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Review Article

Biological actions and molecular effects of resveratrol, pterostilbene, and 3′-hydroxypterostilbene

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ABSTRACT

Stilbenes are a class of polyphenolic compounds, naturally found in a wide variety of dietary sources such as grapes, berries, peanuts, red wine, and some medicinal plants. There are several well-known stilbenes including *trans*-resveratrol, pterostilbene, and 3′-hydroxypterostilbene. The core chemical structure of stilbene compounds is 1,2-diphenylethylene. Recently, stilbenes have attracted extensive attention and interest due to their wide range of health-beneficial effects such as anti-inflammation, -carcinogenic, -diabetes, and -dyslipidemia activities. Moreover, accumulating *in vitro* and *in vivo* studies have reported that stilbene compounds act as inducers of multiple cell-death pathways such as apoptosis, cell cycle arrest, and autophagy for chemopreventive and chemotherapeutic agents in several types of cancer cells. The aim of this review is to highlight recent molecular findings and biological actions of *trans*-resveratrol, pterostilbene, and 3′-hydroxypterostilbene.

1. Introduction

The natural active compounds from plant or herbal origins are being investigated for their bioactivities [1]. Stilbenes are phytochemicals with ~200–300 g/mol molecular weight, a subclass of polyphenolic compounds [2]. They are naturally found in a wide variety of dietary sources such as grapes, blueberries, red wine, and some other plants [3–5]. Family members of the stilbene have a C_6-C_2-C_6 basic skeleton and consist of two phenyl groups linked by an ethene double bond. There are several well-known stilbenes such as *trans*-resveratrol, pterostilbene, and 3′-hydroxypterostilbene (Figure 1).

Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) is the most extensively studied stilbene found in grape skin, berries, peanuts, and some medicinal plants [3,4,6]. Hundreds of studies have shown that resveratrol plays a critical role in human health and diseases due to its diverse biological and

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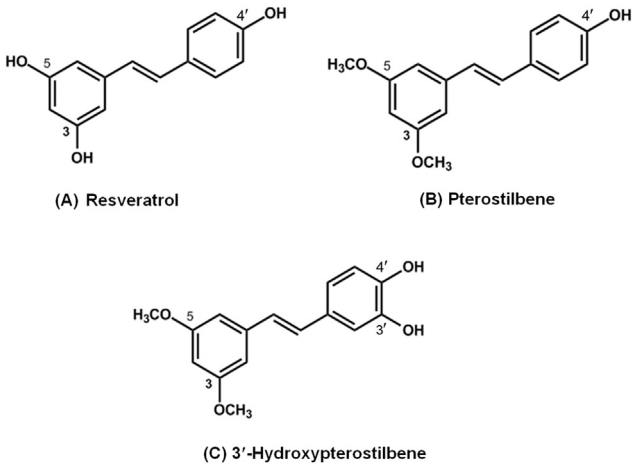

Figure 1 – Chemical structures of (A) resveratrol, (B) pterostilbene, and (C) 3′-hydroxypterostilbene.

pharmacological actions including antioxidation, -inflammation, -carcinogenic, and -diabetic potencies [7–13]. However, one potential issue surrounding resveratrol is that resveratrol has a very low bioavailability that may lower its biological effectiveness [14–16].

Pterostilbene, the 3,5-dimethoxy motif at the A-phenyl ring of resveratrol, has recently received tremendous attention due to its promising chemopreventive and chemotherapeutic properties [17–26]. Due to its structural characteristic, pterostilbene is more lipophilic, exhibits better bioavailability, and is more biologically active than resveratrol [16]. Pterostilbene is primarily found in a tree wood, *Pterocarpus marsupium*, which is a traditional herbal medicine used for the treatment of diabetes [27]. Moreover, in recent studies, pterostilbene have been reported to have powerful growth-inhibitory effects in several different types of cancer cells, notably breast, colon, and prostate cancer cells. [18,25,28]. In multiple research findings, pterostilbene was shown to be an effective apoptotic and autophagic agent that is able to inhibit cancer cell viability, induce cell cycle arrest, alter apoptosis expression gene, promote autophagy-related proteins, and inhibit cancer cells from metastasizing [18,25,28,29].

3′-Hydroxypterostilbene (*trans*-3,5-dimethoxy-3′,4′-dihydroxystilbene), one of metabolites of pterostilbene [30], can also be isolated from whole plant of the herb *Sphaerophysa salsula*, a shrub widely distributed in central Asia and northwest China [20,31]. The latest researches showed that 3′-hydroxypterostilbene appeared to contribute stronger biological activities than pterostilbene on human colon cancer cells [28].

This article reviews the recent advances in understanding the biological activities, molecular effects, and bioavailability of resveratrol, pterostilbene, and 3′-hydroxypterostilbene, and summarizes their clinical potential for the prevention and treatment of chronic diseases.

2. Resveratrol

Resveratrol (*trans*-3,5,4′-trihydroxystilbene), is a natural polyphenolic phytoalexin compound produced by plants to protect them from injury, uv irradiation, and fungal attack [32,33]. It is one of well-studied stilbenes mainly found in grapes and red wine; however, the presence of resveratrol has also been detected in other plants such as peanuts, pistachios, and berries [3,4,34]. In the past few years, the interest in resveratrol has extensively increased and a lot of scientific evidence has demonstrated that resveratrol exerts a plethora of biological functions, especially in the protective effects of chronic diseases, such as anti-inflammation, -cancer, -diabetes, and -obesity activities [7–10,12] (Table 1).

2.1. *Inflammation*

Chronic inflammation has been recognized as the root cause of various human diseases. The inflammatory processes may induce DNA mutations in cells via oxidative or nitrosative stress, which may influence normal cell functions and consequently lead to inflammatory diseases and cancer [35]. In an experiment conducted by Cui et al [36], it was demonstrated that resveratrol significantly suppressed inflammation markers such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and tumor necrosis factor-α (TNF-α) in dextran sulfate sodium (DSS) mouse model of colitis. In addition, resveratrol inhibited neutrophils infiltration in the mesenteric lymph nodes and lamina propria, and decreased the numbers of $CD3^+$ T cells that express TNF-α and interferon gamma (IFN-γ) in DSS-treated mice [36]. Sánchez-Fidalgo and co-workers [37] also found similar results. In their study using DSS-induced colitis model, it was determined that resveratrol supplementation attenuated chronic colonic inflammation with reduced proinflammatory cytokines, including interleukin-1 beta (IL-1β), IL-10, prostaglandin E synthases-1 (PGES-1), TNF-α, iNOS, and COX-2, via downregulation of the p38 MAPK (mitogen-activated protein kinases) signaling pathway [37].

Recently, the study performed by Lee et al [9] suggested that resveratrol could increase the bioavailability of apigenin, which is a bioactive flavonoid with strong anti-inflammation activities. Cotreatment of apigenin and resveratrol increased the levels of plasma apigenin up to 2.39 times compared to the apigenin-alone group. Moreover, cotreatment of apigenin and resveratrol significantly reduced the paw edema caused by carrageenan-induced inflammation in mice. These findings indicated that resveratrol could act as a biological enhancer to strengthen the anti-inflammatory activity of apigenin [9].

2.2. *Breast cancer*

A number of researchers have considered the anticarcinogenic effects of resveratrol in breast cancer [38–40]. A study conducted by Scarlatti et al [38] reported that resveratrol could inhibit human breast cancer cell proliferation and promote death via multiple pathways including apoptosis, cell cycle arrest in the S phase, and autophagy. Resveratrol was shown to induce cell death in both caspase-3 sensitive ($MCF\text{-}7^{casp\text{-}3}$) and caspase-3 insensitive ($MCF\text{-}7^{vc}$) human breast cancer cells. Thus, the effects of resveratrol on breast cancer cell death might not be fully dependent on caspase-3 [38]. Besides, resveratrol stimulated autophagy by activating noncanonical (Beclin-1 independent) routes in both cell lines. The molecular