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New Resveratrol Analogues for Potential Use in Diabetes and Cancer

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Abstract

Resveratrol is a well notorious compound that may play a role in the prevention of diabetes complications and different cancers. Along, resveratrol, a naturally occurring phytoalexin, is known to exert numerous beneficial effects in the organism. Isolation of resveratrol from plants, however, has been proved being difficult. Importantly, the bioavailability in the body is poor therefore capability is reduced and not enough resveratrol reaches the target organ. In this study we generated different methoxylated resveratrol analogues using Wittig reaction. Trans stilbene obtained was 0.08 g and the *cis* one was 0.01 g. Additionally with the Horner-Witting method a yield of 0.15 g trans stilbene was obtained. By substituting the hydroxyl group with methoxy group at different positions on the aromatic rings, we could increase the efficacy and bioavailability of the Trans form of resveratrol.

Keywords: Cancer; Diabetes; Horner-Wittig Reaction; Resveratrol; Stilbene; Wittig Reaction

Introduction

Diabetes is known as a chronic metabolic condition of having higher than normal blood sugar levels [1]. It involves β cells in the pancreas, which secrete a hormone called insulin. There are two types of diabetes: Type 1 and Type 2. Type 1 diabetes occurs when no insulin is being produced by the pancreas and is also known as insulin-dependent diabetes. Type 2 diabetes appears when there is relative insulin deficiency as such it increased glucose production by the liver and decreased utilization of glucose in the peripheral tissues [2]. It is well known that Type 2 diabetes can be genetically inherited and can be influenced by a number of factors such as diet, stress, alcohol consumption and lack of exercise [3]. Since the number of people diagnosed with diabetes has increased enormously, this disease is nowadays considered the 6th cause of worldwide mortality [4]. Because of the heightened aging of population and overweight people, it is estimated that by 2025 roughly 5 million people will have diabetes [4,5].

There are distinct classes of drugs which treat diabetes. Essentially, different types of insulin and as a second line treatment are the Sulphonylureas class. This class of drug cannot be taken by obese people because one of the adverse reactions is weight gain [6]. It appears clear that new treatments are urgently required to properly manage the different forms of diabetes [7-10]. Resveratrol is a stilbenoid and a phytoalexin which belongs to the large group of polyphenols found in different plant species [1]. The name stilbene (Figure 1), 1,2-diphenylethylene was derived from the Greek word stilbos, which means shining [3]. Phytoalexins are a group of phytochemicals of low molecular weight which are produced when plants are attacked by pathogens [2,3]. The richest natural source of resveratrol is *Polygonum cuspidatum* [3,5]. Also, resveratrol is synthesized in the skin cells of the grapes [11].

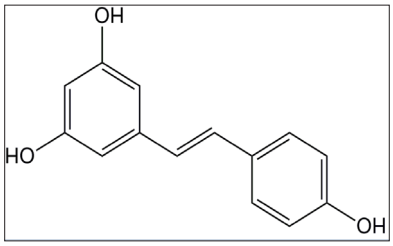

Figure 1: Structure of resveratrol

It is found 5-10% of biomass in the grape skin and absent or low in the fleshy fruit [5,11]. Trans-resveratrol is more efficient as an antioxidant than *cis*-resveratrol. However, *cis*-resveratrol has shown anti-inflammatory properties through significant modulatory effect

on the nuclear factor kB related genes [9]. Nowadays, resveratrol is available in tablet form and is recommended as dietary supplement [5,10]. According to Szkudelska K et al. [5], resveratrol has calorie restriction mimetic effect which can prevent some diseases of ageing such as insulin resistance and type 2 diabetes. The proposed mechanism for this effect may be related to inducing genes for phosphorylation and mitochondrial biogenesis [5,12]. Mitochondrial biogenesis is a process when new mitochondria are formed in the cell and it is activated by many different regulators such as peroxisome proliferator activated receptor gamma (PGC-1α) during times of cellular stress. Indeed, common complications of type 2 diabetes are metabolic syndrome and oxidative stress [8-15].

Many in vitro studies [10] have tried to demonstrate resveratrol potential in both cancer initiation and progression i.e. resveratrol's can promote cell cycle arrest leading to apoptosis of tumor cells [16-19]. Moreover, the role of resveratrol in cyclooxygenese (COX) inhibition is well-known [20-24]. With the epigenetic landscape enlargement, resveratrol has been under light even more. Indeed, its capacity to reduce DNA binding activity of nuclear factor κB (NF-κB) has been proved [24-29], but a lot of investments need still to be done in term of epigenetic cancer therapies [30]. Despite its potential, there are many problems associated with resveratrol. Firstly, according to the literature, the isolation of resveratrol from plants has proved to be difficult [31,32]. In the second place, the bioavailability of resveratrol in the body is poor therefore potency is reduced and not enough resveratrol reaches the target organ [31,32].

To increase the bioavailability, resveratrol analogues with similar activity that lack the hydroxyl groups are being looked at [33,34]. Taken together these data highlight the fact that it is crucial to continue exploring the design and synthesis of resveratrol analogous. Stilbene, which the most famous derivatives is resveratrol as we mention above, is an unreactive colorless compound practically insoluble in water. There are two isomeric forms of 1,2-diphenylethylene: *trans*-stilbene, which is not sterically hindered, and *cis*-stilbene, which is sterically hindered and therefore less stable [2,35,36]. Trans-Stilbene melts around 125°C and the *cis*-stilbene melts around 6°C. From literature we know that under the influence of light trans-stilbene could isomerize to *cis*-stilbene and the reverse path can be induced by heat or light.

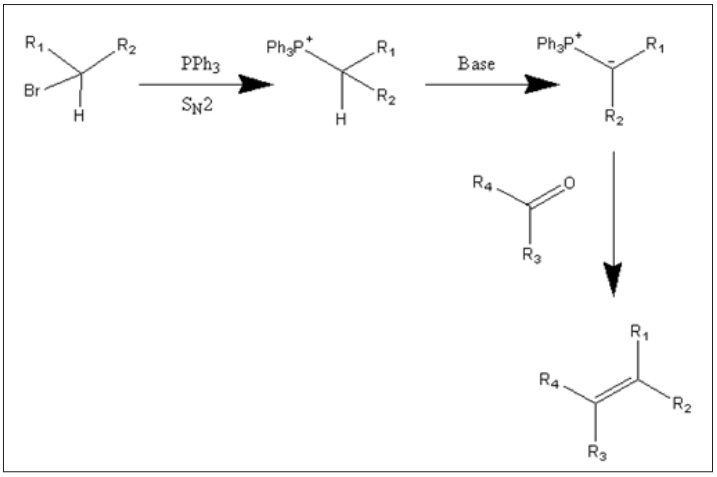

Figure 2: Wittig Reaction.

Different methods have been reported to synthesize stilbene derivatives such as Perkin reaction, Heck reaction, Aldo-type reaction, Wittig-type olefination reaction and Horner-Wittig reaction [35,36]. In this study we aim to use Wittig-type olefination reaction and demonstrate the potential to give both *cis* and *trans* isomers with an increasing yield. Wittig-type olefination reaction is used for the synthesis of alkenes [35]. The phosphorus yield, or Wittig reagent, is attacked by a carbonyl compound used as an electrophile. Addionally, to create the alkene double bond the smaller carbon units are conjoined. These interactions allow quick assemblement of molecules increased in size and complexity [35]. By increasing the stability of phosphorus yield, this will allow an increase in the Trans stilbene [36] (Figure 2).

Materials and Method

Materials

4-methoxybenzltriphenylphosphonium chloride, 3,4,5-trimethoxybenzaldehyde, n–butyllithium, anhydrous THF, ethylacetate, magnesium sulphate, 4-methoxybenzylchloride, triethylphosphite, diethyl-4-methoxybenzylphosphonate, dimethylfarmamide (DMF), sodium *tert*-butoxide, 2,4-dimethoxybenzaldehyde were supplied by Sigma Aldrich.

Chemistry

Preparation of trans and *cis*-stilbene was accomplished by means of the Wittig reaction between 3,4,5-trimenthoxybenzaldehyde and methyl-triphenyl-phosphonium chloride. 4-methoxybenzylchloride and triethylphosphite underwent Arbusov reaction to produce diethyl-4-methoxybenzylphosphonate which then was used to react with 3,4,5- trimethoxy-benzyl-phosphonate using Horner-Wittig reaction to produce trans-stilbene derivative. The reactions were carried out under nitrogen gas using solvent anhydrous THF. Production of 2, 4, 4'-trimethoxy-stilbene was synthesized using Horner–Wittig reaction only. The reaction was carried out under nitrogen gas and solvent DMF. Final products were characterized by NMR and melting point, which were in full accordance with the depicted structures.

Mechanisms

Mechanism of Wittig Reaction: This mechanism requires the use of a strong base (commonly butyl lithium) to carry out the deprotonation and moister free conditions. Thus, the phosphonium ion is deprotonated by base [34,35]. Phosphorus atom is a strong electron-withdrawing group positively charged and able to activate the neighboring carbon atom as a weak acid [36] (Figure 3). Methoxylated analogues of resveratrol such as *trans* 3,4,5,4'-tetramethoxystilbene (DMU 212) was synthesized using Wittig reaction. Other methoxylated analogues are synthesized using Horner-Wittig reaction such as 2,4,4'-trimethoxy stilbene and 3,4',5- trimethoxy stilbene. The mechanism of Horner-Wittig reaction is similar to Wittig reaction, it is a variation made by Leopold Horner [35-37]. The only difference is Horner-Wittig reaction selectively produces *trans*-formation of stilbene whereas Wittig reaction produces both *trans* and *cis* products.

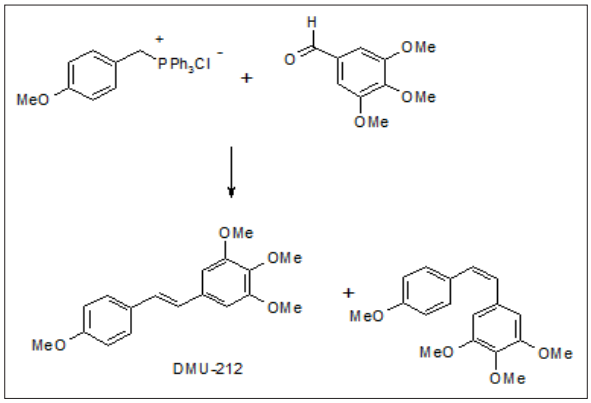

Figure 3: DMU212 synthesis by Wittig reaction.

A General Wittig procedure for synthesis of *trans* and *cis*-stilbenes: (Figure 3) To a stirred suspension of the 4-methoxybenzyltriphenylphosphonium chloride (1.194mmol, 0.5g) in anhydrous THF (20mL), at -20°C, under N_2 was added drop wise a solution of *n*-butyllithium in hexanes (0.78mL, 1.19 mmol, 2.5M). A TLC plate was carried out with the mobile phase of ethyl acetate/hexane (7:3). Reaction mixture is spotted against the starting material on the TLC plate. From the plate no starting material was present in the reaction mixture and Rf values were obtained. The resulting red suspension was stirred for 20min at -20°C and then the 3, 4, 5- trimethoxy benzaldehyde (1.194mmol, 0.23g), in anhydrous THF (10ml) was added drop wise. The reaction was stirred for 1h at -20°C and then allowed to warm to room temperature and stirred overnight.

The reaction mixture was quenched with ice-water (40ml) and extracted with ethyl acetate (3 x 20ml). The combined organic extracts were washed with water (2 x 20ml), brine (2 x 20ml) and dried over anhydrous magnesium sulphate. The solvent was removed in vacuum. The solution was collected from the vacuum and placed in the round bottom flask and attached to the rotary evaporator. Crude product was obtained. Flash column chromatography (petroleum ether/ ethyl acetate 5:5) afforded the *cis*- and *trans*- stilbenes respectively. 3',4,4',5'-tetramethoxystilbene. A cream solid; Yield: 0.7g (30%); mp 157°C; ^{1}H NMR (CDCl3): e 7.44 (d, J = 8.8Hz,2H), 6.98 (d, J = 16.3Hz, 1H), 6.91-6.83 (m, 3H), 6.71 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$): e 159.2, 153.3, 137.7, 133.3, 129.9, 127.6, 127.5, 126.4, 114.1, 103.2, 60.9, 56.0, 55.2.

A Horner-Wittig Procedure for synthesis of trans-3,4,4',5'- tetramethoxystilbene (DMU 212): (Figure 4) A mixture of 4-methoxybenzylchloride (6.39mmol/ 3.6ml) and triethylphosphite (7.98mmol/ 5.46ml) was heated to reflux for 3h. A TLC plate was carried out to observe if the reaction had gone to completion. According to the TLC plate there was some starting material present. The reaction mixture was left for a further of five days. Another TLC plate was carried out after five days the reaction had gone to completion. After controlling by thin layer chromatography (TLC: Rf. = 0.17 ethyl acetate/ petroleum ether 2:8) that the reaction was complete, the excess triethylphosphite was removed in vacuo to afford diethyl-4-methoxybenzylphosphonate as viscous straw colored oil. A cooled solution of diethyl-4-methoxybenzylphosphonate (20mmol, 5.06g) in DMF (20ml) was added to the stirred suspension of sodium tert-butoxide (40mmol, 3.84g) in DMF (20ml) at 0°C under N_2. The pale yellow solution was stirred at 0°C for a further 40min.

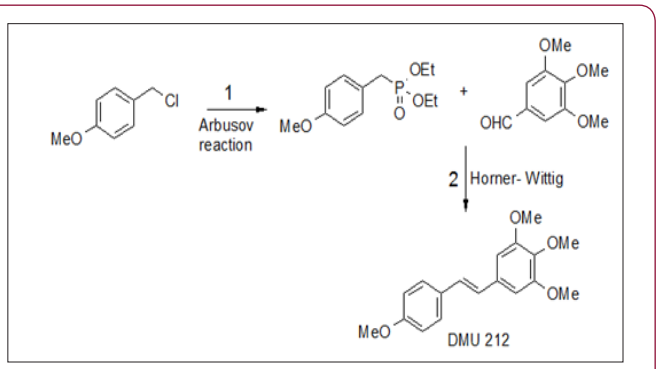

Figure 4: DMU212 synthesis by Horner-Wittig reaction.

A cooled solution of 3,4,5-trimethoxybenzaldehyde (20mmol, 3.92g) in DMF (10ml) was siphoned in the mixture. The resulting pale yellow mixture was stirred for further 1h and then allowed to cool to room temperature over 1.5h. A TLC plate was carried out to ensure reaction has gone to completion. The mixture was heated to 95°C for 20min and then allowed to cool to room temperature. The mixture was quenched with water (50ml) and the white precipitate formed was removed by filtration, washed with water (20ml) and cooled ethanol (20ml). Recrystallization from ethylacetate afforded DMU 212 as white crystalline solid. 3',4,4',5'-tetramethoxystilbene. A white solid; Yield: 3g (76.5%) m.p. 157°C; ^{1}H NMR ($CDCl_3$): δ H 7.44 (d, J = 8.8Hz,2H), 6.98 (d, J = 16.3Hz, 1H), 6.91-6.83 (m, 3H), 6.71 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$): e 159.2, 153.3, 137.7, 133.3, 129.9, 127.6, 127.5, 126.4, 114.1, 103.2, 60.9, 56.0, 55.2.

Synthesis of Diethyl-4-Methoxybenzylphosphonate: A mixture of 4-methoxybenzylchloride (27.2mmol, 3.69ml) and triethylphosphite (32.7mmol, 5.6ml) was heated to reflux for 3h. A TLC plate was made using mobile phase of ethyl acetate/ petroleum ether (2:8) to observe if the reaction mixture had gone

to completion. From the TLC plate, starting material was showed in the reaction mixture. The reaction was left for another three days to go to completion. After controlling by thin layer chromatography (TLC:Rf. = 0.17 ethyl acetate/petroleum ether 2:8) that the reaction was complete, the excess triethylphosphite was removed in vacuo to afford diethyl-4-methoxybenzylphosphonate. Total stock material collected was 5.32g of diethyl-4-methoxybenzylphosphonate.

Horner-Wittig Synthesis of 2,4,4'-Trimethoxystilbene: Figure 5 A cooled solution of diethyl-4-methoxybenzylphosphonate (77mmol, 2g) in DMF (20ml) was added to the stirred suspension of sodium *tert*-butoxide (15.4mmol, 1.48g) in DMF (20ml) at 0°C under N_2. The pale yellow solution was stirred at 0°C for a further 40min. A cooled solution of 2,4-dimethoxybenzaldehyde (77mmol, 1.29g) in DMF (10ml) was siphoned into the mixture. The resulting pale yellow mixture was stirred for further 1h and then allowed to warm to room temperature over 1.5h. A TLC plate was carried out against the diethyl-4-methoxybenzylphosphonate to ensure the reaction had gone to completion. From the TLC plate it showed there was starting material present in the reaction mixture. Therefore, the reaction mixture was left on the ice-bath for further five days.

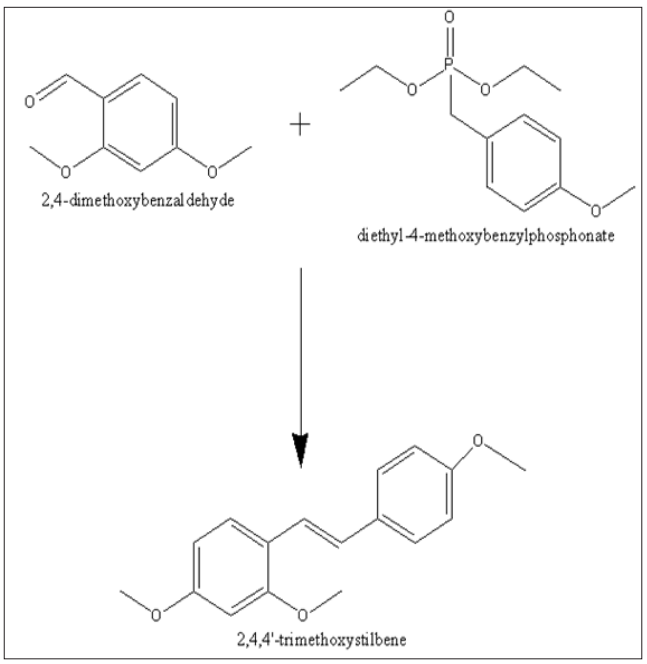

Figure 5: 2,4,4'-trimethoxystilbene synthesis with Horner-Wittig reaction.

Afterwards, another TLC plate was carried out which showed the reaction had gone to completion. The mixture was quenched with water (50ml) and the grey precipitate formed was removed by filtration, washed with water (50ml) and cold ethanol (50ml). The solution was placed on the rotary evaporator to remove the DMF. Recrystallization from ethyl acetate afforded 2,4,4'-trimethoxystilbene. 2,4,4'-trimethoxystilbene. White solid; Yield: 0.56g (43.4%), TLC: Rf. = 0.65 (ethyl acetate/ petroleum ether 1:9); m/z [FAB] 271 [M+1]+, 45%); δ H (CDCl3) 3.80 (9H, s, 3 x OMe), 6.40 (1H, t, ArH), 6.65 (2H, d, ArH), 6.85 (1H, d, J=16Hz, C=CH), 6.90 (2H, d, ArH), 7.10(1H, d, J=16Hz, C=CH), 7.4(2H, d, ArH); δ C (CDCl3), 55.37, 55.40, 99.67, 104.38, 113.69, 126.62, 127.86, 128.33, 128.79, 129.97, 139.75,159.45, 161.02; Anal. Calcd $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found C, 75.60; H, 6.67; HRMS found [M+1]+ 271.1329, $C_{17}H_{19}O_3$ requires [M+1]+ 271.1129.

Results and Discussion

Synthesis of *Trans* and *Cis*-Stilbene

The method we used for the synthesis of *Trans* and *cis*-stilbene is the Wittig reaction [35-37]. This reaction is used to form a double bond between the two compounds. The reaction is used in organic synthesis and to obtain *cis* and *Tran's* form of the product. According to a study of Alonso et al. [38], they used nickel nanoparticles to promote Wittig olefination of benzyl alcohols with benzyidene-triphenyl-phosphorane, a new synthesis of resveratrol, DMU-212 and analogues. In this study we used benzyltriphenylphosphonium chloride and *n*-butyllithium which produced a red suspension. The deep red color is an indication of the "Wittig reagent" ylides. The product alkene and phosphonium salt are normally not colored. Thus, Wittig reactions can be monitored by the formation of red color when ylide is made and the disappearance of the color shows that the ylide has reacted and gone to the final product. When the 3,4,5-trimethoxybenzaldehyde was added to the reaction mixture the suspension changed color from red to yellow.

To see if the reaction had gone to completion a TLC plate was carried out by quenching the reaction. TLC plate showed that the reaction needed an hour to complete. Furthermore, the suspension changed color from yellow to cream. After freeze drying and Büchner filtering the solid and liquid product, they were weighed to obtain the yield. *Trans* stilbene was a cream product and the amount obtained from the experiment was 0.08g. The *cis* stilbene appeared as a straw colored oily liquid and the quantity obtained was 0.01g. Using Wittig reaction, *trans* and *cis* form of stilbene were obtained however the yield of both forms were much less than what was predicted. The retention factor (Rf) value were measured and the Rf value of trans and *cis* stilbene was compared to the DMU-212 rf value. Rf value for *trans, cis* and DMU-212 was 0.34, 0.42 and 0.32. The value of *trans* and DMU-212 is similar to each other which proves the *trans*-stilbene is 3,4,4',5-tetramethoxystilbene which is the same as DMU-212. The yield produce for *trans*-stilbene was 16%. We assume that the reason of low yield is due to some of the material lost during the reaction. *Cis* isomer of the stilbene was also produced therefore some of it must be taken up by the *cis*-isomer and reducing the yield for *trans*-isomer. We are tempted to speculate that to improve the yield of the product Heck reaction could be used in the future. Heck reaction is also selective for *trans* isomer and the yield produced by this reaction can be used to compare with the yield produced by Wittig reaction.

Synthesis of *Trans* 3,4,4',5-Tetramethoxystilbene

We elect to use the Horner-Wittig method because this reaction gives a good *trans* selectivity. The diethyl-4-methoxy-benzyl-phosphonate which was used was synthesized earlier. The second half of the reaction was left longer than the actual method. This is because the reaction had not gone to completion as the red suspension was still visible showing that the ylide was formed, present and had not gone to completion in the product as there is not color change spotted. To confirm a stilbene has been formed, a

purple spot was visible under the U.V. light indicating the presence of stilbene when carrying out a TLC plate. Rf values were measured from the TLC plate when the reaction had gone to completion which was 0.136 and this value was compared against the literature Rf value which was 0.17. This reaction produced a greater yield, 0.15 g, of *trans* 3,4,4',5-tetramethoxystilbene compared to the general Wittig reaction. The major difference in yield could be possibly because in the general Wittig reaction, *trans* and *cis* isomers were produced whereas in the Horner-Wittig reaction only *trans* isomer was produced. Again, we may argue that in future Heck reaction can be used to compare.

Synthesis of 2,4,4'-Trimethoxystilbene

Horner-Wittig reaction was used as *trans* isomer of the product needs to be obtained. During the reaction a red suspension had been formed and had changed to a grey color, which showed that ylide had been formed and gone to the product due to the disappearance of the red color. When a TLC plate was made a purple spot was shown under the U.V. light stating that stilbene has formed. This methoxylated analogue has not previously been made, therefore it was hard to compare.

Conclusion

Here, resveratrol analogues were designed to improve potency and biopharmaceutical properties of resveratrol itself. The Horner Wittig reaction produced exclusively *trans* stilbene with high yields. To form the alkene bond between the two aromatic rings, Wittig olefination reaction is essential. Wittig reaction requires a phosphonium ylide to form a phosphonium ion, the increase in stability of this ylide will favors *trans* form of stilbene. Non-polar solvents and salt free conditions induce *cis* formation of stilbene due to the diminish of the ylide. The number and position of the methoxy group exerts significant influence on the yield and efficacy of methoxylated resveratrol analogues.

Structural modification of resveratrol by substituting the hydroxyl group with methoxy group on the aromatic ring could possibly have an effect on insulin sensitivity. Indeed, resveratrol has low bioavailability due to being metabolized by sulfation and glucuronation in the liver. Bioavailability can be increased by designing resveratrol analogues which would reduce the activity of hydroxyl group on resveratrol. Methoxylation of hydroxyl groups is supposed to prevent polyphenol metabolism and enhance stilbene bioactivity. Methoxylated analogues of resveratrol possess increased lipophilicity which would increase its bioavailability as it will stay longer in the body rather than getting excreted out of the body. Further studies should be addressed for the effectiveness and efficacy of such new analogues considering the crucial role of resveratrol in some of the most human deleterious diseases [39-42].

Acknowledgement

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