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Obtaining Resveratrol: from Chemical Synthesis to Biotechnological Production

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Abstract: Given the pharmacological importance of resveratrol, preparation methods, including plant extraction, chemical synthesis and biotechnological production are evolving rapidly aiming at a large scale production. Plant extraction is the classical method providing major amount of this compound, however, it suffers from low abundance of resveratrol in natural material and environmental, seasonal, or regional variations of natural sources. Complexity of synthetic pathway and the low total yield constrain the industrial application of chemical synthesis. In contrast, biotechnological means offer significantly promising and scalable strategies for resveratrol production while using low-cost and renewable resources. In the present paper, both advantages and disadvantages of these preparation methods as well as the bioavailability and structure-activity relationship of resveratrol have been summarized and discussed aiming to provide valuable information for future improvement of resveratrol production and for searching of a stable and effective resveratrol analogue for therapeutic purposes.

Keywords: Resveratrol, plant extraction, chemical synthesis, biotechnological production, bioavailability, structure-activity relationship.

INTRODUCTION

As the most important contributor to "French Paradox", a phenomenon of low occurrence for cardiovascular diseases despite of a fat-rich diet in France [1], resveratrol (**1** in Figure) has attracted extensive interests in recent years. *In vitro*, *ex vivo* and animal experiments have demonstrated that it possesses a wide range of biological benefits for cardiovascular diseases, cancer, neurodegenerative diseases as well as others [2-8].

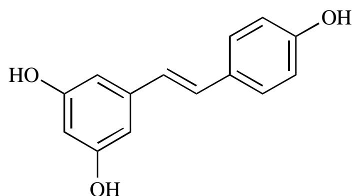

Fig. (1). Resveratrol (*trans*-isomer) (**1**).

The pharmacological importance of resveratrol has stimulated extensive analysis of the best sources as well as its chemical and biotechnological production. In nature, resveratrol is found in more than 72 plant species, like peanuts, eucalyptus, spruce, lily and mulberries. Among them, grapes (and their product-wine), Japanese knotweed and peanuts have been reported to be the most abundant natural sources [7, 8]. Naturally, resveratrol is synthesized through a branch of phenylpropanoid pathway as a part of the plant defense system under stress conditions [9-11]. Its synthesis is stimulated by UV exposure, pathogen (such as bacteria or fungi) attack and some other stress conditions. Furthermore, different elicitors (like heavy metal ions and chemical compounds) or treatments (like different gaseous and abiotic treatments) have also been successfully applied to enhance the resveratrol synthesis for postharvested grapes or cultured grapevine cells [12-16].

Resveratrol occurs as two isomeric forms-*trans*- and *cis*-resveratrol. Although both forms are naturally occurring, most of the recorded health benefits are attributed to the *trans* form. Because the *cis* isomer can be easily transformed from the *trans* form under intense UV light [17], the published data mainly concern the *trans*-resveratrol preparation, therefore in this paper, our concerns mainly focused on this version and its production methods can be grouped into three categories: (1) plant extraction, (2) chemical synthesis, (3) and biotechnological production. In the present review, we are trying to summarize the recent progresses from these three perspectives.

1. PLANT EXTRACTION

Naturally, the skins and seeds of grapes as well as Huzhang (also known as Japanese knotweed, *Polygonum cuspidatum*) are the most abundant sources of resveratrol, which enables the possibility for resveratrol preparation from them. Typically, the carefully selected raw materials are sliced and heated up in large metal chambers for extraction. Ethanol or methanol is widely used as the solvent to produce a crude liquid extract. By passing through a silica column under high pressure, or using some other purification methods, the crude extract is further processed and finally it is dried under vacuum, which protects resveratrol from degradation, to remove the solvent and produce resveratrol powder. The powder finally can be used directly or combined with fillers such as rice flour or hydroxypropylcellulose to manufacture pills and capsules for marketing purposes. However, due to the too complicated factors impacting on the resveratrol extraction efficiency, more detailed optimizations have also to be investigated [18, 19].

Moreover, it is interesting to mention that several biotic and abiotic treatments have been shown to improve resveratrol content in different tissues [12-16]. Although the molecular basis of the resveratrol increase is not clear under such situations, it was shown that the mRNA expression of resveratrol synthase increases, which is followed also by an increase of the protein level, after biotic and/or abiotic treatment [20, 21]. It seems therefore likely that these treatments could induce the resveratrol synthase gene expression leading to a further resveratrol synthesis. Another possibility is that the activity of resveratrol synthase is activated by abiotic and/or biotic factors thus leading to further resveratrol synthesis. Of course, the increase of resveratrol synthesis might also be due to the cross-reactive of the both possibilities. Whatever, these observa-

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tions might be useful to improve the production of resveratrol by the plant extraction method.

In recent years, several new technologies, including supercritical fluid extraction [22], pressurised liquid extraction [23], high-speed counter-current chromatography [24] and macroporous resin extraction [25], have been developed for resveratrol extraction from plants. However, because of the low concentrations existing in the plants, disadvantages of the plant extraction method are: it is not environmentally friendly, high-costs of production and the plant resources are limited. Concerning the last point, it is interesting to mention that the by-products from wine industry, which is treated as waste generally, should also be investigated for resveratrol extraction considering resveratrol was found in grape skin as well as the seeds and grape stalks and their transfer into wine are only with limited amounts during normal wine-making process [26]. In this way, one can transfer these waste into high-value products because only a very small amount of these waste materials is used all over the world [27].

2. CHEMICAL SYNTHESIS

Extensive efforts have also been made on chemical synthesis of resveratrol. Based on the published reports, chemical synthesis of this compound is mainly achieved through Perkin reaction, Wittig reaction, Horner-Wadsworth-Emmons reaction and Heck reaction.

2.1. Perkin Reaction

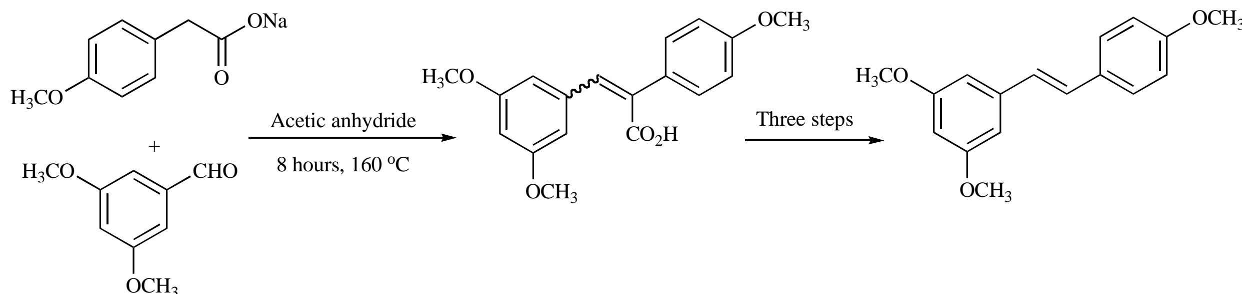
As shown in Scheme **1**, one of the pioneering syntheses of resveratrol was performed by Späth *et al.* [28] through Perkin reaction with *p*-anisyl acetic acid sodium salt and 1,3-dimethoxy benzaldehyde as the starting material in the presence of acetic anhydride. After decarboxylation with quinoline-Cu salt, *trans*-3, 5, 4'-trimethoxystilbene (trimethyl ether derivative of resveratrol) was obtained and its chemical structure was identical to the natural product [28] reported by Takoaka, who isolated resveratrol from roots of *Veratrum grandifluorum* for the first time [29, 30]. An improved method was also described by Solladie *et al.* recently [31].

However, Perkin reaction requires multiple steps including sequential protection, condensation, decarboxylation and deprotection. Particularly the decarboxylation of Perkin reaction needs extreme harsh conditions (like high temperature, polluting metal catalyst) for resveratrol synthesis which constrains its general utility. Recently, a modified Perkin reaction between benzaldehydes and phenylacetic acids bearing 4- or 2-hydroxy substitution at the aromatic ring performed in the presence of piperidine-methylimidazole and polyethylene glycol under microwave irradiation has been reported [32] (Scheme **2**). The authors observed a simultaneous condensation-decarboxylation which significantly reduces the synthetic steps required for resveratrol synthesis through Perkin reaction. The reported protocol also correlates with a recent recommendation that relatively mild conditions should be used to effect the overall transformation for Perkin condensation after revising the condensation mechanism [33]. It is also more environmentally friendly compared to the previous reports as it is devoid of employing toxic quinoline-Cu salt and harsh protection-deprotection conditions [32].

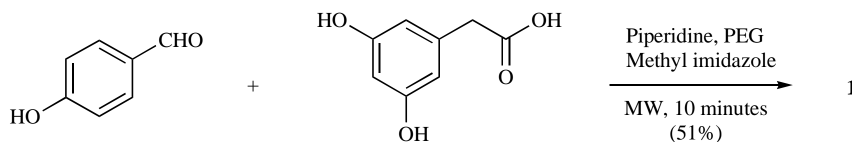
2.2. Wittig and Horner-Wadsworth-Emmons (HWE) Reaction

Wittig Reaction, a chemical reaction between an aldehyde or ketone and a triphenyl phosphonium ylide for production of an alkene and triphenylphosphine oxide, is a general approach for carbon-carbon double bond formation. In 1985, Moreno-Manas and Pleixatas performed resveratrol synthesis by Wittig reaction through reacting a phosphorus ylide, that is prepared from 3, 5-dihydroxytoluene, with a silylated hydroxybenzaldehyde (total yield 10%) [34]. Subsequent modifications have also been reported [35, 36]. Later on, a new Wittig reaction between 3, 5-bis-(tertbutyldimethylsilyloxy) benzaldehyde and the phosphonium ylid obtained from (4-methoxybenzyl)-triphenyl-phosphonium chloride has also been reported, which produces a mixture of *cis* and *trans*-resveratrol with a ratio of 2.3:1 [37]. Although further improvements have been made aiming at a higher overall yield and a better separation of the synthesized resveratrol from those by-products like triphenylphosphine oxide or compounds used for isomerization [38-42], a major disadvantage for resveratrol synthesis by classical Wittig reaction is the lack of stereoselectivity thus resulting in a mixture of *trans*- and *cis*-isomers, which often requires relatively harsh reaction conditions for their isomerization [43-45].

Whatever, because of the efficiency to construct carbon-carbon double bonds and recent development of the potential to control the stereoselectivity [46], the majority of reported synthetic routes for resveratrol production are based on the Wittig reaction and several Wittig-related deviations have also been reported to overcome the above mentioned problems. As an analog of Wittig reaction, the HWE reaction uses phosphonate-stabilized carbanions instead of phosphonium ylides for double bond formation [47]. Prominently, this reaction usually gives excellent *trans*-selectivity. By reacting benzylphosphonic acid diethyl ester with substituted benzaldehydes under HWE conditions, *O*-methylated resveratrol as well as its analogs have been successfully synthesized in exclusive *trans*-conformation in a relatively high overall yield and purity [48,



Scheme 1. Späth's synthesis of trimethylated resveratrol.



Scheme 2. A modified Perkin reaction to synthesize resveratrol.

49] (Scheme **3**). Furthermore, a so-called solid-phase reactive chromatography (SPRC), which combines reaction, separation, and purification into a single unit for the preparation of resveratrol analogues, was reported recently, which is devoid of long liquid-liquid extraction procedures and purification protocols thus enabling a fast reaction procedure [50].

2.3. Heck Reaction

The Heck reaction, a palladium-catalyzed olefination of aryl or vinyl halides, is one of the commonly used strategies for stilbene synthesis due to its remarkable chemoselective and amenability to a wide range of functional groups [43]. Different Heck-coupling reactions used as the key steps for resveratrol synthesis are summarized in Scheme **4**. In 2002, Guiso *et al.* performed resveratrol synthesis by palladium acetate catalyzed reaction between 3,5-diacetoxy- styrene and *p*-acetoxyiodobenzene to form 3,5,4'-triacetoxystill- bene, which was converted to resveratrol by treatment with sodium methoxide [51, 52]. In 2003, Andrus *et al.* used a decarboxylative Heck reaction by coupling 3,5-diacetoxybenzoic acid chloride with 4-acetoxystyrene in the presence of palladium acetate and *N,N'*-bis-(2,6-diisopropylphenyl) dihydroimidazolium chloride to give a resveratrol triacetate [53]. Notably, the starting material, benzoic acid derivatives, used in this report can be easily obtained which makes the synthesis more feasible. In the same year, a two sequential Heck-type coupling route was reported for the construction of unsymmetrical (or symmetrical) *trans*-stilbene derivatives, which is convenient and shows highly chemo-, regio-, and stereoselective properties [54]. Very recently, a palladium catalyzed Heck-Matsuda arylation of styrenes with arenediazonium salts as the key step for the synthesis of resveratrol within 3 steps reaching an overall yield of 72%, and DMU-212 (a resveratrol analogue) in a single step with 93% yield was also reported [55].

However, preparation of the required precursors for Heck reaction still takes several steps and more recently, a two-step synthesis of *trans*-3,5,4'-trimethoxystilbene using commercially available 1,3-dimethoxybenzene and 4-vinylanisole *via* an advanced Heck reaction was reported [56]. Moreover, considering the conveniency, expenses, overall yield and specificity, Heck reaction is still a more attractive strategy than others like Horner-Emmons route.

2.4. Other Methods

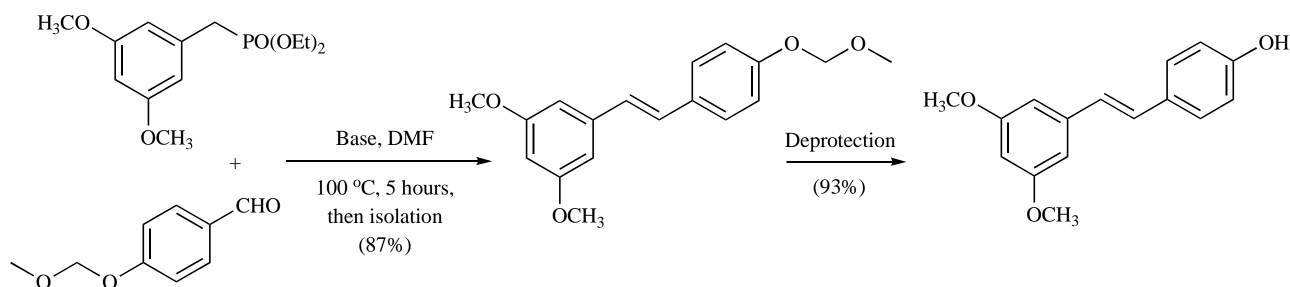
In 1997, Alonso *et al.* performed a lithiation/condensation reaction using 4-methoxy-benzaldehyde and the silyl derivative of 3,5-dimethoxy-benzyl alcohol as starting material for resveratrol synthesis. The elimination of H_2O led to the formation of *trans*-double bond exclusively, and only *trans*-resveratrol was therefore obtained in the end. The overall yield, however, was only 21% [57].

Julia olefination is one of the important tools for the preparation of alkenes and the Julia-Kochienski olefination is a further refinement which enables the formation of a double bond in one step with a very high *trans*- selectivity [58]. As depicted in Scheme **5**, Alonso *et al.* utilized this type of reaction for trimethylresveratrol and its analogue synthesis with a satisfactory yield and stereoselectivity [59, 60].

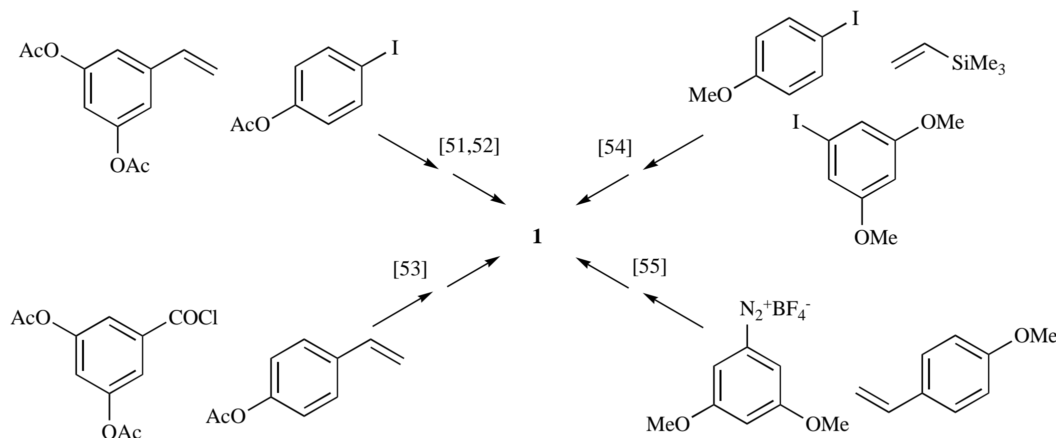
Several other methods were also applied for stilbene synthesis [61]. While most have both advantages and disadvantages, future efforts would target at a more convenient, atom economic (i.e., the reactant atoms are made used of efficiently), environmentally friendly and high yielding synthetic route. At this point, Heck reaction seems more attractive for resveratrol and its analogues preparation because of its mild reaction conditions which tolerate the presence of diverse functional groups, high stereoselectivity, as well as fewer synthetic steps.

3. BIOTECHNOLOGICAL SYNTHESIS

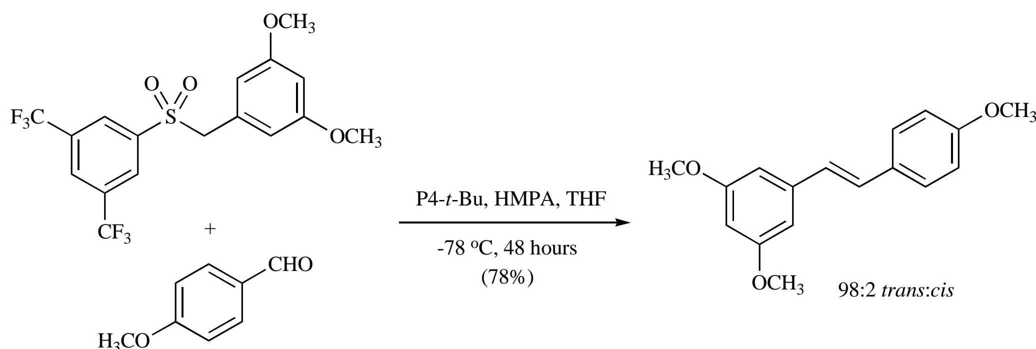
Because of the limitations for large scale preparation of resveratrol by plant extraction or chemical synthesis, intensive inter-



Scheme 3. Application of HWE reaction in resveratrol derivative synthesis.



Scheme 4. Synthesis of resveratrol (1) *via* Heck reactions.



Scheme 5. A Julia-Kochienski pathway to trimethylresveratrol synthesis.

ests arise in recent years for resveratrol production in a biotechnological means by use of microorganisms or plant cell cultures. Generally this technology represents a low cost and rapid production of the target products which are always biologically active. Basically, the genetic modifications for resveratrol production are based on the natural synthetic pathway of resveratrol, namely the phenylalanine/polymalonate pathway, in which one molecule of 4-coumaroyl-CoA was condensed with three molecules of malonyl-CoA to form resveratrol by stilbene synthase (STS), a key enzyme that is uniquely distributed in certain groups of plants [9, 10]. Several excellent reviews published recently on this topic [10, 11, 62], therefore here we only outline the current successes.

3.1. Utilization of Bacteria and Yeast

Engineering of both bacteria like *E. coli* strain JM109 [63], BL21 (DE3) [64, 65] as well as BLR (DE3) [66, 67] and yeast like *Yarrowia lipolytica* (ATCC20362 strain) [68], *Lactococcus lactis* (FSAO-VST strain), *Aspergillus niger* (FGSC A913 strain) and *Aspergillus oryzae* (MG1363 strain) [69] as well as *Saccharomyces cerevisiae* (RESV11 strain, CEN.PK113-3b strain, WAT11 strain and FY23 strain) [64, 70-72] have been reported to be successfully used for a heterogenous biosynthesis of resveratrol, although with variable yields ranging from 0.32×10^{-3} mg/l to 6 mg/l for yeast and from 3.6 mg/l to 171 mg/l for bacteria [10, 11]. The biotechnological engineering in these microorganisms was performed either by introducing the complete phenylalanine/polymalonate pathway using aromatic amino acids as substrates or only by transforming the genes of the key enzymes, i.e. STS and coumaroyl-CoA ligase (4CL), the latter one catalyzing the formation of 4-coumaroyl-CoA when 4-coumarate is supplemented as precursors [11]. Both strategies have their own advantages and disadvantages. For example, the complete pathway engineering represents a closer situation towards the natural biosynthetic pathway and thus it always starts from the precursors L-phenylalanine or L-tyrosine, which seems very attractive in terms of production cost [11]. However, on the one hand it has been shown that the heterologous biosynthetic ability of the system for an interested compound is decreasing when the number of genes required for the biosynthesis is increasing [70]. Of course, the more genes required for transformation, the more genetic works are required. On the other hand, it was shown that in *E. coli*, the expression of phenylalanine/tyrosine ammonia lyase, which is required at earlier steps for the formation of 4-coumaroyl-CoA formation [10], heavily depends on the addition of higher amount of coumaric acid (20 mg/l). However, it was shown that *p*-coumaric acid inhibits the growth of *E. coli* [73]. Therefore, direct transformation of 4CL and STS and supplementation of 4-coumaric acid as a building block might be more straightforward and fast, but the genes introduced for this purpose should be carefully selected as the production yield of resveratrol varied significantly depending on the genes' originating species [for a direct comparison, see ref. 11]. At this point, probably the host strains, the expression vectors, the physical distance of the paired genes (as a consequence the spatial location of the two enzymes) as well as the precursors used all seem to have an important effect [11, 65, 71]. Therefore, further optimizations concerning all the potential parameters are required.

A direct comparison by transforming the same genes into bacteria (*E. coli* BL21 strain) and yeast (*Saccharomyces cerevisiae* CEN.PK113-3b strain) for resveratrol production was performed and it is shown that *E. coli* produced 16 mg/l in average in 24 hours while yeast produced in average 6 mg/l which takes about 96 hours. However, *E. coli* requires higher amount of *p*-coumaric acid precursors (20 g/l) and yeast needs only 5 g/l [64]. Obviously, *E. coli* seems to more efficiently produce resveratrol in a relatively short time. However, by engineering yeast as a host for resveratrol production has another potential advantage, which is the utilization of this kind of yeast for wine industry during fermentation [74, 75]. Although at this point, further investigations are critically and thoroughly required to ensure the safety and quality of this kind of wines before it comes into reality as the genetically modified organisms are concerned [76].

3.2. Utilization of Plant Related Technologies

Several lines of plants, including grape, pea, apple, kiwi, tomato, rice, wheat and so on [for a complete list, see 62] have been engineered for resveratrol production, but mainly for a purpose of improved disease resistance to pathogenic attacks. The amounts of produced resveratrol varied significantly from different reported plants. For example, the mRNA of STS gene could be detected in transgenetic strawberry (*Fragraria*), while the STS protein could not be verified by mass spectrometry due to its rather low amount, and accordingly no resveratrol or its derivatives were detected [77]. Similarly, in transformed Kiwi fruits with STS genes isolated from Vitis spp. (*V. vinifera, V. labrusca* and *V. riparia*), piceid - resveratrol glucoside - was accumulated instead of resveratrol even mRNA of STS gene was transcripted too. Accordingly, no resistance against *Botrytis cinerea* was observed [78]. Nevertheless it was shown that piceid, similarly as resveratrol, improves the pathogen resistance of apple leaves to *Venturia inaequalis* under *in vitro* conditions [79]. The mechanisms underlying these discrepancies are not clear, however, the following parameters might have a contribution: (1) Promoter differences. The expression of STS gene was driven by either constitutive promoters, which leads to the accumulation of resveratrol throughout the plant, or by inducible promoters, which directs the resveratrol synthesis under inducible conditions [10, 62]. (2) Gene differences. At present, a large array of STS genes was identified [62, 80], therefore it is understandable that the individual members of the STS gene family might show different expression profiles. For example, the expression rate of grapevine (*Vitis vinifera L.*) *Vst1* gene has been shown to be 4-6 folds higher than *Vst2* in wheat [81] and 10 to 100 fold differences in grapevine [82]. Furthermore, the differences of the expression kinetics and the stability of mRNAs from respective STS genes were also recorded [9]. (3) Host differences. When *Vst1* gene was

transformed into apple (*Malus domestica Borkh.*) [83], peas (*Pisum sativum*) [84] or papaya (*Carica papaya L.*), the resulted transgenetic plants accumulate different amounts of piceid. This might be explained in part because different plants response differentially to different biotic and abiotic factors, environmental factors, the state of the plants and so on, which are well documented factors that affect the resveratrol synthesis in nature [18, 85, 86]. (4) Other factors, like events resulting from the gene insertion [87] and the other related metabolism pathways or events (like chalcone synthesis, transport and glycosylation of resveratrol, and so on), all might have an effect on resveratrol synthesis. Therefore, more molecular mechanism elucidations and investigations are required before a general strategy (if it exists!) could be introduced for resveratrol accumulation purposes in transgenetic plants.

Although theoretically the transgenetic plants enriching resveratrol could be used for resveratrol production in combination with plant extraction method, the complication to obtain and grow these kinds of plants still limits their utilization in reality. At this point, using plant cell cultures is a more attractive alternative due to its established track record for valuable secondary metabolites production [88]. At present, the mainly used cell cultures for resveratrol production are based on grapevine (*Vitis vinifera*) [11], although a cotton cell suspension has been reported [89]. In order to increase the resveratrol production, several inducers or elicitors have been used, including methyljasmonate (MeJA), cyclodextrins, chitosan, L-Alanine, fungal cell wall fragments, Na-orthovanadate, jasmonic acid and so on [summarized in 11]. Among them, modified β-cyclodextrins, namely the methylated and hydroxypropylated version, was the most efficient one which gives the highest production of resveratrol [90]. More interestingly, a combination of MeJA and cyclodextrin gives a synergistic effect on resveratrol production, which generates a final concentration higher than the sum of the individual additions [91]. The stimulation effect of these elicitors is not only due to their ability to induce the gene expression of those involved in resveratrol synthesis [91-94], but also due to their ability to form inclusion complexes (in case of cyclodextrin) which stabilize resveratrol as it inhibits the lipoxygenase catalyzed resveratrol oxidation [95]. Furthermore, in most cases the plant cell culture produced resveratrol was secreted into the extracellular medium, while piceid, the stabilized form [96], located inside the cell. Therefore, enhancement of the secretion of resveratrol from its glycosylated form across the cell wall would further benefit their production. Although the secretion mechanism of resveratrol is not well characterized, the ATP-binding cassette (ABC) transporters might be a potential candidate as they are involved in the secretion of other phenolic compounds [97]. Interestingly, after treatment with the modified β-cyclodextrins, heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (DIMEB) which shows the most effective resveratrol elicitation in plant cell cultures, induction of genes encoding putative secondary metabolite transporters, such as the ABC transporter family, was observed [93].

Other culture systems, like hairy root cultures of peanut and callus cultures, for resveratrol production were also reported [98, 99]. Recently, a new hairy root line from peanut cultivar was used to establish the culture system and the factors, including nutrient conditions of the media, pH and conductivity of the culture system, nutrient metabolism and induction of the culture at different ages, all affecting the biosynthesis of resveratrol were characterized and optimized [100]. Hairy root cultures enable a high and continuous yield for a wide range of metabolites with high growth potential and long term stability properties [101]. However, scaling up hairy roots to an industrial level is still a big challenge at present and more optimizations are requried before its industrial exploitation. Additionally, calli of peanut (*Arachis hypogaea*) and grapevine (like *Vitis amurensis* Rupr., *Vitis vinifera* L., *Vitis thunbergii* sieb.et zucc) were also used for resveratrol production and it was shown that several elicitors, such as UV irradiation, sodium nitroprusside treatment, as well as growth regulators like 6-benzyl-aminopurine all could stimulate resveratrol synthesis [102-105]. Interestingly, transformation of *Vitis amurensis* callus culture by the *rolB* gene of *Agrobacterium rhizogenes* led to a 100-fold increase of resveratrol production [103] in a Ca^{2+} dependent manner [106] resulting from the selective enhancement of individual gene expression from PAL and STS gene families induced by *rolB* transformation [107]. However, further system optimizations, space requirements and required long time of culturing have to be improved in the future before a large scale production of resveratrol comes into reality by this technology [11].

3.3. Other Systems

Human kidney cell line (HEK293) was also engineered successfully for resveratrol production in aglycone form [71]. This observation might be particularly interesting for future gene therapy purposes because the introduced TAL gene can directly uses the tyrosine pool of the mammalian cells thus directly enables the resveratrol production in combination with the introduced 4CL and STS gene fusion [10]. At this point, all the concerns like the feasibility, expression regulation, safety and so on would have to be extensively and thoroughly investigated as it has been observed that toxic effects appear when resveratrol concentration reaches at or above 1 g per kg (body weight) [108].

Streptomyces, belonging to the family of Actinobacteria which is a group of Gram-positive bacteria, is the largest antibiotic producing genus and has been widely used for production of antibacterials, antifungals as well as a wide range of other bioactive compounds [109]. Recently, an engineered strain of *Streptomyces venezuelae* DHS2001 was used for the production of plant polyketide, including resveratrol [110]. Although the production yield in this report is lower when compared with others like *E. coli*, it is believed there are still rooms for its improvement [110].

4. STABILITY AND BIOAVAILABLITY

Under intense UV light, the *trans*-isomer can be easily transformed into the *cis*-configuration [17, 111]. Theoretically, the *cis*-resveratrol is less stable because of the two center chain hydrogen atoms located on the same side. Indeed, *trans*-resveratrol was shown to be stable for months when protected from light, unless in high pH buffer. In contrast, the *cis*-form is stable only at neutral pH when completely protected from light [17]. Under consumable conditions, we found that resveratrol (*trans*- and *cis* together) decreased by approximately 50% in sunlight and by approximately 25% under UV illumination within the first hour. For both conditions the loss continues with time but eventually with reduced efficiency [111]. Loss of resveratrol by UV treatment is contrast to the original thought as it is believed that this treatment of *trans*-resveratrol generates only *cis*-resveratrol. Interestingly, unknown substances in addition to the *trans* and *cis* isomers after exposure of *trans*-resveratrol solution to UV light were noticed [111-113] and recently, the MS/MS analysis has identified that the compound is derived from oxidation, where the double bond at the centre of the resveratrol molecule, changes into a triple bond, forming a diphenylacetylene derivative (3,4',5-trihydroxy-diphenylacetylene) [114]. Together, these data indicate that, as with all antioxidant compounds, resveratrol is very unstable and tends to act as a reducing agent when exposed to light, and will be oxidized on exposure to air. Oxidation may eventually lead to complete degradation and substantial loss of its biological activity. Therefore it is necessary to protect resveratrol from direct exposure to light and air during storage and analysis.

Under physiological conditions, though no phase I reactions like oxidations, reductions, or hydrolysis were reported under reported *in vitro*, *in vivo* or *ex vivo* conditions, resveratrol mainly undergoes glucuronidation and sulfation process after administra-

tion as investigated using liver and duodenum samples as well as Caco-2 cells *in vitro* [115]. *In vivo* analysis with animal models like rabbits and rats or mice as well as humans have shown that resveratrol is absorbed efficiently and distributed into various organs including brain, heart, lung, liver, kidney, etc., although with low levels (always below 1 nmol per g fresh tissue) [8, 115]. However, since only trace amounts of free resveratrol were found in plasma samples while its conjugated glucuronide and sulfate forms were still detectable after a prolonged time, it is suggested that probably most of resveratrol is metabolized under *in vivo* conditions too [116-120]. Therefore, the rapid metabolism is one of the constraints concerning the low bioavailability of resveratrol under *in vivo* conditions [8, 108]. In this respect of bioavailability, another determinant concerns the resveratrol transport across the plasma membrane to its cellular targets. In hepatic cells, it was shown that transport of resveratrol involves a passive and a carrier-mediated transport process [121]. This later process might be particularly interesting to improve the uptake efficiency of resveratrol. On the other hand, it was demonstrated that resveratrol conjugates are secreted back to the intestinal lumen through the multidrug resistance-associated protein (MRP2, ABCC2) and the breast cancer resistance protein (BCRP, ABCG2), both belonging to the ABC transporter family [116]. Therefore, reduction of this efflux might improve the pharmacokinetic efficacy of resveratrol as it was proposed that these resveratrol metabolites might be or served as the pool for the bioactive form *in vivo* [122], even this issue is not yet fully addressed and other opinions exist [108, 123, 124]. Additionally, resveratrol was shown to interact with several proteins like serum albumin or haemoglobin, which might also contribute to the regulation of its bioavailability [8, 121].

5. RESVERATROL ANALOGS (STRUCTURE-ACTIVITY RELATIONSHIPS)

As discussed above, the main drawbacks of resveratrol are its low stability and lability to inactivation potentially caused by natural modifications. Its rapid metabolism is another concern although the produced metabolites might be the real functional form, a topic requiring a thorough investigation in the future to find out the actual functional form in terms of certain diseases. Additionally, besides the widely known beneficial effects of resveratrol, genotoxic effect was also reported [125]. Therefore, evaluation on the biological activity of resveratrol derivatives or analogs is obviously required and more stable and equally or more effective forms of resveratrol derivatives/analogues with reduced genotoxicity would be highly desirable.

Theoretical calculations based on the molecular structure of resveratrol have been performed [126-129] and it was concluded that resveratrol has potent antioxidant activity and the dominant feature of its radical was a semiquinone structure, which determined the radical stability. The unpaired electron is mainly distributed to the O-atom and its *ortho* and *para* positions. Because of resonance effects, the 4'-OH group is more reactive than 3- and 5-OH groups and the acidity of this group as well as the subsequent transfer of protons or hydrogen atoms to reactive species seem to be crucial for its antioxidant activity. The importance of this 4'-OH was also confirmed by experimental studies concerning its requirement for cell proliferation inhibition [130], its genotoxic activity [131] as well as its efficacy for free radicals scavenge [132]. It was also found that the antioxidant activity of resveratrol is related to its spin density and unpaired electron distribution of the oxygen atom [128]. Therefore, the type of substitution groups would have an important effect on its activity. For example, it was shown that in HL-60 leukemic cells hydroxystilbenes with *ortho*-hydroxyl groups exhibited higher cytostatic activity compared to hydroxystilbenes with other substitution patterns because of the formation of *ortho*-semiquinones, which undergo redox-cycling thereby consuming additional oxygen and forming cytotoxic oxygen radicals, during metabolism or autoxidation [133]. Furthermore, introduction of methyl groups into the ortho position of the 4′-hydroxyl group of resveratrol significantly increased its antioxidative ability but surprisingly decreased its genotoxicity [134]. Because delocalization of the unpaired electron density was mainly on the oxygen atom and its *ortho* and *para* positions [128], therefore the introduced methyl groups contribute to the delocalization of the unpaired electron by hyperconjugation thus results in the stronger antioxidative ability of *o*-methyl derivatives as compared to resveratrol [134]. In addition, hydroxylated but not methoxylated resveratrol derivatives showed a high rate of selective inhibition of cyclooxygenase-2 (COX-2), while resveratrol shows non-selective effect on COX-1 and COX-2 [135] indicating that selective substitution would be very helpful for specific purposes.

Further experimental analysis on the structure-activity relationship of resveratrol and its analogues has identified that their biological activity not only depends significantly on the structure of the molecules, such as the number and position of hydroxyl groups, intramolecular hydrogen bonding, stereoisomery and double bond [136], but also with the electron environment [137]. These informations are very helpful in screening for more effective alternatives for pharmacological purposes since the biological activities of resveratrol are often ascribed to its antioxidant activity, however, one have to keep in mind that for certain purposes, careful evaluation is definitely required as it was concluded that neither the cytotoxic or cytostatic activities of hydroxystilbenes nor their cytoprotective and antioxidant activities in living cells can be predicted from their antioxidant and prooxidant activity, respectively, in cell-free systems [138]. Indeed, in an array of inhibition test for the human tumor necrosis factor alpha-induced activation of transcription factor nuclear factor kappaB, numerous resveratrol derivatives that potentially inhibits the activation of NFkappaB generally did not exhibit antioxidant activity and even there are compounds that were devoid of hydroxy groups but shows 100-fold more potent than resveratrol [49]. Interestingly, even *trans*-resveratrol was known to be more active than *cis*-resveratrol, the modified *cis*-isomer derivatives displayed a higher activity than their corresponding *trans*-isomer derivatives in several cases [139-141].

6. FUTURE PERSPECTIVES

Resveratrol preparation from natural sources may suffer from its low abundance in nature and environmental, seasonal, or regional variations of natural materials. While the complexity of synthetic pathway and the low total yield as well as production of by-products, which further complicate its purification, limit the industrial application and is commercially infeasible, therefore, biotechnological means offer significant promising and scalable strategies for resveratrol production while using low-cost and renewable resources [142]. However, the slow growth and genetic intractability of certain natural product-producing bacteria present significant challenges for metabolic engineering [143]. In case of resveratrol, a big success has been made by use of microorganism, however, obviously further optimizations are required concerning optimal gene overexpression and regulation as well as final resveratrol production yield. At this point it is worth to mention that, the functional overexpression of heterologous genes, particularly of mammalian origin, using standard bacterial expression hosts such as *E. coli* is often suffered from incorrect folding, assembly or targeting of recombinant proteins, as well as inclusion body formation, therefore characterization of all these parameters might be useful to achieve a large scale production of resveratrol. In addition, recent successes by *in vitro* enzymatic total synthesis of natural products [144, 145] provide additional opportunities for metabolic engineering [143], which might be also worth to give a try for resveratrol synthesis. In contrast to microorganism, plant cell culture might be more attractive to produce higher amounts of resveratrol, therefore further scale-up to industrial level has to be set up [11] even several

limitations have to be kept in mind like the costs of the equipments under large scale production condition as well as the easy infection property of such system during generation.

Extensive investigations on resveratrol have been performed under *in vitro* conditions, i.e. with cultured cells, which exposed to unmetabolized resveratrol at concentrations that are often 10-100 times greater than peak concentrations observed in human plasma after oral consumption [146], while pharmacokinetic analysis using animal or limited numbers in humans suggest that resveratrol undergoes rapid metabolism and other tissues are exposed primarily to resveratrol metabolites. Because little is known about the biological activity of resveratrol metabolites, and it is not known whether some tissues are capable of converting resveratrol metabolites back to resveratrol [122], further investigations on resveratrol analogues should be thoroughly evaluated, which should also be highly valuable to find more effective and stable one to serve as substitute of resveratrol. Additionally, specific targeting strategies should be also considered which might improve the specificity and efficacy [147]. Finally, translating the knowledge obtained from epidemiological and *in vitro* studies into clinical level should be extremely careful since the testing experimental system might be of particularly importance as evidenced from the research of beta carotene [148].

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