THERAPEUTIC POTENTIAL OF PLANT-DERIVED OLIGOSTILBENES AND STILBENE GLYCOSIDES

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ABSTRACT

Stilbenoids constitute a major class of plant-derived secondary metabolites occurring in abundance across several families and are well-known for their nutritional and health-promoting benefits. Several investigations have established their therapeutic potential in the management of different types of cancer, neuroinflammation, arthritis, disorders in lipid metabolism, microbial infection etc. Studies on resveratrol monomer, oxyresveratrol, their synthetic analogs, piceatannol, pterostilbene can be found in the literature. But a collective and comprehensive review on chemistry, pharmacological effects, structure-activity relationship and pharmacokinetics of plant-derived oligostilbenes and stilbene glycosides is missing. These phytochemicals are generally characterised by poor oral bioavailability due to extensive first-pass metabolism and conjugation. The present review attempts to fill up these lacunae and also focuses on further studies that can be performed in the future to translate these immensely potential secondary metabolites into human clinical setting from cell culture and animal studies at the preclinical level for effective therapeutic intervention of various pathological conditions.

Keywords: Bioavailability, Chemopreventive, Cytotoxicity, Neuroinflammatory, Pharmacokinetics, Oligostilbene, Resveratrol, Secondary metabolite, Stilbene glycoside and SAR

INTRODUCTION

Stilbenoids are non-flavonoid polyphenolic multi-faceted bioactive secondary metabolites found in abundance in fruits, leaves, bark and wood of numerous plants belonging to Vitaceae, Dipterocarpaceae, Leguminosae, Fabaceae, Gnetaceae, Moraceae, Polygonaceae and Cuperaeaceae families. Dietary items such as grapes and other related substances constitute major sources of this group of secondary metabolites, primarily resveratrol [1, 2]. High concentration of stilbenes has been reported in passion fruit (Passiflora edulis) [3]. Stilbenoids, a prominent group of secondary metabolites, are considered as phytoalexins as they are synthesised naturally from phenylpropanoids in response to pathogenic attack and diseases, biotic and abiotic stress factors, environmental stress and UV light-induced damage, confer selective advantage and contribute significantly to bacterial root nodulation and coloration and provide protection against toxins [4, 5]. The most commonly occurring monomeric stilbenes are E-resveratrol and E-piceid in berry skin and these isomers may undergo different types of biotransformation reactions to produce glycosylated, methoxylated derivatives and also to yield isomers and oligomers. Stilbene glycosides synthesized de novo in plants participate in storage, confer protection against peroxidation and are transported form cytoplasm to apoplasms [3]. Apart from their antimicrobial defense actions, hydroxystilbene glucosides, isorhapontin (isorhapontigenin-O-glucoside), astringin (piceatannol-O-glucoside) and piceid (resveratrol-O-glucoside) are considered as lignin monomers and are incorporated by coupling and cross-coupling reactions during lignification in Norway spruce bark to form stilbenolignans, gnetominin B, gnetominin C, gnetofuran A and gnetucleristol [6]. Stilbenes have demonstrated a diverse range of biological functions, health-promoting effects through complex specific and non-specific mechanisms. Stilbenes may be developed as chemopreventive and chemotherapeutic agents against different forms of cancers in animals and humans, as evident from various in vitro and in vivo studies on different cancer cell lines such as colon, breast, prostate, pancreas, melanoma, lung and others [7–9]. Although the trans-isomer of stilbene is usually the most stable one and found to possess anticancer activity, combrestatin A-4 (3,4,5,4’-tetramethoxy-3’-hydroxy-cis-stilbene), isolated from Combretum zeylanicum is a cis-stilbene which is reported to show cytotoxic activity against several cancer cell lines [10]. Numerous studies in the past have focussed on production, biosynthesis, isolation, characterization, and various pharmacological effects of dietary stilbenes or stilbene glycosides from medicinal plants of Africa or Croatia or Australia [11–15]. Several investigations have revealed interesting observations on the therapeutic potential of resveratrol, oxyresveratrol, piceatannol, pterostilbene and naturally occurring resveratrol analogs as well as structurally modified oxyresveratrol [16–29]. Synthetic derivatives of resveratrol and other stilbene analogs are also reported [30–32]. Although oligostilbenes also have been subject of attention, but no comprehensive review could be found on different aspects of oligostilbenes of plant origin, focusing on pharmacological effects, structure-activity relationship (SAR), pharmacokinetics etc. Stilbene glycosides as a group have been particularly left out as evident from literature survey. Drug discovery and development based on natural products exploiting privileged scaffolds present in Mother Nature’s laboratory is the key to success in pharmaceutical industry. Therefore, elucidation of the mechanism of action of oligostilbenes and stilbene glycosides will undoubtedly create unforeseen scope for scientists in the future. Keeping this in mind, the present review aims to provide an insight into the therapeutic potential of plant-derived oligostilbenes and stilbene glycosides.

Chemistry and biosynthesis of stilbenes: Brief background

The basic skeleton of stilbene is characterized by a 1,2-diphenylethylene nucleus, composed of two benzene rings (A and B), joined by an ethylene bridge, due to which cis-and trans-isomers may be obtained. Most commonly occurring phytostilbenes are based on trans-resveratrol structure and may exist in free form (aglycone) as a mixture of monomers, dimers, octamers and other complex oligomers formed by condensation of monomers and also as metabolites (glucosides) [5, 14, 33, 34]. Stilbenes with...
substituents of different types and at different positions in any of the rings, of different steric configurations in free form or in their glucosidic form were isolated from leaves, heartwood and bark of pine and Eucalyptus species [35]. Prenylated stilbenes, trans-4-isopentenyl-3,5-dihydroxystilbene and trans-4-(3-methyl-E-but-1- enyl)-3,5,2'-4'-tetrahydroxystilbene were obtained from the stem bark of Arctocarpuscommunis, M. swinefurthii and M. alnifolia [13, 36].

Stilbenes, plant polyketides are biosynthesised through shikimate derived phenylpropanoid and acetate-malonate pathways [37]. p-coumaroyl-CoA acts as precursor for biosynthesis of stilbenes in plants. Stilbene synthase converts cinnaamoyl CoA, utilises 3 units of malonyl CoA and is involved in aldol-type cyclisation (carbon 2 to carbon 7) and decarboxylation to produce resveratrol [4, 5]. Occurrence of pinoxylin synthase and dihydro-pinoxylin synthase is reported in the literature [38]. Biosynthesis of plant stilbenes in reconstituent E. coli has been reported to yield functionalized stilbenes [39].

Oligostilbenes

Peroxidase isoenzymes located in the cell wall, apoplast and vacuole catalyse oxidative coupling of E-resveratrol or other stilbene monomers to form oligomer stilbenoids or oligostilbenes which are bioavailable hydroxystilbenes [3]. Stilbene, sp. and it is a dimer of oligostilbenes namely, heimiol B, hopeaphenol, vaticanol A, stepnophyllol C and hopeaphenol A in acetone extract of the stem bark of Artocarpuscommunis, M. schweinfurthii var. taivansiana [42]. A resveratrol dimer, ampelmosin A was detected in grapevine shoot extracts and in Ampelopsis glandulosa [37]. Other oligostilbenes extracted from grapevine root extract include (+)-e-vininferin, wilsonol C, vitsin A and vitsin B [43]. Acetone extract of stem bark of Shoreahopelifolia revealed the presence of oligostilbenes of (e)-viniferin, (-)-amenoisepin C, (-)-hopeaphenol and (-)-hopeaphenol isolated from Anchopteris species, acetone extract of the rhizome of Ampelocissuscontusa (L.) and stem bark of Vateria indica Linn [2]. Similar oligostilbenes, vitsinol A, (+)-e-vininferin, (-)-vitisin A, (-)-vitisin B and (+)-hopeaphenol were also isolated from Ampelopsis brevipedunculata var. hancei, of which the last three are tetramers [44]. (-)-e-vininferin, a dimer and a chiral molecule is regarded as the chemical marker of plants belonging to Dipterocarpaceae family and acts as a precursor of oligostilbenes found in Shorea, Hopea, Vatica and Dipterocarpus species. A trimer stilbene, ampelmosin E was isolated from Ampelopsis brevipedunculata and Shoreagibbosa. Shoreaphenol may be considered as the chemical marker of Shorea sp. and it is a dimer containing benzofuran ring [45]. Latifoliol A, B and C were detected in ethylacetae fraction of the Gnetumlatifolium extract. The first two compounds are characterised by a bridged 3-oxabicyclo [3.3.0] octane moiety, whereas latifoliol C was produced by the condensation of gnetomarin G with trans-oxyresveratrol. Several oligostilbenes, such as cis-shegansu B, trans-shegansu B, gnetofolin F, (+)-gnemontalin G, parvifolol C, lehmbachol B, gnetijolin C, gnetin H and a second group lacking oxygen-containing heterocyclic ring, with (+)-gnemontalin G, parvifolol C, lehmbachol B, gnetijolin C, gnetin H were detected in different plant species [40]. Preparative high performance liquid chromatography, NMR spectroscopy and mass spectrometric fragmentation pattern revealed the presence of several oligostilbenes namely, heimiol B, hopalexin vatalcanol A, balanocarpol and vaticaophilin A in the crude extract of the leaves of Neobalanocarpus heimi [41]. The electrospay ionization ion-trap time-of-flight multistage mass spectrometry (ESI-IT-TOF-MS') fragmentation study on (−)-7,8-cis-vininferin, carasphilin A, saturestin A and saturestin C proved valuable information for the first characterization of oligostilbenes [46]. Several other resveratrol oligomers include trans-miyababenol C, kobophenol A and kobophenol B isolated from Carexespecies (Carexfuliculata and Carexynglandra) and acuminol, a dimer obtained from stem barks of Shoreauncinata [47]. Miyababenol was isolated from Vitis sp. Instrumental methods of analyses revealed the presence of vatanol C, stepphyllol C and hopalexin A in acetone extract of the stem bark of Shorea bracteolata [48]. Gnetulin is an isorhapontiginin dimer with 2,3-diphenyl-1-indane and exocyclic double bond framework isolated from different plants of Gnetum (Gnetaceae) and other analogs such as gnetomarin C and D, gnetuinham, parthenocissus have also been reported [49]. With respect to stability, stilbenoids are vulnerable to effects of light, oxygen and temperature as well as oxidative enzymes. For example, exposure to UV and visible lights causes trans-to cis-isomerization of resveratrol [5]. Trans-gnetin H was converted to its cis-form on exposure to UV light for 6h [50]. Dryobalanopobilin A was found to be a source of (−)-amenoisepin C, A and two trimers, namely cis-and trans-diptodinsolin B [51]. Structures of some representative oligostilbenes are presented in fig 1.

Stilbene glycosides

Bioactivity-guided fractionation of the methanolic extract of Acer mori leaves revealed the presence of two new stilbene glycosides, 5-O-methyl-(E)-resveratrol 3-α-D-glucopyranoside and 5-O-methyl- (E)-resveratrol 3-O-D-apiofuranosyl-(1→6)-β-D-glucopyranoside [52]. HR-ESI-MS, GC-MS, HPLC, NMR and other instrumental methods of analyses revealed five new stilbene glycosides, (E)-2,3,5,4-tetrahydroxyoligostilbene-2-O-(4”-O-α-D-glucopyranosyl)-α-D-glucopyranoside, (E)-2,3,5,4’-tetrahydroxyoligostilbene-2-O-(6”-O-α-D-glucopyranosyl)-α-D-glucopyranoside, (E)-2,3,5,4’-tetrahydroxyoligostilbene-2-O-α-D-glucopyranosyl-4’-O-α-D-glucopyranoside, (E)-2,3,5,4’-tetrahydroxyoligostilbene-2-O-α-D-glucopyranosyl-5-O-α-D-glucopyranoside, and (E)-2,3,5,4’-tetrahydroxyoligostilbene-2-O-(2”→6”)-O-α-D-fructofuranosyl)α-D-glucopyranoside from the roots of Polygonummultiflorum [53].

Pharmacological effect and therapeutic potential of oligostilbenes

Ampelmosin A reportedly inhibited Aβ aggregation in vitro [37]. Oligostilbenesgnetin C (resveratrol dimer), gnetin L, gmenoside C and gmenoside D obtained from ethanolic extracts of the seeds of melinjo (Gnetumnamol L.) exhibited free radical scavenging activity and antimicrobial activity against food-contaminating microbes and Enterobacteriaceae [54]. The oligostilbenes isolated from G. macrostachyum inhibited lipoxygenase (sHOX-1) either via non-competitive or mixed-competitive mechanisms. It is to be mentioned that their enzyme inhibitory activity was not an outcome of their anti-oxidant effect. The compounds did not gain access to the enzyme catalytic site owing to their large molecular size [55]. Synergistic effect shown by a resveratrol tetramer with resveratrol monomer on inhibition of inflammatory arthritis was found to be stronger than the other oligomers isolated from stem part of Vitis [42]. Vitsinol A, a resveratrol dimer demonstrated potent effect in vitro anti-inflammatory effect in LPS-induced RAW264.7 cells. It was found to be less cytotoxic compared to other dimer and tetramers isolated from Ampelopsis [44]. cis-shegansu B and latifoliol exhibited potential inhibitory activity against LPS-induced inflammation by transfection of A541-42 gene into microglial BV-2 cell line. The tested compounds significantly lowered the secretion of NO in BV-2 cells [40]. Among the oligostilbene isomers, cis-and trans-suffruticosol D, obtained from the seeds of Paeoniauffruticosa, trans-isomer showed greater cytotoxic effect (lower IC50 values) against several human cancer cell lines such as A549 (lung), BT20 (breast), MCF-7 (breast), and U2OS (osteosarcoma) versus normal human cell lines (HMEC (breast) and HPLA (lung)). Antitumor effects were characterised by the hall mark features of apoptotic pathway, including alteration in nuclear size and cell membrane permeability, decrease in mitochondrial transmembrane potential and lowering of cell motility. Excessive ROS generation by the oligostilbene isomers in lung cancer cells inhibited cytotoxic production and blocked the NFkBpathway [56]. Oligostilbenes, cis-c-vininferin, trans-c-vininferin, suffruticosol A, suffruticosol C, gmenoside C, gmenoside D, cis-suffruticosol D, trans-suffruticosol D, cis-gnetin H and trans-gnetin H, from the seedcases of P. suffruticosa demonstrated anti-proliferative activity and induced apoptosis in three representative subtypes of human breast carcinoma cells, including basal A phenotype BT20 cells [estrogen receptor (ER)-progesterone (PR)-human epidermal growth factor receptor 2 (HER2)]. Luminol A phenotype MCF-7 cells (ER+PR+HER2-) and basal B phenotype MDA-MB-231 cells (ER-PR-HER2-). Higher efficacy was shown against BT20 cells than MCF-7 and MDA-MB-231 cells. Of the various compounds investigated, resveratrol dimers, trans and cis gnetin H exhibited...
maximum cytotoxic effect. Trimmers were observed to be more potent than the dimers [50]. Ampelopsin E demonstrated selective cytotoxicity against cancer cells and thus could be developed as a promising chemotherapeutic agent [45]. cis-ampelopsin E inhibited LPS-induced inhibitor kinase (IERK/β) phosphorylation, c-myc signaling and NF-κB (NF-κB)-dependent expression of COX-2, active form and prostaglandin E2 (PGE2) production. Additionally, degradation of IκBα was prevented and upregulation of NF-κB transcriptional activity was inhibited via reduction of translacion of transcription factor p65 into the nucleus [57]. Cell cycle arrest has been linked to the mechanism of antiproliferative effect of oligostilbenes [47]. Mechanistic studies on deoxyrhapontigenin, a natural stilbene dimer derived isolated from the root extract of Rheum undulatum displayed the compound to induce apoptosis and dilate endoplasmic reticulum (ER) upregulate the expression of ER stress markers GRP78, IRE1α, eIF2α, CHOP, JNK, and p38 in breast cancer cell line, chemoresistant MCF-7/ADR (Chemoresistant) (Doxorubicin/adriamycin cell line) [58]. Acuminat exhibited antioxidant activity, similar to resveratrol [47]. Among the oligostilbenes purified from grapevine root extract, vittisin B was identified as the most potent replication suppressor of hepatitis C virus (HCV) in vitro where it disrupted the activity of an essential viral enzyme, helicase NS3 [43]. (+)- and (-)-hopeaphenol exerted antiangiogenic effect via facilitation of glucose uptake in muscle cells by binding to the active sites of the proteins 18VN, 3A4A and 3A7F, thereby inhibiting α-glucosidase in a dose-dependent fashion. (–)-hopeaphenol inhibited bacterial virulence factor type III secretion system. An earlier research paper discussed several biological effects of hopeaphenol [2]. trans-viniferin, trans-resveratrol dehydrodimer showed antimicrobial effect against Acetobacteraceae, Acetobacterenoni, Bacillus cerasus, Bacillus subtilis, Dekkerabruxellensis, Escherichia coli, Listeria innocua, Listeria monocytogenes, Pseudomonas fluorescens, Pseudomonas aeruginosa, Streptococcus spp., Zygocacharomycesbaillii, and Zygocacharomycesrouxii. Anti-obesity effect was also reported in rats. Adipogenesis was inhibited in 3T3-L1 cells by lowering levels of gene markers involved in lipid accumulation and expression of adipogenesis (PPARgamma) and anti-inflammatory (MCP-1) proteins [59]. Rhapontigenin and isorhapontigenin were found to possess weaker anti-staphylococcal activity against six standard strains and two clinical isolates of S. aureus, compared to hydroxypterostilbene, pinostilbene and pterostilbene [1]. (-)-viniferin, (-)-α-viniferin, (-)-hopeaphenol, vaticanol A, B, C and G were reported to be weak inhibitors of murine tyrosinase [60]. Astringin, pallidal, ω-viniferin, and ω-viniferinexhibited anti-angiogenic effect. VEGF-induced PI3K/Akt phosphorylation was significantly inhibited. Moreover, ω-viniferin and palidal significantly induced NOS activation and thus could provide guard against the side effects caused by anti-VEGF hypertension drugs. Pallidal also inhibited VEGFR-2 activation [61]. Anti-malarial activity was shown by (–)-hopeaphenol, (–)-hopeaphenol, vaticanol, vaticanol C, and ε-viniferinexhibiting anti-obesity activity. VEGF-induced PI3K/Akt phosphorylation was significantly inhibited. SAR of oligostilbenes and stilbene glycosides: General principles

Biological activity, therapeutic effects and pharmacokinetic behaviour of stilbenoids depend greatly on the degree and position of hydroxylation and methoxylation. Introduction of methoxy substituent increases lipophilicity, prevents metabolic degradation in vivo and facilitates easy penetration of the molecule across cell membrane, enhances the apoptotic activity of the phytocompound and ultimately improves the anticancer effect. However, too manymethoxy groups hinder interaction with the target protein and therefore becomes a barrier to its therapeutic efficacy [35, 69, 70]. Number of hydroxyl groups in the stilbene derivatives enhances aqueous solubility, alters the anti-oxidant property of the molecule and improves the antimicrobial action [1]. It has been observed that presence of hydroxyl groups is essential for selective inhibition of COX-2 [71]. There are several studies confirming higher cytotoxic potential of cis-derivatives [10]. However, in a study on role of oligostilbenes in cancer management, trans-isomers have been found to be more effective. Antitumor efficacy of Paeonia oligostilbene was governed by degree of polymerization i.e. the number of repeating units of resveratrol, presence of double bond, steric arrangement and their conformation. Both the isomers suppressed 3T3-L1 induced fibroblasts, but fibroblasts did not exhibit wound healing and can be considered to possess anti-angiogenic activity [68].
Pharmacokinetic studies on oligostilbenes and stilbene glycosides

It has been reported that relatively small fraction of orally administered stilbenes are readily absorbed from the upper intestine. Stilbenes are characterised by low stability, rapid in vivo metabolism, poor bioavailability and low target specificity. Their bioavailability is affected by the compounds’ pharmacokinetic parameters i.e., their absorption, distribution, metabolism and elimination. They may be excreted as metabolites either renally or non-renally [5]. A characteristic feature of plant polyphenols is that after oral administration, they are usually bioactive in their conjugated metabolite form produced as a result of enteric as well as hepatic Phase II biotransformation [7]. Colonic microflora also is involved in metabolic breakdown of large molecular weight non-absorbed compounds to their lower MW derivatives [72]. Other factors governing their poor bioavailability include their chemical structure, degree of glycosylation/acylation, conjugation with other phenolic compounds, molecular size, degree of polymerization, solubility, route of administration etc [33]. Bioavailability studies help in planning the therapeutic uses and efficacy of the oligostilbenes.

Pharmacokinetic analysis of rhaponticin (rhapontin) in rats demonstrated rapid distribution and elimination and hence, extremely poor oral bioavailability. However, the plasma concentration of rhapontigenin increased and eliminated gradually after parenteral administration [1]. Rhapontigenin was reported to...
have better bioavailability than resveratrol with a longer t1/2 (3h) and it was also converted to its glucuronide and excreted via biliary route. The oligostilbene is characterized by high apparent volume of distribution suggesting its extensive tissue distribution [8]. Following oral administration at a dose of 100 mg/kg body weight in rats, half-life of oral bioavailability of resveratrol was found to be 4.2 h and 6.59%, respectively. Biotransformation of genetol into its glucuronide and its reconversion back into parent stilbene accounted for its comparatively longer biological half-life. The glucuronide conjugate could be detected for 72 h in serum [5]. Poor bioavailability of vitisin B after ingestion is attributed to its large molecular size, poor aqueous solubility and low absorption across the intestinal epithelium. Rapid and extensive in vivo metabolism of viniferin contributed to its low bioavailability. Enzymes UDP-glucuronosyl transferase (UGT) and sulfotransferase (SULT) are involved in glucuronidation and sulfation of viniferin, leading to conjugates circulating in blood. However, intraperitoneal injection of viniferin reportedly improved its pharmacokinetic parameters with 85% bioavailability compared to 0.77% via oral route [43]. High bioaccumulation of the native compound was seen in white adipose tissues indicating them as body reservoir from where trans-viniferin could be released slowly. Free oligostilbene was found in plasma as early as 15 min after intraperitoneal injection. A greater percentage of glucuronide metabolites could be detected in liver and kidney. Hepato-biliary excretion may be considered as major route of elimination for the particular isomer of viniferin as either native compound or its metabolites could be found more in faeces than in urine [59]. Poor bioavailability of trans-8-viniferin after oral administration was attributed to low absorption and extensive metabolism involving mainly glucuronidation and sulfation to a lesser extent. The molecule was excreted primarily in its unchanged form in the faeces [73]. Oral bioavailability of genetin C was found to be better than resveratrol [50]. Rate and extent of absorption of ampelopsin E were higher via intravenous route compared to oral route, owing to extensive first-pass metabolism (glucuronidation and sulfation) in the liver and small intestine [62].

Future scope

Translation of preclinical positive data for plant-derived oligostilbenes and stilbene glycosides on cell culture models and animals to human clinical setting require long-term randomized clinical studies with larger population samples of different age groups and longer follow-up periods [5]. Results obtained from these studies will establish therapeutic dose, and safe concentration of the bioactive phytochemicals. Although the whole plant or its parts form a part of the traditional diet due to their health-promoting effects, there are limited studies on safety of the therapeutically active stilbenoids [63]. Trans-generational effects of stilbenoids. Int J Mol Sci 2018;19:25.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally. CONFLICT OF INTERESTS

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