resveratrol is reportedly derived from the Latin word 'res' meaning 'which comes from' the plant 'veratrum' and 'ol' indicating the presence of an alcohol moiety. Resveratrol is obtained from plants. The function of resveratrol in plants is thought to be protection since it is produced when the plant is under environmental stress, whether ultraviolet radiation, infection, or insect infestation. Resveratrol's introduction into the dietary supplement market a few years back was based upon the consideration that intake of it and other polyphenol compounds from red wine may contribute to the "French paradox", the unexpectedly low rate of death from cardiovascular disease in the Mediterranean population, despite a diet that is relatively high in saturated fat. Since then, interest in resveratrol has increased due to research suggesting additional antioxidant, anti-inflammatory, anticancer, antiviral, and anti-aging effects; as well as possibly playing a role in weight loss and athletic performance. Resveratrol has emerged as a leading candidate for improving healthspan through potentially slowing the aging process and preventing chronic diseases. This review summarizes the ethnopharmacological aspects of resveratrol and provides suggested directions for future research in this realm.

Keywords: Resveratrol, Polyphenols, Pharmacological actions, Red wine

Introduction

Resveratrol is a phytoalexin found in many plant species [1], including those often consumed by humans such as grapes, peanuts, and berries; it is produced in plants in response to mechanical injury, fungal infection, and UV radiation [2]. Resveratrol (3, 5, 4-trihydroxystilbene) (Figure 1) was first isolated from the roots of white hellebore (*Veratrum grandiflorum* O. Loes) in 1940 and later, in 1963, from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine [3]. Initially characterized as a phytoalexin [4], resveratrol attracted little interest until 1992, when it was postulated to explain some of the cardioprotective effects of red wine [5]. Resveratrol is not only found in these plants (Figure 2), but also in processed products such as wine. In fact, many attribute the 'French Paradox' in which moderate wine consumption is associated with decreased risk of coronary heart disease [6], to be the result of red wine's relatively high resveratrol concentration (0.1–14.3 mg/l). Since then, dozens of reports have shown that resveratrol can prevent or slow the progression of a wide variety of illnesses, including cancer [7], cardiovascular disease [8] and ischaemic injuries [9, 10] as well as enhance stress resistance and extend the lifespans of various organisms from yeast [11] to vertebrates [12].

Resveratrol is a strong anti-oxidant and acts in many chemical reactions in the cell [13]. It can also bind to an estrogen receptor in the cell, therefore it can be considered as an estrogenic com-pound [14]. As an estrogenic compound, it could be effective against hormone related cancers. Resveratrol enhances the internal functions of the cell, particularly mitochondria, which is the energy source for the cell [15]. Mitochondria convert food energy in to energy that the cell can use. Decreased mitochondrial function has been linked to insulin resistance, metabolic syndrome, and cardiovascular disease. Resveratrol has been found to be linked to decreased incidence of many chronic diseases such as neurodegenerative diseases, cancer and heart disease [1]. The mechanism by which resveratrol exerts such a range of beneficial effects across species and disease models is not yet clear. Attempts to show favourable effects *in vitro* have met with almost universal success, and have led to the identification of multiple direct targets for this compound. However, results from pharmacokinetic studies indicate that circulating resveratrol is rapidly metabolized, and cast doubt on the physiological relevance of the high concentrations typically used for *in vitro* experiments. Further experiments are needed to show whether resveratrol or its metabolites accumulate sufficiently in tissues to recapitulate *in vitro* observations, or whether alternative higher-affinity targets, such as quinone reductase 2 (QR2; also known as NQO2) [16], have the key roles in its protective effects. *In vivo* results have therefore become increasingly important in our attempts to understand how resveratrol is effective in the treatment of disparate diseases. This review summarizes the ethnopharmacological aspects of resveratrol and provides suggested directions for future research, as they relate to the development of human therapeutics.

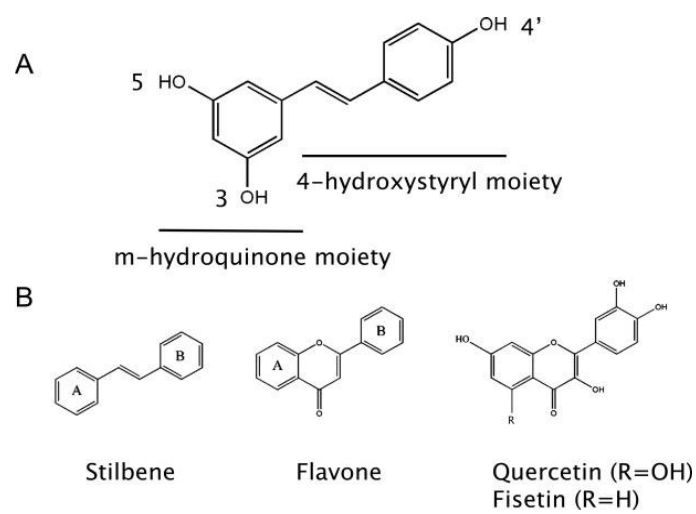

Figure 1: (A) Chemical structure of resveratrol, 3, 4', 5-tri-hydroxyl trans stilbene. The two moieties are shown, as well as the numbering of the hydroxyl group. (B) from left: Chemical structures of stilbene and similar flavone, the common phenyl rings are lettered. Chemical structures of the flavone derivatives quercetin and fisetin, which share common targets with resveratrol.

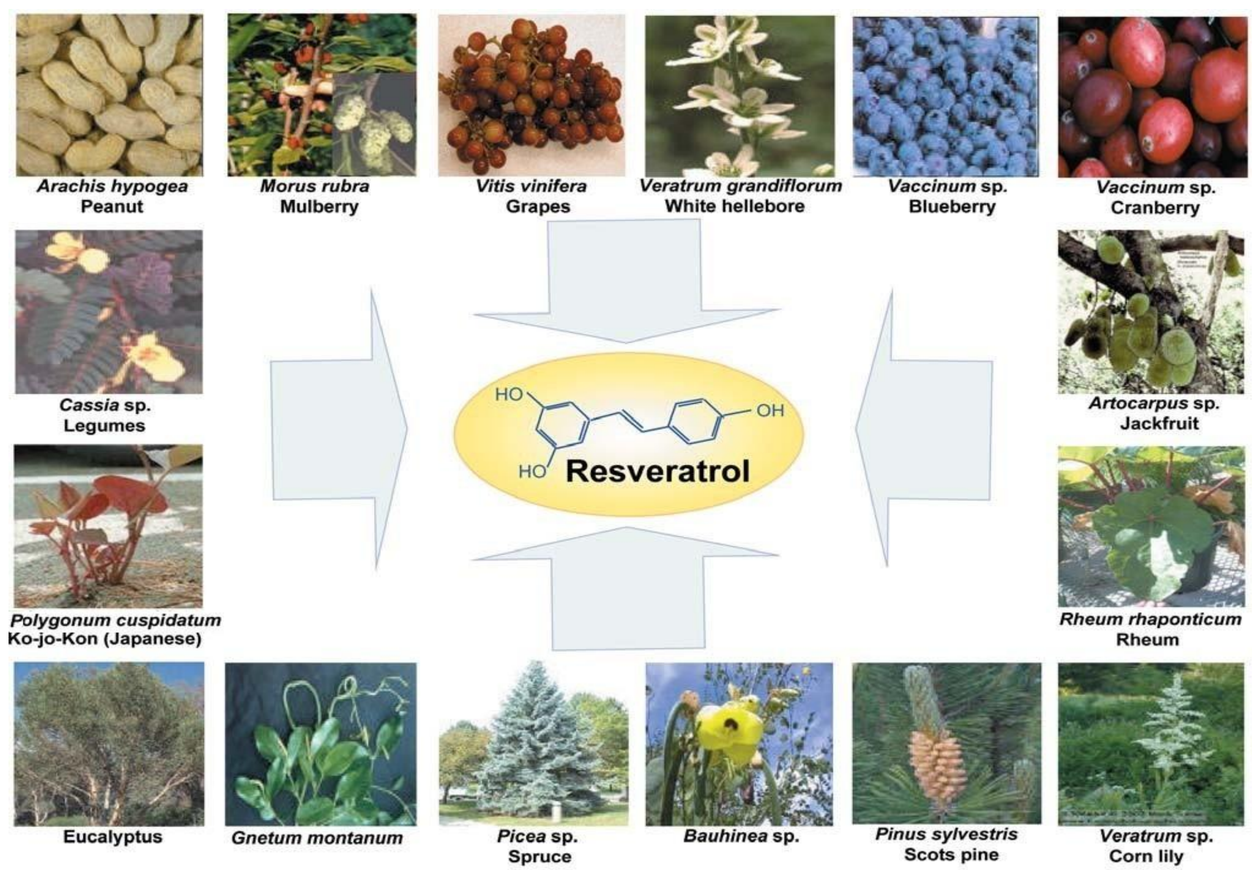

Figure 2: Herbal sources of resveratrol

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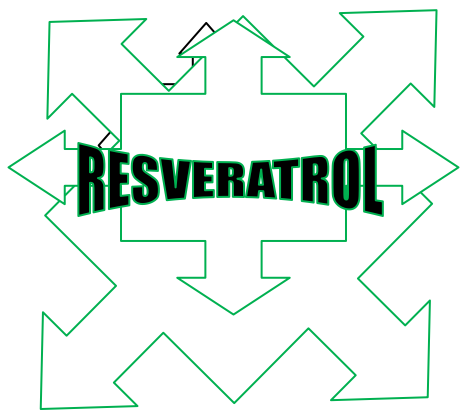
Rajesh Singh Pawar, E-mail:- dr_pawar14@rediffmail.com

Table 1: Properties and products of resveratrol

Physical-chemical properties of resveratrol	
Physical State	Solid, powder
Color	Off white
Melting Point (°C)	253-255
Herbal products	
Bio vin full spectrum grape seed and skin extracts, Biochem olive leaf extract, Cardio cholestamax™, ORAC+ Biosynergistic super fruit powder, ActiVin™ + Resveratrol, Protykin®, Resveratrol synergy™	

Table 2: Therapeutic potential of resveratrol

Anti-inflammatory agent [17]	**Circulation enhancing agent** [25]
Pain blocker [18]	**Hormone replacement agent** [26]
Antibiotics [19]	**Cardio Protective agent** [27]
Antidepressant [20]	**Anti-hypertensive agent** [28]
Anticholesterol agent [21]	**Vasodilator** [29]
Anti blood clotting agent [22]	**Aromatase Inhibitors** [30]
Anti-angiogenic agent [23]	**5-Alpha reductase inhibitors** [31]
Alzheimer's drug [24]	**Anti-osteoporosis agent** [32]



Ethnopharmacological considerations

Resveratrol has emerged as a leading candidate for improving healthspan through potentially slowing the aging process and preventing chronic diseases. There is growing evidence that resveratrol can prevent or delay the onset of cancer, heart disease, ischaemic and chemically induced injuries, diabetes, pathological inflammation and viral infection. The poor bioavailability of resveratrol in humans has been a major concern for translating basic science findings into clinical utility (Table 1 & 2).

The hope and hype surrounding resveratrol was sufficient to lead to the development of human clinical trials in the absence of a full understanding of its mechanism of action or optimal dosage protocols to attain sufficient concentrations in humans. Human clinical trials exploring the health effects of resveratrol continue to emerge, but remain somewhat limited in scope and number. Much of the human literature has yielded promising results consistent with data from laboratory animal models [33], such that resveratrol reduces biomarkers of inflammation in healthy individuals [34-36], improves clinical biomarkers in diabetes [37, 38], increases blood flow to the brain [39] and enhances vascular function in general [40, 41].

A number of theoretical solutions have been developed to improve the bioavailability of resveratrol, including consumption with various foods, micronized powders, combining it with additional phytochemicals, controlled release devices, and nanotechnological formulations. While laboratory models indicate these approaches all have potential to improve bioavailability of resveratrol and optimize its clinical utility, there is surprisingly very little data regarding the bioavailability of resveratrol in humans. One possible explanation for this seemingly coordinated response is that resveratrol resembles an endogenous signalling molecule. Indeed, resveratrol's structure is reminiscent of molecules that stimulate the oestrogen receptors. However, attempts to characterize resveratrol as an *in vivo* oestrogen mimetic have met with limited success [42, 43]. Another alternative is the 'xenohormesis hypothesis', which proposes that organisms have evolved to respond to chemical cues in their diets [44, 45].

Discussion

According to hindu mythologies it is mentioned in Vedas and Puranas, that besides Demon, God and Goddess also consumed *Somarasa* (a kind of intoxicating drink made from extract of grapes). In Vedas and Puranas, *Somrasa* has been mentioned many times behind the fact that increased the life span of people dwelling at that era. This led to a concept about the hidden therapeutics metabolites present the fruit. Days are not far when Resveratrol will be replacing multi vitamins supplements, protein diets, and other nutraceuticals products in the pharmaceutical sector throughout the world. In

Rajesh Singh Pawar, E-mail:- dr_pawar14@rediffmail.com

a nut shell, resveratrol is still a *Tricky molecule* and matter of research molecule which has multipurpose role in therapeutic curing of many dreadful diseases like Cancer and AIDS. So, one can assume that resveratrol will be the next *Genetic Tsunami* in medical research field. Despite the therapeutic effects of resveratrol, its pharmacokinetic properties are not favorable since this compound has poor bioavailability being rapidly and extensively metabolized and excreted. To overcome this problem, drug delivery systems have been developed to protect and stabilize resveratrol and to enhance its bioavailability. Herein is presented an up-to-date revision covering the literature reported for nano and micro formulations for resveratrol encapsulation that include liposomes, polymeric nanoparticles, solid lipid nanoparticles, lipospheres, cyclodextrins, polymeric microspheres, yeast cells carriers and calcium or zinc pectinate beads. Regarding the interaction of resveratrol with cell membranes, only few studies have been published so far. However, it is believed that this interaction can be implied in the biological activities of resveratrol since transmembranar proteins are one of its cellular targets. Indeed, resveratrol presents the capacity to modulate the membrane organization which may consequently affect the protein functionality. Therefore, the intracellular effects of resveratrol and the effects of this compound at the membrane level were also revised since their knowledge is essential for understanding the pharmacological and therapeutic activities of this bioactive compound.

Whether resveratrol can stimulate endogenous pathways to promote health and longevity, such as those that are active during caloric restriction or whether it produces its effects through a series of fortuitous interactions are important issues to address.

Conclusion

There is little evidence from animal or human studies that resveratrol can serve as a viable treatment for various diseases in the near future. There is a need for more extensive and consistent studies in animal models. In addition, much work needs to be done on optimizing the bioavailability of the drug and determining its pharmacokinetic, pharmacodynamics, and safety profile in different patient populations (e.g. adults *vs* pregnant women *vs* children). In addition to its other properties, resveratrol is reported to act as an analgesic, protect against hearing loss and enhance lipopolysaccharide-induced anorexia in rats, although it has no anorexic effect when given alone. Resveratrol has also been shown to reduce injuries to the kidneys, spinal cord, liver, lungs, intestine and colon. These additional results indicate that the protective effects of resveratrol are not limited to the heart and brain *in vivo*. This is especially concerning, given that conclusions about resveratrol's future are being generated from human clinical trials which are currently being performed without a full understanding of the optimal dosage protocols. While there are many reports on the various effects of resveratrol derivatives in *in vitro* test systems, little is known about their absorption, metabolism, bioavailability, and more important biological effects *in vivo*.

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Rajesh Singh Pawar, E-mail:- dr_pawar14@rediffmail.com

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Rajesh Singh Pawar, E-mail:- dr_pawar14@rediffmail.com