Journal of Berry Research 3 (2013) 181–196
DOI:10.3233/JBR-130062
IOS Press

Invited Review

Beyond resveratrol: A review of natural stilbenoids identified from 2009–2013

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Received 25 November 2013; accepted 2 December 2013

Abstract. Polyphenols constitute a large chemical class of phytochemicals among which the stilbenoid sub-class has attracted significant attention due to their elaborate structural diversity and biological activities. Resveratrol, a well-known stilbene, has been extensively studied due to its wide range of biological activities and occurrence in plant foods, including grape and some berries. Apart from the intact resveratrol molecule and closely related analogs, this compound can be regarded as a monomer which occurs as a primary building block for subsequent polymerization which leads to extensive structural diversity. Consequently, stilbenoids exhibit a vast array of polymerization and oligomeric construction, with over 60 such naturally occurring stilbenes being isolated and identified in the last five years alone, adding to the hundreds which are already known to date. This review updates the literature on natural stilbenoids which have been isolated and identified since 2009 and discusses the biological activities of this sub-class of bioactive polyphenols as a whole.

Keywords: Polyphenols, stilbenes, resveratrol, oligomers, bioactive

1. Introduction

1.1. Stilbenes

Over the past few decades, significant research attention has been directed towards the investigation of polyphenols, a large class of secondary metabolites which are abundant in plants and plant-derived foods including grapes, and some berries and nuts. Within the large chemical class of (poly)phenolic compounds, the stilbenoids, which occur in ca. 33 plant families, have been extensively studied both as pure compounds and enriched plant derived extracts [1, 2]. Consequently, their potential applications either as botanical supplements or as active constituents in medicinal and cosmetic preparations have been evaluated [1]. Notably, stilbenoids have been isolated and studied as monomers and oligomers, as well as glycosylated derivatives with the best known example being resveratrol as well as others including α-viniferin, and astringin (see Fig. 1) [2].

The carbon skeleton of stilbenes occurs as a C6–C2–C6 unit, namely, a 1, 2-diphenylethylene moiety, however, the commonly hydroxylated derivatives provide the class with a wide variety of polymerization and oligomeric construction. Stilbenes are produced by plants as a woody metabolite, as well as constitutive and inductive defense agents. The antimicrobial activity of plant stilbenes, and the nature of these compounds as being both constitutive and

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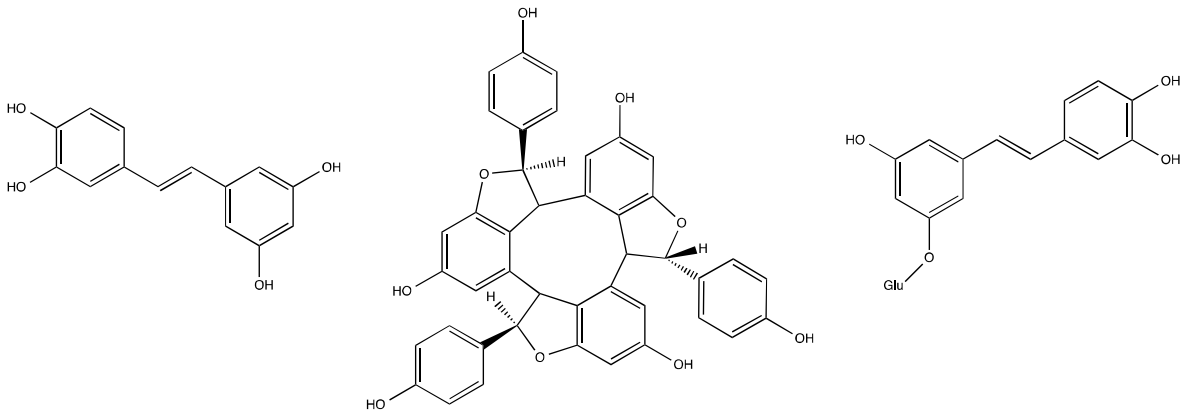

Fig. 1. Stilbene derivatives highlighting the common monomer, resveratrol (left), a trimer α-viniferin (center), and a glycosylated derivative, astringin (right).

inducible secondary metabolites, suggests that their *in situ* concentrations are a good indication of disease resistance [2]. Historically, significant research has focused on the role of stilbenes and their activity as anti-bacterial agents, antioxidants, anti-inflammatory agents, anticancer and cancer chemopreventive agents, and more recently their role in the regulation of several human degenerative diseases [3–9].

1.2. Occurrence of resveratrol in berries

The occurrence of stilbenes in berries has largely been reported for the so called 'model stilbenoid' compound, namely, resveratrol (Fig. 1) which was originally isolated from the roots of *Veratrum grandiflorum* in 1940 [10]. Notably, as mentioned previously, in nearly every case highlighted in the current review, resveratrol has been used as the primary building block during the polymerization into larger stilbenes.

In many grape varieties, *trans*-resveratrol is a phytoalexin produced to combat the growth of fungal pathogens such as *Botrytis cinerea*, a necrotic fungus whose most notable host is wine grapes [11]. Resveratrol's presence in *Vitis vinifera* grapes is also constitutive, with a natural accumulation in the skin of ripe berries. In muscadine grapes (*Vitis rotundifolia*), a species native to the southeastern United States, resveratrol has been isolated from the seeds as well as the skin [12]. The concentration of resveratrol present in grape skins varies with the grape cultivar, its geographic origin, and exposure to infections. As red wine is fermented with the skins, it contains a higher concentration of resveratrol as compared to white wines. Depending on the grape variety, the concentration of resveratrol in red wines ranges between 0.2–5.8 mg/L, with a direct correlation in the amount of fermentation time a wine spends in contact with the grape skins [13].

Resveratrol has also been detected in several other berry varieties. It has been identified in blueberry, bilberry, cowberry, red currant, cranberry and strawberries; however these berries contained less than 10% of that present in grapes [14, 15]. The content of *trans*-resveratrol in the fresh weight of the above fruit ranges from 3–30 μg/g [15]. Additionally, it has been reported that heating and cooking the berries will contribute to the degradation of resveratrol [14].

1.3. Occurrence of resveratrol and other stilbenes in non-berry food sources

Resveratrol and polymeric stilbenes have been found in other food sources apart from the various berry varieties. Interestingly, a source of resveratrol derivatives is peanuts (*Arachis hypogea*), in particular, sprouted peanuts, where the resveratrol content rivals that of grape skins. Depending upon peanut cultivar, the resveratrol content ranges from 2.3–4.5 μg/g before sprouting and 11.7–25.7 μg/g after sprouting [16]. Two new resveratrol dimers were recently

isolated from peanut seeds and are discussed later in this review [17]. Cocoa powder, baking chocolate, and dark chocolate have also been reported to contain small concentrations of resveratrol in normal consumed quantities i.e. 0.35–1.85 mg/kg [18].

1.4. Previous review articles on stilbenes

To date, there are several reviews available on the pharmacological benefits of resveratrol and its analogs [19–21]. Most recently, in 2009, Shen and co-workers have published a comprehensive examination of the novel chemistry related to stilbenes discovered over the time period from 1995 to late 2008 [2]. Therefore, in this review, we examine new stilbene chemistry that has been reported from 2009 to late 2013, bridging the gap in period previously reported by Shen and co-workers [2]. During the current period covered herein, over 60 naturally occurring stilbenes have been isolated and identified with structures ranging from glycosylated monomers to a hexamer. Current scientific interest in determining the biological activity of this class of compounds will also be highlighted.

2. Stilbenes isolated and identified since 2009

2.1. Compound classification

While more complex classification systems for stilbenes have been proposed by Sootheeswaran and Pasupathy [22], for the purpose of this review, the novel chemistry isolated has been grouped into: monomers, dimers, trimers, tetramers, and hexamer units. Additionally there was one norstilbene isolated, as well as stilbenes containing glycoside moieties which are differentiated based on their carbon-carbon or carbon-oxygen connectivity. These compounds are discussed below.

2.2. Stilbene monomers

Only two stilbene monomer derivatives were isolated during this time period. While the stilbene structure provides a large variety in the ways of polymerization, the diphenylethylene unit does not have many locations for potential modifications into novel monomers. Although the discovery of new monomers is less common, two prenylated derivatives were successfully isolated and identified. From black skin peanut seeds challenged with the fungal strain *Rhizopus oligoporus*, Liu et al. [23] isolated the methoxy-prenylated derivative shown in Fig. 2 (compound shown on the left). Shan and co-workers [24] successfully isolated the additional monomer, cudrastilbene, from the roots of *Cudrania tricuspidata*, an ethnobotanical plant used commonly in China, Korea, and Japan for medicinal purposes. The two new compounds can be found in Fig. 2.

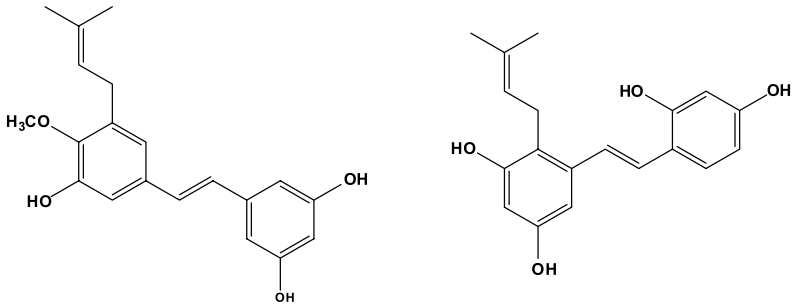

Fig. 2. 3,5,3′-trihydroxy-4′-methoxy-5′-isopentenylstilbene (left) and cudrastilbene (right) isolated from fungal challenged black skin peanut seeds and *Cudrania tricuspidata* respectively.

2.3. Stilbene dimers

During the time period of this review, a total of 17 dimeric stilbenes were reported. Among the oligomeric stilbenes, the resveratrol monomer is most commonly used for construction. There are many combinations of C–C and C–O bonding patterns that can arise during the polymerization of the resveratrol units. However, the most common is the formation of the benzofuran moiety. This is apparent, as it is seen in almost all of the newly isolated stilbene dimers.

Arguably, most structurally unique of the dimers are the two phytoalexins isolated by Sobolev et al. [17]. Interestingly, the production of these two compounds was induced by subjecting peanut seeds (*Arachis hypogaea*) to fungal (*Aspergillus caelatus*) infection. Isolation and purification of the fungal challenged seed's chemical constituents resulted in the discovery of two new prenylated dimers of resveratrol, arahypin 6 and 7 (Fig. 3).

Plants of the genus *Gnetum* have previously been reported to be rich sources of oligomeric stilbene derivatives [25]. Similarly, in the current time period of 2009–2013, for this review, this was also true with the isolation and characterization of macrostachyols C and D from the roots of *Gnetum macrostachyum* (Fig. 4) [25]. Interestingly, macrostachyol C does not contain a benzofuran moiety as observed in the majority of the stilbene dimers.

The genus *Shorea* had previously been reported to contain stilbenoids, although the work done by Patcharamun and co-workers in 2011 was the first phytochemical investigation conducted on *Shorea ruxburghii* [26], a medicinal plant used in India. This work resulted in the isolation of roxburghiol A (Fig. 5).

Vaterioside A (Fig. 6), was isolated from the leaves of *Vateria indica* by Ito et al. [27]. Previously, studies have shown that this carbon skeleton can be produced by exposing ε-viniferin to photo-oxidative conditions [28]. However,

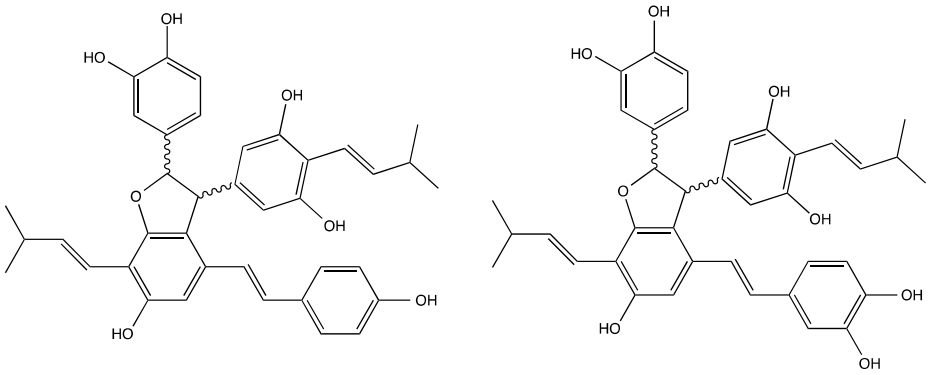

Fig. 3. Arahypin 6 (left) and arahypin 7 (right) isolated from peanuts (*Arachis hypogaea*).

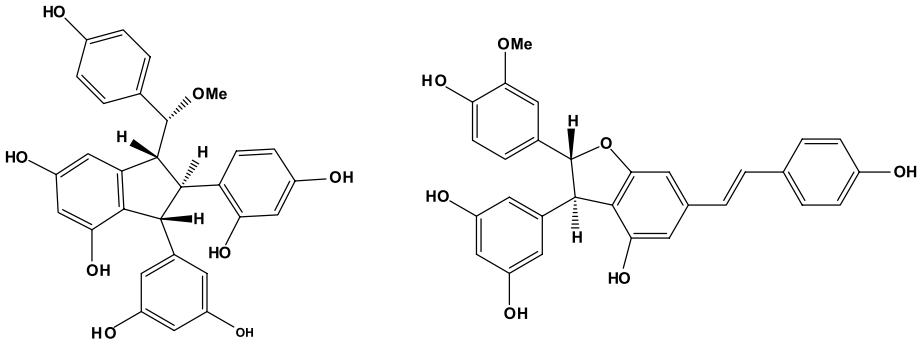

Fig. 4. Macrostachyols C (left) and macrostachyol D (right) isolated from *Gnetum macrostachyum*.

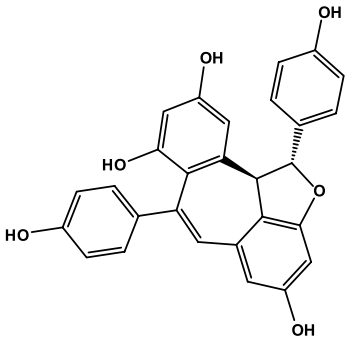

Fig. 5. Roxburghiol A isolated from *Shorea roxburghii*.

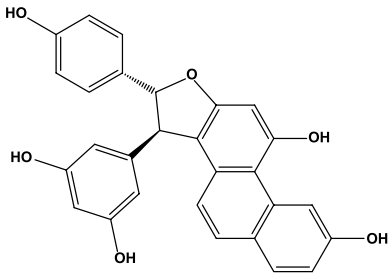

Fig. 6. Aglycone of vaterioside A isolated from *Vateria indica*.

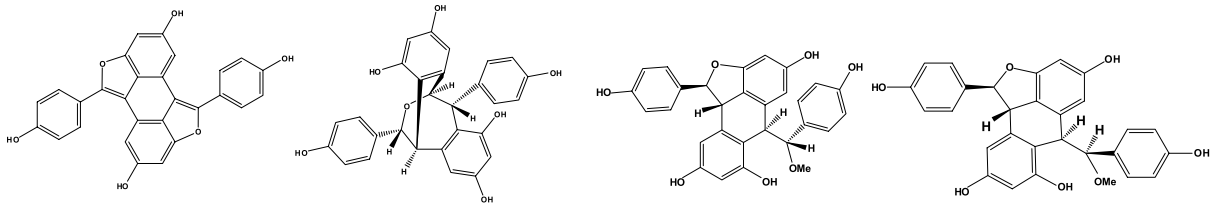

Fig. 7. Hopeahainols C-F (left to right, respectively) isolated from *Hopea hainanensis*.

this is the first chemical isolation from natural sources. A glycosylated form of vaterioside A was additionally isolated during this phytochemical investigation (compound is shown in Fig. 22).

Four new dimers were reported from the stem wood of *Hopea hainanensis* by Ge et al. [29]. This group has previously isolated and characterized several other stilbene oligomers from the *Hopea* genus. This recent work resulted in the isolation and characterization of four new structures, each of which has notable differences (Fig. 7). Hopeahainol C is more unsaturated when compared to the other dimers of this review, lacking a single sp^3 hybridized carbon. The relatively stereochemistry of these compounds were unambiguously determined using NOESY experiments [29].

Examination of the branches and twigs of the tropical plant *Vatica mangachapoi* by Qin et al. [30] afforded the three new dimers shown in Fig. 8. The compounds were isolated in a bioassay guided fractionation targeting compounds with xanthine oxidase (XO) and acetylcholinesterase (AChE) inhibitory effects. Interestingly, vaticahainol A shows rearrangement from the original resveratrol unit. The structure contains a lactone moiety, which is not seen in the other dimers discussed in this review. Vaticahainol B contains a quinone ring, which also has not been seen in many other isolated stilbenes. The quinone moiety is recognized by four quaternary sp^2 C-atoms and two protonated sp^2 C-atoms, which suggests the presence of a cyclohexa-2,5-dienone system. The final structure, vaticahainol C, contains a distinctive phenanthrene moiety [30].

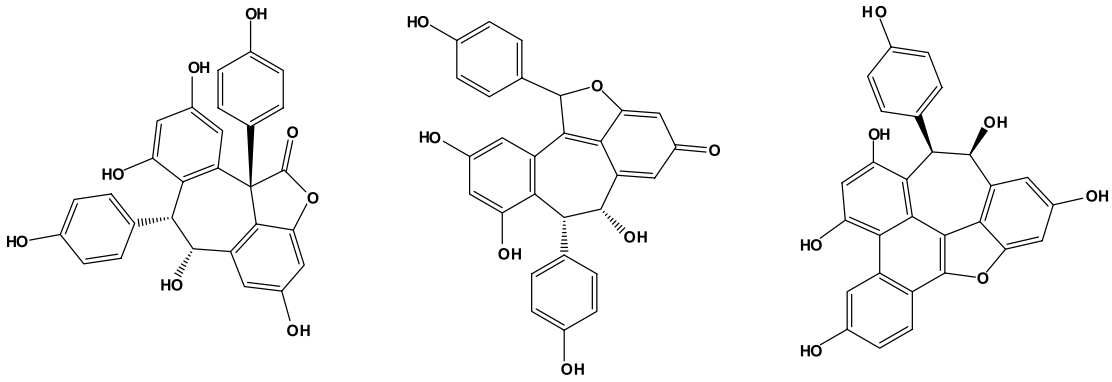

Fig. 8. Vaticahainols A-C (left to right, respectively) isolated from *Vatica mangachapoi*.

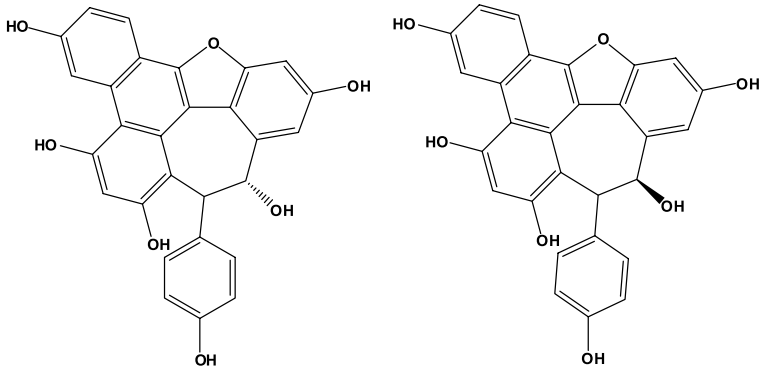

Fig. 9. Albiraminol B (left) and malibatol A (right) isolated from *Vatica albiramis*.

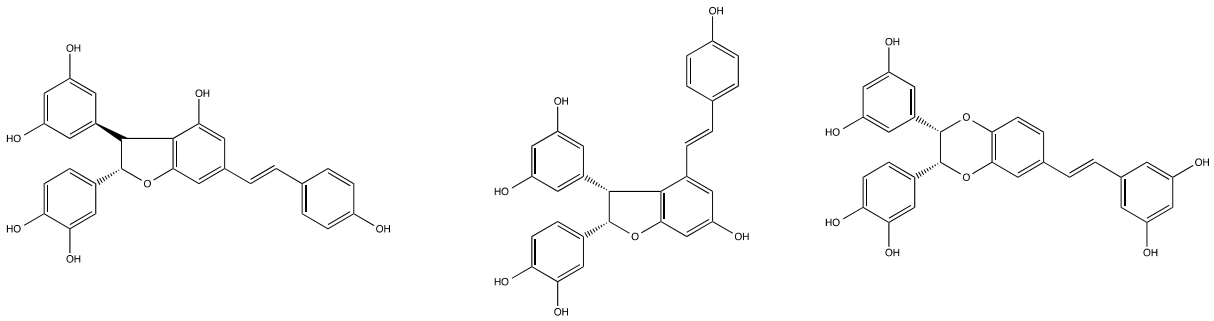

Fig. 10. Longusol A-C (left to right, respectively) isolated from *Cyperus longus*.

While studying the stems of *Vatica albiramis*, Abe et al. [31] isolated several new stilbenes oligomers [31]. These include the dimer, albiraminol B, which is nearly identical to a previously known compound, malibatol A (Fig. 9). The only difference between these two compounds is stereochemistry in the connectivity between the A1 and A2 rings. Notably, malibatol A was also isolated by this group from the same fraction.

Working with the methanol extract of the whole plant *Cyperus longus* which is used traditionally in Egyptian medicine as a tonic and a diuretic, Morikawa et al. [32], using bioassay guided fractionation, were able to identify three stilbenes (Fig. 10) [32]. These include longusol A and B which contain similar connectivity using the common

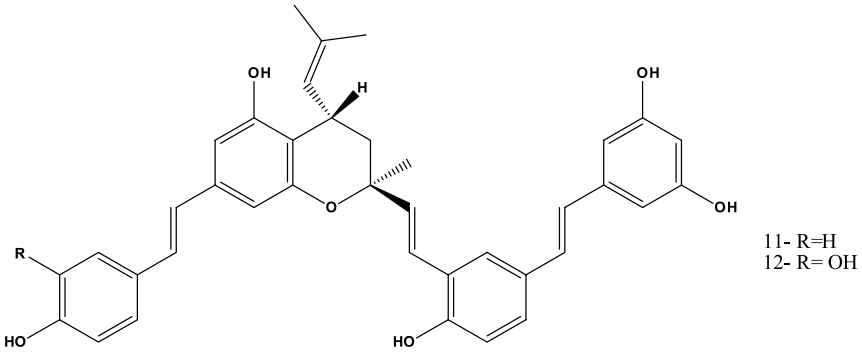

Fig. 11. Arahypin-11 and -12 isolated from fungal challenged black skin peanuts.

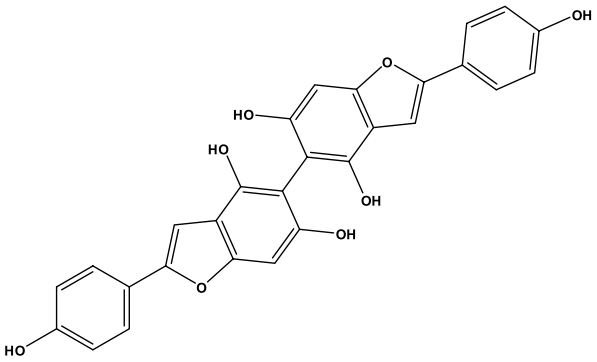

Fig. 12. Dimer isolated from the roots and stems of *V. amurensis*. The compound contains an aryl carbon-carbon linkage of two benzofuran monomers.

benzofuran ring to connect the two resveratrol monomers. The carbon skeleton presented by these two structures has been previously reported as opposing stereoisomers, as well as re-isolated by this group during the investigation of *C. longus.* Longusol C contains a 1,4-dioxane moiety to connect the resveratrol units, however its stereoisomer was also previously reported. The stereoisomer was again re-isolated by the group.

While working with fungal challenged black skin peanut seeds Liu et al. [23] isolated two new prenylated stilbene dimers, arahypin-11 and arahypin-12, along with the monomer previously mentioned in Fig. 2. Their isolation of prenylated stilbenes from fungal challenged peanut seeds follows previous publications, most notably the previously mentioned Sobolev et al. [17]. Arahypin-11 and -12 can be found in Fig. 11 below.

The last dimer isolated contains an aryl coupling between two benzofuran stilbene monomers. The roots and stems of *Vitis amurensis* have been used ethnobotanically as pain relievers, and in this investigation yielded the isolation of the novel dimer [33]. The compound can be found in Fig. 12.

2.4. Stilbene trimers

Of the compounds isolated during this time period, only 4 were stilbene trimers. Three of these four compounds were isolated from the plant *Paeonia suffruticosa* by He et al. [34], two of which are a pair of stereoisomers (Fig. 13) [34]. The third compound, isolated from *P. suffruticosa* is *cis*-gnetin H. The three compounds contain the same carbon skeleton and the resveratrol monomer units are connected by benzofuran rings. The absolute stereochemistry of the three trimers was determined using NOESY NMR and circular dichroism [34].

As previously mentioned, plants of the genus *Gnetum* are rich sources of oligomeric stilbene derivatives [25]. Along with the isolation of the two dimers, macrostachyol C and D, Sri-in et al. isolated a novel trimer from *Gnetum*

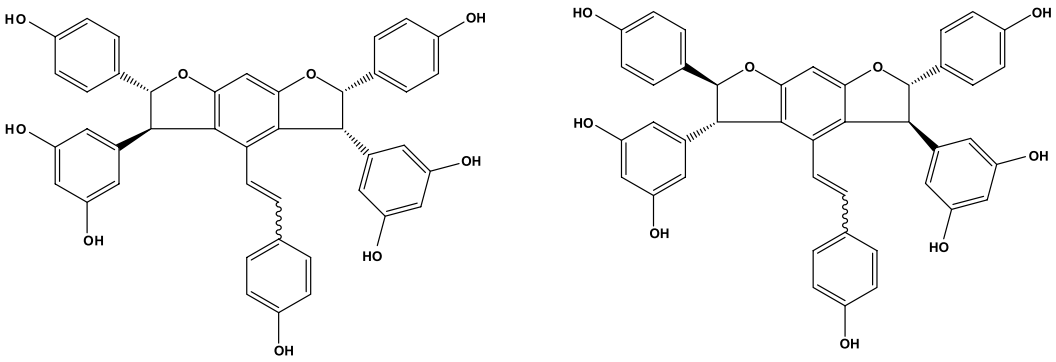

Fig. 13. *cis/trans*-suffruticosol D and *cis*-gnetin H (left to right, respectively) isolated from *Paeonia suffruticosa*.

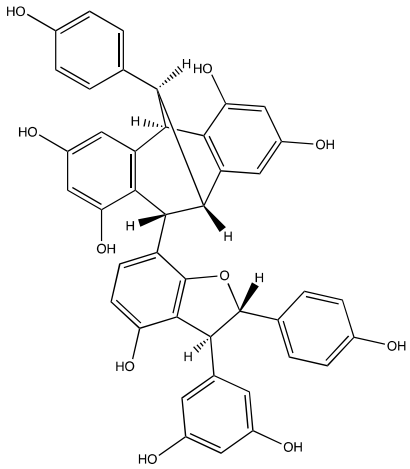

Fig. 14. Macrostachyol B isolated from *Gnetum macrostachyum*.

macrostachyum, named macrostachyol B (Fig. 14) [25]. The structure contains an interesting carbon bridge creating the bicyclic internal ring system.

2.5. Stilbene tetramers

Similarly to the stilbene dimers, the majority of the stilbene tetramers contain a benzofuran moiety. This is due to the fact that the tetramers are primarily 'dimers of dimers'. As shown in the current review, as well as the most recent other review reported by Shen et al. [2], the diversity of stilbene dimers is quite extensive. Due to the number of active functional groups that allow for the ease as well as variety in polymerization, once a dimer is formed, there are several positions whereby these newly formed dimers can polymerize to form tetramers of resveratrol. This ease in polymerization is responsible for the increasing diversity of resveratrol dimers and tetramers.

Two new tetramers were isolated from *Upuna borneensis*, conducted by Ito et al. [35]. The group has previously reported a structural variety of resveratrol oligomers from *U. borneensis*, while in this report they were investigating the acetone extract of the plant's stems. Their work afforded the two new tetramers, upunaphenols O and P (Fig. 15) [35]. Upunaphenol O consists of the resveratrol dimers ampelopsin A and *cis*-ε-viniferin. Additionally both of the dimer-subunits were isolated by the group, who hypothesized that they are indeed the building blocks of the tetramer [35]. Upunaphenol P contains a similar dimer unit to upunaphenol O, however the determination of whether it is derived from ampelopsin A or B is inconclusive. Additionally it contains a unique C–C bridge between the two dimer pieces.

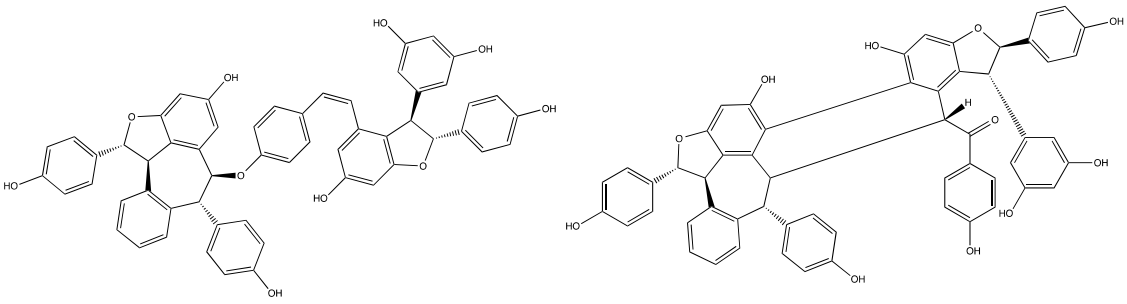

Fig. 15. Upunaphenol O (left) and Upunaphenol P (right) isolated from *Upuna borneensis*.

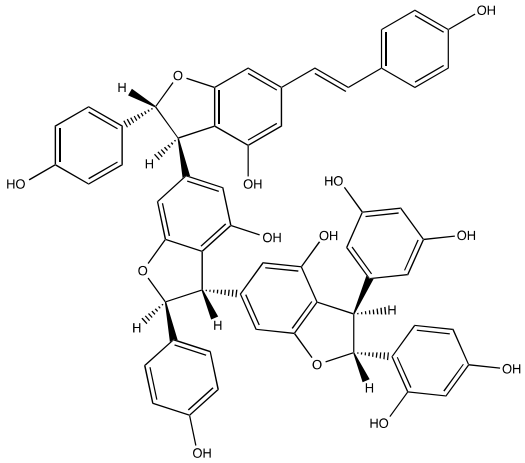

Fig. 16. Macrostachyol A isolated from *Gnetum macrostachyum*.

Along with the isolation of the two dimers, macrostachyol C and D, and the trimer macrostachyol B, this group also isolated a novel tetramer from *Gnetum macrostachyum*, macrostachyol A (Fig. 16) [25]. Macrostachyol A differs from other common tetramers, as based on the bonding pattern it does not appear to be a dimer of a dimer. Instead, the bonding suggests that macrostachyol A is derived from latifolol, a resveratrol trimer, combined with yet another resveratrol unit through oxidative coupling [25]. It is noteworthy to add that this group also isolated latifolol, which adds credibility of their oxidative coupling hypothesis.

The next two resveratrol tetramers return to the commonality of a dimer of dimers and include cajyphenol A and B which were isolated from *Cayratia japonica* by Bao et al. [36] (Fig. 17). These two tetramers contains the same carbon skeleton, however differ in their attachment of the two dimer sub-pieces. Additionally the southern portion of each the two molecules contains opposing relative stereochemistry.

The final resveratrol tetramer isolated during the time of this review, is also the only tetramer that displays a carbon-symmetric structure (Fig. 18). Vateriaphenol F was isolated from the leaves of *Vateria indica* by Ito et al. [27]. The dimer of dimers is constructed from two ε-viniferin pieces. In this example, the use of the furan moiety has been used to polymerize each step of the oligomer from the resveratrol monomers.

2.6. Stilbene hexamer

There was only one hexamer isolated during the time period covered by this review, and it is only the fifth instance of a resveratrol hexamer being isolated from a natural source (Fig. 19). This hexamer was isolated from the acetone extract of *Vatica albiramis* stems by Abe et al. [31]. The structure consists of a tetramer, vacticanol A, and a dimer

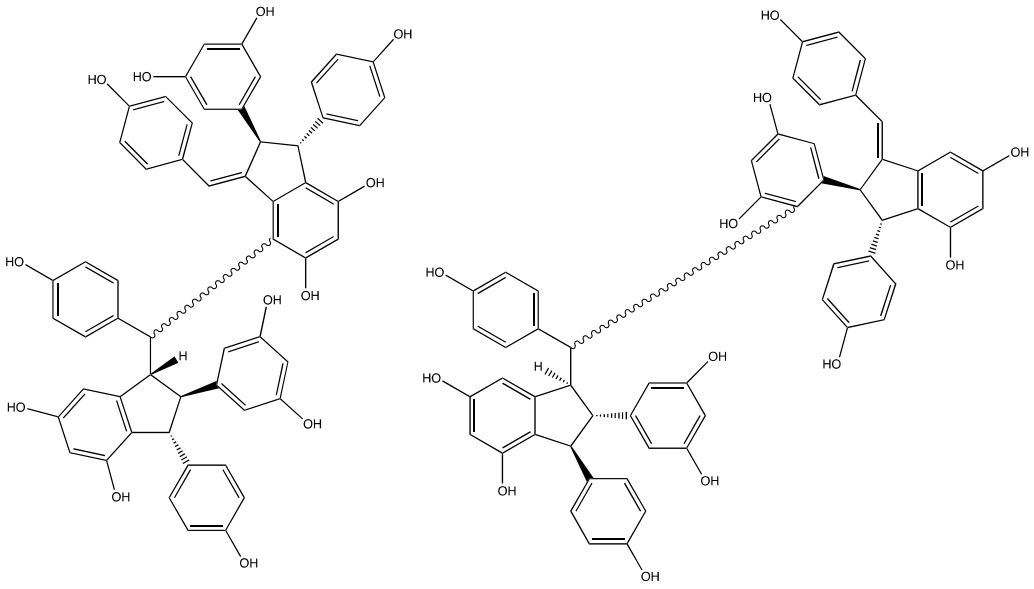

Fig. 17. Cajyphenol A (left) and cajyphenol B (right) isolated from *Cayratia japonica*.

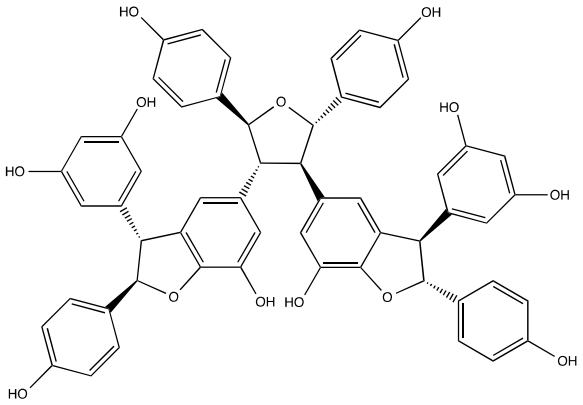

Fig. 18. Vateriaphenol F isolated from *Vateria indica*.

unit. Additionally it is important to note the 1,2-aryl shift which occurred in resveratrol F has rarely been seen in isolated oligomers [31].

2.7. Norstilbene

An interesting structure, longusone A, was isolated from the methanol extract of the whole plant *Cyperus longus* by Morikawa et al. [32] (Fig. 20). When compared to those structures in this review, this compound has several unique features. As stated previously, the majority of the stilbene oligomers were constructed using resveratrol as the monomeric unit. However, the building block in this molecule contains an additional hydroxyl functional group. The presence of the hydroxyl group in the ortho position on the southern-most di-substituted ring, although uncommon, is not improbable as it is present from the portion of resveratrol that is constructed from the shikimate biosynthetic pathway.

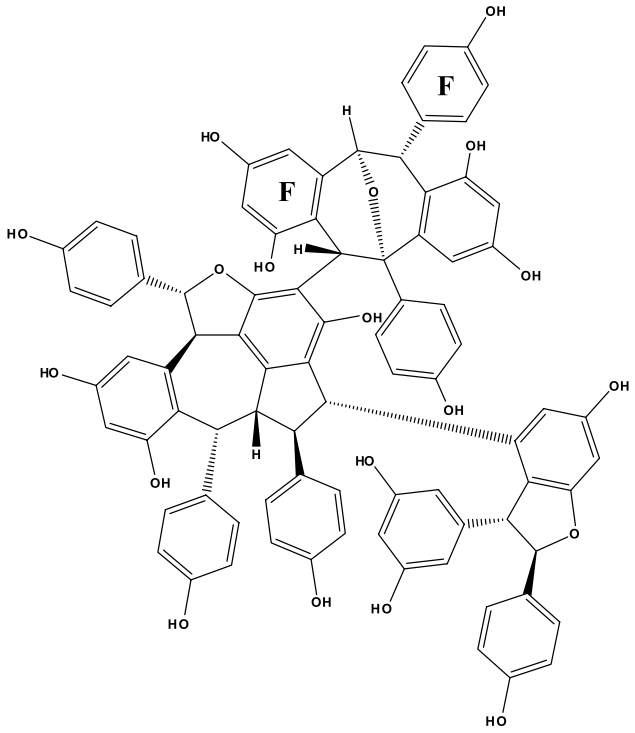

Fig. 19. Albiraminol A isolated from *Vatica albiramis*.

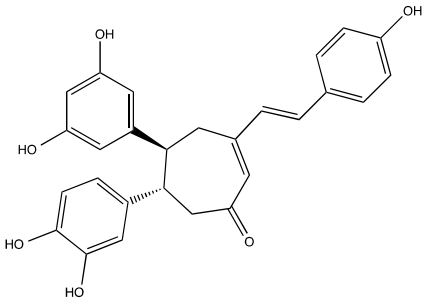

Fig. 20. Longusone A isolated from *Cyperus longus*.

Additionally this compound contains a tropilene moiety, in which for the purpose of this review, had not been previously observed in natural stilbenes. The author, Morikawa et al. [32], describes this molecule as a norstilbene dimer, however it seems unlikely that the molecule's origin is a true stilbene dimer (Fig. 20).

2.8. O-glycosylated stilbenes

The previous stilbenes reported in this review have not been glycosylated. During the period in which this review covers, there were 13 O-glycosylated structures reported. Of which, four were monomers, six dimers, and three tetramers. Like many other classes of compounds, the most common sugar moiety added is glucose and in the case of this review, all of the sugar moieties added through O-glycosylation were glucose.

Upon fractionation of the aerial portions of the Mongolian medicinal plant, *Scorzonera radiata*, Wang et al. [37] isolated four new glycosylated monomers (Fig. 21) [37]. These monomers differ from the typical resveratrol monomer

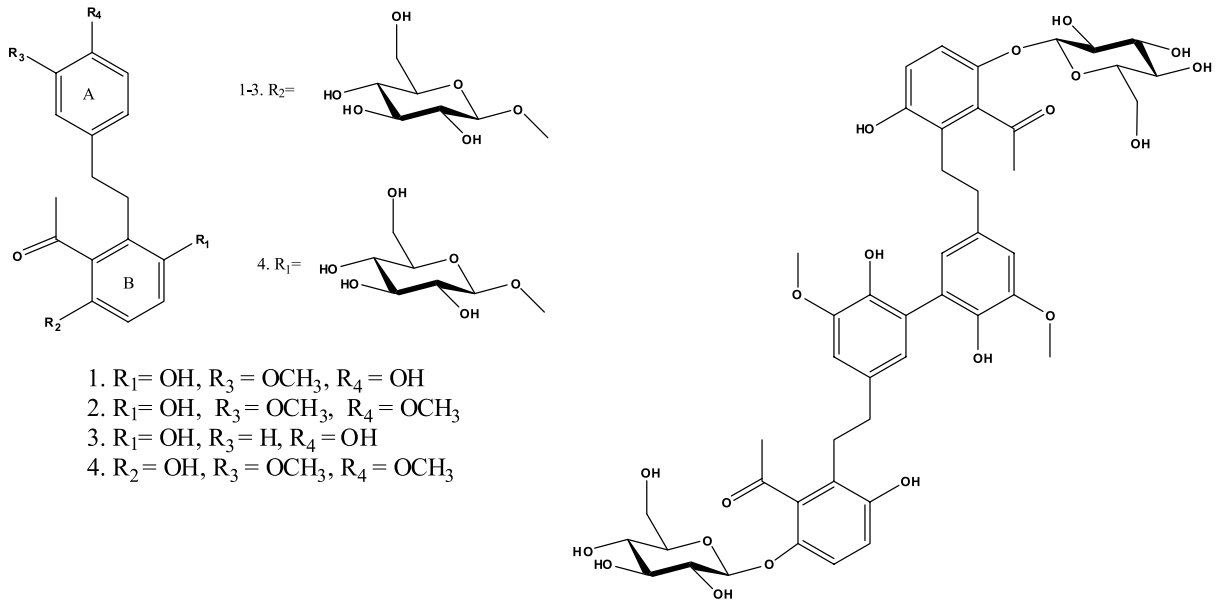

Fig. 21. Four glycosylated monomers and a dimer isolated from *Scorzonera radiata*.

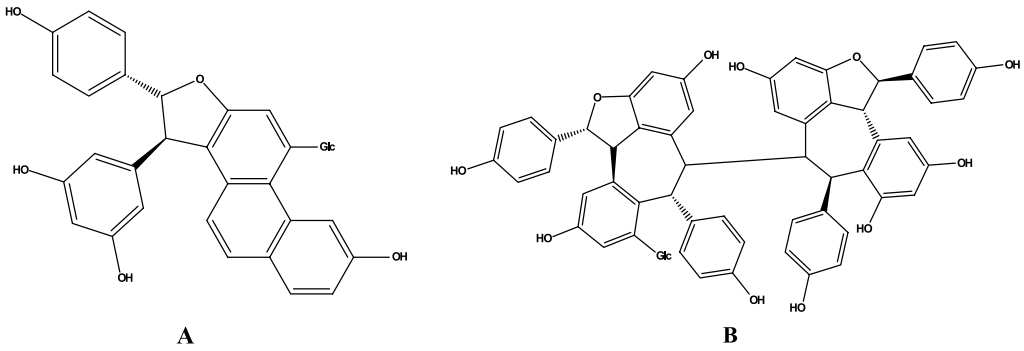

Fig. 22. Vaterioside B isolated from *Vateria indica*.

with the addition of the acetate unit at C1, as well the substitution pattern in ring B. Additionally, several of these monomers have methyl modifications at various locations generating methoxyl functional groups. The group also isolated a dimer of Fig. 21's compound 1, which was connected through a C–C bond and the 5′ carbon (Fig. 21) [37].

Two new glycosylated compounds were isolated in the leaves of *Vateria indica* by Ito et al. [27]. One of the structures, a dimer, is previously mentioned in this review as having an aglycone that had previously not been isolated in nature (Fig. 5). The group also isolated a tetramer with an aglycone, consistent with that of hopeaphenol, a dimer of two ampelopsin units (Fig. 22) [27].

Two publications from the same group, Abe et al. [31, 38], resulted in the final six O-glycosylated stilbenes isolated in the time frame of this review [31, 38]. All six were isolated from the stems of *Vatica albiramis* and named vatalbinosides A-F (Fig. 23). The group isolated 4 dimers and 2 tetramers. While these glycosylated versions are newly isolated compounds, each of the compounds respective aglycones are previously described skeletons.

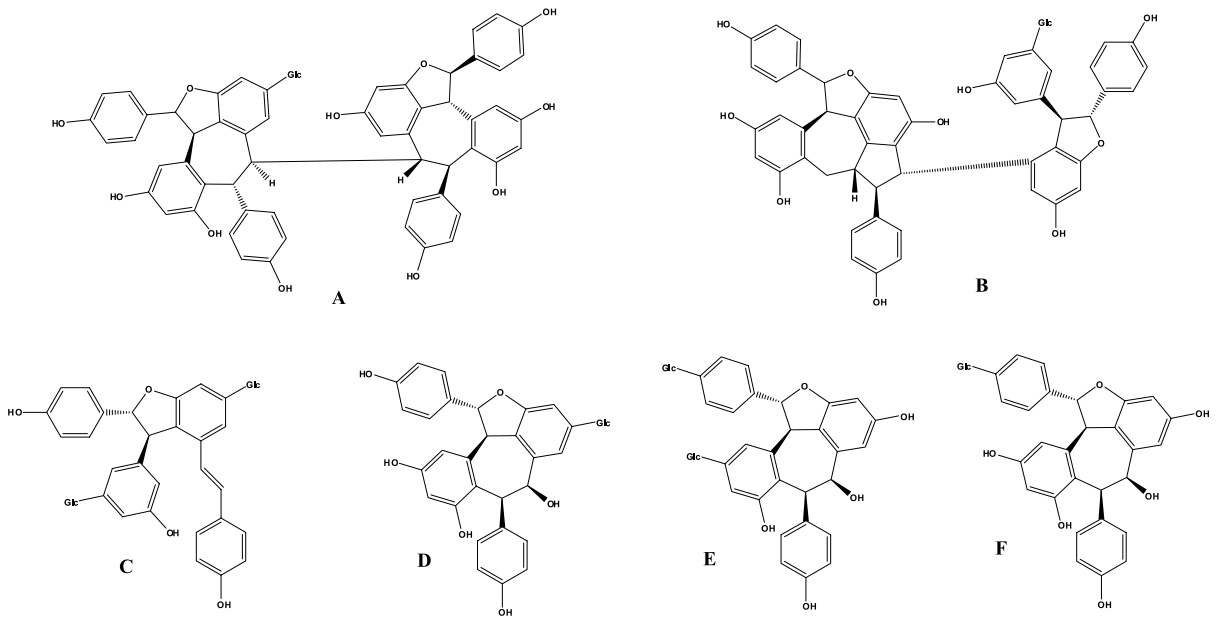

Fig. 23. Vatalbinosides A-F isolated from *Vatica albiramis*.

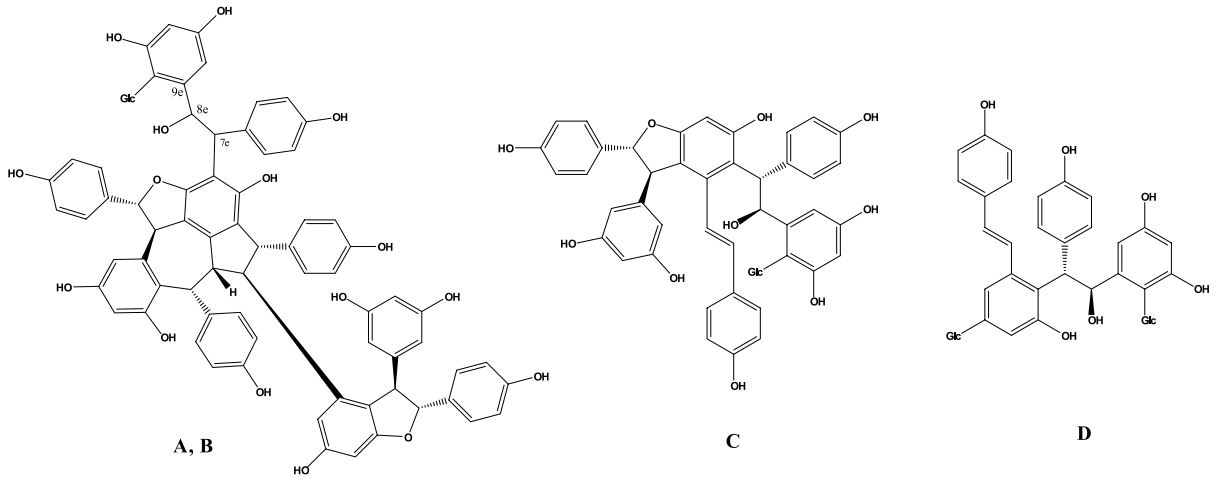

Fig. 24. Hopeasides A-D (left to right) isolated from *Hopea parviflora*.

2.9. C-glycosylated stilbenes

While O-glycosylated structures are much more common, occasionally C-glycosylated structures are also reported among stilbenoids. Abe et al. [39] isolated four new C-glycosylated structures from *Hopea parviflora*, namely, 2 pentamers, a trimer, and a dimer. These compounds have been named hopeasides A-D (Fig. 24). The two pentamers are the first C-glucopyranosyl resveratrol oligomers isolated to date. Moreover, they are stereoisomers of each other but the orientation in which the two differ remains unknown. The orientation, interestingly, is in regard to the orientation of the C–C bonds between 7e-8e-9e. Theoretically, these are sp^3 hybridized freely rotatable bonds, however due to the steric hindrance within the molecule, rotation is restricted creating the two stereoisomers.

3. Biological activity of stilbenoids

Historically, there has been significant work done on the role of stilbenes and their activity as anti-bacterial agents, antioxidants, several anticancer properties, NFκB and hemeoxygenase moderators. For example, kobophenol-A and -B are tetrastilbenes that were first isolated from *Carex kobomugi* and *Carex pumila*, respectively. These compounds have been shown to have moderate inhibitory activity against *Staphylcoccus aureus* [3, 4]. Due to the inherent (poly)phenolic structure of stilbenes, there has been extensive research conducted on their role as antioxidants. Reactive oxygen species (ROS) are generated in bio-organic redox processes. Deregulation of this dynamic biological process leads to oxidative stress, which has been linked to many chronic human diseases including cancer, diabetes, and cardiovascular diseases [5]. The direct efficacy of stilbenes ability for the scavenging of ROS, or induce NADPH oxidase and xanthine oxidase inhibition, however still remains unclear [1].

An additional biological property that stilbenes exhibits is the inhibition of topoisomerase II. Topoisomerases play a critical role in the unwinding of coiled DNA during cellular transcription [6]. Upon discovering this mechanism for oligomeric stilbenes, Yamada et al. [6] conducted a study on over 40 stilbenes and their ability to inhibit topoisomerase II and identified α-viniferin as being highly active. In addition to its ability to inhibit topoisomerase II, α-viniferin has also been reported to not induce apoptosis, but interestingly arresting cell-cycle in the S-phase in human colon tumorigenic cells [7].

Resveratrol has also been implicated in the modulation of several proteins involved in a variety of degenerative diseases. It has been shown that resveratrol down regulates NFκB, an important protein complex involved in cell survival and proliferation. Incorrect regulation of NFκB has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development [8, 9]. Resveratrol has also been linked to moderate hemeoxygenase activity, which catalyzes the cleavage of heme to form iron, CO and bilirubin. Incorrect activity within hemeoxygenase has been linked to Parkinson's and Alzheimer's diseases [8, 9]. Finally, resveratrol has been shown to alleviate some of the problems associated with type II diabetes, such as myocardial ischemia [40].

More recently, resveratrol and some of its analogs, have been linked to anti-aging properties. It was shown that through mimicking caloric restriction, resveratrol prolonged the lifespan of budding yeast, *Saccharomyces cerevisiae*. Supporting results followed with additional organisms, including the nematode, *Caenorhabditis elegans*, the fruit fly, *Drosophila melanogaster*, and the honey bee, *Apis mellifera* [41–44]. With mammals, the first experiments carried out in mice confirmed that resveratrol mimicked the effects of calorie restriction including reduced albuminuria, decreased inflammation, and apoptosis in the vascular endothelium, increased aortic elasticity, greater motor coordination, reduced cataract formation, and preserved bone mineral density [45].

Since aging is a complex process, one could anticipate that the role that stilbenes play in exerting anti-aging effects could be achieved by targeting multiple physiological processes. In fact, resveratrol appears to fit such a hypothesis, although its exact mechanism is not yet fully established. The most intriguing observation linking resveratrol with longevity was its ability to activate some members of the sirtuin (SIRT) family, especially SIRT1 [41]. SIRT1 has been shown to mediate the beneficial effects of calorie restriction on longevity extension [46]. Resveratrol was also shown to reverse a variety of age-related conditions by counteracting mitochondrial dysfunction and metabolic diseases [47]. Several of these effects are SIRT1-dependent, but many others are mediated through independent pathways, such as a cAMP-PKA-AMPKA cascade [48].

4. Summary and concluding remarks

In summary, this review covers the chemical structures of natural stilbenoids isolated and identified from 2009–2013. It is apparent that stilbenes are an exciting chemical class of natural polyphenolic compounds with a unique carbon backbone that allows them to polymerize into complex structures and to be biologically active in a variety of systems. They have been implicated in the inhibition of growth of microbes, as well as to be strong anti-oxidants. In addition, this class of compounds has the ability to inhibit the growth of cancer cells *in vitro*. These compounds display great potential in their chemical diversity but understanding of their role in human health prevention and disease risk reduction would need further studies into their *in vivo* biological potential and mechanisms of action.

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