Chemistry, Biosynthesis and Pharmacology of Viniferin: Potential Resveratrol-Derived Molecules for New Drug Discovery, Development and Therapy

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Abstract: Viniferin is a resveratrol derivative. Resveratrol is the most prominent stilbenoid synthesized by plants as a defense mechanism in response to microbial attack, toxins, infections or UV radiation. Different forms of viniferin exist, including alpha-viniferin (α-viniferin), beta-viniferin (β-viniferin), delta-viniferin (δ-viniferin), epsilon-viniferin (ε-viniferin), gamma-viniferin (γ-viniferin), R-viniferin (vitisin A), and R2-viniferin (vitisin B). All of these forms exhibit a range of important biological activities and, therefore, have several possible applications in clinical research and future drug development. In this review, we present a comprehensive literature search on the chemistry and biosynthesis of and the diverse effects of viniferin, especially with regards to its anti-inflammatory, antipaposisis, antidiabetic, antiplasmodic, anticancer, anti-angiogenic, antioxidant, anti-melanogenic, neurodegenerative effects, antiviral, antimicrobial, antifungal, anti-diarrhea, anti-obesity and anthelmintic activities. In addition to highlighting its important chemical and biological activities, coherent and environmentally acceptable methods for establishing viniferin on a large scale are highlighted to allow the development of further research that can help to exploit its properties and develop new phyto-pharmaceuticals. Overall, viniferin and its derivatives have the potential to be the most effective nutritional supplement and supplementary medication, especially as a therapeutic approach. More researchers will be aware of viniferin as a pharmaceutical drug as a consequence of this review, and they will be encouraged to investigate viniferin and its derivatives as pharmaceutical drugs to prevent future health catastrophes caused by a variety of serious illnesses.
Keywords: viniferin; oligostilbenoid; chemistry; biosynthesis; pharmacology; drug discovery

1. Introduction

Stilbenoids, also known as phytoalexins, are plant phenolics that are synthesized as a defense mechanism in response to abiotic and biotic stresses, such as microbial attack, toxins, infections or UV radiation [1,2]. The best known sources of stilbenoids are from Vitis vinifera [3]. Based on their structural characteristics, stilbenoids containing C6-C2-C6 backbone structures are further divided into five categories: stilbenes, oligostilbenes, bibenzyls, bisbibenzyls and phenanthrenes [1,2]. Among the stilbenoids, resveratrol is the most prominent and most investigated [1,4], while viniferins are more known as “resveratrol derivative” [5].

Several different forms of viniferin exist (Figure 1). The α-viniferin form is an oligostilbene of trimeric resveratrol [6] and was first found in Caraganachamlagu Lam as a compound that exhibits anti-inflammatory activities [7]. Furthermore, one of the major products of resveratrol-derived dehydrodimers is called δ-viniferin [8,9]. The δ-viniferin form is an isomer of ε-viniferin [10], which is also a dimer of resveratrol, extracted from Vitis vinifera; it has been extensively investigated for its potential benefits for human health [11–13]. Other oligomer stilbenoids that can be extracted and are found in the roots of Vitis vinifera are the resveratrol tetramers, R2-viniferin (Vitisin A) and R-viniferin (Vitisin B), which may mediate some other important biological activities [14].

To complete this review, relevant research was collected from several scientific databases, including Google Scholar, Scopus and PubMed. The literature search was performed using keywords such as “viniferin” AND “stilbenoid oligomers” OR “Vitis vinifera” AND “in-vitro” OR “in-vivo” OR “Biological studies” OR “Pharmacological studies” OR “Chemistry” OR “Toxicity studies” OR “Pharmacokinetics” for studies that had been published up until the date of the search. Studies that were not written in the English language or did not have abstracts were excluded. After applying the inclusion and exclusion criteria, as well as eliminating duplicates between the databases, a total of 73 studies were selected. The studies, classified into two major categories, phytochemistry and pharmacology, were further categorized based

Figure 1. Different types of viniferin.
on the key findings, with no restriction on the dose, route, duration of administration, or type of study (animal or human). After a complete screening, the obtained information was summarized and included.

The studies indicated that viniferin is a potentially active molecule and that structural modifications to viniferin may lead to new drug development, with improved bioavailability and pharmacological action. The objective of this review is to discuss the chemistry and pharmacology of viniferin in order to examine how its derivatives might be useful molecules in the discovery of novel drugs to treat a variety of disorders.

2. Chemistry

2.1. Sources and Distribution of Viniferin

Viniferin is found in many plant species, among which grapes (Vitis vinifera) is a primary source. Table 1 summarizes details about the sources and distribution of various types of viniferin from medicinal plants.

Table 1. Source and distribution of Viniferin.

| Source of Viniferin | Plant Parts | Type of Viniferin | References |
|---------------------|-------------|-------------------|------------|
| Astilbe grandis     | Root        | α-viniferin       | [15]       |
| Bombax malabarica   | Root bark   | ε-viniferin       | [16]       |
| Carexana chamaeleon | Not stated  | α-viniferin       | [17]       |
| Carex sinica        | Root and Stems | α-viniferin   | [18-21]    |
| Carex humilis       | Root        | α-viniferin       | [22]       |
| Caryatia trifolia   | Root        | α-viniferin       | [23,24]    |
| Cyphostemma crotal梁 | Root and leaves | cis- and trans-ε-viniferin | [26] |
| Cyphostemma crotalaxioides | Root and leaves | cis- and trans-ε-viniferin | [26] |
| Diptercarpus litteralis | Stem bark   | ε-viniferin       | [27]       |
| Dryobalanops lanceolata | Stem bark   | ε-viniferin       | [28]       |
| Hopea exalata       | Stem bark   | α-viniferin       | [29]       |
| Hopea parviflora    | Stem bark   | ε-viniferin       | [30]       |
| Iris clarkei        | Seeds       | ε-viniferin       | [31]       |
| Iris lacta          | Seeds       | ε-viniferin       | [32]       |
| Rheum undulatum     | Not stated  | ε- and δ-viniferin | [33] |
| Paonia lactiflora   | Seeds       | cis- and trans-ε-viniferin | [34] |
| Paonia ostii        | Seeds       | cis- and trans-ε-viniferin | [35] |
| Parthenocissus quinquefolia | Not stated | ε-viniferin       | [36]       |
| Rheum lhasaense     | Roots       | ε-viniferin       | [37]       |
| Shorea maxwelliana  | Stem bark   | ε-viniferin       | [38]       |
| Shorea avatilis     | Stem bark   | ε-viniferin       | [39]       |
| Shorea seminis      | Tree bark   | α-viniferin       | [40]       |
| Gnetum microcapum   | Not stated  | ε-viniferin       | [41]       |
| Vitis amurensis     | Leaves, petioles, berry, skins and seeds | cis- and trans-ε-viniferin | [42] |
| Vitis heyneana      | Not stated  | ε-, R- and R2-viniferin | [43] |
| Vitis labrusca      | Not stated  | trans ε- and δ-viniferin | [44] |
| Vitis quinquangularis | Not stated | ε-viniferin       | [45]       |
| Vitis rotundifolia  | Hairy root  | ε-viniferin       | [46]       |
| Vitis thunbergii    | Root        | ε-viniferin       | [47]       |
| Vitis vinifera      | Root, stems, canes, leaves, buds and internodes | α-, ε-, ω-, trans, R- and R2-viniferin | [48] |

2.2. Structural Characterization of Viniferin

A large number of resveratrol derivatives of higher structural complexity exist compared to simple substituted resveratrol analogues. The most common compounds found in nature are a variety of resveratrol dimers, such as ε-viniferin (A), δ-viniferin (B), and trimers, i.e., α-viniferin (C) (Figure 2).

Nevertheless, several important factors relating to stilbenoids’ nomenclature and structure may complicate its identification and classification. Another potential confusion lies in the structure and naming of viniferins. For example, although the compound itself takes the form of simple resveratrol dimers and trimers, there are two stereochemical centers at positions 7α and 8α on the dihydrofuran ring, allowing the formation of four potential stereoisomers. The trans-configuration of the two hydrogens in the saturated ring system provides alpha and beta hydrogen, unlike in the cis configuration, in which both hydrogens are either on the alpha side or in the beta position. The naming of the cis
and trans conformations for these hydrogens is an area of confusion when dealing with viniferins, which also contain a trans (E) or cis (Z) double bond.

Determining the absolute configuration to differentiate between (+) and (−)-ε-viniferin, however, is more challenging. For known compounds, their [α] D values can be compared with those in the literature. Nevertheless, due to the difficulties in assigning absolute configurations to stilbenoid oligomers, many compounds have been reported with only their relative configurations assigned. Since (+)-ε-viniferin is considered a major stilbenoid intermediate for larger oligomers, the structures containing viniferin moieties are normally presented as containing the same configuration when not otherwise determined. In the many reports of complex oligomers, only the relative configuration is assigned [62].

trans-ε-Viniferin

The UV spectra in methanol (MeOH) showed λmax (log ε) values at 203 (5.05), 230 (4.87) and 324 nm (4.57), while in MeOH and sodium hydroxide (NaOH), they indicated λmax (log ε) at 211 (5.52), 244 (5.06) and 347 nm (4.84) [63,64]. The infra-red (IR) spectral data exhibited characteristic bands at 3393 cm⁻¹ (OH), 1606, 1513, 1443 cm⁻¹ (C=C aromatic) and 832 cm⁻¹ (para-disubstituted benzene). The 1H-NMR spectra [63,64] were recorded in deuterated acetone with pairs of doublets appearing at δ 7.21 (2H, d, J = 9.0 Hz, H-2A and H-6A) and δ 6.83 (2H, d, J = 8.0 Hz, H-3A and H-5A), integrating two protons. They were assigned to the protons present in the aromatic ring A. The strong singlet at δ6.24 (3H, s, H-2B, 4B, 6B) for three protons was attributed to the protons present on ring B. The pair of doublets at δ 5.42 (1H, d, J = 5.0 Hz, H-1C) and 4.49 (1H, d, J = 5.0 Hz, H-2C) were due to the protons on ring C, while the signal at δ 6.32 (1H, d, J = 1.7 Hz, H-4D) was due to the meta-coupled proton H-4 on ring D. The H-2 proton of ring D appeared at δ 6.71, along with the protons of H-3E and H-5E of ring E. The signal at δ 7.18 (2H, d, J = 9.0 Hz, H-2E and H-6E) was attributed to the presence of the H-2E and H-6E protons on ring E. The alkene protons lying in between the two aromatic rings, D and E, appeared at δ 7.00 (1H, d, J = 15.1 Hz, H-â) and as a partially overlapped signal at δ 6.71.

The structural elucidation of α-viniferin is discussed in greater detail by Kitanaka et al. [65]. For example, α-viniferin with a molecular formula (C42H30O9) showed a peak for its pseudomolecular ion at m/z 701 [M + Na]+ and at m/z 678 for [M+] ion in its field-desorption–mass-spectrometry (FD-MS). In the UV spectra, the λmax peak appeared at 285 nm and in its IR spectra absorption bands at 3400 cm⁻¹ for −OH group and at 1613 cm⁻¹ for C=C, which are characteristic bands for the polyphenols observed.

In its 13C-NMR spectrum [65], α-viniferin exhibited forty-two signals, out of which six methine aliphatic carbon signals appeared between δ 46.4 and 95.6, twelve aromatic –CH groups appeared between δ 96.9 and 128.66, and a total of eighteen quaternary aromatic carbon atoms appeared between δ 118.0 and 161.7, including nine signals assigned to quaternary aromatic carbons under oxygen functions. The 1H-NMR spectrum exhibited

Figure 2. Chemical structures of ε-viniferin (A), δ-viniferin (B), and α-viniferin (C).
three pairs of doublets for vicinally coupled methine protons at δ 3.97 (H₆) and 6.07 (H₈), 4.61 (H₇, J = 6.4 Hz), 4.90 (H₄, J = 6.4 Hz), 4.71 (H₅, J = 9.7 Hz) and 5.95 (H₆, J = 9.7 Hz). In addition, it also exhibited signals characteristic of three 1,2,3,5-tetrasubstituted benzene rings and three 1,4-disubstituted benzene rings.

The ¹H-¹H-COSY NMR spectrum confirmed the relationship between the three methine signals at δ 3.97 (H₆), 4.71 (H₅), 4.61 (H₄), as well as the six meta-coupled signals at δ 5.99 (H₇), 6.22 (H₈), 6.72 (H₉m), 6.25 (H₉), 6.59 (H₉) and 6.23 (H₈). There were cross peaks between the three signals of methine with the attached oxygen seen at 6.77 (H₉), 5.95 (H₇), 4.90 (H₄) and the six 4-hydroxy phenyl proton signals at δ 7.03 (H₉), 6.72 (H₈), 7.22 (H₉), 6.77 (H₉), 7.08 (H₉) and 6.79 (H₈). The plane structure of the α–viniferin was a ring structure with three 2-phenyl-2,3-dihydrobenzofuran units (I, II and III). All the proton signals were assigned to the three units according to the coupling, beginning with the resonance of H₆. The stereochemical configuration of the α–viniferin was determined based on the ²H-¹H- heteronuclear shift correlation spectrum.

### Table 2. The ¹³C and ¹H-NMR spectral data for α–viniferin.

| Carbon No. | Unit I | H (δ), C(δ), J in Hz | Unit II | Unit III |
|------------|--------|---------------------|---------|---------|
| 2          | 6.07 (br.s) | 86.4 | 5.95 (d, J = 9.7) | 90.0 | 4.90 (d, J = 6.4) | 95.6 |
| 3          | 3.97 (br.s) | 46.4 | 4.71 (d, J = 9.8) | 52.8 | 4.61 (d, J = 6.4) | 55.6 |
| 3a         | -      | 118.8 | -                    | 120.9 | -                  | 119.7 |
| 4          | -      | 141.2 | -                    | 139.7 | -                  | 138.7 |
| 5          | 5.99 (d, J = 1.8) | 108.5 | 6.72 (d, J = 1.8) | 106.2 | 6.59 (d, J = 1.8) | 105.8 |
| 6          | -      | 159.3 | -                    | 159.3 | -                  | 160.8 |
| 7          | 6.22 (d, J = 1.8) | 98.0 | 6.25 (d, J = 1.8) | 96.6 | 6.22 (d, J = 1.8) | 96.9 |
| 7a         | -      | 161.6 | -                    | 160.6 | -                  | 161.7 |
| 1¹        | -      | 132.0 | -                    | 132.3 | -                  | 132.5 |
| 2′, 6²     | 7.03 (d, J = 8.5) | 128.2 | 7.22 (d, J = 8.5) | 128.1 | 7.08 (d, J = 8.5) | 128.6 |
| 3′, 5²     | 6.72 (d, J = 8.5) | 115.7 | 6.77 (d, J = 8.5) | 116.1 | 6.79 (d, J = 8.5) | 116.1 |
| 4²        | -      | 157.8 | -                    | 158.2 | -                  | 158.3 |

The biochemical synthesis of reverastrol in plants has been elucidated and occurs via a series of enzymatic processes, as highlighted in Scheme 1. The synthesis begins with the amino acid phenylalanine, which is transformed into cinnamic acid and occurs by deamination; it is catalyzed by the enzyme phenylalanine ammonia lyase. The enzymatic hydroxylation to p-coumaric acid followed by the conversion of free acid into p-coumaroyl...
CoA occurs with the aid of CoA ligase. The final step in the synthesis involves the condensation of p-coumaroyl CoA (%) with malonyl CoA in the presence of stilbene synthase to furnish trans-resveratrol. Largely, resveratrol biosynthesis is controlled by stilbene synthase (STS), which controls the entry point into the stilbene biosynthetic pathway (Scheme 1).

![Scheme 1. Biosynthesis pathway for viniferin.](image)

It was hypothesized that in nature, oligomerization proceeds via the formation of phenoxyl radical intermediates. Resveratrol oligomerization appears to proceed via the coupling of oxidatively generated phenoxyl radicals, as originally proposed by Langcake and Pryce [67]. The dimerization typically occurs (Scheme 2) through two region-isomeric modes: the 8–10′ coupling (as found in ε-viniferin) and the 3–8′ coupling (δ-viniferin).
Scheme 2. Hypothesis to explain the biosynthetic process involved in oligomerization of resveratrol. Resveratrol’s (S1) oligomerization occurs via radical intermediates, S1a–c, to afford the C3–C8′ and C8–C10′ bond connections to form δ-viniferin (S2) and (+)-ε-viniferin (S3), respectively.
2.4. Bioavailability and Pharmacokinetics of Viniferin

Courtois et al. [68] reported that ε-viniferin is rich in carbons and hydrogens, which means that a) it is extremely poorly soluble in water, b) it has low bioavailability, and c) it easily undergoes isomerization under the influence of UV radiation. Nevertheless, by encapsulating the compound in phospholipid-based multi-lamellar liposomes (MLLs) called spherulites or onions, the photosensitivity is improved and the water solubility significantly increased [68]. In humans, ε-viniferin is mostly converted to glucuronides, and less often, to sulfates, whereas glucuronidation is the main pathway involved in rats [68]. The compound is rapidly glucuronidated by hepatic clearance [69], which explains its low bioavailability. In a study in 2018, it was reported that ε-viniferin accumulated in white adipose tissue, suggesting that these tissues may act as a reservoir for the native form, allowing slow release and long-term presence in the organism. Furthermore, ε-viniferin and its metabolite were found in higher concentrations in feces than in urine, signifying the main elimination pathway [70]. In addition, another form of viniferin, δ-viniferin, has a low bioavailability due to its low absorption and extensive metabolism, especially following oral administration compared to intravenous injection. The main metabolite found was glucuronide, followed by sulfates. It was further revealed that unmodified δ-viniferin and its metabolites were eliminated rapidly after intravenous injection and that δ-viniferin is primarily excreted unchanged in the feces after oral administration, with most appearing to be unabsorbed, according to the drug’s concentration in plasma [71]. A resveratrol trimer, α-viniferin is rapidly absorbed into the circulation and slowly eliminated, with only 4.2% bioavailability, following oral administration [7].

All the above-mentioned results indicate that viniferin has the potential to become a drug molecule for enhancing life span by potentially delaying ageing and preventing chronic illnesses. However, the limited bioavailability of viniferin is a major problem for converting these findings from fundamental research into clinical utility as a drug. Viniferin can potentially be made highly bioavailable through consumed with various foods, combination with other phytochemicals, the use of controlled-release technology, and the development of formulations using nanotechnology.

2.5. Medicinal Uses of Plants Containing Viniferin

*Paonia suffruticosa* is an important traditional Chinese herb used to treat osteoarthritis (OA); oligostilbenes are the main active ingredients of its seeds [38]. Another plant, *vitis heymiana*, which is widely distributed in northern Vietnam, has been used in Vietnamese traditional medicine as an agent against arthritis, bronchitis, carbuncles, inflammatory conditions, and menstrual irregularities [35]. The dipterocarpaceae plant, *Cotylelobium melanoxylon*, which is widely distributed in Southeast Asia, has been used as an astringent, antilaxative and blood-coagulation agent in traditional Thai medicine [72]. *Dipterocarpus littoralis*, commonly known as Meranti Jawa in Indonesia, is traditionally used to treat diseases such as diarrhea, diabetes and malaria [27] (Figure 3). Another important plant is *Shorea roxburghii* (Dipterocarpaceae), which is widely distributed in Thailand and its neighboring countries, such as Cambodia, India, Laos, Malaysia, Myanmar and Vietnam. The bark of *Shorea roxburghii* (“Phayom” in Thailand) has been used as an astringent or a preservative in traditional beverages in Thailand [73]. In Indian folk medicine, the plant has been used in the treatment of dysentery, diarrhea and cholera [46].

The genus Hopea (Dipterocarpaceae), which consists of over 104 species, is distributed primarily in southern parts of India and China and in Sri Lanka. *Hopea ponga* (Dennst.) Mabb is an endemic tree found mainly in the tropical evergreen forests of the South Western Ghats of India. The plant was reportedly used in traditional medicine in the treatment of diabetes, piles and snake bites [32]. Another plant, *Vitis amurensis* Rupr. (Vitaceae) is a wild-growing grape, widely distributed in Korea, China and Japan. Its fruit has been used as a raw material for juice and wine in three different countries. The root and stem have been used to relieve pain from injury, rheumatalgia, stomach ache, neuralgic pain and abdominal pain [74].
Figure 3. Biological attributes of viniferin against multiple conditions.

*Caragana sinica* (Buchoz) Rehd. (Fabaceae), a deciduous shrub, is widely distributed in Korea, China and Japan. Its dried roots have been used in the treatment of asthenia syndrome, vascular hypertension, leukorrhagia, bruises, contusion, rheumatism, neuralgia, arthritis and migraine as a folk medicine [19]. The underground parts of *C. chamlague*, which have been used in Korea and China as folk medicine, are purported to be effective against neuralgia, rheumatism and arthritis [75].

3. Biological Properties of Viniferin

3.1. Anti-Inflammatory Effects

A study by Vion et al. [76] reported that trans \( \varepsilon \)-viniferin decreased the amount of inflammatory mediators, such as TNF\( \alpha \) and IL-6. In another study on knee damage associated with arthritis, it was reported that the active constituents of *Vitis thunbergii* var. taiwaniana, including resveratrol, hopeaphenol and (+)-\( \varepsilon \)-viniferin, significantly scavenged 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and inhibited prostaglandin E2 (PGE2) production in lipopolysaccharide (LPS)-induced penehyclidine hydrochloride (PHC)s. Additionally, there was a significant decrease in serum PGE2 and 2-18F-fluoro-2-deoxy-D-glucose (18F-FDG) levels in LPS-induced acute inflammatory arthritis in rabbits [53]. In a recent study, ten oligostilbenes extracted from the seed of *Paeonia suffruticosa* showed protective effects at low concentrations on osteoarthritis chondrocytes. One of the compounds is trans-viniferin, which tends to be most effective in promoting the expressions of Collagen Type II Alpha 1 Chain (COL2A1) and SRY-Box Transcription Factor 9 (SOX9) [38]. On the other hand, the oral and IV administration of \( \alpha \)-Viniferin at >30 mg/kg and >3 mg/kg, respectively, showed significant anti-inflammatory effects on carrageenin-induced paw edema in mice. The compound also showed an inhibitory effect on COX-2 activity and a very weak inhibitory effect on COX-1 activity [24]. These findings are supported by the report by Chung et al. [77], who investigated the anti-inflammatory effects of \( \alpha \)-viniferin and established that it inhibits ERK-mediated STAT-1 activation in IFN-\( \gamma \)-stimulated macrophages, thus downregulating STAT-1-inducible inflammatory genes [77].
Among the many oligostilbenoids extracted from *Vitis heyneana*, α-viniferin has the highest potential inhibitory activities. Overall, LPS-induced COX-2 expression and PGE2 production were suppressed, nitric oxide (NO) release was significantly reduced in a dose-dependent manner and the activation of the transcription factor of NF-κB was inhibited [47]. A study on *Vitis vinifera* root extract, including seven stillbenoids (resveratrol, piceatannol, trans-ε-viniferin, ampelopsin-A, miyabenol C, R-2-viniferin (Vitisin A) and R-viniferin (Vitisin B)) established that the extract has potent free-radical-scavenging activity in terms of DPPH, hydroxyl and galvinoxyl, in a dose-dependent manner; the superoxide radicals are also scavenged when the extract is used in high concentrations. Additionally, it protects against DNA damage caused by hydrogen peroxide while downregulating pro-inflammatory gene expression, including IL-1β and iNOS in cultured macrophages [59].

3.2. Antidiabetic Effects

An earlier study established that the methanolic extracts from the wood and bark of *Cotylelobium melanoxylon* could inhibit elevations in plasma glucose following sucrose loading in rats and ameliorates triglyceride elevation following olive-oil loading in mice. In the study, cis- (±)-ε-viniferin was isolated from the bark extract, while (+)-ε-viniferin was isolated from both wood and bark extracts [72]. The ε-viniferin caused a significant reduction in the concentrations of fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG) and low-density-lipoprotein cholesterol (LDL-C). Additionally, Liu et al. [78] found that the glucose-tolerance and liver- and kidney-damage indices, such as alanine aminotransferase (ALT), aspartate aminotransaminase (AST), creatinine (CR) and blood urea nitrogen (BUN) of diabetic rats also improved. Furthermore, the activation of AMP-activated protein kinase (AMPK) was also increased and the histopathological changes were attenuated in the livers of diabetic rats by binding to the hinge region between the α- and β-units of AMPK, as well as interacting with the active site of AMPK [78].

The progression of diabetes mellitus (DM) can be ameliorated by inhibiting α-glucosidase, which delays glucose absorption and lowers postprandial blood-glucose levels. Lulan et al. [27], who extracted α-viniferin from *Dipterocarpus littoralis*, established its antidiabetic potential, which acts by inhibiting the activities of the α-glucosidase and α-amylase of rats in the intestine. The study compared the extract’s activity with that of acarbose as a standard. The finding was also supported by an earlier study by Morikawa et al. [46], who reported that oral (+)-α-viniferin showed an inhibitory activity against plasma glucose elevation in sucrose-loaded rats at 100–200 mg/kg through the inhibition of intestinal α-glucosidase and aldose reductase activities [46].

In another study, for the first time, acetone and ethanol extracts from the stem bark of *Hopea ponga* (Dennst.) Mabb were tested for their antidiabetic activity. Both (−)-ε-viniferin and (−)-α-viniferin, which were among the ten compounds isolated, showed inhibition towards the activities of α-glucosidase and α-amylase, with prominent antiglycation activity seen. It was also observed that α-viniferin can increase glucose uptake, mainly due to AMPK upregulation, which eventually leads to the translocation of the glucose transporter (GLUT-4) into the cell membrane [32]. A recent study by Oranje et al. [79] investigated sodium-glucose co-transporter 1 (SLGT 1) and 2 (SLGT 2), which are targets for glycemic control in type 2 diabetes mellitus. They established that the isomers of the resveratrol dimers (+)-ε-viniferin and (−)-ε-viniferin inhibit the sodium-glucose co-transporter, while (+)-ε-viniferin inhibits SLGT 1 by 44%, with little inhibition shown towards SLGT2. Nevertheless, by contrast, (−)-ε-viniferin did not inhibit SLGT1, but did show a 35% inhibition of SLGT2. Another study on racemic forms of trans-β-viniferin and trans-ε-viniferin also found that both had higher efficacy in inhibiting pancreatic alpha-amylase compared to pure enantiomers [9].

3.3. Anticancer Effects

Most studies on resveratrol oligomers, including viniferin, are focused on its anticancer activity. It has been reported that a combination of a first-generation platinum complex,
the anti-cancer drug cisplatin (CDDP), and ε-viniferin, a natural antioxidant, has strong apoptotic effects on the glioma cell lines (C6) when used in low concentrations, compared to using the compound alone [80]. Previously, researchers have reported that the apoptosis of hepatocellular carcinoma (HepG2) cells may be induced by using a combination of vincristine and ε-viniferine [81]. Their finding was supported by another study, which investigated the anticancer activity of the combination of vincristine and ε-viniferine loaded with PLGA-b-PEG nanoparticles and also established that the combination induces apoptosis in HepG2 cells [80].

Another study was conducted on the anticancer activity in human hepatocellular carcinoma (HCC) cell lines p53 wild-type HepG2 and p53-null Hep3B. R2-viniferin inhibited HepG2 but not Hep3B, arrested the cell cycle at G2/M and increased the intracellular reactive oxygen species (ROS), caspase 3 activity and the ratio of Bax/Bcl-2 proteins, indicative of apoptosis [82] (Figure 4). R2-viniferin was also tested on the canine glioblastoma cell line D-GBM and the canine histiocytic sarcoma cell line DH82. The author used Vineatrol®30, which contains resveratrol and its oligomers (R2-viniferin and hopeaphenol) which were confirmed to exert a potent anti-proliferative effect on the two canine tumor-cell lines. The effect, at least in D-GBM cells, is due to the induction of apoptosis via the activation of caspase 9 and 3/7 [83]. Subsequently, the researchers performed a comparison of the anticancer activity of R-viniferin and resveratrol against the prostate cancer cell line lymph node carcinoma of the prostate (LNCaP). They established that both compounds can inhibit cell growth and arrest the G1 phase cell cycle, although R-viniferin was more potent and tended to increase the apoptotic cellular fraction, along with increasing the activity of apoptosis-associated enzymes [14].

Additionally, α-viniferin was also reported to be effective against colon cancer cell lines (HCT-116, HT-29, Caco-2) by blocking the S-phase of the cell cycle. Nevertheless, no apoptotic effect was induced [84]. Additionally, α-viniferin has antiproliferative effects against chronic myelogenous leukemia (CML). In vitro, the said compound, along with resveratrol, significantly inhibited the proliferation of K562 cells in both dose- and time-dependent manners by reducing the expression of the BCR-ABL protein. A high dose of α-viniferin caused serious cell death, cell fragmentation, and nuclei lysis, indicating apoptosis [85].

A study on the anticancer activity of α-viniferin against human prostate cancer (PCa) cells reported that it has antiproliferative effects on LNCaP, DU145 and PC-3 cancer cells, depending on the dose and timing of treatment, while conferring strong cytotoxicity in non-androgen-dependent PCa cells. The compound inhibited AR downstream expression in LNCaP cells and inhibited the activation of the GR signaling pathway in the DU145 and PC-3 cell lines. Additionally, it also induced cancer cell apoptosis through the AMPK-mediated activation of autophagy and inhibited the expression of the glucocorticoid receptor (GR) in castration-resistant prostate cancer (CRPC) [86]. In terms of testing the anticancer activity on human melanoma cells, ε-viniferin blocks the cell cycle of melanoma cells in the S-phase by modulating the key regulators of the cell cycle, i.e., cyclins A, E, D1 and their cyclin-dependent kinases 1 and 2, which are associated with the induction of cell death, including apoptosis and necrosis [87].

On the other hand, a study [29] discovered that (+)-α-viniferin and resveratrol possessed antiproliferative action against SK-MEL-28 melanoma cells, where (+)-α-viniferin was reported to be more potent. The compound arrests the G1 cell cycle, as well as inducing DNA damage followed by the induction of apoptosis in SK-MEL-28 cells, which was confirmed by an increased expression of γ-H2AX and cleaved caspase-3. Additionally, (+)-α-viniferin and resveratrol significantly decreased the expression of cyclin B1, which is important for G2/M phase transition in the cell cycle.
which confirmed the inhibition of vascular arginase activity involved in the production of (SHRs). It also exhibits anti-angiotensin-converting enzyme (ACE-I) and vasodilating effects against phenylephrine-induced tensions in an endothelium-intact aortic ring of spontaneously hypertensive rats. Furthermore, the bioactive compound can also aid in lowering the level of pro-inflammatory cytokines, such as TNFα and IL-6. Abbreviations: ROS, Reactive oxygen species; MAPK, Mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinase; JNK, Jun N-terminal Kinase; GSH, Glutathione; LPO, Lipid peroxides; GPx, Glutathione Peroxidase; SOD, Superoxide dismutase; CAT, Catalase; c-Myc, Cellular Homologue of Avian Myelocytomatosis Virus; NF-kB, Nuclear factor kappa B; TNFα, Tumor necrosis factor alpha; IL-6, Interleukin 6; Bcl-2, B-cell lymphoma-2; Cyt-c, Cytochrome complex; Bax, Bcl-2-associated X Protein.

### 3.4. Anti-Angiogenic Effects

Atherosclerosis can be prevented by protecting the vascular endothelial cells (VECs). In fact, low concentrations of ε- and δ-viniferin significantly stimulate wound repair via nitric oxide (NO) production, the activation of endothelial NO synthase and the induction of sirtuin 1 (SIRT1) and HO-1 expression [88]. These findings were supported by another study, which confirmed the inhibition of vascular arginase activity involved in the production of NO by ε-viniferin [89]. The anti-angiogenic effects of α-viniferin were observed when it inhibited mitogen-induced human-umbilical-vein endothelial cell (HUVEC) proliferation through the hypophosphorylation of retinoblastoma protein. It also suppressed mitogen-induced HUVEC adhesion, migration, invasion, and microvessel outgrowth, as mediated by the downregulation of cell-cycle-related proteins, vascular endothelial growth factor receptor-2 (VEGFR-2), and matrix metalloproteinase-2. The inactivation of the VEGFR-2/p70 ribosomal S6 kinase signaling pathway was involved in the α-viniferin-mediated modulation of endothelial cell responses [20].

In addition, (+)-vitisin A can effectively reduce 24-hour systolic and diastolic blood pressures following a single oral dose administered at spontaneously hypertensive rats (SHRs). It also exhibits anti-angiotensin-converting enzyme (ACE-I) and vasodilating effects against phenylephrine-induced tensions in an endothelium-intact aortic ring of
In addition to (+)-vitisin A, it was confirmed that ε-viniferin possessed similar activity. The compound induces the proliferation and wound repair in VECs via NO production and is involved in the protection of VECs from oxidative-stress-induced cell death. It also induced tACE activity in vitro and eventually reduced blood pressure to improve the cardiac mass in SHRs [91].

3.5. Anti-Melanogenic Effects

Facial hyperpigmentation was reported to be improved following the skin application of topical products containing α-viniferin on the skin. It has been reported that α-viniferin inhibited melanin production in α-melanocyte-stimulating hormone (α-MSH)-, histamine- or cell-permeable cAMP-activated melanocyte cultures. It also decreased the melanin index on facial melasma and freckles in humans. The α-viniferin accelerated protein kinase A (PKA) inactivation via the reassociation between catalytic and regulatory subunits in cAMP-elevated melanocytes, a feedback loop in the melanogenic process. Consequently, the cAMP/PKA-signaled phosphorylation of cAMP-responsive element-binding protein (CREB) coupled with the dephosphorylation of cAMP-regulated transcriptional co-activator 1 (CRTC1), which was inhibited; hence, the expression of the MITF-M or Tyro gene was downregulated with decreased melanin pigmentation [92].

3.6. Anti-Obesity Effects

A study compared both the in vitro and the in vivo anti-obesity effect of ε-viniferin and t-resveratrol. The ε-viniferin was confirmed to have a higher anti-adipogenesis activity in 3T3-L1 cells. It significantly suppressed lipid accumulation and the expression of the adipogenesis marker gene, PPAR gamma. When compared with a high-fat-diet control mice group, there was reduced body weight, as well as liver triglyceride levels following ε-viniferin treatment. In the meantime, the levels of plasma insulin and leptin were significantly improved [93]. The (+)-ε-viniferin extracted from the roots of Vitis thunbergii var. taiwaniana 1 (VTT-R) significantly reduces the lipid deposits in 3T3-L1 adipocytes and inhibits 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (Figure 5). The compound is believed to lower the body weights of mice, the weight ratio of mesenteric fat, blood glucose, total cholesterol, and low-density lipoprotein in high-fat-diet-induced obesity groups [52].

3.7. Antidiarrheal Effects

Yu et al. [93] reported that trans-ε-viniferin and R2-viniferin possess antisecretory effects and are useful in the treatment of diarrhea. Additionally, the compound inhibited the activation of intestinal calcium-activated chloride channel (CaCC) when tested on a neonatal mouse model of rotaviral diarrhea. It suppressed diarrhea without affecting the rotaviral infection. Furthermore, the trans-ε-viniferin inhibited the physiologically relevant, long-term CaCC current following agonist stimulation, without affecting cytoplasmic Ca2+ signaling, with both compounds believed to inhibit short-circuit currents in the mouse colon [93]. Subsequently, the author investigated the role of trans-δ-viniferin in rotavirus-infected diarrhea and inflammatory-bowel-syndrome diarrhea IBS-D. They found that the resveratrol dimer could inhibit TMEM16A activity in TMEM16A-expressed Fischer rat thyroid (FRT) cells, as well as preventing Ca2+-activated Cl− current in HT-29 cells and in the colonic mucosa. Moreover, the compound prevents diarrhea caused by rotaviral infection and reduces the pellet number in IBS-D mice [94].
In the control mice group, there was reduced body weight, as well as liver triglyceride levels following ε-viniferin treatment. In the meantime, the levels of plasma insulin and leptin were significantly improved [93]. The (+)-ε-viniferin extracted from the roots of Vitis thunbergii var. taiwaniana 1 (VTT-R) significantly reduces the lipid deposits in 3T3-L1 adipocytes and inhibits 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (Figure 5). The compound is believed to lower the body weights of mice, the weight ratio of mesenteric fat, blood glucose, total cholesterol, and low-density lipoprotein in high-fat-diet-induced obesity groups [52].

**Figure 5.** Anti-adipogenesis activity of ε-viniferin. The ε-viniferin suppressed PPAR-γ and HMG-CoA, which resulted in an anabolic process that stimulated adipogenesis and reduced body weight, liver triglycerides, total cholesterol and blood glucose. Abbreviations: HMG-CoA, β-Hydroxy β-methylglutaryl-CoA; PCSK9, Proprotein convertase subtilisin/kexin type 9; LDLR, Low-density lipoprotein receptor; LPL, Lipoprotein lipase; VLDL, Very LowDensity Lipoprotein Receptor; LDL, Low-density lipoprotein; ApoB, Apolipoprotein B.

### 3.8. Neuroprotective Effects

Alzheimer’s disease (AD) affects many cellular and molecular targets; therefore, its therapy requires multi-target molecules. Caillaud et al. [95] evaluated the effects of trans-ε-viniferin as a neuroprotective agent on transgenic APPswePS1dE9 mice. They reported that the compound can cross the blood–brain barrier and reduce the size, as well as the density, of amyloid deposits to ameliorate astrocyte and microglial reactivity. The effect was shown only after 3-to-6-month-old mice were intraperitoneally injected (10 mg/kg) every week [96]. Additionally, a study found that AD may be caused by the accumulation and aggregation of abnormal b-amyloid peptide and suggested that the inhibition of b-amyloid (Ab) fibril formation is helpful in treating AD. The researchers reported that ε-viniferin glucoside inhibits Ab (25–35) fibril formation in vitro. Additionally, the effects of ε-viniferin on the aggregation of the full-length peptides Ab (1–40) and Ab (1–42) and on b-amyloid-induced toxicity was investigated in PC12 cells; ε-viniferin was confirmed to inhibit Ab cytotoxicity [96].

Furthermore, (+)-α-viniferin was also confirmed to be one of the most important natural constituents to exhibit anti-acetylcholinesterase (AChE) activity, being a significantly specific, reversible and non-competitive AChE inhibitor. Overall, AChE inhibitors increase the efficiency of cholinergic transmission by preventing the hydrolysis of released ACh, allowing more ACh to become available at the cholinergic synapse [75]. In addition, α-viniferin can prevent and treat AD by enhancing alpha-secretase ADAM10 gene expression. Consequently, it prevents the formation of toxic amyloid beta peptides, but also provides
a neuroprotective fragment of the amyloid precursor protein (sAPPalpha). However, a challenge remains due to its limitation in crossing the blood–brain barrier [21], making the design of new formulations a necessity in the future.

In addition to AD, there is also an inherited neurodegenerative disorder known as the Huntington disease (HD). HD is an incurable disease occurring due to an abnormal polyglutamine expansion in the protein named Huntingtin. A study demonstrated that trans-(−)-ε-viniferin can increase the levels of mitochondrial Sirtuin 3 (SIRT3), activates AMPK and protects cells in models of HD [97]. Moreover, ε-viniferin can upregulate SIRT3 expression, which promotes FOXO3 deacetylation and nuclear localization as well as increasing ATP production and decreasing ROS production. The compound also maintains mitochondrial homeostasis, thus inhibiting rotenone-induced cell apoptosis, making ε-viniferin a potential treatment for neurodegenerative disorders [98].

3.9. Antioxidant Effects

A recent study demonstrated that scratched vascular endothelial cells (VECs) treated with resveratrol (10 µM), ε-viniferin (10 µM) and δ-viniferin (5 µM) significantly reversed decreased cell viability after the addition of hydrogen peroxide to the cells, indicating that these compounds are resistant to oxidative stress by increasing the catalase protein level [88]. In addition, ε-viniferin is a potent antioxidant when tested on muscadine grape (Vitis rotundifolia) hairy root cultures, acting via its radical scavenging capacity [50]. Furthermore, α-viniferin exhibited antioxidant activity in cupric ion-reducing antioxidant-capacity, ferric-reducing antioxidant-power, DPPH scavenging, and 2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide radical-scavenging assays. The author concluded that this involved redox-mediated mechanisms, especially electron and H+-transfer, as well as non-redox-mediated mechanisms, including Fe2+-chelation or radical adduct formation [99].

The dimer of resveratrol, trans-δ-viniferin, exhibited moderate antioxidant activity when tested using in vitro model systems, including hydroxy radical scavenging, DPPH and lipid peroxidation. Among the oxygen radicals, the hydroxyl radical is the most reactive and causes great damage to living cells due to its ability to react with various molecules, such as phospholipids, DNA and organic acids. The effects of this compound on human erythrocytes have also been confirmed to protect red blood cells from hemoglobin oxidation [100,101].

trans- and cis-ε-viniferins were among the stilbene derivatives isolated from the seeds of Paonia lactiflora. The compounds were evaluated against the 2-deoxyribose degradation and rat-liver microsomal lipid peroxidation induced by the hydroxyl radical generated via a Fenton-type reaction. It was found that trans-ε-viniferin significantly inhibited the degradation of 2-deoxyribose and rat-liver microsomal lipid peroxidation, whereas cis-ε-viniferin exerted only moderate antioxidant activity [102].

3.10. Antiplasmodic Effects

Malaria is a life-threatening disease caused by parasite species that can infect humans. Among these, Plasmodium falciparum and Plasmodium vivax are the most dangerous. It has been reported that in 2020, nearly 50% of the world’s population was at risk of malaria [103]. To date, many attempts have been made to both prevent and treat malaria, one of which involved the use of medicinal herbs in traditional remedies. The World Health Organization (WHO) has recommended preventive strategies to combat the disease by using antimalarial drugs. Many studies are conducted to determine suitable compounds in plants as health interventions. It has been reported [27] that the bioactive compounds isolated from Dipterocarpus littoralis, especially α-viniferin, has good antimalarial activity. Based on their comprehensive spectrum analyses, including IR, 1D, and 2D NMR, as well as comparisons with research data, the structure of α-viniferin (referred to as “Compound 1”) was determined. It showed alpha-glucosidase and alpha-amylase inhibitory activities with 50% inhibitory concentration (IC₅₀) values of 256.17 and 212.79 µg/mL respectively.
The antiplasmodial activity was tested in vitro against the plasmodium falciparum strain 3D7 at 100 g/mL and demonstrated substantial antiplasmodial inhibitory activity (IC₅₀ value of 2.76 g/mL). Based on the findings, the isolated extract from *Dipterocarpus littoralis*, α-viniferin, is a potential source to be developed into an antiplasmodial agent [27] (Figure 6).

3.11. Antimicrobial Effects

According to the WHO, antimicrobial resistance (AMR) is one of the most significant threats to global public health. Antimicrobial resistance (AMR) develops when bacteria, viruses, fungi and parasites evolve over time and lose their ability to respond to antibiotics, making infections more difficult to treat, as well as raising the risk of disease transmission, severe illness, and death [104].

According to Schnee et al. [105], crude extracts of *Vitis vinifera* canes have considerable antifungal activities. The six identified compounds (ampelopsin A, hopeaphenol, trans-resveratrol, ampelopsin H, ε-viniferin, and E-vitisin B) are active against *Plasmopara viticola*, the pathogen considered the most damaging, affecting grapevines. Moreover, ε-viniferin exhibited low antifungal activity against *Botrytis cinerea*. Nevertheless, none of the identified compounds has been reported to inhibit the germination of *E. necator* [105].

The study conducted by Yadav et al. [106] indicated that viniferin compounds restrained *S. pneumoniae* growth and destroyed bacteria in biofilms. Viniferin treatment
impairs the membrane integrity of biofilm bacteria, according to scanning electron microscopy (SEM) examination and live/dead biofilm staining of pre-established biofilms. Viniferin affects bacterial cell permeability and eventually kills bacteria, according to crystal violet absorption, total protein, and DNA and RNA release. Therefore, viniferin’s fatal action is purported to cause a change in cell-membrane permeability. Although viniferin is commonly reported to have anti-cancer and anti-obesity effects, the investigators focused on its unique antibacterial and antibiofilm against S. pneumonia, which make viniferin and its derivatives good candidates for the development of novel pneumococcal antimicrobial drugs [106].

Another study reported that the resveratrol dimer (dehydro-δ-viniferin), a natural stilbenoid with a benzofuran core, is a potential antimicrobial agent against Gram-positive bacteria, especially the foodborne pathogen, Listeria monocytogenes [107]. Listeria monocytogenes can infect both humans and animals, although it is difficult to control the pathogen due to its ability to build biofilms. The virus has been isolated from a wide range of foods, including raw milk, cheese, raw meat products and salads, making it extremely common in food production and distribution. This bactere can cause several diseases, mainly gastroenteritis, endocarditis, rhombencephalitis, invasive listeriosis, septicemia, meningitis and neonatal infections; it can also lead to abortion [108]. Mattio et al. [107] utilized various protocols to derive stilbenoid-derived 2,3-diaryl-5-substituted benzofurans and found that key stages, such as the demethylation of phenolic groups, are required. Staphylococcus aureus (S. aureus) ATCC29213 was used to test antibacterial activity and the results showed that 5,5′-(2-(4-hydroxyphenyl)benzofuran-3,5-diyl)bis(benzene-1,3-diol) analogue is an important potential compound for further investigation.

In addition, Rahim et al. [109] tested another form of viniferin, α-viniferin, as a potential antibacterial agent against S. aureus, a multidrug-resistant bacterium that is prone to serious healthcare-associated and community-acquired infections globally. The nasal-colonization bacterium can result in a variety of diseases, ranging from mild to life-threatening, including pneumonia, chronic osteomyelitis, and bacteremia. The aim of the study was to use culture-based procedures to explore the antibacterial efficiency of α-viniferin against the normal nares microflora, S. aureus and methicillin resistance staphylococcus aureus (MRSA). The experiment involved a ten-day clinical trial and indicated that α-viniferin demonstrated 50% minimum inhibitory concentrations (MIC50 values) of 7.8 g/mL in culture broth medium throughout the ten-day clinical experiment. A sterile cotton swab stick was used to deliver α-viniferin three times a day for ten days in the nares. The nasal-swab samples were collected at baseline and after 10 days and evaluated. The number of S. aureus was greatly reduced in the cultures, as further confirmed by the reverse transcriptase polymerase chain reaction (RT PCR)-based analysis (0.01). Furthermore, the 16S ribosomal RNA-based amplicon-sequencing study revealed a reduction from 23.99 to 51.03% in the S. aureus at the genus level. The findings showed that α-viniferin is an effective antibacterial agent against the Staphylococcus group, especially against S. aureus and MRSA, but showed no activity against other nasal microflora. Furthermore, α-viniferin enhanced skin moisture content to maintain skin plasticity and barrier integrity in the absence of toxicity. In conclusion, the research used a clinical trial to demonstrate the clinical effectiveness of viniferin as a possible candidate against S. aureus [109].

According to Mattivi et al. [110], vinifers are a small group of trans-resveratrol oligomers, detected in the Vitaceae family, with antifungal characteristics, thus allowing plants to resist attacks from pathogens. The study was performed by isolating and characterizing the entire class of vinifers accumulated in the leaves of hybrid Vitis vinifera genotypes infected by Plasmopara viticola. Six days after infection, the infected leaves of resistant plants were collected, extracted with methanol and pre-purified using ENV+ and Toyopearl HW 40S resins by flash chromatography.

Seven dimers (six stilbenes and one stilbenoid) were detected in infected leaves. Ampelopsin D, quadrangularin A, E-ε-viniferin and Z-viniferin were four compounds new to the grapevine. Next, four trimers (three stilbenes and one stilbenoid), two of which
(Z-miyabenol C and E-cis-miyabenol C) were found that were new to the grapevine, as well as three tetramer stilbenoids, isoheopeaphenol, ampelopsin H, all new to the grapevine, as well as a vaticanol C-like isomer. Other preformed phenolics are structurally changed in tissues infected with *P. viticola*, as evidenced by the isolation of a dimer derived from the condensation of (+)-catechin with trans-caffeic acid [110].

Ultra-high-performance liquid-chromatography–mass spectrometry (UHPLC-MS) was used to evaluate stilbene-enriched extracts from the waste of *Vitis vinifera* (cane, wood, and root). Eleven stilbenes were identified (ampelopsin A, (E)-piceatannol, pallidol, (E)-resveratrol, hopeaphenol, isoheopeaphenol, (E)-ε-viniferin, (E)-miyabenol C, (E)-ω-viniferin, R2-viniferin and r-viniferin) and quantified. The IC$_{50}$ for *Plasmopara viticola* sporulation growth was calculated. The R-viniferin had the lowest IC$_{50}$ (highest efficacy) against *Plasmopara viticola*, followed by hopeaphenol and R2-viniferin. The antifungal activity of the stilbene extracts was highest in the wood extract, followed by the root extract. Overall, the findings indicate that the four most active chemicals (R-viniferin, R2-viniferin, hopeaphenol, and isoheopeaphenol) of the stilbene complex combinations derived from the *Vitis vinifera* waste found in both wood and roots can be exploited for the development of natural fungicides as a low-cost source of bioactive stilbenes [111].

3.12. Antihelmintic Effects

Viniferin has been investigated for its potential antihelminthic effects. Roy and Giri [22] reported that α-viniferin is an active compound found in *Carex baccans* (*C. baccans*) L., a plant known to have anti-diabetic, anti-inflammatory and anticancer activities. Different tribes in Northeast India have traditionally consumed *C. baccans* to treat intestinal worm infections. In in vitro tests, helminths were exposed to different amounts of α-viniferin (50, 100, and 200 M/mL in physiological buffered saline), followed by measurements of motility and mortality. The activity of vital tegumental enzymes, such as acid phosphatase, alkaline phosphatase and adenosine triphosphatase, was reduced in parasites exposed to α-viniferin in histochemical and biochemical studies. The extensive structural and functional alterations observed in the treated parasites are indicative of the compound’s cestocidal activity. The deformation and destruction of suckers seen in resveratrol-exposed *Raillientina echinobothrida* (*R. echinobothrida*) add to the phytochemical’s anthelmintic potential. The NOS and AChE activities change in *R. echinobothrida* following exposure to resveratrol and α-viniferin imply that both phytochemicals have anthelmintic potential [112].

4. Industrial Application of Viniferin

Stilbenoids are a group of organic compounds with C6-C2-C6 as the structural formula. They are found in a range of plant species, including *Vitis vinifera*; as with those in grapes, they are naturally occurring. Resveratrol is the most prominent and frequently investigated stilbenoid [4], while viniferins are also known as resveratrol derivatives [5]. Some resveratrol derivatives, such as piceatannol, pterostilbene and ε-viniferin have recently piqued the interest of industries [113]. Stilbenes are a family of phenolic secondary metabolites known for their important roles in plant protection and human health [114]. The potential applications of viniferins in medical technology and pharmaceutical industries are essential to health, since resveratrol derivatives have a wide range of positive health effects (anti-inflammatory, antidiabetic, anticancer, antiangiogenic, antimelanogenic, anti-obesity, anti-diarrheal and antioxidant). For example, a substantial number of traditional Chinese medications (TCM) have been shown to contain stilbene α-viniferin and confer some effects on leukemic cells. According to the National Cancer Institute Developmental Therapeutics Program records (NSC 655524), leukemia and central-nervous-system cell lines are responsive to α-viniferin treatments in vitro.

In the agricultural industry, numerous studies have shown that vine shoots, one of the most abundant winery wastes, are useful sources of bioactive compounds, such as stilbenes. The predominant stilbenoids in vine shoots are trans-resveratrol and ε-viniferin,
whose content varies depending on numerous intrinsic and extrinsic factors [114]. Since other sources of stilbenoids, such as peanuts, pistachios, peanut butter and chocolates, can also offer health benefits, consuming them in ideal quantities is recommended [58]. Given the potential and influence of stilbenoids, particularly on plant physiology, the agriculture sector is the most affected in terms of their usage. Overall, when contemplating the industrial applications of stilbenoids, for example, the antifungal properties of resveratrol in various leaves and berries are critical [115].

Viniferin is used for both its nutraceutical and its cosmeceutical effects. According to Malinowska et al. [116], grape canes are viticulture-waste biomasses that contain bioactive polyphenols that are useful in cosmetics. Although various studies have examined the cosmetic properties of E-resveratrol, only a few have investigated the potential of ε-viniferin, the second most abundant ingredient in grape cane extracts (GCE). GCE from polyphenol-rich grape types can be used as a multifunctional cosmetic component. The skin-whitening potential of GCE was compared to those of pure ε-resveratrol and ε-viniferin using a tyrosinase-inhibition assay and the activation capability of the cell-longevity SIRT1 protein of GCE. Overall, the current findings allowed the GCE from polyphenol-rich types to be considered as multifunctional cosmetic components, in compliance with green chemistry principles. For example, the Vitis vinifera-derived ingredients included in the safety assessment are reported to have many possible functions in cosmetic formulations. Vitis Vinifera (grape) seed extract is reported to function as an anti-caries, anti-dandruff, anti-fungal, anti-microbial, antioxidant, flavoring, light stabilizer, oral care, oral-hygiene and sunscreen agent. A panel that reviewed the safety of Vitis vinifera-derived components (n = 24) determined that their application is safe in current cosmetics use and concentrations. The chemicals are most commonly applied as skin conditioners in cosmetics. Antioxidants, flavoring agents, and/or colorants are confirmed to be present in some of these components. Additionally, certain grape compounds have been evaluated for safety as cosmetic additives in the past; others have not [117].

5. Structurally-Related Viniferin Molecules for New Drug Discovery and Development

Various nomenclature and structures exist in the literature, which complicate the identification and classification of stilbenoids, particularly viniferins. Viniferins are oligomers of resveratrol; however, there are two stereochemical centers on the dihydrofuran ring, allowing the formation of four potential stereoisomers. The naming of cis and trans-conformations for hydrogen is an area of confusion and is further complicated when stilbenoids also contain a trans- (E) or cis- (Z) double bond. Determining the absolute configuration (the difference between (+) and (−) viniferins) is more challenging. Due to the challenges in assigning absolute configurations to stilbenoid oligomers, many compounds have been reported, with only their relative configurations assigned thus far [62].

E-δ-viniferin (1) (E-resveratrol dehydrodimer) has been reported to be present in V. vinifera cell-suspension cultures, leaves and wine [115]. Its glycosides, E-δ-viniferin-11-O-β-D glucopyranoside (1a) (resveratrol dehydrodimer 11-O-β-D-glucopyranoside) and E-δ-Viniferin 11′-O-β-D-glucopyranoside (E-resveratrol dehydrodimer 11′-O-β-D-glucopyranoside) (1b), are reported from V. vinifera cell-suspension cultures [118]. Z-δ-viniferin (4) and Z-ε-viniferin (5) are reported from V. vinifera leaves following UV irradiation, while (+)-E-ε-viniferin (6) has been reported in V. heynnea stems and V. vinifera stems, as well as leaves [110].
E-ε-viniferin (7) was reported in V. vinifera leaves, roots, stems and red wine [10]. Z-ω-viniferin (7a, 8a-cis-Z-ε-viniferin) (8) and E-ω-viniferin (7a, 8a-cis-E-ε-viniferin) (9) were reported in V. vinifera leaves [110], whereas Z-ε-viniferin diglucoside (10) and E-ε-viniferin diglucoside (11) were reported in V. vinifera wine [119].
Furthermore, the presence of ε-viniferin diol (Betulifol B) (12) was reported in *V. betulifolia* stems [120] and Viniferifuran (13) (Amurensin H) was reported in *V. amurensis* roots [121].

Several research groups have focused on the synthesis of new resveratrol-derived chemical scaffolds with improved pharmacodynamics and pharmacokinetics with respect to the natural precursors. To develop synthetic procedures in order to investigate their biological activities, some methylated viniferins (14–16) were synthesized and characterized by spectral data [122].
Recently, a collection of dehydro-viniferin analogues were synthesized and evaluated for their antimicrobial activities [107].
A chemical-structure analysis indicated that resveratrol was a polyphenol biphenyl, and that multiple hydroxyl groups affected its biological activities as well as cis- or trans-structures [123–125]. Resveratrol oligomers are characterized by the polymerization of two to eight resveratrol units and are the largest group of oligomeric stilbenes [126]. Resveratrol oligomer polyphenols were mainly isolated from five plant families, namely Vitaceae, Leguminosae, Gnetaceae, Dipterocarpaceae and Cyperaceae [126–129]. Nevertheless, although several studies showed various biochemical and pharmacological properties of resveratrol oligomers, so far, no systematic review has been conducted on these compounds. Their intricate structures and diverse biological activities are of significant interest for drug research and development and may provide promising prospects as cancer-preventive and therapeutic agents [84].

Resveratrol dimers: ε-viniferin (A) δ-viniferin (B), Heimiol A (23), Pallidol (24), Balanocarpol α-H (25), Ampelopsin β-H (26), Malibatol A (27) and Malibatol B (28). The phenol ε-viniferin, first isolated from Vitis vinifera (Vitaceae), is classified as a model for its biosynthesis from resveratrol [127]. Similar to resveratrol, ε-viniferin also attracted attention as a phytoalexin and was reported to have antifungal, antibacterial and antiviral activities. Furthermore, δ-viniferin, an isomer of ε-viniferin, only exists in plants in low concentrations.

Resveratrol trimers: α-viniferin (C), miyabenol C (29), suffruticosol A α-H (30), suffruticosol B β-H (31) and gnetin H (32). Resveratrol trimers are formed by three resveratrol monomers through head-to-ligation or circular structure. The α-viniferin is a stilbene trimer isolated from Caragana snice, Caragana chamlagu and the stem bark of Dryobalanops aromatica [130].
Resveratrol trimers: α-viniferin (C), miyabenol C (29), suffruticosol A α-H (30), suffruticosol B β-H (31) and gnetin H (32). Resveratrol trimers are formed by three resveratrol monomers through head-to-ligation or circular structure. The α-viniferin is a stilbene trimer isolated from Caragana sinese, Caragana chamiag and the stem bark of Dryobalanops aromatica [130].

Resveratrol tetramers: Vaticanol C (33), kobophenol A (34) and hopeaphenol (35) from Vitis vinifera, a dimer, trans-ε-viniferin (33), as well as two tetramers, R2-viniferin (34) and r-viniferin (35) were obtained and evaluated for their cytotoxic activity to human hepatocellular carcinoma (HCC) cell lines p53 wild-type HepG2 and p53-null Hep3B. The distinctive toxicity of R2-viniferin on HepG2 was reported [82]. R-viniferin, also known as vitisin B [131] was found in a variety of grapevine-plant species [62].
trans-δ-viniferin (36) was identified in downy-mildew-infected grapevine leaves and identified by HPLC coupled to mass spectrometry using atmospheric pressure photoionization (APPI–MSn) [132].

An acetyl cholinesterase inhibitor, γ-viniferin (36a), was reported in *Vitis vinifera* and a pharmaceutical composition made out of it was patented [133].
Overall, the focus of this review is on the chemistry and biological action of viniferin, as well as the development of consistent and ecologically friendly ways of commercializing the natural molecule on a large scale, since resveratrol has significant market potential. According to a survey in the Global Resveratrol Market Research Report (2020), the value of the global resveratrol market will reach USD 99.4 million by the end of 2026, as cited in Noviello et al. [114]. Only a small number of the viniferin-derived compounds mentioned above underwent pre-clinical research, which includes very few pharmacological studies. Researchers could forecast a few potential compounds in the near future, at least using in-silico studies; subsequently, they could work on them to develop molecules for clinical studies of various disorders. Future views should therefore emphasize the development of new therapeutics in relation to resveratrol-derived molecules, i.e., viniferins, which are capable of treating various diseases, as crucial sources of pharmaceuticals, as well as in other industries that can benefit humans. Therefore, further research may help to exploit its properties and its potential development into phyto-pharmaceuticals. This research will also have a significant impact on our understanding and provide the tools for novel and successful drug-discovery strategies.

In the Structure 36b and 36c the hydroxyl groups are substituted with methyl and propyl groups and are called “cis viniferins”. When this is treated with 12M HCl in THF gives ampelopsin B [122].
6. Conclusions

The current review presents an all-inclusive literature search on various of viniferin studies through the years, especially on its anti-inflammatory, antipsoriasis, antidiabetic, antiplasmodic, anticancer, antiangiogenic, antioxidant, antimelanogenic, neurodegenerative effects, antiviral, antimicrobial, antifungal, anti-diarrhea, anti-obesity and anthelmintic activities. The review shows the diverse collection of biological activities and possible applications in clinical research of all of the different forms of viniferin, such as α-viniferin, β-viniferin, δ-viniferin, ε-viniferin, γ-viniferin, vitisin A and B. Viniferins are resveratrol derivatives, one of the stilbenoids produced by plants as a defense mechanism in response to microbial attack, poisons, diseases, or UV-radiation. To mitigate the research, the confirmation of viniferin concentrations’ therapeutic efficacy in humans is still required. The pharmaceutical industry faces a significant challenge in applying this molecule clinically; it needs to be studied in greater depth to understand its bioavailability, metabolic pathways and human toxicity and, thus, the need to improve the field of clinical medicine is a challenge in producing commercially viable medicine. It may be quite cheap to produce large quantities while also being relatively safe, non-toxic, cost-effective and widely available. In the context of this review, viniferin has the potential to be used as a treatment for a wide range of human illnesses. Overall, viniferins are useful in medical technology and in the pharmaceutical, agricultural, nutraceutical and cosmeceutical sectors. We are confident that the information in this review will be more beneficial to researchers and industrial stakeholders working on the development of vinferin-based therapeutic medications.

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References
1. Ramawat, K.G.; Mérillon, J.-M. Natural Products: Phytochemistry, Botany and Metabolism of Alkaloids, Phenolics and Terpenes; Springer: Berlin/Heidelberg, Germany, 2013.
2. Riviere, C.; Pawlus, A.D.; Merillon, J.-M. Natural stilbenoids: Distribution in the plant kingdom and chemotaxonomic interest in Vitaceae. Nat. Prod. Rep. 2012, 29, 1317–1333. [CrossRef] [PubMed]
3. Houillé, B.; Besseau, S.; Delanoue, G.; Oudin, A.; Papon, N.; Castre, M.; Simkin, A.J.; Guerin, L.; Coudrauav, V.; Giglioli-Guivarc’h, N. Composition and tissue-specific distribution of stilbenoids in grape canes are affected by downy mildew pressure in the vineyard. J. Agric. Food Chem. 2015, 63, 8472–8477. [CrossRef] [PubMed]
4. Akinwumi, B.C.; Bordun, K.-A.M.; Anderson, H.D. Biological activities of stilbenoids. Int. J. Mol. Sci. 2018, 19, 792. [CrossRef] [PubMed]
5. González-Barrio, R.; Beltrán, D.; Cantos, E.; Gil, M.I.; Espín, J.C.; Tomás-Barberán, F.A. Comparison of ozone and UV-C treatments on the postharvest stilbenoid monomer, dimer, and trimer induction in var. ‘Superior’ white table grapes. *J. Agric. Food Chem.* 2006, 54, 4222–4228. [CrossRef]

6. Dilshara, M.G.; Lee, K.-T.; Kim, H.J.; Lee, H.-J.; Choi, Y.H.; Lee, C.-M.; Kim, L.K.; Kim, G.-Y. Anti-inflammatory mechanism of α-viniferin regulates lipopolysaccharide-induced release of proinflammatory mediators in BV2 microglial cells. *Cell. Immunol.* 2014, 290, 21–29. [CrossRef]

7. Fan, Y.; Zhao, L.; Huang, X.; Jia, Q.; Wang, W.; Gao, M.; Jia, X.; Chang, Y.; Ouyang, H.; He, J. Pharmacokinetic and bioavailability studies of α-viniferin after intravenous and oral administration to rats. *J. Pharm. Biomed. Anal.* 2020, 188, 113376. [CrossRef]

8. Wilkers, A.; Paulsen, J.; Wray, V.; Winterhalter, P. Structures of two novel trimeric stilbenes obtained by horseradish peroxidase catalyzed biotransformation of trans-resveratrol and (−)α-viniferin. *J. Agric. Food Chem.* 2010, 58, 6754–6761. [CrossRef]

9. Mattio, L.M.; Marengo, M.; Parravicini, C.; Eberini, I.; Dallavalle, S.; Bonomi, F.; Iametti, S.; Pinto, A. Inhibition of Pancreatic α-amylase by Resveratrol derivatives: Biological activity and molecular modelling evidence for cooperativity between viniferin enantiomers. *Molecules* 2019, 24, 3225. [CrossRef]

10. Pezet, R.; Perret, C.; Jean-Denis, J.B.; Tabacchi, R.; Gindro, K.; Viret, O. α-Viniferin, a resveratrol dehydrodimer: One of the major stilbenes synthesized by stressed grapevine leaves. *J. Agric. Food Chem.* 2003, 51, 5488–5492. [CrossRef]

11. Cho, H.S.; Lee, J.-H.; Ryu, S.Y.; Joo, S.W.; Cho, M.H.; Lee, J. Inhibition of *Pseudomonas aeruginosa* and *Escherichia coli* O157: H7 by α-viniferin. *Biol. Pharm. Bull.* 2009, 32, 204–207. [CrossRef] [PubMed]

12. Roy, B.; Giri, B.R. Caragasinin C: A new oligostilbene from the roots of *Caragana sinica*. *Bioorganic Med. Chem. Lett.* 2012, 22, 973–976. [CrossRef] [PubMed]

13. Empl, M.T.; Albers, M.; Wang, S.; Steinberg, P. The Resveratrol Tetramer r-Viniferin Induces a Cell Cycle Arrest Followed by Apoptosis in the Prostate Cancer Cell Line LNCaP. *Phytother. Res.* 2015, 29, 1640–1645. [CrossRef]

14. Schuck, F.; Schmitt, U.; Reinhardt, S.; Freese, C.; Lee, I.-S.; Thines, E.; Efferth, T.; Endres, K. Extract of *Caragana sinica* as a multi-lamellar liposomes increases its solubility and its photo-stability and decreases its cytotoxicity on Caco-2 intestinal cells. *Fitoterapia* 2019, 139, 104376. [CrossRef]

15. Saad, N.M.; Sekar, M.; Gan, S.H.; Lum, P.T.; Vaijanathappa, J.; Ravi, S. Resveratrol: Latest scientific evidences of its chemical, biological activities and therapeutic potentials. *Pharmacog. J.* 2014, 69, 1307–1312. [CrossRef]

16. Jeong, W.; Ahn, E.-K.; Oh, J.S.; Hong, S.S. Caragasinin C: A new oligostilbene from the roots of *Caragana sinica*. *Planta Med.* 2006, 72, 6754–6761. [CrossRef]

17. Sim, J.; Iang, H.W.; Song, M.; Kim, J.H.; Lee, S.H.; Lee, S. Potent inhibitory effect of alpha-viniferin on human cytochrome P450. *Food Chem. Toxicol.* 2014, 69, 276–280. [CrossRef]

18. Jeong, W.; Ahn, E.-K.; Oh, J.S.; Hong, S.S. Caragasinin C: A new oligostilbene from the roots of *Caragana sinica*. *J. Asian Nat. Prod. Res.* 2017, 19, 1143–1147. [CrossRef]

19. Empl, M.T.; Albers, M.; Wang, S.; Steinberg, P. The Resveratrol Tetramer r-Viniferin Induces a Cell Cycle Arrest Followed by Apoptosis in the Prostate Cancer Cell Line LNCaP. *Phytother. Res.* 2015, 29, 1640–1645. [CrossRef]

20. Cho, Y.R.; Ahn, E.K.; Park, Y.J.; Park, K.; Hong, S.S.; Seo, D.W.; Oh, J.S. A novel role for α-viniferin in suppressing angiogenesis by blocking the VEGFR-2/p70S6K signaling pathway. *Phytother. Res.* 2020, 34, 2697–2705. [CrossRef]

21. Schuck, F.; Schmitt, U.; Reinhardt, S.; Freese, C.; Lee, I.-S.; Thines, E.; Efferth, T.; Endres, K. Extract of *Caragana sinica* as a potential therapeutic option for increasing alpha-secretase gene expression. *Phytochemistry* 2015, 122, 1027–1036. [CrossRef]

22. Roy, B.; Giri, B.R. α-Viniferin-induced structural and functional alterations in Raillietina echinobothrida, a poultry tapeworm. *Microsc. Microanal.* 2015, 21, 377–384. [CrossRef] [PubMed]

23. Lee, S.-H.; Shin, N.-H.; Kang, S.-H.; Park, J.S.; Chung, S.R.; Min, K.R.; Kim, Y. α-Viniferin: A prostaglandin H2 synthase inhibitor from root of Carex humilis. *Planta Med.* 2019, 64, 204–207. [CrossRef] [PubMed]

24. Chung, E.Y.; Kim, B.H.; Lee, M.K.; Yun, Y.-P.; Lee, S.H.; Min, K.R.; Kim, Y. Anti-inflammatory effect of the oligomeric stilbene α-viniferin and its mode of the action through inhibition of cyclooxygenase-2 and inducible nitric oxide synthase. *Planta Med.* 2003, 69, 710–714. [PubMed]

25. Arora, J.; Roat, C.; Goyal, S.; Ramawat, K.G. High stilbenes accumulation in root cultures of *Cayratia triloba* (L.) Domini grown in shake flasks. *Acta Physiol. Plant.* 2009, 31, 1307–1312. [CrossRef]

26. Bala, A.; Kollmann, A.; Ducrot, PH.; Majira, A.; Kerhaos, L.; Leroux, P.; Delorme, R.; Einhorn, J. Cis α-Viniferin: A New Antifungal Resveratrol Dehydrodimer from Cyphomandra crotalariaeoides Roots. *J. Phytopathol.* 2000, 148, 29–32. [CrossRef]

27. Lulan, T.Y.; Fatmawati, S.; Santoso, M.; Ersam, T. α-Viniferin as a potential antidiabetic and antiplasmodal extracted from Dipterocarpos littoralis. *Heliyon* 2020, 6, e04102. [CrossRef]

28. Ahmat, N.; Wibowo, A.; Mohamad, S.A.S.; Low, A.L.M.; Sufian, A.S.; Yusof, M.I.M.; Latip, J. A new symmetrical tetramer oligostilbenoid containing tetrahydrofuran ring from the stem bark of Dryobalanops lanceolata. *J. Asian Nat. Prod. Res.* 2014, 16, 1099–1107. [CrossRef]

29. Moriyama, H.; Moriyama, N.; Ninomiya, K.; Morikawa, T.; Hayakawa, T. Inhibitory effects of oligostilbenoids from the bark of *Shorea roxburghii* on malignant melanoma cell growth: Implications for novel topical cancer biocides. *Biol. Pharm. Bull.* 2016, 39, 1675–1682. [CrossRef]

30. Ge, H.M.; Huang, B.; Tan, S.H.; Shi, D.H.; Song, Y.C.; Tan, R.X. Bioactive oligostilbenoids from the stem bark of *Hopea exalata*. *J. Nat. Prod.* 2006, 69, 1800–1802. [CrossRef]
55. Goufo, P.; Singh, R.K.; Cortez, I. A reference list of phenolic compounds (including stilbenes) in grapevine (Vitis vinifera L.) roots, woods, canes, stems, and leaves. Antioxidants 2020, 9, 398. [CrossRef]
56. Becker, L.; Bellow, S.; Carré, V.; Latouche, G.; Poutaraud, A.; Merdinoglu, D.; Brown, S.C.; Cerovic, Z.G.; Chaimbault, P. Correlative analysis of fluorescent phytoalexins by mass spectrometry imaging and fluorescence microscopy in grapevine leaves. Anal. Chem. 2017, 89, 7099–7106. [CrossRef]
57. Brüsson, S.; Maillot, P.; Schellenbaum, P.; Walter, B.; Gindre-Benbrahim, L. Arbuscular mycorrhizal symbiosis stimulates key genes of the phenylpropanoid biosynthesis and stilbenoid production in grapevine leaves in response to downy mildew and grey mould infection. Phytochemistry 2016, 131, 92–99. [CrossRef]
58. Guerrero, R.F.; Cantos-Villar, E.; Puertas, B.; Richard, T. Daily preharvest UV-C light maintains the high stilbenoid concentration in grapes. J. Agric. Food Chem. 2016, 64, 5139–5147. [CrossRef]
59. Esatbeyoglu, T.; Ewald, P.; Yasui, Y.; Yokokawa, H.; Wagner, A.E.; Matsugo, S.; Winterhalter, P.; Rimbach, G. Chemical characterization, free radical scavenging, and cellular antioxidant and anti-inflammatory properties of a stilbenoid-rich root extract of Vitis vinifera. Oxidative Med. Cell. Longev. 2016, 2016, 8591286. [CrossRef]
60. Qsaib, S.; Mateus, N.; Ibkal, F.E.-z.; Rifai, L.A.; De Freitas, V.; Koussa, T. Direct identification and characterization of phenolic compounds from crude extracts of berries and internodes of grapevine (Vitis vinifera cv Merlot). Nat. Prod. Commun. 2014, 9, 1934578X1400901110. [CrossRef]
61. Lambert, C.; Richard, T.; Renouf, E.; Bisson, J.; Waffo-Tine, V.; Bordenave, L.; Ollat, N.; Métrion, J.-M.; Cluzet, S. Comparative analyses of stilbenoids in canes of major Vitis vinifera L. cultivars. J. Agric. Food Chem. 2013, 61, 11392–11399. [CrossRef]
62. Pawlus, A.D.; Waffo-Tine, V.; Shaver, J.; Métrie, J.-M. Stilbenoid chemistry from wine and the genus Vitis, a review. Oeno One 2012, 46, 57–111. [CrossRef]
63. Privat, C.; Telo, J.P.; Bernardes-Genisson, V.; Vieira, A.; Souchard, J.P.; Nepveu, F. Antioxidant properties of trans-ε-viniferin as compared to stilbene derivatives in aqueous and nonaqueous media. J. Agric. Food Chem. 2002, 50, 1213–1217. [CrossRef]
64. Sahidin, I.; Wahyuni, W.; Malaka, M.; Imran, I. Antibacterial and cytotoxic potencies of stilbene oligomers from stem barks of baoti (Dryobalanops laneolata) growing in Kendari, Indonesia. Asian J. Pharm. Clin. Res. 2017, 10, 139–143.
65. Kitanaka, S.; Ikezawa, T.; Yamasaki, K.; Yamanouchi, S.; Takida, M.; Sung, H.K.; Kim, I.H. (+)-α-viniferin, an anti-inflammatory compound from Caragana chamaglu root. Chem. Pharm. Bull. 1990, 38, 432–435. [CrossRef]
66. Teng, B.-H.; Zhu, Q.-B.; Fan, Y.-Y.; Yao, C.-S. Total synthesis of the active resveratrol dimer dehydro-ε-viniferin. J. Asian Nat. Prod. Res. 2020, 22, 947–955. [CrossRef]
67. Langcake, P.; Pryce, R. A new class of phytoalexins from grapevines. Experientia 1977, 33, 151–152. [CrossRef]
68. Courtois, A.; Jourdès, M.; Dupin, A.; Lapèze, C.; Renouf, E.; Blais, B.; Teisseder, P.-L.; Métrie, J.-M.; Richard, T.; Krisa, S. In vitro glucuronidation and sulfation of ε-viniferin, a resveratrol dimer, in humans and rats. Molecules 2017, 22, 733. [CrossRef] [PubMed]
69. Willenberg, I.; Brauer, W.; Empl, M.T.; Schebb, N.H. Development of a rapid LC-UV method for the investigation of chemical and metabolic stability of resveratrol oligomers. J. Agric. Food Chem. 2012, 60, 7844–7850. [CrossRef] [PubMed]
70. Courtois, A.; Atrié, C.; Marchal, A.; Hornedo-Ortega, R.; Lapèze, C.; Faure, C.; Richard, T.; Krisa, S. Tissular distribution and metabolism of trans-ε-viniferin after intraperitoneal injection in rat. Nutrients 2018, 10, 1660. [CrossRef] [PubMed]
71. Mao, P.; Lei, Y.; Zhang, T.; Ma, C.; Jin, B.; Li, T. Pharmacokinetics, bioavailability, metabolism and excretion of δ-viniferin in rats. Acta Pharm. Sin. B 2016, 6, 243–252. [CrossRef] [PubMed]
72. Matsuda, H.; Asao, Y.; Nakamura, S.; Hamao, M.; Sugimoto, S.; Hongo, M.; Pongpiriyadacha, Y.; Yoshikawa, M. Antidiabetogenic constituents from the Thai traditional medicine Cotylelobium melanoxylon. Chem. Pharm. Bull. 2009, 57, 487–494. [CrossRef]
73. Ninomiya, K.; Chaiech, S.; Kunikata, Y.; Yagi, R.; Pongpiriyadacha, Y.; Muraoka, O.; Morikawa, T. Quantitative determination of stilbenoids and dihydroscolocoumarins in Shorea roxburghii and evaluation of their hepatoprotective activity. Int. J. Mol. Sci. 2017, 18, 451. [CrossRef]
74. Ha, D.T.; Chen, Q.C.; Hung, T.M.; Youn, U.J.; Ngoc, T.M.; Thuong, P.T.; Kim, H.J.; Seong, Y.H.; Min, B.S.; Bae, K. Stilbenes and ologostilbenes from leaf and stem of Vitis amurensis and their cytotoxic activity. Arch. Pharmacal Res. 2009, 32, 177–183. [CrossRef]
75. Sung, S.H.; Kang, S.Y.; Lee, K.Y.; Park, M.J.; Kim, J.H.; Park, J.H.; Kim, Y.C.; Kim, J.; Kim, Y.C. (+)-Alpha-viniferin, a stilbene trimer from Caragana chamaglu, inhibits acetylcholinesterase. Biol. Pharm. Bull. 2002, 25, 125–127. [CrossRef]
76. Vion, E.; Pagé, G.; Bourdeaud, E.; Paccalin, M.; Guillard, J.; Bilan, A.R. Trans ε-viniferin is an amyloid-β disaggregating and anti-inflammatory drug in a mouse primary cellular model of Alzheimer’s disease. Mol. Cell. Neurosci. 2018, 88, 1–6. [CrossRef]
77. Chung, E.Y.; Roh, E.; Kwak, J.-A.; Lee, H.-S.; Lee, S.H.; Lee, C.-K.; Han, S.-B.; Kim, Y. α-Viniferin suppresses the signal transducer and activation of transcription-1 (STAT-1)–inducible inflammatory genes in Interferon–γ–stimulated macrophages. J. Pharmacol. Sci. 2010, 112, 405–414. [CrossRef]
78. Liu, R.; Zhang, Y.; Yao, X.; Wu, Q.; Wei, M.; Yan, Z. ε-Viniferin, a promising natural oligostilbene, ameliorates hyperglycemia and hyperlipidemia by activating AMPK in vivo. Food Funct. 2020, 11, 10084–10093. [CrossRef]
79. Oranje, P.; Gouka, R.; Burggraaff, L.; Vermeer, M.; Chalet, C.; Duchateau, G.; van der Pijl, P.; Geldof, M.; de Roo, N.; Clauser, F. Novel natural and synthetic inhibitors of solute carriers SGLT1 and SGLT2. Pharmacol. Res. Perspect. 2019, 7, e00504. [CrossRef]
80. Özdemir, F.; Apaydin, E.; Önder, N.I.; Şen, M.; Ayirim, A.; Öğünç, Y.; Incész, Z. Apoptotic effects of ε-viniferin in combination with cis-platin in C6 cells. Cytotechnology 2018, 70, 1061–1073. [CrossRef]
81. Özdemir, F.; Akalin, G.; Şen, M.; Önder, N.I.; Işcan, A.; Kutlu, H.M.; Incesu, Z. Towards Novel anti-tumor strategies for hepatic cancer: ε-Viniferin in combination with vincristine displays pharmacodynamic synergy at lower doses in HepG2 Cells. OMICS J. Integr. Biol. 2014, 18, 324–334. [CrossRef]

82. Aja, I.; Ruiz-Larrea, M.B.; Courtois, A.; Krissa, S.; Richard, T.; Ruiz-Sanz, J.-I. Screening of natural stilbene oligomers from Vitis vinifera for anticancer activity on human hepatocellular carcinoma cells. Antioxidants 2020, 9, 469. [CrossRef]

83. Empl, M.; Macke, S.; Winterhalter, P.; Puff, C.; Lapp, S.; Stoica, G.; Baumgärtner, W.; Steinberg, P. The growth of the canine glioblastoma cell line D-GBM and the canine histiocytic sarcoma cell line DH82 is inhibited by the resveratrol oligomers hoophephanol and r2-viniferin. Vet. Comp. Oncol. 2014, 12, 149–159. [CrossRef]

84. González-Sarrias, A.; Gromek, S.; Niesen, D.; Seeram, N.P.; Henry, G.E. Resveratrol oligomers isolated from Carex species inhibit growth of human colon tumorigenic cells mediated by cell cycle arrest. J. Agric. Food Chem. 2011, 59, 8632–8638. [CrossRef] [PubMed]

85. Chai, B.-y.; Gong, F.-K.; Chen, Z.-H.; Li, Z.-X.; Zhang, B. System Prediction and Validation of TCM for Chronic Myeloid Leukaemia Treatment from the Perspective of Low-Toxicity Chemotherapy: A Stilbene α-Viniferin Has a Proapoptotic Effect on K562 Cells via the Mitochondrial Pathway. Evid. Based Complementary Altern. Med. 2020, 20196962. [CrossRef] [PubMed]

86. Cheng, K.; Liu, X.; Chen, L.; Lv, J.-M.; Qu, F.-J.; Pan, X.-W.; Li, L.; Cui, X.-G.; Gao, Y.; Xu, D.-F. α-Viniferin activates autophagic apoptosis and cell death by reducing glucocorticoid receptor expression in castration-resistant prostate cancer cells. Med. Oncol. 2018, 35, 105. [CrossRef] [PubMed]

87. Nivelle, L.; Aires, V.; Rioulot, D.; Martiny, L.; Tarpin, M.; Delmas, D. Molecular analysis of differential antiproliferative activity of resveratrol, epsilon viniferin and labruscena on melanoma cells and normal dermal cells. Food Chem. Toxicol. 2018, 116, 323–334. [CrossRef] [PubMed]

88. Wu, C.W.; Nakamoto, Y.; Hisatome, T.; Yoshida, S.; Miyazaki, H. Resveratrol and its dimers ε-viniferin and δ-viniferin in red wine protect vascular endothelial cells by a similar mechanism with different potency and efficacy. Kaohsiung J. Med. Sci. 2020, 36, 535–542. [CrossRef]

89. Arraki, K.; Totoson, P.; Decendit, A.; Badoc, A.; Zedet, A.; Jolibois, J.; Pudlo, M.; Demougeot, C.; Girard-Thernier, C. Cypereaceae species are potential sources of natural mammalian arginase inhibitors with positive effects on vascular function. J. Nat. Prod. 2017, 80, 2432–2438. [CrossRef]

90. Lin, Y.-S.; Lu, Y.-L.; Wang, G.-J.; Chen, L.-G.; Wen, C.-L.; Hou, W.-C. Ethanic extracts and isolated compounds from small-leaf grape (Vitis thunbergii var. taiwania) with antihypertensive activities. J. Agric. Food Chem. 2012, 60, 7435–7441. [CrossRef]

91. Zghonda, N.; Yoshida, S.; Ezaki, S.; Otake, Y.; Murakami, C.; Mliki, A.; Ghorganel, A.; Miyazaki, H. ε-Viniferin is more effective than its monomer resveratrol in improving the functions of vascular endothelial cells and the heart. Biosc. Biotechnol. Biochem. 2012, 76, 954–960. [CrossRef]

92. Yun, C.-Y.; Ko, S.M.; Choi, Y.P.; Kim, B.J.; Lee, J.; Kim, J.Y.; Song, J.Y.; Kim, S.-H.; Hwang, B.Y. α-Viniferin improves facial hyperpigmentation via accelerating feedback termination of cAMP/PKA-signalized phosphorylation circuit in facultative melanogenesis. Thranostics 2018, 8, 2031. [CrossRef]

93. Yu, B.; Jiang, Y.; Zhang, B.; Yang, H.; Ma, T. Resveratrol dimer trans-ε-viniferin prevents rotoviral diarrhea in mice by inhibition of the intestinal calcium-activated chloride channel. Pharmacol. Res. 2018, 129, 453–461. [CrossRef]

94. Yu, B.; Xie, R.; Jin, L.; Tian, X.; Niu, Y.; Ma, T.; Yang, H. trans-δ-Viniferin inhibits Ca2+-activated Cl– channels and improves diarrhea symptoms. Fitoterapia 2019, 139, 116376. [CrossRef]

95. Caillaud, M.; Guillard, J.; Richard, D.; Milin, S.; Chassaing, D.; Paccalin, M.; Page, G.; Rioux Bilan, A. Trans ε-viniferin decreases amyloid deposits and inflammation in a mouse transgenic Alzheimer model. PLOS ONE 2019, 14, e0212663. [CrossRef]

96. Richard, T.; Poupard, P.; Nassra, M.; Papastamoulis, Y.; Iglesias, M.-L.; Krisa, S.; Waffo-Teguo, P.; Merillon, J.-M.; Monti, J.-P. Protective effect of ε-viniferin on β-amyloid peptide aggregation investigated by electrospray ionization mass spectrometry. Bioorganic Med. Chem. 2011, 19, 3152–3155. [CrossRef]

97. Fu, J.; Jin, J.; Cichewicz, R.H.; Hageman, S.A.; Ellis, T.K.; Xiang, L.; Peng, Q.; Jiang, M.; Arbez, N.; Hotaling, K. trans-(−)-ε-Viniferin increases mitochondrial sirtuin 3 (SIRT3), activates AMP-activated protein kinase (AMPK), and protects cells in models of Huntington disease. J. Biol. Chem. 2012, 287, 24460–24472. [CrossRef]

98. Zhang, S.; Ma, Y.; Feng, J. Neuroprotective mechanisms of ε-viniferin in a rotenone-induced cell model of Parkinson’s disease: Significance of SIRT3-mediated FOXO3 deacetylation. Neuro Regen. Res. 2020, 15, 2143.

99. Li, X.; Xie, Y.; Xie, H.; Yang, J.; Chen, D. π- π Conjugation Enhances Oligostilbene’s Antioxidant Capacity: Evidence from α-Viniferin and Caraphenol A. Molecules 2018, 23, 694. [CrossRef]

100. Kim, H.J.; Chang, E.J.; Bae, S.J.; Shim, S.M.; Park, H.D.; Rhee, C.H.; Park, J.H.; Choi, S.W. Cytotoxic and antimutagenic stilbenes from seeds of Paeonia lactiflora. Arch. Pharmacal Res. 2002, 25, 293–299. [CrossRef]

101. Kovacic, P.; Somanathan, R. Multifaceted approach to resveratrol bioactivity: Focus on antioxidant action, cell signaling and safety. Oxidative Med. Cell. Longev. 2010, 3, 86–100. [CrossRef]

102. Kim, H.J.; Chang, E.J.; Cho, S.H.; Chung, S.K.; Park, H.D.; Choi, S.W. Antioxidative activity of resveratrol and its derivatives isolated from seeds of Paeonia lactiflora. Biosci. Biotechnol. Biochem. 2002, 66, 1990–1993. [CrossRef]

103. Zekar, L.; Sharman, T. Plasmodium Falciparum Malaria. StatPearls: Treasure Island, FL, USA, 2022.

104. WHO. Antimicrobial Resistance. Available online: https://www.who.int/health-topics/antimicrobial-resistance (accessed on 25 May 2022).
105. Schnee, S.; Queiroz, E.E.; Voinescu, F.; Marcourt, L.; Dubuis, P.-H.; Wolfender, J.-L.; Gindro, K. Vitis vinifera canes, a new source of antifungal compounds against Plasmopara viticola, Erysiphe necator, and Botrytis cinerea. J. Agric. Food Chem. 2013, 61, 5459–5467. [CrossRef]

106. Yadav, M.K.; Mailar, K.; Nagarajappar Masagalli, J.; Chae, S.-W.; Song, J.-J.; Choi, W.J. Ruthenium Chloride—Induced Oxidative Cyclization of Trans-Resveratrol to (+)-ε-Viniferin and Antimicrobial and Antibiofilm Activity Against Streptococcus pneumoniae. Front. Pharmacol. 2019, 10, 890. [CrossRef]

107. Mattio, L.M.; Pinna, C.; Catinella, G.; Musso, L.; Pedersen, K.J.; Krogfelt, K.A.; Dallavalle, S.; Pinto, A. Synthesis and Antimicrobial Activity of δ-Viniferan Analogues and Isosteres. Molecules 2021, 26, 7594. [CrossRef] [PubMed]

108. Thakur, M.; Asrani, R.K.; Patial, V. Listeria monocytogenes: A food-borne pathogen. In Foodborne Diseases; Elsevier: Amsterdam, The Netherlands, 2018; pp. 157–192.

109. Rahim, M.A.; Seo, H.; Kim, S.; Jeong, Y.K.; Tajdozian, H.; Kim, M.; Lee, S.; Song, H.-Y. A Clinical Trial to Evaluate the Efficacy of α-Viniferin in Staphylococcus aureus–Specific Decolonization without Depleting the Normal Microbiota of Nares. Pol. J. Microbiol. 2021, 70, 117. [CrossRef] [PubMed]

110. Mattivi, F.; Vrhovsek, U.; Malacarne, G.; Masuero, D.; Zulini, L.; Stefanini, M.; Moser, C.; Velasco, R.; Guella, G. Profiling of resveratrol oligomers, important stress metabolites, accumulating in the leaves of hybrid Vitis vinifera (Merzling × Teroldego) genotypes infected with Plasmodora viticola. J. Agric. Food Chem. 2011, 59, 5364–5375. [CrossRef] [PubMed]

111. Gabaston, J.; Cantos-Villar, E.; Biais, B.; Waffo-Teguo, P.; Renouf, E.; Corio-Costet, M.-F.; Richard, T.; Mérillon, J.-M. Stilbenes from Vitis vinifera L. waste: A sustainable tool for controlling Plasmodora viticola. J. Agric. Food Chem. 2017, 65, 2711–2718. [CrossRef] [PubMed]

112. Giri, B.R.; Roy, B. Resveratrol-and α-viniferin-induced alterations of acetylcholinesterase and nitric oxide synthase in Raillietina echinobothrida. Parasitol. Res. 2015, 114, 3775–3781. [CrossRef]

113. Arbo, B.D.; André-Miral, C.; Nasre-Nasser, R.G.; Schmith, L.E.; Santos, M.G.; Costa-Silva, D.; Muccilo-Baisch, A.L.; Hort, M.A. Resveratrol derivatives as potential treatments for Alzheimer’s and Parkinson’s disease. Front. Aging Neurosci. 2020, 12, 103. [CrossRef]

114. Noviello, M.; Caputi, A.F.; Squeo, G.; Paradiso, V.M.; Gambacorta, G.; Caponio, F. Vine Shoots as a Source of Trans-Resveratrol and α-viniferin: A Study of 23 Italian Varieties. Foods 2022, 11, 553. [CrossRef]

115. Jeandet, P.; Chaudruc, D.; Robillard, B.; Peters, F.; Tusseau, D.; Conreux, A.; Duteurte, B. Determination of the trans-resveratrol content of Champagne wines by reversed-phase HPLC. OENO One 2006, 40, 117–119. [CrossRef]

116. Malinowska, M.A.; Billet, K.; Drouet, S.; Munsch, T.; Unlubayir, M.; Tungmunnithum, D.; Giglioli-Guivarc’h, N.; Hano, C.; Lanoue, A. Grape can extracts as multifunctional rejuvenating cosmetic ingredient: Evaluation of sirtuin activity, tyrosinase inhibition and bioavailability potential. Molecules 2020, 25, 2203. [CrossRef]

117. Fiume, M.M.; Bergfeld, W.F.; Belsito, D.V.; Hill, R.A.; Klaassen, C.D.; Liebler, D.C.; Marks Jr, J.G.; Shank, R.C.; Slaga, T.J.; Snyder, P.W. Safety assessment of Vitis vinifera (Grape)-derived ingredients as used in cosmetics. Int. J. Toxicol. 2014, 33, 485–835. [CrossRef]

118. Waffo-Teguo, P.; Lee, D.; Cuendet, M.; Maffi, F. An oligostilbenol from Riesling roots. Phytochemistry 1995, 38, 1501–1504. [CrossRef]
132. Jean-Denis, J.B.; Pezet, R.; Tabacchi, R. Rapid analysis of stilbenes and derivatives from downy mildew-infected grapevine leaves by liquid chromatography–atmospheric pressure photoionisation mass spectrometry. *J. Chromatogr. A* **2006**, *1112*, 263–268. [CrossRef] [PubMed]

133. Jo, T.H.; Woo, S.S.; Cha, J.; Kim, D.S.; Do, S.; Ryu, J.; Oh, M. Inhibitor for Acetylcholinesterase Containing Gamma-Viniferin or Visitin a. China Patent WO2006025708A2, 2 September 2005. Available online: https://patents.google.com/patent/WO2006025708A2/en (accessed on 2 August 2022).