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STILBENES: CHEMISTRY AND PHARMACOLOGICAL PROPERTIES

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ABSTRACT: Medicinal plants are the most important source of life saving drugs for the majority of the Worlds' population. The compounds which synthesized in the plant from the secondary metabolisms are called secondary metabolites; exhibit a wide array of biological and pharmacological properties. Stilbenes a small class of polyphenols, have recently gained the focus of a number of studies in medicine, chemistry as well as have emerged as promising molecules that potentially affect human health. Stilbenes are relatively simple compounds synthesized by plants and deriving from the phenyalanine/ polymalonate route, the last and key enzyme of this pathway being stilbene synthase. Here, we review the biological significance of stilbenes in plants together with their biosynthesis pathway, its chemistry and its pharmacological significances.

INTRODUCTION

Plants are source of several drugs of natural origin and hence are termed as the medicinal plants. These drugs are various types of secondary metabolites produced by plants; several of them are very important drugs. Essentially, plant cell produced two types of metabolites: primary metabolites involved directly in growth and metabolism, viz., carbohydrates, lipid and protein, and secondary metabolites considered as the end product of primary metabolism and in general not involved in metabolic activity, viz., alkaloids, phenolics, essential oils, steroids, lignins, tannins etc. The plant biomasses cultivated *in vitro* are capable of biosynthesis of secondary metabolites typical for intact plants or they may serve as sources of entirely new molecules, not identified in nature. In effect, a path was opened for intensive biotechnological research into the potential use of *in vitro* cultures to produce highly valuable secondary metabolites, including compounds for which medical application could be found[1] . Polyphenolics are important constituents of grapes in determining the colour, taste and body of wines. Unlike other alcoholic beverages, red wine, which is obtained after maceration, contains phenolic compounds in high concentration up to 4 g/l, but relatively low quantities are present in white and rosé wines, i.e. about a tenth of those of red wines. Among these phenolic compounds, *trans*-resveratrol, belonging to the stilbene family, is a major active ingredient which can prevent or slow the progression of the major diseases, as well as extend the lifespans of various organisms from yeast to vertebrates [2,3]. Other natural stilbenes derived from resveratrol such as pterostilbene or piceatannol, display higher oral bioavailability and bioactivity than the parent compound, but are far less abundant in natural sources[4]. Some t-resveratrol analogues such as polyhydroxy and polymethoxy derivatives exhibit higher pharmacological activity than the parent compound [5].

Epidemiology

Some epidemiologic studies in United States have examined the relationship between wine consumption and the risk of cancer. Contrary to other alcoholic beverages, the moderate wine consumption was associated with a decrease (or no increase) in the risk of oral and pharyngeal cancer [6] and breast cancer[7] using small cohorts in Italy found a minimum risk of cancer and cardiovascular disease associated with moderate alcohol consumption (wine being the main beverage).

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Chemistry

Stilbenes naturally occur in several plant families, such as the Cyperaceae, Dipterocarpaceae, Gnetaceae, and Vitaceae[8]. Grapes (Vitaceae) and products manufactured from grapes are viewed as the most important dietary sources of these substances[9] .They are a family of molecules belonging to the non-flavonoid polyphenol group. The essential structural skeleton comprises two aromatic rings joined by an ethylene bridge (C_6-C_2-C_6).From this relatively simple structure, there is a large array of compounds: - monomers which varying in the number and position of hydroxyl groups, the substitution with sugars, methyl, methoxy and other residues and the steric configuration of the molecules (Fig. 1), - oligomers resulting from the different oxidative condensation of resveratrol monomer (dimers, trimers, tetramers,……).

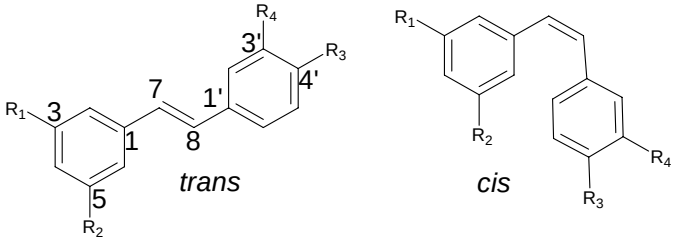

Figure 1: Structure of the main stilbene monomer derivatives from *Vitis vinifera*

names	R_1	R_2	R_3	R_4
cis- and *trans*-resveratrol	OH	OH	0H	H
trans-pterostilbene	OCH_3	OCH_3	OH	H
cis- and *trans*-piceid	OGlc	OH	OH	H
cis- and *trans*-resveratroloside	OH	OH	OGlc	H
cis- and *trans*-resveratrol 3,5-*O*-*β*-diglucoside	OGlc	OGlc	OH	H
cis- and *trans*-resveratrol 3,4'-*O*-*β*-diglucoside	OGlc	OH	OGlc	H
trans-resveratrol 3,5,4'-*O*-*β*-triglucoside	OGlc	OGlc	OGlc	H
trans-piceatannol	OH	OH	OH	OH
cis- and *trans*-astringin	OGlc	OH	OH	OH

Monomers (Fig 1)

Among stilbene monomers, resveratrol (3, 5, 4'-trihydroxystilbene) has been identified as the major biological active compound, and most of the studies have focused on it. The two isomeric forms of resveratrol (*cis*- and *trans*-) have different chemical characteristics and biological activities. The *trans*-isomer is usually the more stable, and *cis*-*trans*-interconversions can occur in the presence of heat or ultraviolet light.Other simple stilbenes have been isolated in *Vitis vinifera* : *trans*-pterostilbene and piceatannol. Besides the aglycone of resveratrol cited above, some resveratrol glucosides derivatives have been identified such as piceid and resveratroloside, two *β*-glucosides of resveratrol [10] together with astringin (piceatannol 3-*O*-*β*-glucoside). These compounds exist in their two isomeric forms, *cis* and *trans* (Waffo-Téguo et al., 1998). Furthermore, resveratrol di- and tri- glucoside derivatives have been recently isolated from *Vitis vinifera* [11.12].

Oligomers

Besides monomers of stilbenes, some oligomers have been isolated from *Vitis vinifera*. They are eithers dimers, trimers and tetramers. These oligomers result from the different oxidative condensation of resveratrol monomer.

Dimmers

The dimers are divided into two major groups. One group (A) contains one five-membered oxygen heterocyclic ring bearing to aromatic ring (benzofuran ring) (Fig 2). Belonging this group, we have *α*-viniferin substituted or not with sugars[13] , *α*-viniferin (also named resveratrol dehydrodimer) glucosylated or not[14] (Waffo et al., 2001) and *α*-viniferifuran[15] (Fig 2).The other group (group B) does not contain any oxygen heterocyclic ring. Among dimers belonging to this group, pallidol have been isolated in *Vitis vinifera* as well as its mono- and di-glucoside [14, 13] and parthenocissin A (Fig 3).

2.2.4 – Trimers

Recently, resveratrol trimer was detected in grapevine infected by downy mildew using HPLC coupled to Atmospheric Pressure Photoionisation (APPI) mass spectrometry. The structure was supposed to be α-viniferin [15] (Fig.4).

2.2.5 – Tetramers

Besides resveratrol dimers and trimer, stilbene tetramers were isolated from *Vitis vinifera*. They are divided into three groups: one group contains a bicyclo[6.3.0]undecane ring system. Into this group we have viniferol A (Fig. 5). Second group has a bicyclo[5.3.0]decane ring system. Resveratrol tetramers belonging to this group are: viniferal B and C, vaticanol B, and vaticaphenol A (Fig.5) third group contains benzofuran system usually *trans*-2-aryl-2,3-benzofuran moiety (Fig 6). Tetramers

belonging this group are: vitisifuran A and B and iso- and hopeaphenol (two cyclic symmetric tetramers) [14] (Ito *et al*., 1997).

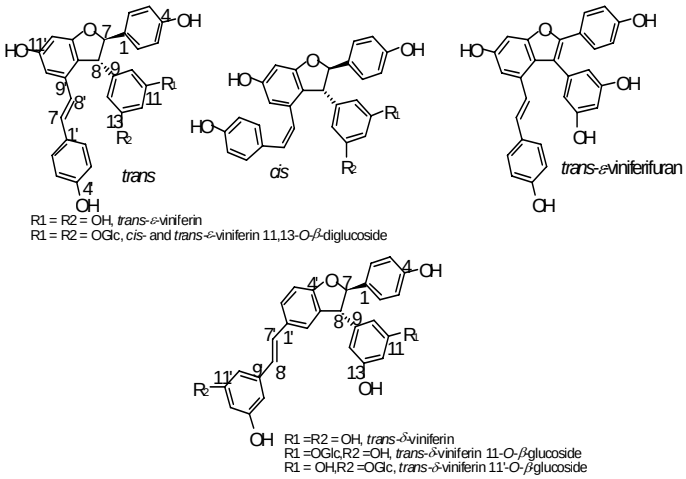

Figure 2: Structure of the main stilbene dimer derivatives (group A) from *Vitis vinifera*

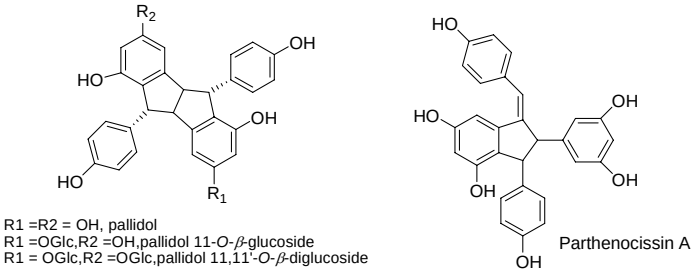

Figure 3: Structure of the main stilbene dimer derivatives (group B) from *Vitis vinifera*

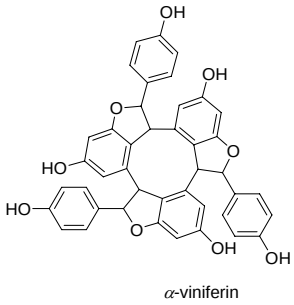

Figure 4: Structure of the stilbene trimer from *Vitis vinifera*

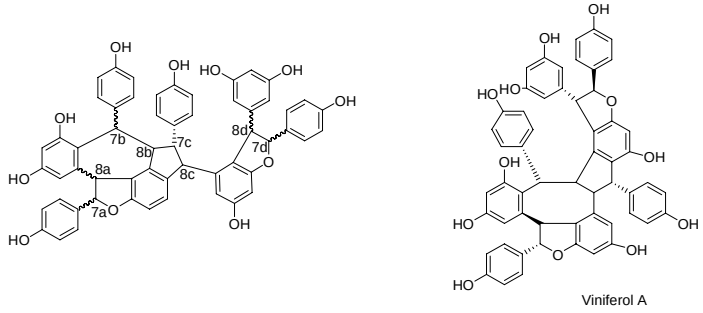

Figure 5: Structure of the stilbene tetramer from *Vitis vinifera*

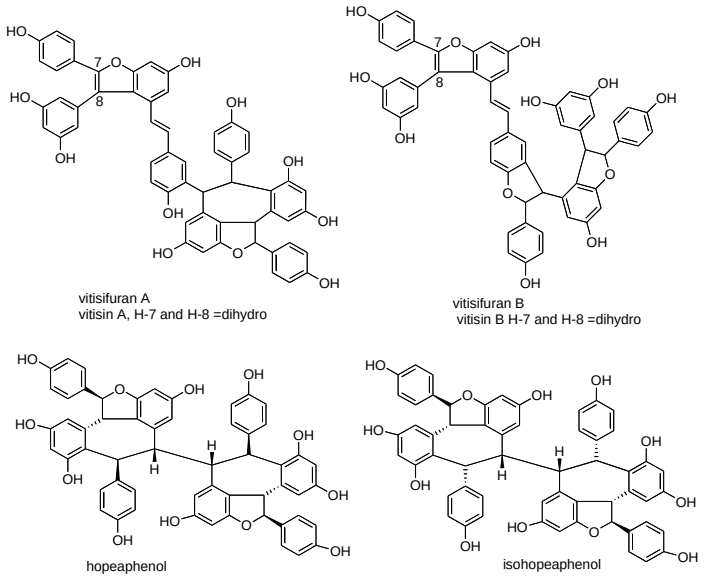

Figure 6: Structure of the stilbene tetramer from *Vitis vinifera*

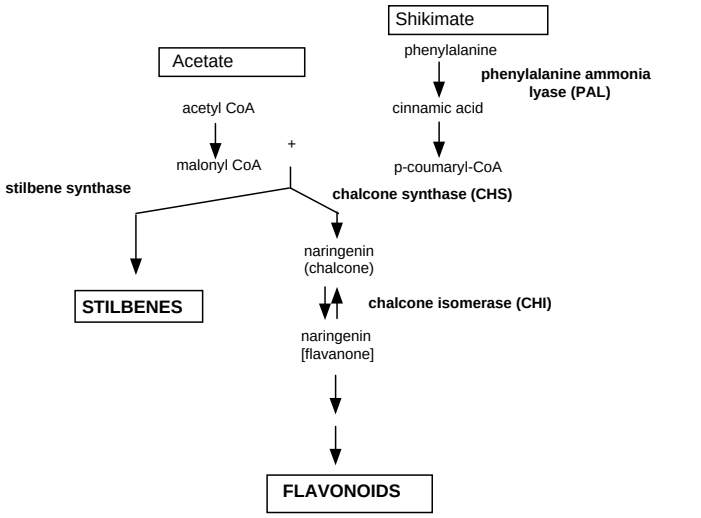

Figure 7: General biosynthesis pathway of stilbenes and flavonoids

Biosynthesis of stilbenes

The immediate precursors of resveratrol are p-coumaroyl CoA and malonyl CoA in a molar ratio of 1 to 3. The latter is derived from elongation of acetyl CoA units and the former from phenylalanine, which can be synthesized from sugars via the shikimate pathway. Following oxidative deamination catalysed by Phenylalanine Ammonia Lyase (PAL), phenylalanine is converted to cinnamic acid which in turn is enzymatically hydroxylated to p-coumaric acid. In the final step, p-coumaroyl CoA is generated from the free coenzyme by a specific CoA ligase. The condensation of p-coumaroyl CoA with 3 molecules of malonyl CoA is accomplished through the

activity of the stilbene synthase (STS), which leads to trans-resveratrol (Fig. 7). However, the exact biosynthetic formation of these derivatives is unknown.

In *Vitis vinifera* varieties, a number of different hydroxystilbenes are present in several parts of the grape plant as constitutive compounds of the lignified organs (roots, canes, seeds, stems, ripe cluster stems), and as induced substances (in leaves and berries) probably acting as phytoalexins in the mechanisms of grape resistance against pathogens. Both resveratrol and piceid can be found in grape products, with the concentration of the glucoside usually being significantly higher than the aglycone .In grape berries, stilbene synthesis is primarily located at the skin cells and it is absent or low in the fruit flesh. The greater part of the resveratrol in the skins is in both glycosidic forms (pieced isomers), whereas pterostilbene is detected in very low levels in healthy and immature grape berries [17] found that piceids were the major components of grape juices, averaging a total of 4 mg/L in red grape juices and 0.5 mg/L in white ones. In seeds, only *trans*- and *cis*-resveratrol was detected. In grape cell suspension cultures, several stilbenes have been isolated: Resveratrol, piceid, resveratroloside and astringin, all in the two isomeric forms *cis*- and *trans* (Fig.1) Recently, three new resveratrol diglucosides, *cis*- and *trans*-resveratrol 3,5-*O*-*β*-diglucoside [12] and *trans*-resveratrol 3,4'-*O*-β-diglucoside [18] (Fig.1) have been isolated together with a new resveratrol triglucoside, *trans*-resveratrol 3,5,4'-*O*-*β*-triglucoside [12] . (Fig.1).Furthermore, resveratrol dimers have been identified, among them, *trans*-*α*-viniferin together with *trans*-*α*-viniferin 11- and 11'-*O*-ß-glucoside and pallidol [14]. Besides the monomers of stilbenes, some resveratrol dimers have been characterized from the wines: - from German commercial white wines (Riesling), *α*-viniferin diglucosides and pallidol mono- and di-glucosides have been identified at very low levels (< 0.05 mg/L) [13] from French commercial red wines low levels (from 0.5 to 4.8 mg/L) of *trans*-*α*-viniferin, parthenocissin A, and pallidol have been isolated [19]; and - from commercial Brazilian red wines, *trans*-*α*-viniferin have been found only in the youngest vintage (2002) with an average level of 11.7mg/L [20] .

BIOLOGICAL & PHARMACOLOGICAL ACTIVITIES

Bioavailability and metabolism

Stilbenes are naturally occurring polyphenolic compounds which have been reported to have potential preventive activities in human diseases. Among these stilbenes, *trans*-resveratrol, which is mainly found in peanuts, grapes and red wine, is one of the most important in terms of biological activities, since it has been reported to exert anticarcinogenic, antioxidant and cardioprotective activities [2].

The absorption of resveratrol using an isolated preparation of luminally and vascularly perfused rat small intestine[21]. Pharmacokinetics of *trans*-resveratrol following oral administration to rat (50 mg/kg)[22]. They determined resveratrol and glucuronide metabolites concentrations in plasma samples. They showed that resveratrol is bioavailable at 38% when administrated in a solution of hydroxypropyl ß-cyclodextrin and its systemic exposure was approximately 46-fold lower that of these glucuronides. Administration of 20 mg/kg mouse, resveratrol glucuronide, but also resveratrol sulfate as the resveratrol metabolites in the serum samples. However, only traces of unconjugated resveratrol were observed[23]

Cardiovascular protection

Antioxidant activity. Free radicals derived from molecular oxygen, such as superoxide, hydroxyl, hydroperoxyl radicals and nitric oxide, are constantly generated *in vivo* for specific metabolic purposes [24] . Free radical concentrations are increased either by their overproduction or by a deficiency in antioxidant defense systems. The reactivity of radicals can cause severe damage to biological molecules, especially to DNA, lipids and proteins [24] This damage probably contributes to the development of major chronic diseases including cancer, Parkinson's disease, senile dementia and atherosclerosis. Resveratrol can also prevent the initial events of atherosclerosis in endothelial cells - by inhibition of the enzymatic systems producing reactive oxygen species such as NADPH oxidase and hypoxanthine/xanthine oxidase, - and by inhibition both the expression of adhesion molecules and the monocyte adhesion to endothelial cells[25]. Resveratrol is able to regulate vasomotion which is impaired in atherosclerosis. The key regulators of the vasomotor function are the vasodilatator NO and the vasoconstrictor endothelin-1 [25]. Taken together, these biological activities *in vitro* of polyphenols such as *trans*-resveratrol, (antioxidant, anti-atherogenic, anti-thrombotic, vasorelaxant and anti-hypertensive) could explain the beneficial effects of wine in the prevention of cardiovascular disease. Biological activities after polyphenols or wine

ingestion. Some *in vivo* studies have been carried out in animals and human volunteers in order to show these protective effects after wine or pure compound consumption found that red wine notably reduced coronary atherosclerosis in rabbit. Using a hamster model of atherosclerosis [26], showed aortic fatty streak area was significantly reduced (76%) in the group receiving resveratrol at a level mimicking a moderate consumption of red wine. Intravenous and intragastric administration of red wine, grape juice and not white wine inhibited *in vivo* platelet activity and thrombosis in canine coronary arteries [27] .

Cancer Chemoprevention

The term « chemoprevention » can be defined as the ingestion of non-toxic quantities of chemical agents (dietary or pharmaceutical) that are able of preventing, inhibiting or reversing the process of carcinogenesis [28] Chemopreventive agents can act by various mechanisms on this process [29] (Alberts et al., 1999): (1) anti-initiating activities (inhibition of carcinogen formation in the body and of uptake ; inhibition of the metabolic activation of carcinogens by Phase I enzymes such as cytochrome P450 enzymes, or increase in their detoxification by Phase II enzymes such as transferases leading to an easier excretion ; scavenging of free radicals and trapping ultimate carcinogens preventing their interactions with DNA). These compounds are referred to as « blocking agents » due to their ability to prevent initiation. In addition, several reports indicate that *trans*-resveratrol inhibits the proliferation of a wide variety of tumor cells [30] . The cancer chemopreventive activity of *trans*-resveratrol was established in various assays reflecting the three major stages of carcinogenesis [31].

Neurodegenerative diseases

Resveratrol promotes antiaging effects in numerous organisms. It modulates pathomechanisms of debilitating neurological disorders, such as ischemia, Huntington's disease (HD), PD, and AD [32]. In rat hippocampal neurons, resveratrol inhibits voltage-activated potassium currents, suggesting that may be useful for treating ischemia brain injury [33] .

In midbrain dopaminergic neurons, resveratrol protects neuron cultures against several type of insults related to PD pathogenesis like cytotoxic effects induced by 1-methyl-4-phenyl pyrimidium, sodium azide, thrombin and DNA damage. In Huntington's disease, resveratrol rescued mutant polyglutamine-specific cell death in neuronal cells derived from HdhQ111 knock-in mice and from transgenic *C. elegans* both models for HD [34]. In gerbil ischemia model, administration of resveratrol during the early stage of cerebral ischemia could protect against neuronal death in hippocampal CA1 area and concomitantly inhibit glial cell activation [35].

CONCLUSION

Stilbenes and its derivatives were found to be potent antioxidant, anticancer, antihyperlipidemic, antidiabetic, and anti-inflammatory. This would offer remarkable potential for the exploitation stilbenes used in nutraceuticals, and pharmaceutical industries.However, further series of studies are required to prove its clinical reliability, safety, and efficacy.

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