Pterostilbene: Biomedical applications*

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Abstract

Resveratrol and its naturally dimethylated analog, pterostilbene, show similar biological activities. However, the higher in vivo bioavailability of pterostilbene represents a fundamental advantage. The main focus of this review is on biomedical applications of pterostilbene. The metabolism and pharmacokinetics of this stilbene in inflammatory dermatoses and photoprotection, cancer prevention and therapy, insulin sensitivity, blood glyceremia and lipid levels, cardiovascular diseases, aging, and memory and cognition are addressed. Safety and toxicity, as well as recommendations for future research and biomedical uses, are discussed. This review includes comparisons between pterostilbene and other polyphenols, with particular emphasis on resveratrol. Potential benefits of using combinations of different polyphenols are considered. Based on present evidences we conclude that pterostilbene is an active phytonutrient and also a potential drug with multiple biomedical applications.

Keywords

Phytochemicals, polyphenols, pterostilbene, resveratrol, stilbenes

Introduction

Pterostilbene (3,5-dimethoxy-4’-hydroxystilbene; Pter) is a phytoalexin (antimicrobial substance synthesized de novo by plants) and a natural dimethylated analog of resveratrol (3,5,4’-tri-hydroxystilbene; Resv) (Figure 1), and is a much stronger antifungal agent (>10 times) than Resv1. Moreover, Pter, with two methoxy groups and one hydroxy group, has greater lipophilicity and a higher potential for cellular uptake than Resv, which has three hydroxy groups.

Pter and Resv exist as two geometric isomers: cis and trans, but naturally occurring structures overwhelmingly exist in the trans form. trans- and cis-Resv can be either free or bound to glucose2. Trans-Resv can undergo isomerization to the cis form when exposed to ultraviolet (UV) irradiation3. Similar chemical features are accepted for Pter.

The widely accepted chemical definition of the term, polyphenol, known as the White–Bate-Smith–Swain–Haslam definition, describes the class as (i) generally moderately water-soluble compounds, (ii) with molecular weight of 500–4000 Da, (iii) >12 phenolic hydroxyl groups, and (iv) 5–7 aromatic rings per 1000 Da, where the limits to these ranges are necessarily somewhat flexible4. The need for clarity of definition, in view of the current enormous literature and the ambiguity of the term, polyphenol, led Stéphane Quideau5 to offer a new definition. Even if there was agreement to include polyphenolic structures with no tanning action in the definition, the term “polyphenol” should be restricted, in a strict chemical sense, to structures bearing at least two phenolic moieties independent of the number of hydroxyl groups they each bear. Quideau5 went on to say that this definition needed additional restrictions, for many natural products of various biosynthetic origins contain more than one phenolic unit. It is, for example, the case for many alkaloids that are derived from the phenylalanine/tyrosine amino acids. The natural occurrence of such alkaloids then gives a problem in any attempt to propose a definition of polyphenol based strictly on the grounds of biosynthetic origin(s), for these amino acids themselves are primary metabolites of the shikimate/phenylpropanoid pathway. Therefore, Quideau5 proposed that the term “polyphenol” should be used to define compounds exclusively derived from the shikimate/phenylpropanoid and/or the polyketide pathway, featuring more than one phenolic...
unit and without nitrogen-based functional groups. The authors of the present review subscribe to this functional/biological definition since this better reflects what is observed in mammalian cells and organisms. It is on this basis that we refer to Pter as a natural derivative of a polyphenol, although those adhering to the strict classical definition would not consider it so.

Pter, a secondary metabolite of plants originally isolated from the heartwood of red sandalwood (*Pterocarpus santalinus*), is also found in other plants such as blueberries (e.g. 9.9–15.1 mg/kg of fresh weight) (and other small berry plants); grapes (e.g. up to 4.7 mg/g of fresh weight of skins in non-UV-induced berries of Chardonnay variety); *Pterocarpus marsupium* (Indian Kino tree, a medium to large, deciduous tree native to India, Nepal, and Sri Lanka); and *Guibourtia tessmanii* (a flowering plant genus in the legume family native to tropical regions of Africa). A Resv-O-methyltransferase, able to catalyze biosynthesis of Pter from Resv, both *in vitro* and *in planta*, has been identified in grapevine leaves where it was induced by different stresses, including downy mildew (*Plasmopara viticola*) infection, UV light, and aluminum chloride treatment. Indeed, Pter is involved (as are other natural polyphenols) in plant defense against many different stressful conditions, including UV radiation, aggression by pathogens, low soil fertility, high/low temperatures, severe drought, and grazing pressure.

Depending on dietary habits, human intake of flavones and flavonols (the most common flavonoids) is ~3–70 mg/day, mainly quercetin (60–75%) (major sources include tea, wine, berries, apples, and onions). However, there are no reported estimates regarding Pter intake. Quantitative studies have shown that, in dark-skinned grapes, for every 10 parts of Resv, there are only one to two parts of Pter and references therein.

Parts of the Indian Kino (heart wood, leaves, and flowers) have long been used for their medicinal properties in Ayurveda medicine. Gum resin, the only herbal product ever found to regenerate β cells that produce insulin in the pancreas, was used by Ayurvedic practitioners in the treatment of diabetes. Pter was also identified as a major phenolic compound in darakchasava, a traditional Ayurvedic herbal preparation (the main ingredient of which is *Vitis vinifera*) used to treat cardiovascular and related problems.

**Metabolism and pharmacokinetics**

**Oral and intravenous administration**

Orally administered polyphenols undergo rapid and extensive conjugation in the intestinal tract of man and rodents. It is in this form that they are absorbed with very little of the free polyphenol gaining access to the blood circulation. Polyphenol metabolites can be detected in the urine, while some metabolites are eliminated via the biliary tract and subsequently recycled by the intestinal tract. Furthermore, it is important to take into account that coexisting compounds in the lumen, inhibition of digestive enzyme activity, and/or alteration of intestinal transport systems can modulate intestinal absorption.

Most polyphenols are not subjected to phase I metabolism in the liver because polyphenolic structures make them partially unfavorable substrates for the cytochrome P450 systems.
enzymes. However, polyphenols can directly undergo phase II metabolism, predominately methylation, glucuronidation and sulfation.

While some studies suggest that multiple enzyme-mediated methylations can increase the bioavailability of polyphenols (e.g. compare Resv and Pter), other studies indicate a marked decrease in the anticancer benefits of methylated polyphenols.

Available experimental data indicate that polyphenol aglycones, when absorbed by intestinal enterocytes, undergo extensive phase II metabolism via UDP-glucuronyl transferase isofoms that markedly decrease the amount of unconjugated/natural compounds reaching the systemic blood circulation. Moreover, hydrophilic polyphenol conjugates need carriers to cross the enterocyte membrane on the luminal (MRP2) and serosal (MRP3 and MRP4) sides. However, these limitations can be circumvented by intravenous administration. Once present in the blood stream, polyphenol aglycones reach the liver, where they are rapidly and extensively metabolized (at rates and percentages that vary depending on the type of polyphenol) to methylated, glucuronidated, and/or sulfated conjugates.

Glucuronidated conjugates are excreted into either bile (via MRP2) or the sinusoidal blood (via MRP3 and MRP4). Breast cancer resistance protein (BCRP)-type carriers are likely involved in the export of conjugated sulfates.

Conjugates released into the duodenum can later be hydrolyzed by intestinal bacterial microflora and free aglycones absorbed through the colon back into the systemic blood.

Physiological sulfatase and glucuronidase activities present in different tissues also contribute to polyphenol pharmacokinetics and bioavailability. Therefore, in the short-term (first hour), depending on whether administration is oral or i.v., blood levels of unconjugated/natural polyphenol structures will be very different. Nevertheless, it is important to point out that further metabolic steps and recycling mechanisms may maintain low or very low levels for a much longer period.

After i.v. administration to mice of 20 mg/kg trans-Pter (a dose representing, in an adult human being of 70 kg body weight, ~1000 times the maximum amount of Pter found in 1 kg of dark grapes), its highest concentration in plasma (~95 μmol/L, 5 min after administration) decreased to ~1 μmol/L in 480 min. Following an identical protocol, we found previously that the highest Resv concentration in plasma (~43 μmol/L, 5 min after i.v. administration to rabbits) decreased rapidly to ~1 μmol/L in 60 min. We calculated a half-life of Resv and Pter, in mouse plasma, of 10.2 and 77.9 min, respectively. Furthermore, after i.v. administration, total blood levels of Pter were not significantly different from those reported for plasma. At least 99% of the Pter measured in plasma or blood was in its trans form.

Remsberg et al. also evaluated preclinical pharmacokinetics and pharmacodynamics of trans-Pter in rats. Right-jugular-vein-cannulated rats were dosed with 20 mg/kg of Pter i.v. and samples were analyzed by a reverse phase HPLC (high-performance liquid chromatography) method. The area under the curve for serum, serum half-life, urine half-life, total clearance and volume of distribution during the terminal exponential phase of drug elimination were 17.5 ± 6.6 μg/h/mL, 1.73 ± 0.78 h, 17.5 ± 5.6 h, 0.960 ± 0.025 L/h/kg and 2.41 ± 1.13 L/kg [mean ± standard error of mean (SEM)], respectively. A Pter-glucuronidated metabolite was detected in both serum and urine.

In vitro metabolism in rat liver microsomes also suggested phase II metabolism of Pter.

Later, Lin et al. validated a HPLC-UV method for quantification of Pter in rat plasma and showed that terminal elimination half-life and clearance of Pter were 96.6 ± 23.7 min and 37.0 ± 2.5 mL/min/kg, respectively, while its absolute oral bioavailability was 12.5 ± 4.7%. This confirmed that Pter has better pharmacokinetic characteristics than its natural occurring analog, Resv.

Kapetanovic et al. also studied these aspects in rats taking 50 or 150 mg/kg/day of Resv and 56 or 168 mg/kg/day of Pter orally for 14 consecutive days. Two additional groups were dosed once i.v. with 10 and 11.2 mg/kg of Resv and Pter, respectively. In these studies, plasma concentrations of agents and metabolites were measured using HPLC–MS (mass spectrometry). Resv and Pter were ~20 and 80% bioavailable, respectively. Following oral dosing, plasma levels of Pter and Pter sulfate were markedly greater than were plasma levels of Resv and Resv sulfate. Although plasma levels of Resv glucuronide exceeded those of Pter glucuronide, those differences were smaller than those of the parent drugs and sulfate metabolites. Therefore, these differences in agent pharmacokinetics suggested that in vivo biological activity of equimolar doses of Pter was greater than that of Resv.

Shao et al. have identified nine mouse urinary Pter metabolites, Pter glucuronide, Pter sulfate, mono-demethylated Pter glucuronide, mono-demethylated Pter sulfate, mono-hydroxylated Pter, mono-hydroxylated Pter glucuronide, Pter glucuronide sulfate, using liquid chromatography/atmospheric pressure chemical ionization and electrospray ionization tandem MS.

Pharmacokinetics of trans-Resv in its aglycone and glucuronide forms, studied following i.v. (15 mg/kg) and oral (50 mg/kg) administration to intact rats, demonstrated a sudden increase in the plasma concentration of these compounds 4–8 h after administration that was linked to enterohepatic recirculation. Based on their chemical similarities (and taking into account differences in the aglycone/metabolite half-life), this type of recirculation might be expected to be seen for Pter as well. Nevertheless, it is important to note that the percentages of Resv aglycone and Resv glucuronide that were due to enterohepatic recirculation were only 24.7 and 24.0%, respectively. Figure 2 summarizes the main features of Pter metabolism and pharmacokinetics under in vivo conditions. Finally, as recently reviewed, although some exceptions have been reported, most available data indicate that natural polyphenols (including Pter) are biologically much more active than their in vivo generated metabolites.

**Cutaneous administration**

Pter metabolism in the skin has not yet been studied. However, some general features may be highlighted as they are common to most polyphenols. As compared to other skin
cells, keratinocytes contain different phase I (reduction/oxidation) and II (biotransformation) enzyme activities (much lower than those expressed in the liver)\(^3\). Human keratinocytes express a variety of CYPs (cytochrome P450 superfamily) that play important roles in xenobiotic, drug and steroid metabolism\(^3\). Many of the CYPs that have been characterized as playing major roles in xenobiotic/drug metabolism in the liver have also been identified in human skin (mainly localized within the epidermis and sebaceous glands); these include those involved in the metabolism of many procarcinogens (e.g. CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6 and CYP3A4) and the majority of pharmaceutical drugs (e.g. CYP3A4/5 and CYP2D6)\(^3\). Many exogenous chemical compounds, including natural polyphenols, can be potential substrates, inducers, or inhibitors of CYP phase I enzymes\(^3\). Interestingly UV irradiation, as well as different environmental factors, can affect CYP activity and thereby alter polyphenol metabolism in the skin\(^3\). In addition, skin peroxidases, which represent an alternate pathway to cytochrome P-450 for xenobiotic metabolism in skin\(^4\), may be also involved in metabolizing polyphenols\(^3\). Other phase I-related enzyme activities, including flavin monoxygenases, prostaglandin H-synthase, cyclooxygenases, alcohol dehydrogenase, or NADPH quinine reductase could be also related to polyphenol metabolism in skin\(^3\). However, to date, none of this has been shown with Pter.

Moreover, phase II detoxification enzyme activities [including glutathione (GSH) S-transferases, UDP-glucuronony transferase, or catechol-O-methyl transferase] are present in the skin, and could be affected by polyphenols\(^3\). These mechanisms may involve Nrf2, Keap1, and antioxidant-responsive elements present in the promoter regions of genes encoding different phase II enzymes\(^4\). Finally, it is important to note that topical drugs can modulate expression of drug-metabolizing enzymes gene expression in human skin \(in vivo\). Therefore, variation in the expression and regulation of these genes could be a determinant of individuality in response to topical (and possibly systemic) therapies for common skin diseases\(^4\).

**Antioxidant activity**

The antioxidant potential of Pter was first evaluated by Rimando et al.\(^1\) who found that peroxyl-radical scavenging activity of Pter was similar to that of Resv, having total reactive antioxidant potentials of 237 ± 58 and 253 ± 53 \(\mu\)mol/L, respectively. Both compounds were found to be more effective than Trolox as free radical scavengers, although Pter showed moderate inhibition (IC\(_{50} = 19.8 \mu\)mol/L) of cyclooxygenase (COX)-1, and was weakly active (IC\(_{50} = 83.9 \mu\)mol/L) against COX-2, whereas Resv strongly inhibited both isoforms of the enzyme with IC\(_{50}\) values of ~1 \(\mu\)mol/L\(^1\).

Studies on the antioxidant activity of hydroxystilbene derivatives (including Pter and Resv) in homogeneous solution (estimated by measuring rate constants for their reactions with peroxy radicals) showed that they behave as mild antioxidants with the notable exceptions of the \(trans\) isomers of 3’,4’-dihydroxy-3,5-dimethoxyxystilbene and 3’,4’-dihydroxy-5’-tert-butyl-3,5-dimethoxyxystilbene, whose activities are only slightly lower than that of \(a\)-tocopherol (vitamin E)\(^4\). Rate constants of the inhibition reaction (which depends on enthalpy factors) showed that the antioxidant activity of \(cis\)-hydroxystilbenes, in all examined cases, was worse, by factors ranging between 2 and 6, than that of the corresponding \(trans\) isomers\(^4\).
Studies by Amarnath and Pan on the antioxidant role of Pter in streptozotocin–nicotinamide-induced type 2 diabetes mellitus in rats showed that, whereas the activity of superoxide dismutase, catalase, GSH peroxidase, GSH S-transferase and reduced GSH was significantly decreased in liver and kidney of diabetic animals when compared with normal controls, there were significant improvements in these activities after treatment with Pter at a dose of 40 mg/kg per day (oral administration) for 6 weeks. Increased levels of lipid peroxidation measured as thiobarbituric acid reactive substances in liver and kidney of diabetic rats were also normalized by treatment with Pter, thus indicating a potential antioxidant activity under in vivo conditions. Later, Remsberg et al. also reported that Pter exhibits a concentration-dependent antioxidant capacity as measured by the ABTS [2,2-azinobis-(3-ethyl-benzothiazoline-6-sulfonic acid)] method.

Studies on the antioxidant effect of Resv, Pter, quercetin and their combinations in human erythrocytes in vitro showed that quercetin and Pter protected erythrocyte membranes against hydrogen peroxide-induced lipid peroxidation (IC50 values = 64 ± 8.7 and 44.5 ± 7.8 μmol/L, respectively). Resv was significantly less effective. However, the three compounds protected erythrocytes against hemolysis and GSH depletion to the same extent, whereas combinations consisting of two compounds (molar ratio 1:1) influenced lipid peroxidation in a concentration-dependent manner. At lower concentrations, Resv with quercetin or Pter inhibited synergistically oxidative injury of membrane lipids, whereas at higher concentrations, an additive effect was observed. These protective effects may support potential health benefits of these bioactive microcomponents when taken together in the diet.

Further studies by Hasiah et al. on the total antioxidant activity [ferric reducing antioxidant power assay] of methoxylated stilbene analogs on HepG2 hepatoma and Chang liver cells showed that compounds possessing hydroxyl groups at the 4′-position, namely (E)-3-methoxy-4′-hydroxy-stilbene, (E)-3,5-dimethoxy-4′-hydroxy-stilbene (Pter), and (E)-4-methoxy-4′-hydroxy-stilbene, displayed the highest antioxidant activity. This suggested that there could be a relationship between chemical structure and antioxidant activity.

In addition, indirect effects could be of greater biological importance than direct chemical reactions of polyphenols. What is meant by this? As the antioxidant strategy is largely based on enzymes, the question has rightfully been posed: “Polyphenolic phytochemicals—just antioxidants or much more?” There is a growing body of evidence that this class of botanicals can address key switches that regulate defense enzymes, i.e., transcriptional regulators such as NF-κB, AP-1, FoxOs, Nrf2, Keap1, as well as changes in nuclear histone acetylation. As a consequence, the ensuing cellular responses could include indirect antioxidant effects and other types of responses.

**Inflammatory dermatoses**

Plant polyphenols have been suggested as possible gold standard skin anti-inflammatory agents. The term “inflammatory dermatoses” refers to a range of skin disorders, including, but not limited to, sebaceous gland disorders, mycotic skin infections, exfoliative dermatitis, and many dermatoses (papulosquamous, allergic, pruritic, vascular, bacterial, viral, granulomatous, parasitic skin, bullous, pigmented, photosensitive, those caused by collagen diseases, and those due to internal diseases). Inflammatory dermatosis can also be associated with an autoimmune condition, in which case it is referred to as autoimmune dermatosis (www.aad.org). Molecular targets and mechanisms of action of some selected polyphenols (e.g., catechins, proanthocyanidins, Resv, or silymarin), in skin inflammatory pathologies, have been recently reviewed. However, at present, just a few observations on the effect of Pter in specific dermatoses, including psoriasis, atopic dermatitis, and contact/allergic dermatitis, have been reported. These primary observations were obtained using standard models and chemically induced skin alterations in mice.

**Mycoses**

Cutaneous mycoses caused by dermatophyte fungi are among the most common infections worldwide, yet treatment is restricted by the limited availability of effective drugs, drug toxicity, and emergence of drug resistance (www.aad.org). Recently, Kingsbury et al. observed that stilbene fluorescent brighteners and stilbene phytolaxins, pinosylvan monomethyl ether and Pter inhibit fungi (representative strains of the dermatophyte Trichophyton rubrum and Candida albicans) by binding chitin in the cell wall and disrupting cell wall integrity; this entails a different mechanism of inhibition than that of currently available antifungal drugs. Previously, it was observed that (1) pinosylvan (a constituent of pine) exhibited more potent growth inhibitory activity against C. albicans and Saccharomyces cerevisiae than Resv; and (2) Resv is not effective against C. albicans and non-C. albicans species (C. dubliniensis, C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei) in vitro. Moreover, when the antifungal effect of three furyl compounds closely related to Resv, (E)-3,4,5-trimethoxy-β-(2-furyl)-styrene, (E)-4-methoxy-β-(2-furyl)-styrene, and (E)-3,5-dimethoxy-β-(2-furyl)-styrene, against Botrytis cinerea was analyzed, their inhibitory effect on conidia germination was determined to be ~70%, while at the same concentration Pter produced complete inhibition. Therefore, it is plausible that Pter, alone or in combination with other selected polyphenol(s) or conventional antifungal agents, may be useful against drug-resistant mycoses.

**Photoprotection**

Solar radiation induces acute and chronic reactions in human and animal skin. Chronic repeated exposure is the chief cause of non-melanoma skin cancer, and it is also a prime factor in the etiology of cutaneous melanoma. Skin cancer is the most common type of cancer in fair-skinned populations in many parts of the world. Consequently, the incidence of non-melanoma skin cancer (squamous-cell and basal-cell...
carcinoma in particular) is a significant public health concern worldwide (http://cancer.gov). Among types of solar radiation, UVB (290–320 nm) radiation is highly mutagenic and carcinogenic in animal experiments compared to UVA (320–400 nm) radiation. Epidemiological studies suggest that solar UV radiation is responsible for skin tumor development and photocaging. Exposure of the skin to solar UV radiation results in inflammation, oxidative stress, DNA damage, dysregulation of cellular signaling pathways and immunosuppression, which promote skin cancer. The use of chemopreventive agents such as plant polyphenols to inhibit these events in UV-exposed skin is gaining attention. Indeed, potential anticancer/photoprotective properties, as well as beneficial effects in skin diseases related to inflammation, oxidative stress, and/or damage to DNA, have been proposed/suggested for different polyphenols, including green tea polyphenols, grape seed proanthocyanidins, Resv, silymarin, luteolin, and genistein. For example, and despite having a minimum sun protection factor (SPF), tea extract (containing epigallocatechin-3-gallate, EGCG) has protective effects against DNA damage and UV-induced immunosuppression (partly because of its ability to reduce oxidative stress, inhibit NF-κB, and facilitate repair of DNA damage). However, recently some concerns have been raised because polyphenols could be a double-edged sword for human skin by exerting both protective and damaging actions. Apart from unintentional or occupational contact with skin-damaging plants, there are numerous cosmetic preparations, skin care products, and food supplements containing plants extracts that could lead to undesirable skin effects in sensitive individuals (e.g. skin sensitization, skin carcinogenesis, or phototoxic reactions).

It has been reported that Pter is as potent as Resv in inhibiting 12-O-tetradecanoylphorbol-13-acetate (TPA)-activated NF-κB, AP-1, COX-2, and iNOS in mouse epidermis, and that Pter potently inhibits 7,12-dimethylbenz[a]anthracene (DMBA)/TPA-induced mouse skin carcinogenesis. However, the only report on Pter and UV-induced carcinogenesis has recently been presented in a patent by our group. Data reported in this patent show that topically administered Pter fully protects against chronic UVB (180 mJ/cm² × 3 doses × week × 7 months)-induced carcinogenesis in SKH-1 hairless mice. Since Pter also has minimal SPF effect, its photoprotective effect must necessarily involve a biological mechanism. In this model, Resv was unable to exert protection (50% by Week 21, and 100% by Week 30). Other polyphenols used with the same protocol (including curcumin, EGCG, epicatechin, apigenin, genistein, ellagic acid, or lutein) did not render better results than Resv (Estrela, unpublished results). Studies to elucidate mechanisms and specific molecular targets to explain the photoprotective effect of Pter (versus other polyphenols) are now underway in our group.

Applications in cancer prevention and therapy
Abundant information is now available on cellular mechanisms by which natural polyphenols may interfere with carcinogenesis, and tumor growth and dissemination. Polyphenols have been shown to act on multiple targets in pathways related to cellular proliferation and death, inflammation, angiogenesis, or drug and radiation resistance. Besides, possible effects of natural polyphenols in cancer prevention and therapy have been reviewed. This includes a recent review focused on Pter and anticancer mechanisms. However, this recent review did not distinguish between cancer prevention and therapy, and did not address the fundamental problem involving the lack of correlation between in vitro observations and in vivo bioavailability.

Cancer prevention
The possibility that fruit and vegetables may help to reduce the risk of cancer has been studied for over 30 years, but no protective effects have been firmly established. Nevertheless, since the seminal article published by Jang et al. on the cancer chemopreventive activity of Resv in a mouse skin cancer model, the role of natural polyphenols in cancer prevention has received substantial support.

The cancer chemopreventive activity of Pter was first reported by Rimando et al., who, using a mouse mammary organ culture model, showed that carcinogen-induced pre-neoplastic lesions were (similarly to Resv) significantly inhibited by Pter (ED₅₀ = 4.8 μmol/L). Later it was shown, in the azoxymethane (AOM)-induced colon carcinogenesis model in rats, that dietary Pter decreased (1) aberrant crypt foci formation (57% inhibition) and (2) mucosal levels of the proinflammatory cytokines, TNF-α, IL-1β and IL-4. Colon tumors from Pter-fed animals showed reduced expression of inflammatory markers as well as nuclear staining for phospho-p65, a key molecule in the NF-κB pathway. In human HT-29 colon carcinoma cells, Pter reduced the protein levels of β-catenin, cyclin D1 and c-MYC, altered the cellular localization of β-catenin, and inhibited the phosphorylation of p65. In addition, studies by Chiou et al., in the same AOM-induced colon carcinogenesis model, showed that dietary Pter inhibited in colon tissue AOM-induced transcriptional activation of iNOS and COX-2, GSK-3β phosphorylation and Wnt/β-catenin signaling, expression of VEGF, cyclin D1, and MMPs, and activation of Ras, phosphatidylinositol 3-kinase/Akt and EGFR signaling pathways. This indicated that Pter inhibited colon carcinogenesis via suppression of multiple signal transduction pathways. Chiou et al. later demonstrated that Pter is more potent than Resv in preventing AOM-induced colon tumorigenesis via activation of the Nrf2-mediated antioxidant signaling pathway.

Pter was found to be as potent as (or in some assays significantly more potent than) Resv in inhibiting TPA-activated NF-kB, AP-1, COX-2, and iNOS in mouse epidermis; this suggested that Pter might show higher biological activity since the substitution of the hydroxyl with the methoxy group increases lipophilicity. In this context, Pter has been shown to potently inhibit DBMA/TPA-induced mouse skin carcinogenesis.

Pan et al. also showed that Pter significantly suppressed TPA-induced invasion, migration and metastasis of human HepG2 cells. Pter inhibited TPA-induced expression of VEGF, EGF and EGFR, and TPA-stimulated NF-kB and AP-1-dependent transcriptional activity. Moreover, Pter...
suppressed in HepG2 cells TPA-induced activation of extra-cellular signal-regulated kinase 1/2, p38 mitogen-activated protein kinase, c-Jun N-terminal kinases 1/2 and phosphatidylinositol 3-kinase/Akt and PKC that are upstream of NF-kB and AP-1. In addition, Pan et al. also reported suppression of heregulin-β1/HER2-modulated invasive and aggressive phenotype of breast carcinoma by Pter via inhibition of matrix metalloproteinase-9, p38 kinase cascade and Akt activation.

Recently, the effects of berry polyphenols (such as cyanidin, delphinidin, quercetin, kaempferol, ellagic acid, Resv, and Pter) on blocking receptor signaling and activating cell-death pathways have been suggested as potential mechanisms for breast cancer prevention. In this context, Wang et al. reported that Pter simultaneously induced apoptosis, cell cycle arrest and cyto-protective autophagy in breast cancer cells. Pter was also found to inhibit lung or prostate cancer in vitro through induction of apoptosis, or breast cancer through mitochondrial depolarization, and induction of caspase dependent, and caspase-independent apoptosis. In addition, Chen et al. have shown chemopreventive effects of Pter on urethane-induced lung carcinogenesis in mice via inhibition of EGFR-mediated pathways and induction of apoptosis and, apparently, autophagy. Furthermore, Pter has an inhibitory effect on leptin-stimulated breast cancer in vitro through reduction of cell proliferation and JAK/STAT3 signaling, a critical regulatory component of tumorigenesis in obesity-related breast cancer. Moreover, microarray analysis of Pter-treated pancreatic cancer cells revealed upregulation of pro-apoptosis genes and altered levels of phosphorylated STAT3, MnSOD/antioxidant activity, cytochrome C, and Smac/DIABLO.

It has been suggested that Pter induces autophagy (early stage) and apoptosis (later stage) in sensitive and chemoresistant human bladder cancer cells; this indicates that Pter can cause cancer cell death through activation of different pathways. However, although several reports have suggested that Pter can induce autophagy in several types of cancer cells, these observations are based on accumulation of LC3II and autophagosomes, which is not sufficient evidence to demonstrate autophagic cell death. To correctly validate the process, LC3II and P62/SQSTM1 expression/levels (which must increase and decrease, respectively, during active autophagy) must be evaluated. In fact, Pter induces autophagy in cancer cells is very limited since autophagosomes and LC3II accumulation are significantly associated not with active autophagy but with hsp70-dependent lysosomal permeabilization.

Moreover, Resv or Pter can promote expression and activity of Argonaute-2, a central RNA interference (RNAi) component, which inhibits breast cancer stem-like cell characteristics by increasing the expression of a number of tumor-suppressive miRNAs (including miR-16, -141, -143, and -200c). This suggests that dietary intake of natural polyphenols may contribute to the prevention and treatment of some cancers by regulating the RNAi pathway.

Thus, reported results support an effective role for Pter in cancer prevention. However, based on the available literature and taking into account the limitations of bioavailability, it appears reasonable to suggest that clinical studies on cancer prevention should first focus on skin (see above under "photoprotection") and colon cancers.

Cancer therapy
Malignant tumors are invasive and may metastasize to distant sites through the circulatory system. Consequently, metastatic spread, not primary tumor burden, is the main cause of cancer-related death. However, cancer spread and invasion of secondary tissues/organisms appears to be poorly effective, a fact biologically expressed as metastatic inefficiency, which implies that only highly resistant cell subsets begin metastatic invasion and start secondary growth. At present, strategies for cancer treatment using combined therapies or combined agents (targeted therapies in combination with established/conventional chemotherapies or radiotherapies), involving distinct molecular mechanisms, are considered more promising than established/conventional therapies. Although such combinations have shown promising efficacy in preclinical models, the results in clinical trials have not been encouraging. This suggests that malignant cells (likely particular cell subsets), treated to block specific pathways, find ways to adapt using alternative survival mechanisms. By increasing efficacy of chemo/radiotherapy and/or by promoting cancer cell death (see above under "cancer prevention"), natural polyphenols may be particularly useful agents in the treatment of an established cancer (recently reviewed by Asensi et al.).

In a primary report, Pter and 3'-hydroxypterostilbene, used at concentrations that elicit significant apoptotic effects in two Fas-ligand resistant lymphoma cell lines (HUT78B1 and HUT78B2) and in multidrug-resistant leukemia cell lines (HL60-R and K562-ADR), did not show any cytotoxicity in normal hematopoietic stem cells. This suggested that these natural stilbenes could be useful in the treatment of resistant hematological malignancies, including imatinib non-responsive neoplasms.

The first report supporting a potential role of Pter in malignant tumor therapy, published by Ferrer et al., showed that i.v. administration of Pter and quercetin (20 mg/kg per day) to mice inhibited by 73% metastatic growth of B16-F10 melanoma cells (high metastatic potential) in the liver, a common site for metastasis development. The anti-metastatic mechanism involved: (1) a Pter-induced inhibition of vascular cell adhesion molecule 1 expression in the hepatic sinusoidal endothelium, which consequently decreases B16-F10 cell adhesion to the endothelium through very late antigen-4; and (2) a nitric oxide-dependent quercetin- and Pter-induced inhibition of Bcl-2 expression in metastatic cells, which sensitized them to vascular endothelium-induced cytotoxicity. These findings open a new window for possible applications of polyphenol associations in cancer therapy, particularly because polyphenol administration can be combined with biotherapy, cytotoxic drugs, and/or ionizing radiation. Further studies by Priego et al. showed that combined i.v. administration of Pter and quercetin facilitated elimination of human HT-29 colorectal cancer xenografts by chemoradiotherapy in a Bcl-2- and superoxide dismutase 2-dependent mechanism. Although combined administration of polyphenols and chemoradiotherapy has side effects as shown...
by alterations in hematological and clinical chemistry parameters\textsuperscript{122}, such alterations are commonly observed and managed in colorectal cancer patients receiving clinical therapies. Moreover, results published by Nutakul et al.\textsuperscript{123} suggested that Pter has more potent inhibitory effects on colon cancer cells than Resv, a fact that may be associated with the superior bioavailability of Pter to Resv (see above).

Regarding drug metabolism systems, Mikstacka et al.\textsuperscript{124} showed that Resv and its natural analogs (including Pter) can inhibit cytochromes P450\textsubscript{1A2} and 2E1 catalytic activities. Structure–activity relationship analysis led to the conclusion that the substitution of hydroxyl groups of Resv with methoxy groups increases the inhibition of CYP1\textsubscript{1A2}, yet the number and position of methylations were not essential. However, the 4′-hydroxyl group in Resv and its analogs may play an important role in the interaction with a binding site of CYP2E1\textsuperscript{129}. These observations are important because they imply that the half-life of drugs, metabolized through systems affected by these polyphenols, could be altered (see also above under “metabolism and pharmacokinetics”). Mikstacka et al.\textsuperscript{124} also reported that Resv analogs, in which the hydroxy groups are substituted by methoxy groups, exhibited a remarkably stronger inhibitory effect toward human CYP1\textsubscript{1A1} in comparison to the parent compound. In contrast, the potency of pinostilbene, desoxyrhabditellin, and Pter toward CYP1\textsubscript{1B1} was comparable to that of Resv\textsuperscript{124}.

A recent report\textsuperscript{125} shows that lipophilic 3-oxo-C(12)-homoserine lactone and stillbe derivatives (including Pter) can be loaded into liposomal lipid bilayers with efficiencies of 50–70%. Liposomes solubilize these compounds and allow i.v. administration without the use of solvents. Indeed, i.v. administration of liposome-associated 3-oxo-C(12)-homoserine lactone (3 mg/kg) and Resv (5 mg/kg) inhibited tumor growth by ~70% in head and neck squamous-cell carcinoma-bearing mice; this demonstrated that simple solubilization can have important therapeutic benefits\textsuperscript{125}.

Although potential applications of Pter in cancer therapy are just beginning to be explored, recent findings are encouraging and support the need for further research. For instance: (1) genomic analysis of Pter predicts its antiproliferative effects against pancreatic cancer under \textit{in vitro} and \textit{in vivo} conditions\textsuperscript{110}; (2) the inhibitory effects of EGCG and Pter on pancreatic cancer growth \textit{in vitro} suggest the benefits of polyphenol combinations\textsuperscript{126}; and (3) Pter promotes cancer cell death via a mechanism involving lysosomal membrane permeabilization, and different grades of susceptibility were observed among different cancer cells (including A375 melanoma, L649 lung cancer, HT29 colon, and MCF7 breast cancer) depending on their lysosomal heat shock protein 70 content, a known stabilizer of lysosomal membranes\textsuperscript{107}.

Table 1 summarizes schematically the potential effects of Pter on different signaling cascades and cellular mechanisms involved in cancer progression and dissemination.

### Effects on insulin sensitivity, blood glycemia and lipid levels

Insulin resistance (hyperinsulinemia) is now recognized as a major contributor to the development of glucose intolerance, dyslipidemia and hypertension in non-insulin-dependent diabetes mellitus patients (www.diabetes.org). Beneficial roles of dietary polyphenols in the prevention of cardiovascular diseases (see below) and control of glucose homeostasis have been considered and studied\textsuperscript{112,132}.

The antihyperglycemic activity of phenolics (marsupsin and Pter, orally administered) from \textit{P. marsupium}, assayed in rats with hyperglycemia induced by streptozotocin, was first reported in 1997 by Manickam et al.\textsuperscript{15} This effect was comparable to that of 1,1-dimethylbiguanide (metformin), a first-line oral antidiabetic drug for the treatment of type 2 diabetes (www.diabetes.org). In agreement with these findings, it was also reported that treatment with a \textit{P. marsupium} extract significantly lowered the serum glucose levels and substantially prevented hypertriglyceridemia and hyperinsulinemia\textsuperscript{133}. Large gene screening analyses revealed that expression of a large number of genes involved in lipid

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<td>Bad\textsuperscript{128}, Bax\textsuperscript{128,127,128}, Bak\textsuperscript{122}, Bid\textsuperscript{122}; caspase 1, 2, 3, 7, 8, 9\textsuperscript{128}, P53\textsuperscript{108,127,128}, Smac/DIABLO\textsuperscript{110}, cytochrome C\textsuperscript{128}</td>
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<td>Increases LC3-II\textsuperscript{102,107,108,111,129,130}, increases P62/SQSTM1\textsuperscript{107}; reduces P62/SQSTM1\textsuperscript{130}</td>
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<td>Necrosis\textsuperscript{107,111}, cleaved PARP\textsuperscript{102,107,122}; mitochondrial depolarization\textsuperscript{128}; reduces p65\textsuperscript{96,122}; reduces NF-κB\textsuperscript{96,122}; increases iκB-α stability\textsuperscript{122}; lysosomal membrane permeabilization\textsuperscript{107}; EGFR inhibition\textsuperscript{108}; decreases ERK1/2\textsuperscript{108}</td>
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metabolism was affected by Pter treatment. More recent data showed that Pter activated AMPK in both p53 positive and negative human prostate cancer cells. Pter-activated AMPK decreased the activity and/or expression of lipogenic enzymes, such as fatty acid synthase and acetyl-CoA carboxylase.

Rimando et al. found that hypercholesterolemic hamsters fed with Pter at 25 parts per million of the diet showed 29% lower plasma low-density lipoprotein (LDL) cholesterol, 7% higher plasma high-density lipoprotein (HDL) cholesterol, and 14% lower plasma glucose levels as compared to the control group. Results from in vitro studies showed that Pter acted as a peroxisome proliferator-activated receptor (PPAR-α) agonist (PPAR-α is expressed in adipose and other tissues) and may be a more effective PPAR-α agonist and hypolipidemic agent than Resv, whereas in vivo studies demonstrated that Pter possesses lipid and glucose lowering effects.

Moreover, the oral administration of Pter in diabetic rats resulted in a significant reduction of glycated hemoglobin and increased total hemoglobin levels, whereas the activities of hepatic enzymes such as hexokinase were significantly increased, and glucose-6-phosphatase and fructose-1,6-bisphosphatase activities were decreased. Furthermore, chronic treatment with Pter remarkably reduced the pathologic changes observed in rat liver and kidney of streptozocin–nicotinamide-induced type 2 diabetes.

Cardiovascular benefits

At present, while there is a large body of knowledge on oxidative risk for atherothrombotic cardiovascular disease, rigorous clinical investigations establishing a direct causality chain between intake of specific dietary polyphenols and improvement of (cardio)vascular function in humans are scarce. Diffusible physiological vasoactive mediators (e.g. endothelin-1, angiotensin II, thromboxane A2, prostacyclin, NO) reach the vascular smooth muscle to modify the degree of arterial contraction, thereby regulating the diameter of the vessel. Polyphenols from red wine increase endothelial NO production and lead to endothelium-dependent relaxation in conditions such as hypertension, stroke and the metabolic syndrome. However, although intracellular pathways involved in the endothelial effects of polyphenols are partially described, the molecular targets of these polyphenols have not been completely elucidated. A suitable experimental approach has been found in what is called flow-mediated dilation, a physiological response measured as the increase in vascular diameter subsequent to resumed blood flow after transient ischemia. Based on this, it has been shown that consumption of certain dietary flavonoids is causally linked to increases in flow-mediated dilation in humans. Consequently, and from evidence obtained by different lines of research, potential benefits of natural polyphenols in ischemia or ischemia-reperfusion-induced tissue/organ damage have been proposed.

Data from a recent human clinical trial, in patients with stable coronary artery disease, showed that Resv improved left ventricle diastolic function and endothelial function, lowered LDL-cholesterol levels, and protected against unfavorable hemorheological changes measured in patients with coronary artery disease.

Pter has been shown to lower plasma lipoproteins and cholesterol in hypercholesterolemic hamsters, to protect vascular endothelial cells against oxidized low-density lipoprotein-induced apoptosis in vitro and in vivo, and to promote cytoprotective macroautophagy in vascular endothelial cells. Moreover, results from a recent phase 2/3 trial at the University of Mississippi Medical Center, USA (www.clinicaltrials.gov) show that pTeroPure (a patented nutritional ingredient that corresponds to a highly purified trans-Pter; Chromadex, Irvine, CA) significantly reduced blood pressure in human adults. These results suggest that further research is warranted on potential Pter-induced cardiovascular benefits.

Effects on aging, memory and cognition

There is abundant literature and there has been strong debate on potential antiaging effects of natural polyphenols. Pearson et al., in a key article, reported that Resv delayed age-related deterioration (including reduced albuminuria, decreased inflammation, and apoptosis in the vascular endothelium, increased aortic elasticity, greater motor coordination, reduced cataract formation, and preserved bone mineral density) and mimicked transcriptional aspects of dietary restriction without extending life span in mice. Recently the effect of Resv, green tea extract, curcumin, oxaloacetic acid, and medium-chain triglyceride oil on the life span of genetically heterogeneous mice was evaluated using the Interventions Testing Program, US National Institute on Aging; however, these studies concluded that none of these five agents had a statistically significant effect on the life span of male or female mice. Nevertheless, these data do not allow the conclusion that any polyphenol present in nature, if given for a long period of time, would be unable to increase life span in mammals. As recently discussed in an excellent commentary, aging is regulated by signaling networks encompassing nutrient-sensing, and mitogen-activated, stress-responsive and DNA damage response signaling pathways. Caloric restriction modulates portions of those signaling networks.

Networks conserved during evolution and including genes that are antagonistically pleiotropic, drive growth and development early in life and aging later in life. Based on the molecular mechanisms involved in polyphenol–cell interactions (see above), a positive effect on life extension in mammals cannot be ruled out.

As reported by Joseph et al., dietary Pter was effective in reversing cognitive behavioral deficits as well as dopamine release, and working memory was correlated with Pter levels in the hippocampus (19-month-old Fischer 344 rats). More recently, it has been shown that, at equivalent and diet-achievable doses, Pter is a more potent modulator of cognition and cellular stress than Resv, likely driven by increased PPAR-α expression and increased lipophilicity (due to the substitution of hydroxyl with methoxy groups in Pter). Therefore Pter appears to show advantages, as compared to Resv, in improving some aging-associated damages.

Safety–toxicity

On September 2011, Chromadex achieved GRAS (generally recognized as safe) status for its ingredient pTeroPure-
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and standard chemotherapy, for the treatment of human to be therapeutically effective, in combination with quercetin derivative, Pter, undergo rapid and extensive conjugation in study of Pter toxicity in mice. In this study mice, fed during was a peer-reviewed article detailing a 28-day subchronic study of Pter toxicity in mice. In this study mice, fed during 28 days at doses of 0, 30, 300, and 3000 mg/kg body weight/day of Pter, showed that the red blood cell number and hematocrit increased after Pter administration compared to control groups; as well, histopathologic examination and evaluation of biochemical parameters revealed no alterations regarding clinical signs or organ weight at any dose. No mortality was observed even with the highest dose administered with the food.

Recently (September 2012), data from the first clinical trial on Pter (Effect of Pterostilbene on Cholesterol, Blood Pressure and Oxidative Stress, www.clinicaltrials.gov, conducted at the University of Mississippi Medical Center, USA) were released. It was concluded that Pter reduced blood pressure in adults (both systolic and diastolic pressures were decreased by Pter at an oral dose of 125 mg given twice per day). The 125 mg dose was obtained by converting the 30 mg/kg animal dose into a human equivalent dose, thus following the formula for dose translation based on body surface area [animal dose (mg/kg) multiplied by animal Km/human Km (where Km is a correction factor reflecting the relationship between body weight and body surface area)] Safety data for this dosage showed that Pter was well-tolerated at the twice daily dosing frequency.

Pter-induced toxicity, after i.v. administration, was also evaluated in mice. Pter was found pharmacologically safe because it showed no organ-specific or systemic toxicity (including tissue histopathologic examination and regular hematology and clinical chemistry data) even when administered i.v. at a high dose (30 mg/kg per day × 23 days) (a lower dose of 20 mg/kg per day × 23 days regimen was found to be therapeutically effective, in combination with quercetin and standard chemotherapy, for the treatment of human colorectal carcinoma xenografted into mice).

Despite these observations, before dietary/therapeutic dosages are standardized for different applications, more rigorous studies are needed. It is worthwhile to mention that a phase II clinical trial (www.clinicaltrials.gov), sponsored by GlaxoSmithKline to assess the safety and activity of SRT501 (a formulation of Resv claimed to increase its in vivo bioavailability) alone or in combination with bortezomb (the first therapeutic proteasome inhibitor tested in patients with multiple myeloma), was terminated due to safety concerns after kidney damage developed in some patients (cast nephropathy, a type of kidney damage that can stem from multiple myeloma and lead to organ failure). In this trial, a high dose of 5 g SRT501/day was administered orally for 20 consecutive days in a 21 day cycle for a maximum of 12 cycles. Despite the large effort that has been put forth by the international research community to understand the mechanisms of Resv’s beneficial effects, the precise dosing, risks, and outcomes in humans remain uncertain.

Conclusions and recommendations

All bioactive polyphenols studied to date, including the derivative, Pter, undergo rapid and extensive conjugation in the intestinal tract of man and rodents. It is in this conjugated form that they are absorbed, with very little of the free natural compound gaining access to the blood. Most available data indicate that natural polyphenols and their derivatives are biologically more active than their metabolites. As stated above, there is clear evidence that oral administration of Pter can have beneficial effects in humans. Nevertheless, the available evidence is insufficient to justify chronic administration of Pter to human beings beyond the dietary recommended dose.

In general, it is important to note that bioavailability and in vivo biological efficacy of natural polyphenols are critical issues that must be correlated before drawing any conclusions on the potential health benefits of polyphenols. As concluded several years ago by Kroon et al., in an excellent commentary, all in vitro studies on the biological responses to polyphenols must use only physiologically relevant concentrations of these molecules or their conjugates. Thus the rationale for in vitro studies to test the biological activities of natural polyphenols at higher than (patho)physiological concentrations, and their practical relevance, must be called into question. Consequently a lot of work must still be done in order to clarify the mechanisms underlying the benefits observed under in vivo conditions. Regarding Pter in particular, it is important to point out the promising data obtained in animals and in different pathologies (see above) that support the need for further animal research and human clinical trials.

Taking into account the experimental evidence presented above, we conclude that: (1) Pter has multiple biomedical applications that need to be further explored; (2) Pter (more lipophilic and showing higher in vivo bioavailability) appears superior to Resv in practically all comparative studies performed to date; (3) different pathways of administration (topical, oral, and i.v.) will require different and optimized pharmaceutical formulations and/or delivery systems (liposomes and other drug delivery systems such as nanoparticles, microemulsions, or polymeric implantable devices are emerging as viable alternatives that have been demonstrated to deliver therapeutic concentrations of e.g., curcumin, ellagic acid, green tea polyphenols, or Resv into the systemic circulation); (4) consequently, standardized formulations and/or delivery structures, and dosages for specific clinical studies, must be developed; (5) studies on the combinatorial effects of Pter and other polyphenols and/or specific disease-related drugs are recommended; and (6) some biomedical applications may be suggested as priorities for research in the coming years: skin and colorectal cancer chemoprevention and treatment; inflammatory dermatoses; type II diabetes; ischemia- or ischemia-reperfusion-induced tissue/organ damage; long-term studies on life extension in healthy mammals; and the incidence of aging-associated pathologies/damages using mammalian models. Nevertheless, other areas where natural polyphenols have potential applications should not be ignored (e.g., neuroprotection and neurodegeneration, microbial infections, therapy of other cancers, and other inflammation-related diseases). In these efforts, it is essential to keep in mind the need of elucidating metabolism and pharmacokinetics features of Pter in humans, possible biological effects of Pter metabolites, and potential interactions of Pter with different drug metabolism systems.
Declarations of interest

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References


133. GROVER JK, VATS V, YADAV SS. Pterocarpus marsupium extract (Vijayasar) prevented the alteration in metabolic patterns induced in the normal rat by feeding an adequate diet containing fructose as sole carbohydrate. Diabetes Obes Metab 2005;7:414–20.


