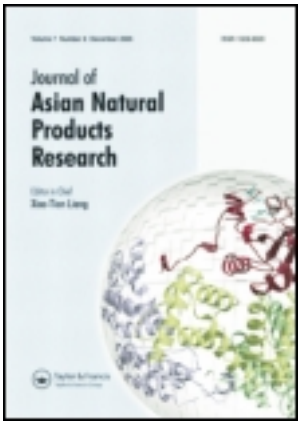

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Advanced research on acteoside for chemistry and bioactivities

Jiang He[a], Xiao-Peng Hu[a], Yong Zeng[b], Yan Li[b], Hai-Qiang Wu[a], Rong-Zhu Qiu[a], Wen-Jie Ma[a], Tao Li[a], Chen-Yang Li[a] and Zhen-Dan He[a]*

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Acteoside is one kind of phenylethanoid glycoside, which has shown a lot of biological activities. This article reviewed the study progress of acteoside, such as distribution, preparation, identification, and bioactivities.

Keywords: acteoside; distribution; preparation; identification; bioactivities

1. Introduction

Acteoside, which is also called kusagin or verbascoside [1], has been isolated from many dicotyledons that are mostly distributed in Asia. It has been reported that acteoside has extensive biological activities including antioxidant [2–5], anti-inflammatory [6,7], hepatoprotect [8,9], and cell apoptosis regulation [9–11]. Besides, because it has few side effects, it may be developed into a promising drug. So far, there are three primary approaches to prepare acteoside, including isolation from plants, preparation by chemical synthesis and biosynthesis. Hence, it is not difficult to produce acteoside on a large scale. In recent years, the researches on acteoside have attracted considerable attention. This article summarized the research progress of acteoside, including its physicochemical properties, distribution, preparation, and bioactivities.

2. Physicochemical properties

Acteoside (Figure 1) is one kind of phenylethanoid glycosides, whose formula is $C_{29}H_{36}O_{15}$, and its molecular weight is 624. Acteoside is a white amorphous powder and tastes bitter, its optical rotation is $[\alpha]_D^{22}$ −70.99 ($c = 0.439$, MeOH). In addition, the UV and IR spectral data of acteoside are shown below: UV λ_{max} (EtOH) (log ε): 202 (4.50), 220 (4.11), 246–247 (3.83), 288 (3.90), 336 (4.11) nm; IR ν_{max} (KBr): 3450, 1700, 1600, 1520, 1450, 1270, 810 cm^{-1} according to the literature [12]. He *et al*. [13,14] studied the fragmentation of acteoside through the FAB-MS, the FAB-MS (positive) *m/z*: 625 $[M + H]^+$, 487 [*M*-(3,4-dihydroxy)-phenethyl]$^+$, 477 [*M*-rhamnosyl]$^+$, 461 [*M*-caffeoyl]$^+$; the FAB-MS (negative) *m/z*: 623 $[M - H]^-$, 163 [*O*-rhamnosyl or caffeoyl]$^-$.

^{1}H NMR (400 MHz, CD_3OD) [14]: aglycone δ 6.69 (1H, d, $J = 2.0$ Hz, H-2), 6.68 (1H, d, $J = 8.2$ Hz, H-5), 6.57 (1H, dd, $J = 8.3$, 2.0 Hz, H-6), 4.05 (1H, dd, $J = 7.9$, 6.9 Hz, H-8a), 3.72 (1H, dd, $J = 11.0$, 7.9 Hz, H-8b), 2.78 (2H, m, H-7); *E*-caffeoyl 7.59 (1H, d, $J = 15.8$ Hz, H-7′), 7.06 (1H, d, $J = 1.6$ Hz, H-2′), 6.96 (1H, dd, $J = 8.4$, 1.6 Hz, H-6′), 6.79 (1H,

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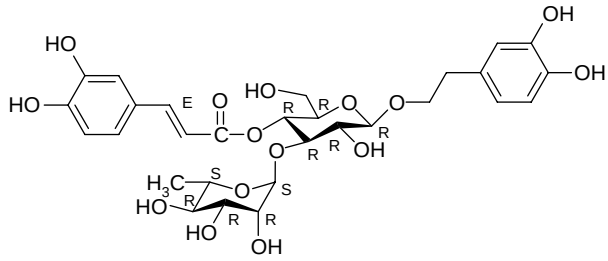

Figure 1. Structure of acteoside.

d, $J = 8.4$ Hz, H-5′), 6.28 (1H, d, $J = 15.8$ Hz, H-8′); glucose 4.38 (1H, d, $J = 7.9$ Hz, Glu-1″); rhamnose 5.19 (1H, d, $J = 1.2$ Hz, Rha-1‴), 1.09 (3H, d, $J = 6.1$ Hz, Rha-6‴). ^{13}C NMR (400 MHz, CD_3OD) [14]: aglycone δ 131.6 (C-1), 116.4 (C-2), 144.6 (C-3), 146.1 (C-4), 117.2 (C-5), 121.3 (C-6), 36.5 (C-7), 72.3 (C-8); *E*-caffeoyl 127.7 (C-1′), 115.4 (C-2′), 146.8 (C-3′), 149.7 (C-4′), 116.4 (C-5′), 123.2 (C-6′), 148.0 (C-7′), 114.8 (C-8′) 168.4 (CO); glucose 104.2 (C-1″), 76.0 (C-2″), 81.7 (C-3″), 70.7 (C-4″), 76.2 (C-5″), 62.5 (C-6″); rhamnose 102.9 (C-1‴), 72.1 (C-2‴), 72.3 (C-3‴), 73.8 (C-4‴), 70.7 (C-5‴), 18.4 (C-6‴).

3. Distribution

So far, more than 150 species of plants have been discovered to contain acteoside, belonging to 20 families and 77 genera (Table 1). Acteoside is widely distributed in dicotyledonous plants, such as Verbenaceae, Scrophulariaceae, Oleaceae, Orobanchaceae, Bignoniaceae, Labiatae, Buddlejaceae, and Acanthaceae. Acteoside has been mainly isolated from arial parts of some plants in Labiatae, Scrophulariaceae, and Verbenaceae, leaves or flowers of some plants in Oleaceae and Buddlejaceae, stems of some plants in Orobanchaceae. Besides, acteoside has been discovered in some traditional medicine plants, such as *Scrophularia ningpoensis*, *Cistanche deserticola*, and *Digitalis purpurea.* Thus, further study of the distribution of acteoside in plants not only can help us to get more information on drug screening, but also to understand the evolution of the plant communities better, because closely related plant species often have the same or similar chemical evolution and biosynthesis pathway.

4. Preparation

Since 1963, Scarpati and Delle-Monache [15] firstly isolated phenylpropanoid glycoside acteoside from the scrophulariaceous medicinal plants, and then the research on acteoside has been rapidly developed, especially the preparation of acteoside.

4.1 Isolation and purification

Traditional methods for the isolation of acteoside from plants are often time consuming and involve repeated chromatographic steps on silica gel, Sephadex LH-20 and preparative high performance liquid chromatography (HPLC). To avoid peak tailing, some kinds of acid have often been added into the mobile phase during thin-layer chromatography (TLC)/HPLC analysis for acteoside [16–18].

In contrast, high-speed counter-current chromatography (HSCCC) has become an effective alternative to the conventional chromatographic techniques for the separation of acteoside from plants. Li *et al.* [19] applied HSCCC to the separation and purification of acteoside from *Plantago psyllium* L. Lei *et al.* [20] also used this technique to separate acteoside from *Cistanche salsa* (C.A. Mey) G. Beck with

Table 1. The distribution of acteoside in plants.

No.	Plants	Parts	Remark	Refs
Magnoliaceae				
1	*Magnolia officinalis*	Stem barks	TCM	[78]
2	*M. rostrata*	Barks	–	[147]
Piperaceae				
3	*Piper aduncum*	–	–	[159]
Polygonaceae				
4	*Polygonum aviculare*	Aerial parts	TCM	[160]
Rosaceae				
5	*Rosa rugosa*	Flowers	TCM	[47]
Loganiaceae				
6	*Buddleja americana*	Leaves	–	[161]
7	*B. Asiatica*	Flowers	TCM	[162]
8	*B. davidii*	Leaves	TCM	[163]
9	*B. madagascariensis*	Leaves	–	[164]
10	*B. officinalis*	Flowers	TCM	[165]
11	*B. purdomii*	–	–	[166]
12	*Polypremum procumbens*	Aerial parts	–	[71]
Oleaceae				
13	*Abeliophyllum distichum*	–	–	[167]
14	*Forsythia koreana*	–	–	[168]
15	*F. suspensa*	Seeds	TCM	[169]
16	*F. viridissima*	Flowers	TCM	[170]
17	*Fraxinus oxycarpa*	Leaves	–	[171]
18	*F. sieboldiana* var. *angustata*	–	–	[172]
19	*F. malacophlla*	Bark and leaves	TCM	[12,180]
20	*Ligustrum delavayanum*	Leaves	–	[173]
21	*L. ovalifolium*	Leaves	–	[174]
22	*L. purpurascens*	Leaves	TCM	[42]
23	*L. robustum*	Leaves	TCM	[176]
24	*Osmanthus fragrans*	Flowers	TCM	[177]
25	*O. fragrans* var. *aurantiacus*	–	–	[178]
26	*Syringa vulgaris*	–	TCM	[179]
Compositae				
27	*Aster smithianus*	–	–	[181]
Plantaginaceae				
28	*Globularia trichosantha*	Aerial parts	–	[182]
29	*P. asiatica*	Seeds	TCM	[175]
30	*P. lanceolata*	Aerial parts	–	[44]
31	*P. ovata*	Seeds	–	[45]
32	*P. palmata*	Leaves and roots	–	[46]
33	*P. psyllium*	Seeds	–	[47]
Campanulaceae				
34	*Craterocapsa tarsodes*	–	–	[48]
Scrophulariaceae				
35	*Brandisia hancei*	Whole herbs	TCM	[49,180]
36	*Buddleja lindleyana*	–	TCM	[50]
37	*Castilleja linariaefolia*	–	–	[51]
38	*D. purpurea*	Leaves	TCM	[52]
39	*Euphrasia pectinata*	Aerial parts	–	[53]
40	*E. regelii*	–	–	[54]
41	*Halleria lucida*	Leaves	–	[55]
42	*Lagotis brevituba*	–	TCM	[56]
43	*L. ramalana*	Whole herbs	Tibetan medicine	[57]
44	*L. stolonifera*	Aerial parts	–	[58]

Table 1 – *continued*

No.	Plants	Parts	Remark	Refs
45	*Monochasma savatieri*	–	TCM	[59]
46	*Oreosolen wattii*	–	Tibetan medicine	[60]
47	*Paulownia tomentosa*	Fruits	TCM	[61]
48	*Pedicularis nordmanniana*	Aerial parts	–	[62]
49	*P. striata*	Whole herbs	–	[63]
50	*Penstemon hirsutus*	Leaves	–	[64]
51	*P. linarioides*	–	–	[65]
52	*P. roseus*	Aerial parts	–	[66]
53	*Picria fel-terrae*	Whole herbs	TCM	[67]
54	*Rehmannia glutinosa*	Roots	TCM	[68]
55	*Rhynchocorys stricta*	Aerial parts	–	[69]
56	*S. ningpoensis*	–	TCM	[13]
57	*S. scorodonia*	–	–	[70]
58	*S. striata*	Aerial parts	–	[26]
59	*Siphonostegia chinensis*	Whole herbs	TCM	[72]
60	*Torenia fournieri*	Flowers	–	[73]
61	*Verbascum macrurum*	Aerial parts	–	[74]
62	*V. pterocalycinum* var. *mutense*	Flowers	–	[75]
63	*V. salviifolium*	Aerial parts	–	[76]
64	*V. sinaiticum*	Aerial parts	–	[77]
65	*V. sinuatum*	Leaves	–	[78]
66	*V. spinosum*	Aerial parts	–	[79]
67	*Veronica chamaedrys*	–	–	[80]
68	*V. Persica*	Aerial parts	TCM	[81]
Orobanchaceae				
69	*Aeginetia indica*	–	TCM	[82]
70	*Boschniakia rossica*	–	TCM	[83]
71	*C. deserticola*	–	TCM	[84]
72	*C. phelypaea*	Aerial parts	–	[85]
73	*C. salsa*	–	–	[84]
74	*C. sinensis*	–	–	[84]
75	*C. tubulosa*	–	TCM	[84]
76	*Orobanche aegyptiaca*	–	–	[86]
77	*O. coerulescens*	–	TCM	[87]
Gesneriaceae				
78	*Mitraria coccinea*	–	–	[88]
Bignoniaceae				
79	*Campsis grandiflora*	Flowers	TCM	[89]
80	*C. chinensis*	–	–	[90]
81	*Incarvillea younghusbandii*	Roots	–	[91]
82	*Jacaranda caucana*	Stems	–	[92]
83	*J. ovalifolia*	Leaves	–	[93]
84	*Spathodea campanulata*	Leaves	–	[94]
Pedaliaceae				
85	*Harpagophytum procumbens*	Roots	–	[95]
Martyniaceae				
86	*Martynia louisiana*	Leaves and stems	–	[96]
Acanthaceae				
87	*Acanthus ilicifolius*	Leaves	TCM	[97]
88	*Strobilanthes sp.*	–	–	[98]
89	*Barleria acanthoides*	–	–	[99]
90	*B. cristata*	Callus cultures	TCM	[100]
Verbenaceae				
91	*Avicennia marina*	–	–	[101]

Table 1 – *continued*

No.	Plants	Parts	Remark	Refs
92	*A. officinalis*	Leaves	–	[102]
93	*Callicarpa dichotoma*	Leaves	TCM	[103]
94	*C. japonica*	Fruits	TCM	[104]
95	*C. pedunculata*	–	TCM	[105]
96	*Clerodendron bungei*	–	–	[106]
97	*C. cyrtophyllum*	–	–	[107]
98	*C. fragrans*	–	–	[108]
99	*C. infortunatum*	Flowers	–	[109]
100	*C. japonicum*	–	–	[110]
101	*C. philipinum*	Roots	–	[111]
102	*C. serratum*	–	–	[112]
103	*C. trichotomum*	–	–	[113]
104	*Duranta repens*	Leaves	–	[114]
105	*Gmelina arborea*	Leaves	–	[115]
106	*Lantana lilacina*	Leaves	–	[116]
107	*Lippia alba*	–	–	[117]
108	*L. canescens*	Aerial parts	–	[118]
109	*L. dulcis*	Aerial parts	–	[118]
110	*L. nodiflora*	–	–	[119]
111	*L. triphylla*	Leaves and stems	Peruvian medicine	[120]
112	*Premna japonica*	Stems	TCM	[121]
113	*Stachytarpheta cayennensis*	Leaves	–	[122]
114	*S. glabra*	Leaves	–	[123]
115	*Verbena brasiliensis*	Aerial parts	–	[124]
116	*V. littoralis*	–	–	[125]
117	*V. officinalis*	–	TCM	[126]
118	*V. tenera*	–	–	[127]
Labiatae				
119	*Anisomeles indica*	Whole plants	TCM	[128]
120	*Ballota pseudodictamnus*	Aerial parts	–	[129]
121	*Colebrookea oppositifolia*	Aerial parts	–	[130]
122	*Lamiophlomis rotata*	–	TCM	[131]
123	*Lamium album*	Flowers	–	[132]
124	*L. maculatum* var. *kansuense*	–	–	[133]
125	*Leonotis nepetaefolia*	–	African medicine	[134]
126	*Leucosceptrum japonicum*	–	–	[135]
127	*Marrubium alysson*	Aerial parts	–	[136]
128	*M. vulgare*	Aerial parts	–	[137]
129	*Phlomis amanica*	–	–	[138]
130	*P. armeniaca*	–	Turkish medicine	[139]
131	*P. aurea*	Leaves	–	[140]
132	*P. carica*	Aerial parts	–	[141]
133	*P. caucasica*	Aerial parts	Iranian medicine	[142]
134	*P. kotschyana*	Aerial parts	–	[143]
135	*P. monocephala*	Aerial parts	–	[141]
136	*P. physocalyx*	Aerial parts	–	[142]
137	*P. sieheana*	Aerial parts	–	[144]
138	*P. sintenisii*	Aerial parts	–	[145]
139	*P. tuberosa*	Aerial parts	TCM	[146]
140	*Pogostemon cablin*	Aerial parts	TCM	[16]
141	*Scutellaria albida colchica*	–	–	[148]
142	*S. alpina*	–	–	[149]
143	*S. baicalensis*	Roots	TCM	[150]
144	*S. galericulata*	–	TCM	[149]

Table 1 – *continued*

No.	Plants	Parts	Remark	Refs
145	*S. incana*	–	–	[149]
146	*S. iyoensis*	–	–	[149]
147	*S. lateriflora*	–	–	[149]
148	*S. orientalis*	–	–	[149]
149	*S. planipes*	Aerial parts	–	[151]
150	*S. pontica*	–	–	[149]
151	*S. salviifolia*	–	Turkish medicine	[139]
152	*S. taurica*	–	–	[149]
153	*S. ventenatii*	–	–	[149]
154	*Sideritis lycia*	Aerial parts	–	[152]
155	*S. stricta*	Aerial parts	–	[153]
156	*Stachys schtschegleevii*	Aerial parts	–	[154]
157	*S. sieboldii*	Aerial parts	TCM	[155]
158	*Wiedemannia orientalis*	Aerial parts	–	[156]
Myoporaceae				
159	*Myoporum laetum*	Leaves	–	[157]
Byblidaceae				
160	*Byblis liniflora*	Plantlets	–	[158]

a quaternary two-phase solvent system composed of ethyl acetate–*n*-butanol–ethanol–water (4–0.6–0.6–5, *v/v*).

High-performance centrifugal partition chromatography (HPCPC) is another effective method to separate the phenylethanoid glycosides. Li *et al*. [21] used this method to isolate acteoside from *Plantago asiatica*.

4.2 Biosynthesis

Hiroshi and Yutaka [22] examined the biosynthesis of acteoside in olive cell cultured by feeding experiments with stable isotope-labeled precursors. The hydroxytyrosol moiety of acteoside is biosynthesized from tyrosine through dopamine, whereas the caffeoyl moiety of acteoside is biosynthesized from phenylalanine via a cinnamate pathway. They also suppressed the acteoside production in olive cells using putative inhibitors, proving that the biosynthesis route is correct.

4.3 Chemical synthesis

Toshinari *et al*. [23] reported the first total synthesis of acteoside in 1999. In the same year, Howard *et al*. [24] also reported the synthesis of acteoside. Toshinari's strategy for the total synthesis of acteoside involved a convergent route from the phenethyl glycoside derivative **5a**, from the glucose derivative **3** and the phenethyl derivative **4** by the Koenigs–Knorr method in the presence of silver carbonate (Figure 2). The next step, the caffeoyl moiety was introduced into the synthesized glycoside **5a** via deacetylation, selective tritylation, acetylation, and esterification (Figure 3). For rhamnosylation (Figure 4), the 3-*O*-allyl group of compound **11** was subjected to oxidative cleavage using selenium dioxide to afford compound **12**. Rhamnosylation of compound **12** was performed with 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate (**13**) in the presence of boron trifluoride diethyl etherate at -20°C to give the expected R-rhamnoside **14** in 73% yield. The acetyl groups of compound **14** were then cleaved to give compound **15**. Compound **15** was then treated with 1,4-cyclohexadiene/Pd-C in a solvent mixture of DMF–EtOH at 40°C. At 10 h, the starting compound **15** was completely consumed to give the desired acteoside.

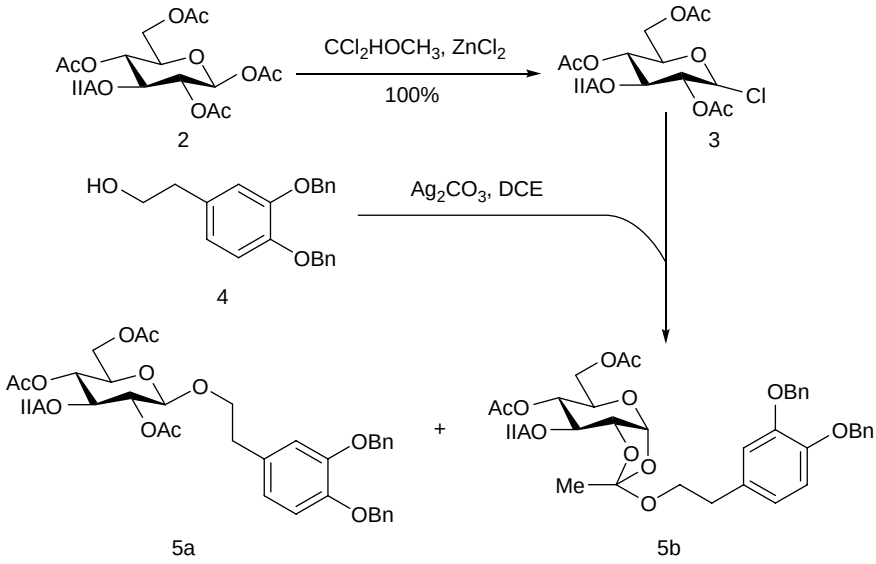

Figure 2. Synthesis of phenethyl glucoside **5a**.

5. Bioactivities

5.1 Antioxidant effect

The antioxidant effect is the major function of acteoside and has been widely demonstrated. He *et al*. [5] confirmed the antioxidant effect *in vitro* according to free radical-induced hemolysis of red blood cells (RBC) and scavenging of superoxide

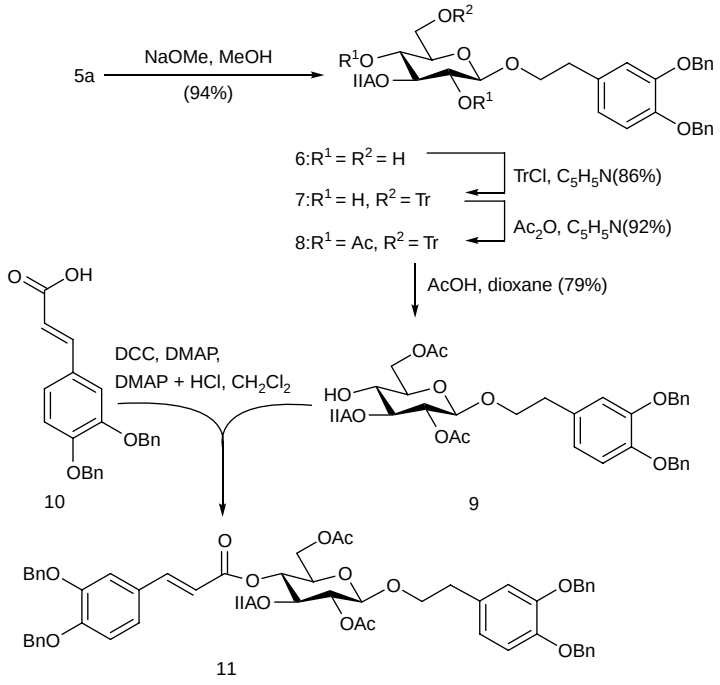

Figure 3. Synthesis of caffeoyl ester **11**.

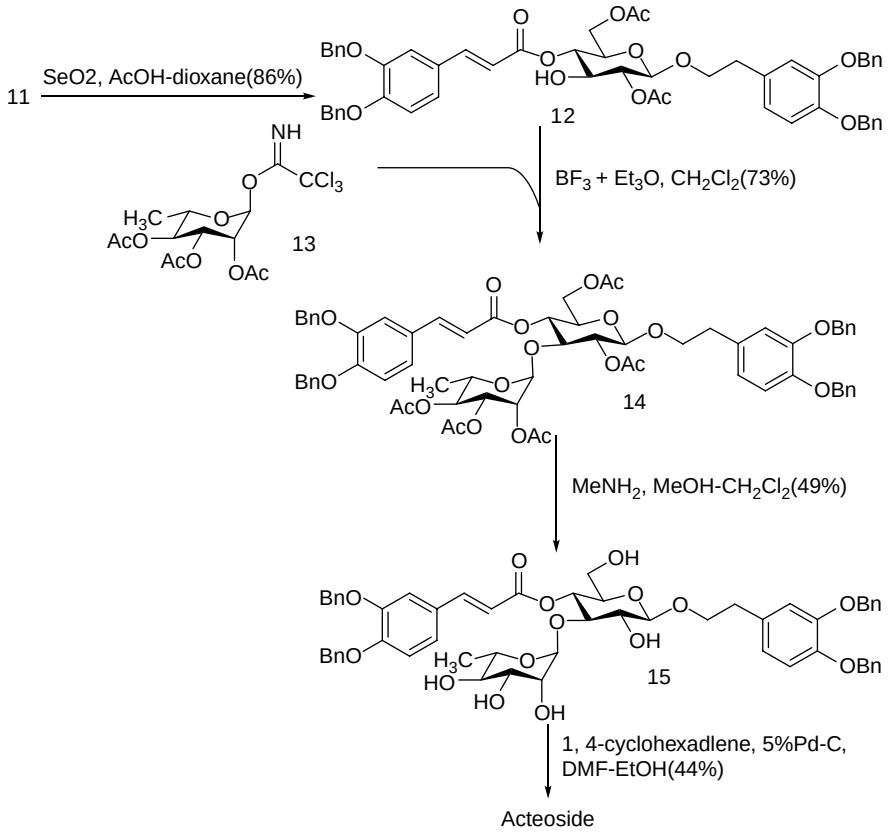

Figure 4. Rhamnosylation and deprotections.

assays. In addition, they also compared the antioxidant effects of acteoside with its derivatives, and the results showed that rhamnosyl at C-6″ and acetyl at C-2″ in the glycosyl part, apparently, contributed to the stronger antioxidant effect of acteoside. Yoon *et al*. [2] demonstrated that acteoside dose-dependently inhibited silica-induced reactive oxygen species (ROS) generation in B16 melanoma cells. Wang *et al*. [3] showed that acteoside could protect SH-SY5Y cells against β-amyloid-induced cell injury by attenuating ROS production. Chiou *et al*. [4] found that acteoside not only effectively minimized the loss of cell viability induced by hydroxyl radicals in cultured endothelial cells but also countered the free radical-induced destruction of the endothelium-dependent relaxation to acetylcholine in rat aorta. Furthermore, acteoside showed a dose-dependent scavenging effect of 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radicals in their experiments. Ohno *et al*. [25] showed that administration of acteoside prolonged survival time to 63.3 ± 3.4 days compared with 52.1 ± 2.5 days in controlled mice using a mouse model injected with B16 melanoma cells intravenously. They thought the antimetastatic effect of acteoside may be related to the antioxidant effect, nitric oxide (NO) synthesis regulation and cytotoxic activity against tumor cells.

5.2 Anti-inflammatory effect

Inflammatory is related to phospholipase A_2 (PLA_2) activation, histamine release,

ROS generation, and NO production in neutrophils, macrophages, and mast cells. Among them, cytosolic PLA_2 plays a key role in inflammatory response via generation of lysophosphatidylcholine or arachidonic acid [6].

Lee *et al*. [6] demonstrated that acteoside inhibited histamine release induced by melittin (an endogenous PLA_2 activator), arachidonic acid (produced by PLA_2 activation), and thapsigargin (a Ca^{2+} pump inhibitor) in the presence or absence of extracellular Ca^{2+} in mast cells. They showed that acteoside does-dependently inhibited 0.5 μM melittin-induced histamine release, 100 μM arachidonic acid-induced histamine release and 1 μM thapsigargin-induced histamine release. They also suggested that cytosolic PLA_2 rather than exogenous PLA_2 seemed to be involved in histamine release in RBL 2H3 cells.

Otherwise, Diaz *et al*. [26] showed that anti-inflammatory function of acteoside was related to the inhibition of lipopolysaccharide (LPS)-induced NO, prostaglandin E_2, and TNF-α production in mouse peritoneal. LPS activate two representative transcription factors, NF-κB and activator protein-1 (AP-1), and the activation of NF-κB and AP-1 cooperatively acts on the induction of the iNOS gene in cells, which is followed by the sustained production of NO. Lee *et al*. [7] found that LPS-inducible NO production was significantly inhibited by 100 μM acteoside. Consistent with the Western blot analysis result, RT-PCR analysis revealed that the iNOS mRNA level was also completely inhibited by 100 μM acteoside in the macrophages. A pre-treatment of the cells with acteoside (100 μM) significantly blocked the LPS-inducible increase in the AP-1 reporter activity. Their experiment demonstrated that acteoside selectively suppressed AP-1 activation, which may be essential for iNOS induction in the LPS-treated macrophages.

5.3 Antinephritis effect

Hayashi *et al*. [27–29] have done a series of experiments to investigate the effect of acteoside on rapidly progressive glomerulonephritis. First, they demonstrated that acteoside was capable of antinephritis. They found that giving 30 mg/kg acteoside once a day significantly inhibited crescentic-type anti-glomerular basement membrane (GBM) nephritis on rat model according to the measurement of urinary protein exertion, plasma cholesterol and creatinine contents, the titer of plasma antibody against γ-globulin, and histological observation. Then, they studied the effect of acteoside on leukocyte accumulation in the glomeruli of nephritic rats. The result showed that acteoside markedly suppressed the increase of total leukocytes and ED-1-positive cells only on the 15th day by 79 and 78%, respectively. Acteoside markedly suppressed the increase in CD4-positive cells, CD8-positive cells, interleukin (IL)-2-receptor-positive cells, and Ia-positive cells on the 5th day by 93, 74, 69, and 90% respectively, and on the 15th day by 82, 90, 100, and 92%, respectively. Later, they demonstrated the inhibitory effect of acteoside on the expression of intercellular adhesion molecule-1 (ICAM-1), which played a crucial role on the development of glomerulonephritis.

Hattori *et al*. [30] also demonstrated acteoside could inhibit mesangial cells proliferation and extracellular matrix overproduction by either inhibiting ICAM-1 expression or increasing activities of matrix metalloproteinases (MMP).

Therefore, these findings suggest that the antinephritic action of acteoside is due to the reduced glomerular influx of leukocytes through the inhibition of leukocytes adhesion to glomerular endothelial cells.

5.4 Cell regulation

Sun *et al*. [10] found that acteoside could promote rat prostate apoptosis and inhibit benign prostatic hyperplasia.

Lee *et al*. [31] clarified the role of acteoside on cell cycle. Acteoside was found to inhibit the proliferation of HL-60 cells not only by inducing differentiation via increased TGF-β1 signaling but also by arresting the G1 phase cell cycle through the downregulation of the CDK4- and CDK6-associated kinase activities in association with the induction of CKIs such as $p21^{CIP1/WAF1}$ and $p27^{KIP1}$. Meanwhile they assessed the inhibitory effects of acteoside and its derivatives on cancer cell growth. In their study, acteoside and isoacteoside, which have two catechol moieties and one rhamnose group, were found to be potently cytotoxic to various cancer cells, suggesting that caffeoyl substituents on the glucose ring of the phenyl ethanoids structure are crucial for cytotoxicity. Moreover, the cytotoxicity of leucosceptoside A was approximately a half of the acteoside derivatives, thus implying that the number of catechol moieties is also an important cytotoxic feature. Consistent with this trend, martynoside and isomartynoside, which have no catechol moiety, showed no cytotoxic effect at $< 150\,\mu M$. On the other hand, calceolariosides A and B were slightly less cytotoxic than leucosceptoside A, although these possess two catechol moieties, which indicate that the rhamnose group is also an important anticancer feature. Moreover, the positions of the caffeoyl substituents on the glucose ring have a secondary effective cytotoxicity, as acteoside and calceolarioside A were more cytotoxic activities to various cancer cells than isoacteoside and calceolarioside B, respectively. Tang *et al*. [32] demonstrated that acteoside would significantly stimulate the proliferation of dendritic cells at a low concentration, while showed an opposite effect at a very high concentration of 1000 μg/ml. On the other hand, the cell proliferation regulation effect of acteoside was also related to its function of the cell cycle regulation.

5.5 Hepatoprotective effect

Zhao *et al*. [8] found acteoside (50, 150, or 300 mg/kg) effectively reduced the Bacillus Calmette-Guérin (BCG)/LPS-induced elevated liver index, liver homogenate aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, hepatic NO, and malondialdehyde (MDA) contents; restored hepatic SOD activity; and reduced the degree of liver injury in immunological liver injury (ILI) mice. Lee *et al*. [34] showed the protective effects of acteoside against the carbon tetrachloride-induced hepatotoxicity. Their studies showed that acteoside-suppressed P450 2E1 protein levels in a dose-dependent manner and significantly reduced the liver damage. Xiong *et al*. [9] demonstrated the inhibition effect of acteoside on apoptosis in D-GalN and on LPS-induced liver injury. It suggested that the hepatoprotective effect of acteoside may be associated with its antioxidant properties, immunoregulatory function, and regulation of hepatic apoptosis.

5.6 Immunoregulation

Hayashi *et al*. [28] have done researches on the effect of acteoside on leukocytes accumulation in the glomeruli of nephritic rats. Their study demonstrated that acteoside suppressed the accumulation of CD4-positive cells, CD8-positive cells, and IL-2-receptor-positive cells in the glomeruli of rats. They suggested that the immunosuppressive action of acteoside might be partly due to the prevention of the activation of antigen-presenting cells such as monocytes and mesangial cells.

5.7 Neuroprotective effect

Gao and Pu [35] showed that pretreatment of acteoside had a potent neuroprotective effect against rotenone-induced SH-SY5Y cells damage. Yang and Pu [11] demonstrated that acteoside could protect

SH-SY5Y cells against rotenone-induced apoptosis. They suggested that the neuroprotective effect of acteoside might be related with its function of reducing ROS level. Zhao and Pu [36] showed acteoside might protect C57 mice against MPTP-induced neuronal damage. Pu *et al*. [37] showed that acteoside could inhibit apoptosis by 1-methyl-4-phenylpyridinium ion in cerebellar granule neurons.

5.8 Other effects

Yoon *et al*. [2] found that acteoside could inhibit tyrosinase activity and melanin production in B16 melanoma cells. Furthermore, Song and Sim [38] demonstrated that acteoside inhibited α-MSH-induced melanin production in B16 cells by the inactivation of adenyl cyclase. Quan *et al*. [39] found that acteoside could enhance the sex function of the male rats by increasing pencil erection. Martins *et al*. [40] found that acteoside had inhibitory activity against HSV-1 and HSV-2 *in vitro*. Molnar *et al*. [33] reported that acteoside had the effect of antibacterial through its antiplasmid function. Shang *et al*. [41] showed that acteoside could reduce the level of uric acid in hyperuricemia mice and significantly inhibit the xanthine oxidase *in vitro*. The prevention and curative effect of acteoside is related to its inhibition of xanthine oxidase. Tam *et al*. [42] demonstrated that acteoside enhanced contraction of rat mesenteric artery due to the endothelial NO. Wong *et al*. [43] showed the relaxing effect of acteoside in rat aortic rings.

6. Discussion

Acteoside, which has extensive biological activities and few side effects, could be isolated from many plants that mostly distributed in Asia. Now, there have been some related health products of acteoside on the market as hepatoprotective, such as 'CHDA Capsules' (G20060728), manufactured by CHD Biotechnology (Shezhen High-Tech Industrial Park Bio-Incubator, Gaoxin C., Shenzhen, Hong Kong) Limited. Researchers are still evaluating whether acteoside can be used as medicine to cure other diseases and developing the products of acteoside to improve human health. For these reasons, it may be developed into a promising drug in the future.

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