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Pharmacological Aspects of Resveratrol

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ABSTRACT

Resveratrol [(E)-5-(4-hydroxystyryl) benzene-1,3-diol], also known as 3,4′,5-trihydroxystilbene also known as resveratrol is classified as a phytoalexin in plants such as nuts, cocoa, berries and grapes for self-defense against injury and pathogenic attacks by bacteria and fungi. Research on this compound did not gain popularity until the 1990s when a published paper implied the relationship between resveratrol and the decrease in cardiovascular complications due to the consumption of grape fermented wine in French populations. This observation sparked research on resveratrol even though its concentration in wine is relatively low, leading to the realization that resveratrol has potential for benefits in other illnesses such as in anti-diabetic, anti-cancer, anti-aging research and benefits towards reproductive organs, among many others that will be discussed in this review. However, most of the research found on the effects of resveratrol have been conducted on animal models, most notably mice, with a limited amount on actual humans. More research is to be expected to compare if the effects on humans will be like those of the animal models.

Introduction

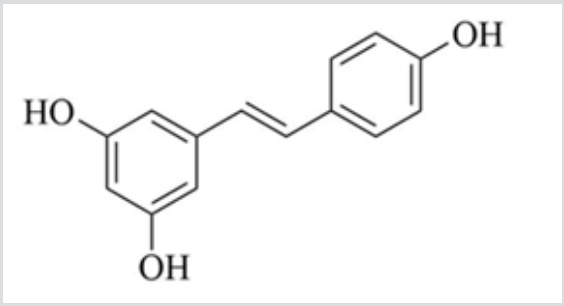

Figure 1: Chemical Structure of Resveratrol.

The non-flavonoid phenolic compound 3,4′,5-trihydroxystilbene, known as resveratrol (Figure 1) or shortened to RSV, is classified as a phytoalexin and is produced naturally in plants such as spermatophytes as a self-defense mechanism in response to injury to the plant by UV irradiation, metallic salts, etc. or by a pathogen attack from bacteria or fungi [1]. The plants include, among others, nuts, cocoa, berries and grapes which then can found in grape fermented wine and grape juice. The Z-isomer of resveratrol is not found in grape extract, however the trans-isomer of resveratrol, trans-3,4′,5-trihydroxystilbene, can only be found in the skin of the grapes with the amount of resveratrol per grape varying by the grape cultivator, geographic origin, and even infection [1-3]. In wine, the amount of resveratrol depends on the type of wine since the process of making white and rose wine requires the grape skin to be removed before wine production, compared to red wine where the skin is kept intact [2].

This compound was first isolated in 1939 from the roots of white hellebore, but research on this compound did not gain popularity until the 1990s when a published paper included the phrase "the French paradox" which stated that even though the French had diets containing high amounts of saturated fats, their chance of cardiovascular complications was low [3-6]. This observation gave way to the implication that the French lifestyle of drinking wine was the cause of their increased health, sparking research on resveratrol even though its concentration in wine is relatively low [4]. These studies led to the realization that resveratrol has potential for benefits in other illnesses such as in anti-diabetic, anti-cancer and anti-aging research, among many others.

Discussion

Scientists have conducted many experiments and studies on resveratrol that have shown how it can be used as treatment for cancer, cardiovascular disease, ischemic and chemically induced injuries, inflammation, viral infections, diabetes, and neurological diseases such as Alzheimer's disease and seizures [7,8]. Alzheimer's disease has been found to elevate inflammatory and cytokine levels which leads to neuroinflammation, a leading contributor to the development of the disease. The release of an increased level of cytokine is caused by the accumulation of fibrillar Aβ-containing plaques which also leads to inflammation. Resveratrol has been known to have neuroprotective effects by decreasing the Aβ levels in the hippocampus therefore protecting the blood brain barrier, and by stopping the brain from increasing anti-oxidation [9]. In cancer treatments, it has been recorded that resveratrol exhibits chemo preventive effects on lung, breast, prostate, colon, skin cancer and other cancers through experiments on animal models. However, the success depends not only on resveratrol but on what other chemicals are being administered in conjunction with resveratrol and what type of cancer is being treated [4].

Resveratrol exists in both the trans and cis-isomer, however the cis-isomer of resveratrol has never been identified in grape extract, though it can be converted from the trans-isomer of resveratrol, which is found in the skin of grapes, by using UV radiation. Compared to the cis-isomer, the trans-isomer is more affective against anti-oxidant, bioactive, and more stable, which is why it is often used in studies. The E-isomer is commercially available as supplements and has been seen to remain stable for months when it is fully protected from UV light [1,10]. Diverse pharmacological effects of resveratrol is discussed in the sequel.

Antidiabetic and Antiobese

Since it was published, the concept of the French Paradox has obtained criticism for its accuracy and research trying to replicate the data. New research states that this concept can be explained by another concept called the Caloric Restriction (CR) which states that a 20-30% reduction of calorie intake can increase organism lifespan and protect against illness [6]. Findings show that resveratrol affects the protein silent information regulator 2 (Sir2), a conserved deacetylase which is responsible for the extended lifespan of yeast through cardiovascular health derived from caloric restriction [11], therefore mimicking the benefits of CR [6]. The mammalian analog of Sir2 is the sirtuin gene, SIRT1, which regulates glucose and insulin production, metabolism, and cell survival, has shown to have activity enhanced by resveratrol including improved cellular function and overall organismal health [11]. Diabetes is a highly studied disease since it is affecting over 5% of people worldwide. It is known that people that are overweight are at higher risk of developing diabetes along with obesity-related related health problems [11]. Diabetes causes hyperglycemia and interferes with the production of insulin with long term effects including cardiovascular disease, inflammatory diseases, and higher risk of developing cancer, similar to obesity. In type 1 diabetes, resveratrol protects that get harmed by the effects of diabetes and decrease blood glucose levels that get elevated from the effects of diabetes as demonstrated in an experiment where rats with streptozotocin induced diabetes had their blood glucose reduced by the effects of resveratrol. In type 2 diabetes, resveratrol was shown to improve insulin action and protects pancreatic β-cells both of which are damaged by inflammation and oxidative stress caused from diabetes [3].

Many studies on obesity, increased calorie intake, and diabetes has been performed on animal models such as rats. A study tested the effect of resveratrol by mimicking metabolic syndrome found in obesity and diabetes by feeding maternal and post-weaning female mice high fat diets. Maternal mice on a high fat diet with no resveratrol treatment were seen to have higher body weight, plasma triglyceride levels, and leptin. The mice that were fed with resveratrol treatment regardless of a high fat diet showed a lower daily calorie intake, decreased plasma leptin levels, and decreased body weight. It reversed the increased cholesterol levels and triglyceride levels and show promise that it can reverse the increased high-density lipoprotein levels found in plasma [12].

Effects on Reproduction and Cancer

Resveratrol is seen to interact with many different types of receptors, leading to the fact that it can act through multiple pathways [8]. It has been seen that resveratrol is a selective estrogen receptor modulator [9] and can compete with the estrogen receptors native ligand, estradiol, for the Ligand Binding Domain (LBD). When it binds to the estrogen receptor, resveratrol has been seen to increase the expression of native regulated genes and at high concentrations it can increase proliferation of breast cancer cells that are regulated by the estrogen receptor [1]. Because resveratrol has been shown to have protective actions to damaging interactions such as those found in cancer, obesity, and diabetes, it has been tested on what effects it can have on reproductive organs. Polyvinyl chloride (PVC) is a type of polymer that is used in the production of plastics. It has also been shown that for mice on resveratrol treatments and high calorie diets, their body functions are similar to those of mice on a normal diet, even without a reduction in body weight of the high calorie mice [11]. In another study involving mice, resveratrol effects the development of brown-like adipocytes, that have been linked to reduce obesity through increased energy and oxygen consumption, that form in White Adipose Tissue (WAT) by increasing its protein expression [13].

These study shows promise to use resveratrol in humans to control metabolism and prevent obesity since it is shown to prevent effects of excess caloric intake and increase longevity. There is a correlation to an increase of PVC found in the human body to an

increase of reproductive health issues and can cause endocrine disruption, an increase in prostate cancer, a decrease in sperm production, and infertility. Resveratrol was used in a study where male rats were exposed to PVC to investigate any protective effect that it can have on reproductive competence. When administered alone, resveratrol did not show any significant changes, however when a mixture of PVC and resveratrol was administered to the mice it resulted in partial restoration of reproductive organ weight, sperm count, and fertility parameters. The androgen receptor is the male equivalent of the female estrogen receptor, both of which are involved with reproductive activities, their ligand binding domain as described above, work the same way, with testosterone replacing estradiol for the androgen receptor.

PVC is known to bind in the LBD of androgen which causes reproductive failures and prostate cancer. Since, as stated above, resveratrol can kick out estradiol from the LBD, then it can also kick out testosterone in the LBD for androgen receptor competing with PVC which also wants to bind to the same binding pocket. This causes the improvement of sperm count, testicular antioxidant defense system, treatments for infertility, and testosterone production [14]. It has been seen that resveratrol readily chelates with copper, but not the ferrous ion, and can scavenge for free radicals. It has also been seen that resveratrol can inhibit peroxidation of membrane lipids [1]. Resveratrol has been shown to be used in conjunction with other chemicals such as melatonin, a hormone that is involved with the regulation of sleep and is even used in birth control, both of which exhibit similar properties such as free radical scavenging, SIT1 activation, and stem cell protection. In a study involving pigs, resveratrol and melatonin are shown to exhibit synergistic effects compared to the individual compounds being used as treatment on their own.

This compound mixture was shown to increase blastocyst formation rates and cell numbers, oocyte nuclear maturation, and total cell numbers of embryo development after parthenogenetic activation of blastocysts, and the development of embryos after somatic cell nuclear transfer [15]. Ovarian cancer can cause ovarian toxicity that damages the sex gland where the female gametes are produced. Cisplatin has been used to treat the damages, however it also produces highly toxic effects which lowers its therapeutic efficacy. In a study on rats, resveratrol was used in conjunction with cisplatin to view if it would offer protection from the toxicity produced. It was shown that at high doses resveratrol offered protection to the rat ovaries in turn increasing fertility, decreasing follicular apoptosis, and stimulating proliferation of granulosa cells. This is theorized to occur due to resveratrol's effect on oxidative stress [16]. Other studies have also shown that resveratrol treatments have cytostatic with no cytotoxic effects on ovaries by reducing the size of adipocytes, improving estrus cyclicity, and anti-tumor efficiency [17,18].

In conclusion, at first glance resveratrol seems like a miracle fix all compound due to its beneficial effects for the treatment of cancer, cardiovascular disease, injuries, inflammation, viral infections, diabetes, neurological diseases, and much more. However, it has been shown to have a low bioavailability after oral administration [19] with toxic effects observed at 1 g per kg of body weight.

It is also shown to be quickly cleared from the blood stream, even though favorable effects are still observed after long-term use [8]. Even with all the emphasis on the effects of drinking wine due to it containing resveratrol, the actual amount found in foods and drinks is very small. Because of this most research studies use resveratrol supplements which are also recommended for human intake. When discussing research, it is also good to know that most of the research found on the effects of resveratrol have been conducted on animal models, most notably mice, with a limited amount on actual humans. This leads to the question of whether mice are like humans enough for the research to have the same effects. It would be interesting to see what future applications resveratrol can have. It has recently been reported how resveratrol can be used as a nanosuspension that can increase the effects of freeze-drying for drug delivery [20]. Another delved into the world of cosmetology in order to use resveratrol in conjunction with glycolic acid to crease a hybrid compound called resveratryl triglycolate that helps reduce UV damage of skin [21]. Resveratrol, indeed, has a promising future full of different applications.

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