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Invited review

Anti-inflammatory activity of natural stilbenoids: A review

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ABSTRACT

Resveratrol and other natural stilbenoids, including piceatannol, pterostilbene, and gnetol, are well-known anti-inflammatory compounds with indisputable activity *in vitro* as well as *in vivo*. Their molecular targets include inducible nitric oxide synthase, cyclooxygenases, leukotrienes, nuclear factor kappa B, tumor necrosis factor α, interleukins and many more. This anti-inflammatory activity together with their antioxidant activity is believed to stand behind their other positive health effects against cancer, cardiovascular and neurodegenerative diseases or diabetes. Thus, they are nowadays commercially marketed as nutraceuticals. Naturally, they are present in wine, grapes or berries. However, there is a rigorous debate about the real effect of these compounds on human health. It is argued that the concentration of stilbenoids in food and beverages is too low to have any therapeutic potential and this concentration is further reduced by their low bioavailability and extensive metabolism. Therefore, this review focuses on *in vitro*, *in vivo*, preclinical as well as clinical data available for various natural stilbenoids and summarizes the anti-inflammatory targets on molecular level, compares the relevance of the experimental studies, discusses the metabolism of stilbenoids and the potential activity of their metabolites and relates this knowledge to human health. Moreover, the ways to augment stilbenoidsí efficacy are suggested with special focus on multitargeted therapy and nanocarriers.

Contents

Abbreviations: AMPK, 5′ adenosine monophosphate-activated protein kinase; AP-1, activator protein 1; CAT, catalase; COX, cyclooxygenase; CRP, C-reactive protein; CSA, cajaninstilbene acid; CYP, cytochrome enzyme; DSS, dextran sulfate sodium; ERK, extracellular signal-regulated protein kinase; GPCR, G protein-coupled receptor; GR, glutathione reductase; HO-1, heme oxygenase-1; HDL, high density lipoprotein; ICAM-1, intracellular adhesion molecule 1; IgE, immunoglobulin E; IKK, I kappa B kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, Jun amino-terminal kinase; LDL, low density lipoprotein; LOX, lipoxygenase; LPS, lipopolysacharides; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MMP, matrix metallopeptidase; mPGES-1, microsomal prostaglandin E synthase-1; NFAT, nuclear factor of activated T-cells; NF-κB, nuclear factor kappa B; NHEK, normal human epidermal keratinocytes; NLC, nanostructured lipid carrier; NO, nitric oxide; NOX, NADPH oxidase; Nrf2, nuclear factor erythroid 2-related factor 2; NSAID, nonsteroidal anti-inflammatory drug; OHDA, 6-hydroxydopamine; PAMP, pathogen-associated molecular pattern; PGD_2, prostaglandin D_2; PGE_2, prostaglandin E_2; PKC, protein kinase C; PMA, phorbol-12-myristate-13-acetate; PME, pinosylvin monomethyl ether; PPARα, peroxisome proliferator-activated receptor α; ROS, reactive oxygen species; SLN, solid lipid nanoparticle; SOD, superoxide dismutase; STAT-1, signal transducer and activator of transcription-1; Syk, spleen tyrosine kinase; TMS, 3,5,4′-*trans*-trimethoxystilbene; TNFα, tumor necrosis factor α; TPA, 12-O-tetradecanoylphorbol-13-acetate; VCAM-1, vascular cell adhesion molecule 1; VPO1, vascular peroxidase 1.

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1. Introduction

Inflammation is a response to pathogens and tissue injury. Cellular damage or pathogen-associated molecular patterns (PAMPs) expressed by microbes are recognized by immune cells (macrophages, leukocytes, neutrophils, and mast cells), which are thus drawn to the site of injury. These cells then release various inflammatory mediators, which include cytokines, histamine, nitric oxide, leukotrienes and prostaglandins. Cytokines such as tumor necrosis factor α (TNFα) and interleukins (ILs) released by macrophages repair local damage and through the binding to G protein-coupled receptors (GPCRs) cause expression of selectins and integrins. Histamine is released by mast cells and causes vasodilation and increases vascular permeability. Nitric oxide, which is released by endothelial cells, diffuses into smooth muscle cells and causes their relaxation and thus promotes vasodilation. Prostaglandins and leukotrienes are synthesized by endothelial cells from phospholipids of damaged membranes and enhance vessel dilation and permeability. Altogether, these inflammatory mediators promote further recruitment of immune cells into the site of injury and there they elicit fever, redness, edema and pain [1]. In addition, during inflammation, an enormous amount of reactive oxygen species (ROS) is generated. Intracellularly produced ROS are key suppressors of inflammation as they initiate neutrophil apoptosis. However, prolonged inflammatory and oxidative reactions lead to chronic inflammation characterized by abnormal accumulation of inflammatory cells and release of inflammatory mediators along with ROS-mediated toxic oxidative reactions damaging lipids, proteins and nucleic acids. Chronic inflammation is the major cause of aging and severe diseases, such as asthma, arthritis, inflammatory bowel diseases, bronchitis, pancreatis, liver fibrosis, cardiovascular diseases, neurodegenerative disorders and cancer [2–8]. Mechanistically, chronic inflammation activates Toll-like receptors expressed on macrophages to induce overproduction of inflammatory mediators. These mediators activate the transcription factors, such as nuclear factor kappa B (NF-κB), nuclear factor of activated T-cells (NFAT), nuclear factor erythroid 2-related factor 2 (Nrf2) and activator protein 1 (AP-1), which are all either directly or indirectly regulated *via* mitogen-activated protein kinases (MAPKs) [9]. In addition, several enzymes are activated, such as I kappa B kinase (IKK), inducible nitric oxide synthase (iNOS), COX-2 (cyclooxygenase) and 5-LOX (lipoxygenase) [10,11].

Genetic and environmental factors play pivotal roles in the development of chronic inflammation. Dietary habits are among the most influential environmental factors. Nowadays, the wealth and fast lifestyle in industrialized countries leads to the higher intake of sugar and high-fat food and lower intake of fruits and vegetables [12]. Nevertheless, the popularity of plant-derived products and return to traditionally used remedies has increased dramatically over the last few years. There is an exponential expansion in the use of medicinal plants for the treatment of various symptoms and ailments, and it seems that these plant-derived products are potential future medicines [13]. Furthermore, there is an extensive amount of nutraceuticals and diverse dietary supplements derived from plants, which are in great demand. For example, an inflammatory plant *Harpagophytum procumbens*, which exerts its effects through the inhibition of COX-2, is a very well-known dietary supplement for arthritis patients [14]. In between dietary supplements and pharmaceuticals stand nutraceuticals, which have a confirmed clinical efficacy in addition to their nutritional value. Nutraceuticals are active substances extracted from plants or other living organisms which are administered in suitable pharmaceutical form. They help to inhibit pathological damage and disease. In this respect, they are similar to food supplements and are unlike pharmaceuticals which cure the already visible symptoms. In general, most of nutraceuticals are antioxidant and/or anti-inflammatory agents with good tolerability and high bioavailability. Plant polyphenols including grape flavonoids and stilbenes are eminent examples [12].

Traditionally, inflammation is treated with so called nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. These drugs are relatively old and possess multiple severe side effects and have limited efficacy, thus there is a continuous demand for new anti-inflammatory agents. NSAIDs are potent inhibitors of cyclooxygenases COX-1 and COX-2. COX-1 is considered to be the constitutive isoform involved in homeostatic processes and its inhibition by NSAIDs is the cause of their side effects (damage to gastrointestinal tract). On the other hand, COX-2 is induced during inflammation and causes onsite production of pro-inflammatory prostaglandins (PGE_2, PGD_2). One of the strategies towards new anti-inflammatory compounds was thus the development of selective COX-2 inhibitors. These selective inhibitors, called coxibs, improved the efficacy of NSAIDs and diminished their damage to gastrointestinal tract, however, they instead increased the risk of cardiotoxicity and hepatotoxicity [15]. For this reason, several already FDA-approved drugs had to be removed from the market. Apart from COX inhibitors, there was a relatively small number of targets to produce successful anti-inflammatory drugs, such as the H1 receptor for histamine, the cytokine TNFα, the receptor for the cysteinyl leukotrienes C4 and D4 and 5-LOX enzyme. Over the past two decades, there has been a significant increase in knowledge about immunology, and thus many additional anti-inflammatory targets have been described (>300 leukocyte surface antigens, >80 cytokines and their receptors, >20 chemokines and their G-protein-coupled receptors etc.) [7]. In spite of this progress, there is still only a limited number of approved anti-inflammatory drugs, but further advances are expected.

2. Stilbenoids and anti-inflammatory activity

As mentioned before, stilbenoids are a class of compounds with multiple pharmaceutically relevant properties. They are a group of plant phytoalexin polyphenols found in high concentrations in grapes, berries, nuts and teas. In plants, their main function is to