Glycosylation of Stilbene Compounds by Cultured Plant Cells

Kei Shimoda 1, Naoji Kubota 1, Daisuke Uesugi 2, Yusuke Kobayashi 2, Hatsuyuki Hamada 3 and Hiroki Hamada 2,*

1 Department of Biomedical Chemistry, Faculty of Medicine, Oita University, 1-1 Hasama-machi, Oita 879-5593, Japan; shimoda@med.oita-u.ac.jp (K.S.); nkubota@med.oita-u.ac.jp (N.K.)
2 Department of Life Science, Faculty of Science, Okayama University of Science, 1-1 Ridai-cho, Kita-ku, Okayama 700-0005, Japan; dshangshan10@gmail.com (D.U.); junfuquan853@gmail.com (Y.K.)
3 National Institute of Fitness and Sports in Kanoya, 1 Shiromizu-cho, Kagoshima 891-2390, Japan; hatsuhama@yahoo.co.jp
* Correspondence: hamada@dls.ous.ac.jp; Tel.: +81-86-256-9473

Received: 29 February 2020; Accepted: 21 March 2020; Published: 22 March 2020

Abstract: Oxyresveratrol and gnetol are naturally occurring stilbene compounds, which have diverse pharmacological activities. The water-insolubility of these compounds limits their further pharmacological exploitation. The glycosylation of bioactive compounds can enhance their water-solubility, physicochemical stability, intestinal absorption, and biological half-life, and improve their bio- and pharmacological properties. Plant cell cultures are ideal systems for propagating rare plants and for studying the biosynthesis of secondary metabolites. Furthermore, the biotransformation of various organic compounds has been investigated as a target in the biotechnological application of plant cell culture systems. Cultured plant cells can glycosylate not only endogenous metabolic intermediates but also xenobiotics. In plants, glycosylation reaction acts for decreasing the toxicity of xenobiotics. There have been a few studies of glycosylation of exogenously administrated stilbene compounds at their 3- and 4′-positions by cultured plant cells of Ipomoea batatas and Strophanthus gratiss so far. However, little attention has been paid to the glycosylation of 2′-hydroxy group of stilbene compounds by cultured plant cells. In this work, it is described that oxyresveratrol (3,5,2′,4′-tetrahydroxystilbene) was transformed to 3′-, 2′-, and 4′-β-glucosides of oxyresveratrol by biotransformation with cultured Phytolacca americana cells. On the other hand, gnetol (3,5,2′,6′-tetrahydroxystilbene) was converted into 2′-β-glucoside of gnetol by cultured P. americana cells. Oxyresveratrol 2′-β-glucoside and gnetol 2′-β-glucoside are two new compounds. This paper reports, for the first time, the glycosylation of stilbene compounds at their 2′-position by cultured plant cells.

Keywords: glycosylation; oxyresveratrol; gnetol; β-glucoside; cultured plant cells; Phytolacca americana

1. Introduction

Oxyresveratrol (3,5,2′,4′-tetrahydroxystilbene) and gnetol (3,5,2′,6′-tetrahydroxystilbene) are the major bioactive stilbenoids. These compounds are contained in plants such as Artocarpus lacucha Buch.–Ham and Gnetum gnemon, which have been used as folk medicines [1]. They have many pharmacological activities such as anti-oxidant, anti-inflammatory, analgesic, antidiabetic, anti-adipogenesis, anticancer, antileukaemic, and antiviral effects [2–15]. In spite of their pharmacological activities, the water-insolubility of stilbene compounds prevents their further exploitation as medicines and functional food ingredients. Furthermore, these compounds are
not necessarily most active within the living body, because of their poor intestinal absorption. The glycosylation of bioactive compounds can enhance their water-solubility and absorption after oral administration [16–18].

Plant cell cultures are ideal systems for propagating rare plants and for studying the biosynthesis of secondary metabolites such as flavors, pigments, and agrochemicals, except for a very limited number of compounds (e.g., pyrethrins, bialaphos, and nicotin). Furthermore, the biotransformation of various organic compounds has been investigated as a target in the biotechnological application of plant cell culture systems [19]. Plant cultured cells can be used to convert organic molecules to more useful compounds by catalyzing hydrolysis, oxidation, reduction, esterification, isomerization, and glycosylation reactions. The glycosylation reaction occurs readily in plant cells, because glucosyltransferases are widespread in plants. It has functions such as increasing solubility and stability of aglycons and activating biosynthetic intermediates. Furthermore, it is well known that higher plants accumulate glycosides as secondary metabolites. They are capable of glycosylating not only endogenous metabolic intermediates but also xenobiotics. In plants, glycosylation reaction acts for decreasing the toxicity of xenobiotics. Many studies on the glucosylation of exogenous phenols in cultured plant cells have been reported so far [20–29]. There have been a few reports describing biocatalytic glucosylation of stilbene compounds [26,27,29]. For example, resveratrol (3,5,4′-trihydroxystilbene) was glucosylated to its 3- and 4′-β-glucosides by cultured plant cells of Ipomoea batatas and Streptanthus gratus [26]. In addition, pterostilbene (4′-hydroxy-3,5-dimethoxystilbene) and pinostilbene (3,4′-dihydroxy-5-methoxystilbene) were converted into their 3- and/or 4′-β-glucosides by using cultured Phyto1acca americana cells or glucosyltransferase from P. americana [27,29]. These studies reported the glycosylation of stilbenoids at their 3- and/or 4′-positions by cultured plant cells or plant glucosyltransferase. However, little attention has been paid to the biocatalytic glycosylation of stilbene compounds at their 2′-position. These encouraged us to investigate biocatalytic glycosylation of stilbene compounds, which possess a hydroxy group at their 2′-position.

We report here the biotransformations of 2′-hydroxy stilbene compounds, oxyresveratrol and gnetol (Figure 1), by cultured plant cells of P. americana. The cultured P. americana cells glycosylated these stilbene compounds to oxyresveratrol 3-β-glucoside, oxyresveratrol 2′-β-glucoside, oxyresveratrol 4′-β-glucoside, and gnetol 2′-β-glucoside (Figure 1), in which oxyresveratrol 2′-β-glucoside and gnetol 2′-β-glucoside are two new compounds.

![Figure 1. Chemical structures of stilbene compounds.](image)

**2. Results**

2.1. **Glycosylation of Oxyresveratrol (1) and Gnetol (2) by Cultured Plant Cells of Phyto1acca americana**

Oxyresveratrol (1) was subjected to a biotransformation system using cultured plant cells of Phyto1acca americana. The compound 1 was administered to flasks containing suspension cell cultures of P. americana and incubated at 25 °C for two days on a rotary shaker, after which three products formed (3–5) were purified by HPLC from the MeOH extract of the cells. Based on the analyses of mass and nuclear magnetic resonance (NMR) analyses including 

$^1$H and $^{13}$C-NMR, and HMBC spectroscopy, the chemical structures of the products were determined to be oxyresveratrol 3-β-glucoside (3, 36% yield), oxyresveratrol 2′-β-glucoside (4, 30% yield), and oxyresveratrol 4′-β-glucoside (5, 22% yield). Two
products, i.e., oxyresveratrol 3-β-glucoside (3) [30] and oxyresveratrol 4′-β-glucoside (5) [31], were known compounds. Oxyresveratrol 2′-β-glucoside (4) has not been identified before.

Next, gnetol (2) was subjected to the same biotransformation system as described above. After two days’ incubation of cultured cells of P. americana with gnetol (2), the product 6 was isolated from the MeOH extract of cultured P. americana cells. The chemical structure of compound 6 was identified as gnetol 2′-β-glucoside (6, 87% yield) based on the analyses of mass and nuclear magnetic resonance (NMR) spectroscopy, i.e., ¹H and ¹³C-NMR, and HMBC spectra. Gnetol 2′-β-glucoside (6) is a new compound.

2.2. Determination of the Chemical Structures of New Compounds, Oxyresveratrol 2′-β-Glucoside (4) and Gnetol 2′-β-Glucoside (6)

The ESIMS spectrum of 4 showed a pseudomolecular ion [M − H]⁻ peak at m/z (405) (Supplementary Materials), consistent with a molecular formula of C₂₀H₂₂O₉ (calcd. 405 for C₂₀H₂₄O₉). The ¹H-NMR spectrum of 4 had a signal at δ 4.74 (1H, d, J = 6.8 Hz) corresponding to its attachment to the anomeric carbon (C-1”) (Table 1). The ¹³C-NMR spectrum of 4 exhibited the anomeric carbon signal at δ 100.7 (Table 1). This ¹³C chemical shift of the anomeric carbon at δ 100.7 indicates the presence of O-glucoside in the structure of 4 [32–34]. From the coupling pattern of the proton signals and the chemical shifts of the carbon resonances due to the sugar moiety (Table 1), the sugar component in 4 was determined to be β-D-glucopyranose. Hydrolysis of 4 using β-glucosidase gave oxyresveratrol (1) as the product. This finding shows that the product has O-β-glucosylation moiety. The HMBC correlation was observed between the anomeric proton signal at δ 4.74 (H-1”) and the carbon signal at δ 155.6 (C-2′) (Figure 2) to establish that the glucopyranosyl residue was attached to the 2′-hydroxy group of 1. Thus, the structure of 4 was determined to be oxyresveratrol 2′-β-glucoside.

| Table 1. ¹H and ¹³C-NMR data of oxyresveratrol 2′-β-glucoside (4) and gnetol 2′-β-glucoside (6). |
|-----------------|--------|--------|--------|--------|
| Position        | δC     | δH (J in Hz) | δC     | δH (J in Hz) |
| Aglycon         | 139.7  | 140.8   | 104.3  | 104.3   |
|                 | 104.3  | 6.34 d (1.6) | 6.38 d (2.0) |
|                 | 158.3  | 104.3   | 104.3  | 6.34 d (1.6) |
|                 | 101.4  | 6.03 s   | 101.6  | 6.10 t (1.6) |
|                 | 158.3  | 158.4   | 158.4  | 158.4   |
|                 | 104.3  | 6.34 d (1.6) | 6.38 d (2.0) |
|                 | 125.7  | 131.7   | 131.7  | 7.46 d (17.2) |
|                 | 122.5  | 119.9   | 119.9  | 7.35 d (16.4) |
|                 | 117.6  | 113.5   | 113.5  | 113.5   |
|                 | 155.6  | 156.4   | 156.4  | 156.4   |
|                 | 102.9  | 6.51 d (1.6) | 106.0  | 6.57 d (8.4) |
|                 | 158.1  | 127.8   | 127.8  | 6.97 t (8.4) |
|                 | 109.4  | 109.6   | 109.6  | 6.64 d (8.4) |
|                 | 7 6.40 dd (8.8, 1.6) | 156.5  | 156.5   |
|                 | 126.5  | 7.40 d (8.4) | 126.5  | 7.40 d (8.4) |
| Glc             | 100.7  | 100.6   | 100.6  | 4.89 d (7.6) |
|                 | 73.3   | 73.6    | 73.6   | 3.30 m   |
|                 | 76.5   | 77.0    | 77.0   | 3.19 t (8.8) |
|                 | 69.5   | 69.7    | 69.7   | 3.31 m   |
|                 | 76.9   | 77.1    | 77.1   | 3.38 m   |
|                 | 60.5   | 60.7    | 60.7   | 3.69 d (10.8) |
|                 | 3.45 m, | 3.73 m  | 3.45 m, | 3.73 m   |
|                 |        | 3.47 dd (12.0, 5.6) | 3.47 dd (12.0, 5.6) |
were capable of glucosylating esculetin to esculetin 7-glucoside and was determined to be glucose on the basis of the chemical shifts of its carbon signals (Table 1) [34]. In most cases, exogenously administered phenols and polyphenols were shown to be converted into their monoglucosides. For example, Datura innoxia cells converted daidzein to daidzein 7-glucoside (daidzin) [25]. Grapefruit (Citrus paradisi) cells in suspension cultures were able to glucosylate exogenous naringenin and hesperetin to naringenin 7-O-β-glucoside (naringin) and hesperetin 7-O-β-glucoside (hesperidin) [24]. Cultured cells of Eucalyptus perriniana converted daidzein to daidzein 7-O-β-glucoside (daidzin) [25].

We recently reported the glycosylation of stilbene compounds by cultured plant cells [26,27]. Resveratrol (3,5,4′-trihydroxystilbene) was glucosylated to give its β-glucosides, i.e., resveratrol 3-O-β-glucoside and resveratrol 4′-O-β-glucoside, by cultured plant cells of I. batatas, S. gratiss, and P. americana [26,27]. It has been reported that piceatannol (3,5,3′,4′-tetrahydroxystilbene) was converted into piceatannol 4′-O-β-glucoside by cultured P. americana cells [27]. Furthermore, piceatannol was subjected to the biocconversion with glucosyltransferase from P. americana expressed in Escherichia coli [28]. The enzyme regioselectively glucosylated piceatannol at its 4′-position to piceatannol 4′-O-β-glucoside. Neither piceatannol 3-O-β-glucoside nor piceatannol 3′-O-β-glucoside were obtained. These demonstrated that cultured plant cells and plant glucosyltransferase can glucosylate stilbene compounds at their 3- and 4′-positions to the corresponding monoglucosides. No studies on glycosylation of stilbene compounds at their 2′-position by biocatalysts have been reported so far.

The present study describes the glycosylation of stilbene compounds using cultured plant cells of P. americana as biocatalysts. When stilbene compounds with hydroxy groups at their 3-, 2′-, and/or 4′-positions were used as substrates, cultured P. americana cells introduced glucosyl residue at these hydroxy groups. Cultured P. americana cells converted oxyresveratrol, which has hydroxy groups at its 3-, 2′- and 4′-positions, into 3-, 2′-, and 4′-β-glucosides of oxyresveratrol. Gnetol with 3- and 2′-hydroxy
groups was transformed to 2′-β-glucoside of gnetol by biotransformation with cultured *P. americana* cells. Gnetol 3-β-glucoside was not formed. This might be explained by substrate specificity of the glucosyltransferases in *P. americana* cells. These results show that cultured cells of *P. americana* can convert exogenous stilbene compounds into their monoglucosides. This paper reports, for the first time, the biocatalytic glycosylation of stilbene compounds at their 2′-position by cultured plant cells.

Oxyresveratrol has been isolated from the roots of *Morus nigra* [35] and from the fruits of *Artocarpus heterophyllus* [36]. A phenolic glycoside was isolated from *Morus ilhou* [37] and *Morus alba* [38], and was identified as oxyresveratrol 3,4′-β-diglucoside. It was found that oxyresveratrol 2′-β-glucoside is not biosynthesized in these plants. On the other hand, gnetol was isolated from stems of *Gnetum klossii* [39]. Gnetol was found to exist as an aglycon in *Gnetum gnemon* products [13]. However, gnetol 2′-β-glucoside was not isolated from these plants. In the present study, cultured plant cells of *P. americana* were capable of transforming oxyresveratrol and gnetol to their 2′-β-glucosides. These suggest that glucosyltransferases, which can glucosylate the 2′-hydroxy group of oxyresveratrol or gnetol, were not included in *A. heterophyllus*, *M. lhou*, *M. alba*, *G. klossii*, and *G. gnemon*, but in *P. americana*.

Despite pharmaceutical properties of stilbene compounds, they have shortcomings such as low solubility in water and poor absorption after oral administration. These shortcomings prevent stilbene compounds from being used as drugs and functional food ingredients. Glycosylation is a characteristic reaction which converts water-insoluble and unstable aromatic compounds into the corresponding water-soluble and stable compounds. It has been reported that curcumin, which was supplied exogenously, was converted to its glycosides with drastically increased water solubility by *Catharanthus roseus* cell suspension cultures [16]. Cultured *C. roseus* cells transformed curcumin to various glucosides not only by introducing individual glucose residues onto its two phenolic hydroxy groups but also by forming β-1,6-glycosidic linkages, leading to the gentiobioside derivatives. Glucosyl conjugation of curcumin drastically enhanced the water-solubility. Curcumin 4′-O-glucoside and curcumin 4′-O-gentiobioside were 230-fold and 2,400,000-fold more soluble than curcumin [16]. On the other hand, it has been reported that the glycosylation of the flavonoid aglycon influences its absorption [17,18]. In the case of quercetin glucoside, the efficiency of absorption was higher than that for quercetin itself [17,18]. Hollman et al. elucidated the mechanism by which glucosylation facilitates quercetin absorption: the glucosides could be transported into enterocytes by the glucose transporter SGLT1 and could then be hydrolyzed inside the cells by cytosolic β-glucosidase [17]. These studies indicate that the glycosylation of bioactive compounds can enhance their water-solubility and intestinal absorption. The glucosides of stilbenes obtained here would be expected as water-soluble food ingredients and drugs. Studies on the pharmaceutical properties of the stilbene glycosides are now in progress in our laboratory.

4. Materials and Methods

4.1. General

The substrates, i.e., oxyresveratrol and gnetol, were purchased from Sigma Aldrich Japan Inc., Tokyo, Japan.

4.2. Analyses

The structures of products were determined based on the analysis of ESIMS, $^1$H- and $^{13}$C-NMR, and HMBC spectra. The $^1$H- and $^{13}$C-NMR, and HMBC spectra were recorded using a JNM-ECS400 spectrometer (JEOL Ltd., Tokyo, Japan) in DMSO-$d_6$ solutions, and chemical shifts are expressed in δ (ppm) with reference to TMS. The ESIMS spectra were measured at 70 eV in negative mode using a JMS-700 MStation (JEOL) in CH$_3$OH solution. Products were analyzed by high-performance liquid chromatography (HPLC) using CrestPak C18S column (column size: 150 × 4.6 mm) at column temperature of 40 °C.
4.3. Cultivation of Plant Callus

Cultured plant cells of *P. americana* were sub-cultured at 4-week intervals on solid medium containing 2% glucose, 1 ppm 2,4-dichlorophenoxyacetic acid, and 1% agar (adjusted to pH 5.7) in the dark. A suspension culture was started by transferring 20 g of the cultured cells to 300 mL of liquid MS medium in a 500 mL-conical flask.

4.4. Glycosylation by Cultured Plant Cells

The substrate was transformed by using plant cultured cells of *P. americana* as biocatalysts. The cultured *P. americana* cells in the stationary growth phase have been used for experiments. To a 300 mL flask containing 100 mL of the culture medium and suspension cultured cells of *P. americana* (25 g) was added 15 mg of substrate, i.e., oxyresveratrol and gnetol. The culture was incubated at 25 °C for 2 days on a rotary shaker (120 rpm). After the incubation period, the cells and medium were separated by filtration with suction. The filtered medium was extracted with ethyl acetate (AcOEt). The cells were extracted by homogenization with MeOH, and the resulting extract was concentrated. The residue was partitioned between H₂O and AcOEt. The AcOEt layer was evaporated and the residue was re-dissolved in MeOH and purified by preparative high-performance liquid chromatography (HPLC) [column: CrestPak C18S (150 × 4.6 mm); flow rate: 1.0 mL/min; column temperature: 40 °C; solvent: CH₃CN:H₂O = 14:86; retention time (min) of the products, oxyresveratrol 3-β-glucoside (8.7), oxyresveratrol 2′-β-glucoside (12.2), oxyresveratrol 4′-β-glucoside (7.2), and gnetol 2′-β-glucoside (15.6)].

5. Conclusions

The present study demonstrated the biotransformation of stilbene compounds that have hydroxy groups at 3-, 2′-, and/or 4′-position by cultured plant cells. It was found that oxyresveratrol and gnetol were glycosylated to 3-, 2′-, and 4′-β-glucosides of oxyresveratrol, and 2′-β-glucoside of gnetol by cultured cells of *P. americana*. Oxyresveratrol 2′-β-glucoside and gnetol 2′-β-glucoside are two new compounds. This paper reports, for the first time, the biocatalytic glycosylation of stilbene compounds at their 2′-position by cultured plant cells.

Supplementary Materials: The following are available online. Figure S1: ESIMS of oxyresveratrol 2′-β-glucoside, Figure S2: 1H-NMR of oxyresveratrol 2′-β-glucoside, Figure S3: 13C-NMR of oxyresveratrol 2′-β-glucoside, Figure S4: HMBC of oxyresveratrol 2′-β-glucoside, Figure S5: HMBC of oxyresveratrol 2′-β-glucoside (enlarged), Figure S6: ESIMS of gnetol 2′-β-glucoside, Figure S7: 1H-NMR of gnetol 2′-β-glucoside, Figure S8: 13C-NMR of gnetol 2′-β-glucoside, Figure S9: HMBC of gnetol 2′-β-glucoside.

Author Contributions: Conceptualization, K.S., N.K., D.U., Y.K., H.H., and H.H.; methodology, H.H.; validation, D.U. and Y.K.; formal analysis, D.U. and Y.K.; investigation, K.S., N.K., D.U., Y.K., H.H., and H.H.; resources, H.H.; data curation, D.U. and Y.K.; writing—original draft preparation, K.S.; writing—review and editing, H.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by The Tojuro Iijima Foundation for Food Science and Technology.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Junsaeng, D.; Anukunwithaya, T.; Songvut, P.; Sritularak, B.; Likhitvitayawuud, K.; Khemawoot, P. Comparative pharmacokinetics of oxyresveratrol alone and in combination with piperine as a bioenhancer in rats. *BMC Compl. Alt. Med.* 2019, 19, 1–10. [CrossRef] [PubMed]

2. Dej-adisai, S.; Parndaeng, K.; Wattanapiromsakul, C. Determination of phytochemical compounds, and tyrosinase inhibitory and antimicrobial activities of bioactive compounds from *Streblus ilicifolius* (S Vidal) corner. *Trop. J. Pharm. Res.* 2016, 15, 497–506. [CrossRef]

3. Likhitvitayawuud, K.; Sornsute, A.; Sritularak, B.; Ploypradith, P. Chemical transformations of oxyresveratrol (trans–2,4,3′,5′–tetrahydroxystilbene) into a potent tyrosinase inhibitor and a strong cytotoxic agent. *Bioorg. Med. Chem. Lett.* 2006, 16, 5650–5653. [CrossRef] [PubMed]
4. Tengamnuay, P.; Pengrungruangkong, W.; Pheansri, I.; Likhitwitayawuid, K. Artocarpus lakoocha heartwood extract as a novel cosmetic ingredient: Evaluation of the in vitro anti-tyrosinase and in vivo skin whitening activities. Int. J. Cosmet. Sci. 2006, 28, 269–276. [CrossRef] [PubMed]

5. Weber, J.T.; Lamont, M.; Chibrikova, L.; Fekkes, D.; Vlug, A.S.; Lorenz, P.; Kreutzmann, P.; Slemmer, J.E. Potential neuroprotective effects of oxyresveratrol against traumatic injury. Eur. J. Pharmacol. 2012, 680, 55–62. [CrossRef] [PubMed]

6. Ashraf, M.I.; Shahzad, M.; Shabbir, A. Oxyresveratrol ameliorates allergic airway inflammation via attenuation of IL-4, IL-5, and IL-13 expression levels. Cytokine 2010, 76, 375–381. [CrossRef]

7. Chung, K.O.; Kim, B.Y.; Lee, M.H.; Kim, Y.R.; Chung, H.Y.; Park, J.H.; Moon, J.O. In-vitro and in-vivo anti-inflammatory effect of oxyresveratrol from Morus alba L. J. Pharm. Pharmacol. 2003, 55, 1695–1700. [CrossRef]

8. Chung, K.O.; Kim, B.Y.; Lee, M.H.; Kim, Y.R.; Chung, H.Y.; Park, J.H.; Moon, J.O. In-vitro and in-vivo anti-inflammatory effect of oxyresveratrol from Morus alba L. J. Pharm. Pharmacol. 2003, 55, 1695–1700. [CrossRef]

9. Galindo, I.; Hernández, B.; Berna, J.; Fenoll, J.; Cenis, J.L.; Escribano, J.M.; Alonso, C. Comparative inhibitory activity of the stilbenes resveratrol and oxyresveratrol on African swine fever virus replication. Antivir. Res. 2011, 91, 57–63. [CrossRef]

10. Lipipun, V.; Sasivimonphun, P.; Yoshida, Y.; Daikoku, T.; Sritularak, B.; Rithidej, G.; Likhitwitayawuid, K.; Pramyoithin, P.; Hattori, M.; Shiraki, K. Topical cream-based oxyresveratrol in the treatment of cutaneous HSV-1 infection in mice. Antivir. Res. 2011, 91, 154–160. [CrossRef]

11. Suwannalert, P.; Povichit, N.; Puchadapirom, P.; Junking, M. Anti-aging activity and non-toxic dose of phytoxyresveratrol from Artocarpus lakoocha Roxb. Trop. J. Pharm. Res. 2012, 11, 69–74. [CrossRef]

12. Chen, W.; Yeo, S.C.M.; Elhennawy, M.G.A.A.; Lin, H.S. Oxyresveratrol: A bioavailable dietary polyphenol. J. Funct. Foods 2016, 22, 122–131. [CrossRef]

13. Remsberg, C.M.; Martinez, S.E.; Akinwumi, B.C.; Anderson, H.D.; Takemoto, J.K.; Sayre, C.L.; Davies, N.M. Preclinical pharmacokinetics and pharmacodynamics and content analysis of gnetol in foodstuffs. Phytotherapy Res. 2015, 29, 1168–1179. [CrossRef] [PubMed]

14. Dvorakova, M.; Landa, P. Anti-inflammatory activity of natural stilbenoids: A review. Pharmacol. Res. 2017, 124, 126–145. [CrossRef] [PubMed]

15. Bolanle, C. Akinwumi 1,2,* ID, Kimberly-Ann M. Bordun 2 and Hope D. Anderson. Biological activities of stilbenoids. Int. J. Mol. Sci. 2018, 19, 792. [CrossRef]

16. Kaminaga, Y.; Nagatsu, A.; Akiyama, T.; Sugimoto, N.; Yamazaki, T.; Maitani, T.; Mizukami, H. Production of unnatural glucosides of curcumin with drastically enhanced water solubility by cell suspension cultures of Catharanthus roseus. FEBS Lett. 2003, 555, 311–316. [CrossRef]

17. Hollman, P.C.H.; Devries, J.H.M.; Vanleeuwen, S.D.; Mengelers, M.J.B.; Katan, M.B. Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. Am. J. Clin. Nutr. 1995, 62, 1276–1282. [CrossRef]

18. Morand, C.; Manach, C.; Crespy, V.; Remesy, C. Quercetin 3-Obeta-glucoside is better absorbed than other quercetin forms and is not present in rat plasma. Free Radical Res. 2000, 33, 667–676. [CrossRef]

19. Ishihara, K.; Hamada, H.; Hirata, T.; Nakajima, N. Biotransformation using plant cultured cells. Phytochemistry 1976, 15, 1225–1229. [CrossRef]

20. Tabata, M.; Ikeda, F.; Hiraoka, N.; Konoshima, M. Glucosylation of phenolic compounds by Datura innoxia suspension cultures. Phytochemistry 1976, 15, 1225–1229. [CrossRef]

21. Mizukami, H.; Terao, T.; Miura, H.; Ohashi, H. Glucosylation of salicyl alcohol in cultured plant cells. Phytochemistry 1983, 22, 679–680. [CrossRef]

22. Tabata, M.; Umetani, Y.; Ooya, M.; Tanaka, S. Glucosylation of phenolic compounds by plant cell cultures. Phytochemistry 1988, 27, 809–813. [CrossRef]

23. Ushiyama, M.; Furuya, T. Glycosylation of phenolic compounds by root culture of Panax ginseng. Phytochemistry 1989, 28, 3009–3013. [CrossRef]

24. Lewinson, E.; Berman, E.; Mazur, Y.; Gressel, J. Glucosylation of exogenous flavanones by grapefruit (Citrus paradisi) cell cultures. Phytochemistry 1986, 25, 2531–2535. [CrossRef]

25. Shimoda, K.; Sato, N.; Kobayashi, T.; Hamada, H.; Hamada, H. Glycosylation of daidzein by the Eucalyptus cell cultures. Phytochemistry 2008, 69, 2303–2306. [CrossRef]
26. Imai, H.; Kitagawa, M.; Ishihara, K.; Masuoka, N.; Shimoda, K.; Nakajima, N.; Hamada, H. Glycosylation of trans-resveratrol by plant-cultured cells. *Biosci. Biotechnol. Biochem.* 2012, 8, 1552–1554. [CrossRef]

27. Sato, D.; Shimizu, N.; Shimizu, Y.; Akagi, M.; Eshta, Y.; Ozaki, S.; Nakajima, N.; Ishihara, K.; Masuoka, N.; Hamada, H.; et al. Synthesis of glycosides of resveratrol, pterostilbene, and piceatannol, and their anti-oxidant, anti-allergic, and neuroprotective activities. *Biosci., Biotechnol, Biochem.* 2014, 78, 1123–1128. [CrossRef]

28. Iwakiri, T.; Imai, H.; Hamada, H.; Nakayama, T.; Ozaki, S. Synthesis of 3,5,3′,4′-tetrahydroxy-trans-stilbene-4′-O-beta-D-glucopyranoside by glycosyltransferases from *Phytolacca americana*. *Nat. Prod. Commun.* 2013, 8, 119–120.

29. Uesugi, D.; Hamada, H.; Shimoda, K.; Kubota, N.; Ozaki, S.; Nagatani, N. Synthesis, oxygen radical absorbance capacity, and tyrosinase inhibitory activity of glycosides of resveratrol, pterostilbene, and pinostilbene. *Biosci., Bioch., Biochem.* 2017, 81, 226–230. [CrossRef] [PubMed]

30. Hanawa, F.; Tahara, S.; Mizutani, J. Antifungal stress compounds from *Veratrum grandiflorum* leaves treated with cupric chloride. *Phytochemistry* 1992, 31, 3005–3007. [CrossRef]

31. Venkataraman, K. Wood phenolics in the chemotaxonomy of the moraceae. *Phytochemistry* 1972, 11, 1571–1586. [CrossRef]

32. Nyemba, A.M.; Ngando Mpondo, T.; Kimbu, S.F.; Connolly, J.D. Stilbene glycosides from *Guibourtia tessmannii*. *Phytochemistry* 1995, 39, 895–898. [CrossRef]

33. Mannila, E.; Talvitie, A. Stilbenes from *Picea abies* bark. *Phytochemistry* 1992, 31, 3288–3289. [CrossRef]

34. Ponrasu, T.; Charles, R.E.; Sivakumar, R.; Divakar, S. Syntheses of α-tocopheryl glycosides by glucosidases. *Biotechnol. Lett.* 2008, 30, 1431–1439. [CrossRef] [PubMed]

35. Zheng, Z.-P.; Cheng, K.-W.; Zhou, Q.; Wang, X.-C.; Lin, Z.-X.; Wang, M. Tyrosinase inhibitory constituents from the roots of *Morus nigra*: A structure-activity relationship study. *J. Agric. Food Chem.* 2010, 58, 5368–5373. [CrossRef] [PubMed]

36. Fang, S.-C.; Hsu, C.-L.; Yen, G.-C. Anti-inflammatory effects of phenolic compounds isolated from the fruits of *Artocarpus heterophyllus*. *J. Agric. Food Chem.* 2008, 56, 4463–4468. [CrossRef]

37. Hirakura, K.; Fujimoto, Y.; Fukai, T.; Nomura, T. Two phenolic glycosides from the root bark of the cultivated mulberry tree (*Morus lhou*). *J. Nat. Prod.* 1986, 49, 218–224. [CrossRef]

38. Jia, Y.-N.; Peng, Y.-L.; hao, Y.-P.; Cheng, X.-F.; Zhou, Y.; Chai, C.-L.; Zeng, L.-S.; Pan, M.-H.; Xu, L. Comparison of the hepatoprotective effects of the three main stilbenes from mulberry twigs. *J. Agric. Food Chem.* 2019, 67, 5521–5529. [CrossRef]

39. Ali, Z.; Tanaka, T.; lliya, I.; Inuma, M.; Furusawa, M.; Ito, T.; Nakaya, K.; Murata, J.; Darnaedi, D. Phenolic constituents of *Gnetum klossii*. *J. Nat. Prod.* 2003, 66, 558–560. [CrossRef]

**Sample Availability:** Samples of the compounds are not available from the authors.

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).