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CHEMICAL CONSTITUENTS OF *RABDOSIA JAPONICA* VAR. *GLAUCOCALYX*

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Rabdosia japonica var. *glaucocalyx* is mainly distributed in northeast Asia and has many bioactivities and good safety. There were over 100 compounds isolated from the plant and 50 derivatives prepared from diterpenoids of this plant. Many of these compounds have good bioactivities. The aim of the present article is to review phytochemical constituents, extraction techniques, and derivatives of diterpenoids, recommend the total diterpenoids and some monomers for pharmaceutical industry, and have a look at the future perspectives. It is expected that still more new compounds having good biological activity will be isolated from the plant.

Keywords: *Rabdosia japonica* var. *glaucocalyx*, chemical constituents, diterpenoid derivatives, review

1. INTRODUCTION

Rabdosia (=*Isodon*) plants belong to a genus of the Labiatae (=Lamiaceae) family, which includes over 100 species mainly growing in eastern parts of Africa, India, Himalayas, Thailand, China and Japan. Various species of *Rabdosia* have been used in indigenous medicine for the treatment of several diseases. For example, the leaves of *R. rubescens*, which is the most studied species and is known in China under the name of "*donglingcao*", are still used by the local people in Henan province for the treatment of respiratory and gastrointestinal bacterial infections, inflammation, and cancer. The aerial parts of *R. ternifolia*, *R. lophanthoides,* and *R. megathyrsa* are empirically employed as antimalarial and anti-inflammatory agents and also for the treatment of enteritis and jaundice. The variety of biological activities made *Rabdosia* plants attractive targets for research on active ingredients which dates back to 1910s. Since the first determination of the molecular structure of enmein, the bitter principle in *R. japonica*, many bioactive diterpenoid compounds have been structurally characterized by Japanese and Chinese researchers. Research on *Isodon* species is being emphasized by much more Chinese researchers.

The genus *Rabdosia japonica* (Burm. f.) Hara var. *glaucocalyx* (Maxim.) Hara is a member of the family Labiatae, subfamily Ocimoideae, tribe Plectrantheae and is mainly distributed in northeast Asia, such as China, Russia, Korea and Japan. It is a widely growing plant species in Northern part of China, which has been used in folk medicine for the treatment of hepatitis, gastricism, mastitis and coughing in China [1]. Recently, it was reported that *R. japonica* has other bioactivities such as antitumor [2], antioxidant [3], anticoagulant [4], antibacterial [5, 6], and anticomplementary [7].

Results of toxicological tests indicated that *R. japonica* is safe to humans within the scope of experimental dosage [8, 9]. The first investigation on chemical constituents of *R. japonica* can be traced back to 1981, when Xu, et al. [10] for the first time isolated two *ent*-kaurane diterpenoids named glaucocalyxin A and B from the plant. Since then, many chemical constituents have been isolated and their structure determined. Phytochemical investigations revealed that diterpenoids, flavonoids and triterpenoids are the major constituents in the whole plant. Diterpenoids have been regarded as the marking composition of the plant.

The aim of the present article is to review phytochemical constituents of *R. japonica* and derivatives of its diterpenoids, recommend the total diterpenoids and some monomers for pharmaceutical industry, and have a look at the future perspectives.

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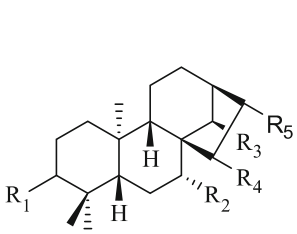
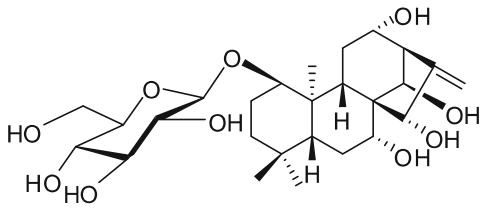
2. DITERPENOIDS

During the period of 1981–April 2014, there appeared a large number of publications about 24 diterpenoids isolated from the plant. Most of these compounds have good cytotoxicity indices. We classify this group of diterpenoids into three subgroups: C-20 non-oxygenated *ent*-kauranes, C-20 oxygenated *ent*-kauranes and 6,7-*seco*-*ent*-kauranes (Figs. 1 – 3). Compound **12** has been the first diterpenoid glycoside isolated from *R. japonica*, and it is the only one so far. Compound **3 – 12** were isolated only from this plant, Compound **1 – 2** and **13 – 24** were also isolated from other *Rabdosia* species.





12 [16]

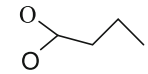
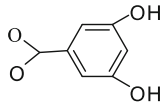
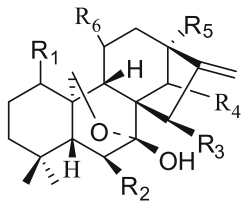
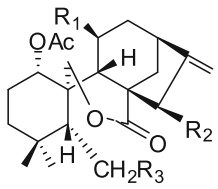
No.	R_1	R_2	R_3	R_4	R_5	Ref.
1	=O	OH	OH	=O	$=CH_2$	[10]
2	=O	OH	OAc	=O	$=CH_2$	[10]
3	=O	OH	OH	α-OH	$=CH_2$	[11]
4	=O	OAc	OH	=O	$=CH_2$	[12]
5	=O	OH	OH	=O	β-CH_3	[12]
6	α-OH	OH	OH	=O	β-CH_3	[13-14]
7	=O			=O	$=CH_2$	[13-14]
8	=O			=O	$=CH_2$	[15]
9	=O	OH	OH	β-OH	$=CH_2$	[15]
10	=O	OH	OH	=O	β-CH_2OCH_3	[15]
11	α-OH	H	H	H	α-OH, β-CH_3	[15]

Fig. 1. Structures of C-20 non-oxygenated *ent*-kauranes.

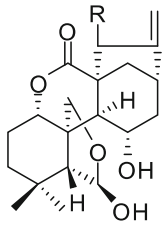


No.	R_1	R_2	R_3	R_4	R_5	R_6	Ref.
13	α-OH	β-OH	=O	β-OH	H	H	[17]
14	H	β-OH	=O	β-OH	H	α-OH	[17]
15	α-OAc	β-OH	=O	β-OH	H	H	[18]
16	β-OH	β-OAc	β-OAc	H	α-OH	H	[19]
17	α-OH	β-OH	=O	H	H	β-OH	[20]

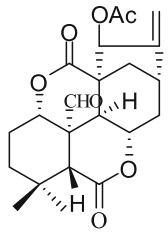
Fig. 2. Structures of C-20 oxygenated *ent*-kauranes.



	R_1	R_2	R_3	Ref.
18	β-OH	=O	OAc	[18]
19	β-OAc	β-OAc	OAc	[18]
20	β-OAc	=O	OAc	[20]
21	β-OH	=O	OH	[20]



	R	Ref.
22	=O	[18]
23	α-OH	[18]



24 [17]

Fig. 3. Structures of 6,7-*seco*-*ent*-kauranes.

2.1. C-20 Non-Oxygenated ent-Kauranes

This is the largest group of known *Rabdosia* diterpenoids, which appear to be the most widely distributed. Their structures are shown in Fig. 1.

2.2. C-20 Oxygenated ent-Kauranes

This group includes compounds **13 – 17** with structures presented in Fig. 2.

2.3. 6,7-Seco-ent-Kauranes

This group includes compounds **18 – 24** with structures presented in Fig. 3.

2.4. Extraction Techniques

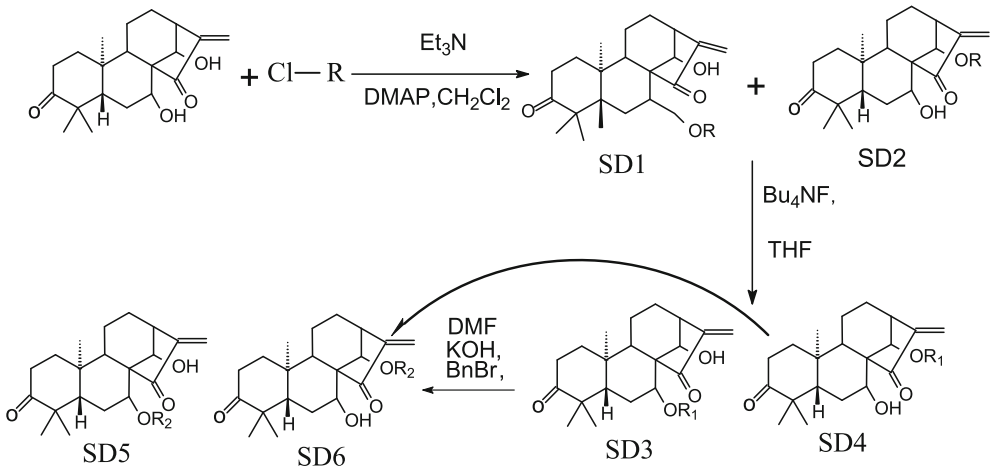
Source of natural products is a big bottleneck, There are a large number of publications about the extraction of total diterpenoids and some monomers from the plant, which are aimed at obtaining more production.

Liu, et al., [21] used solvent extraction, decoloration with activated carbon, hyperfiltration and macroporous resin purification to obtain total diterpenoids from leaves of the plant. The method has the advantages of simple operation, low energy consumption, high product quality, it is suitable for commercial production. Shu, et al., [22] used supercritical fluid extraction and macroporous resin purification to obtain total diterpenoids from the plant. This method has the advantages of high efficiency and low pollution, so it is also suitable for commercial production. Zhang, et al., [23] used solvent extraction, macroporous resin purification and decoloration with activated carbon to obtain total diterpenoids from the plant. Glaucocalyxin A was obtained by the recrystallization of total diterpenoids from ethanol. The method has the advantages of high product quality and high purity: the purity of Glaucocalyxin A is above 90% and its yield is above 7%.

Shen, et al. [24] used L_9 (3^4) orthogonal experiment to optimize the extraction of Glaucocalyxin A. The optimum conditions are as follows: double methanol reflux extraction, each 1.5 h, at the ratio of liquid to solid 15 : 1. The yield of Glaucocalyxin A was 0.028% [24]. Static and dynamic adsorption by macroporous resin were used to optimize the adsorption and elution process [25]. The result showed that the purification of glaucocalyxin A by D101 macroporous resin was better than that by AB-8, and the optimal conditions were as follows: liquid concentration 0.5 – 0.8 $g \cdot mL^{-1}$, absorption rate 2.0 $BV \cdot h^{-1}$, resin adsorption capacity 2.7 $g \cdot g^{-1}$, elution solvent 60% ethanol, elution speed 3.0 $BV \cdot h^{-1}$, elution solvent volume 30 BV.

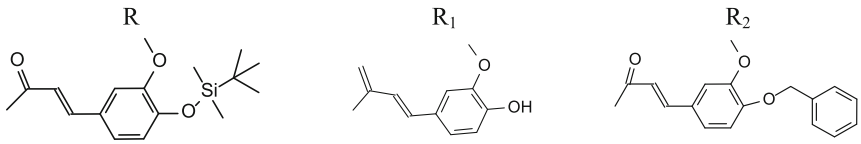
Zhang, et al., [26] used 75 – 80% aqueous ethanol solution, reflux extraction, silica gel column chromatography for purification, and recrystallization to obtain Glaucocalyxin A from the plant. The purity of obtained Glaucocalyxin A is above 95%, its yield is above 10%, and there is no residual solvent. Shu, et al., [27] used supercritical CO_2 fluid extraction with entrainer and high speed counter current chromatography purification to obtain Glaucocalyxin A from the plant. This method has the advantage of high efficiency and low pollution, so it is suitable for commercial production. Liu, et al., [28] used ethanol reflux extrac-

tion, two-phase solvent system allocation, high speed counter current chromatography, and crystallization purification to obtain Glaucocalyxin A from the plant. This preparation method has the advantages of partial removal of impurities through two different solvent system allocation, lossless separation of product through high speed counter current chromatography process, short preparation period, and the avoidance of defects of the traditional silica gel column separation process, such as die adsorption,

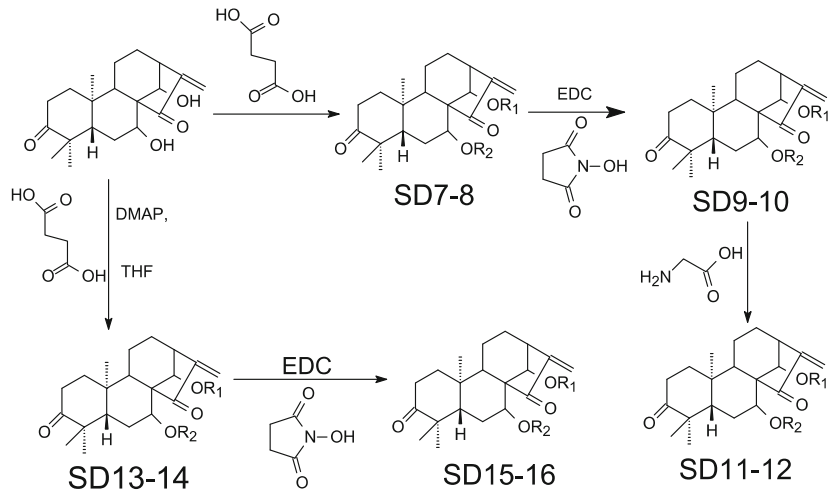


DMAP: 4-dimethylaminopyridine; Bu_4NF: Tetrabutylammonium fluoride

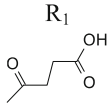
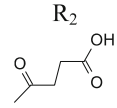
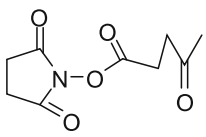
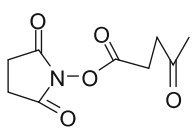
THF: Tetrahydrofuran; DMF: N,N-Dimethylformamide

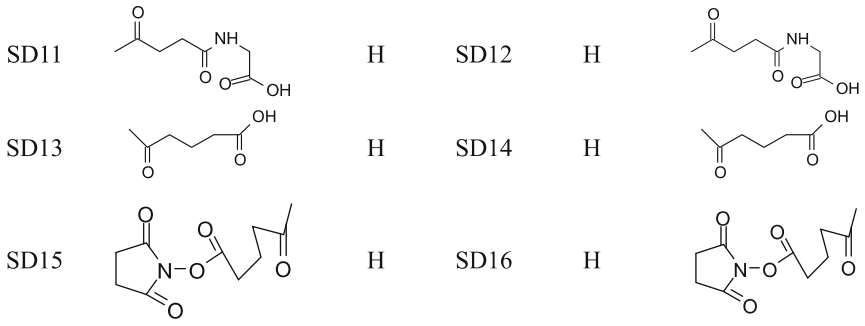


Scheme 1. Synthesis of SD1 – 6 [30].



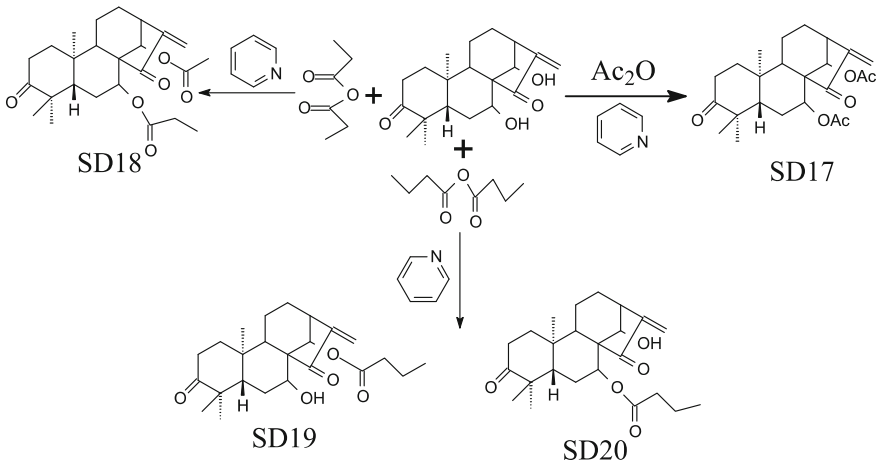
EDC: 1-(3-Dimethylaminopropyl)-3-Ethyl Carbodiimide

No.	R_1	R_2	NO.	R_1	R_2
SD7		H	SD8	H	
SD9		H	SD10	H	



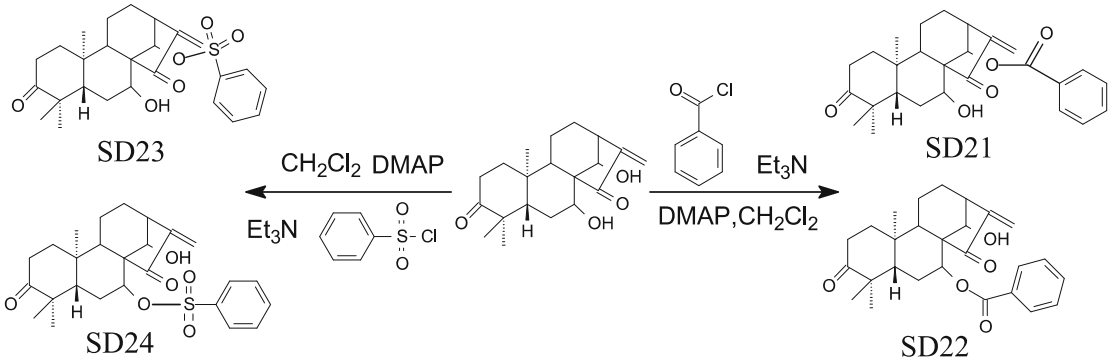
Scheme 2. Synthesis of SD7 – 16 [31].

complex technology, and poor reproducibility. Bai, et al., [29] used aqueous ethanol solution reflux extraction, and repeated sil-

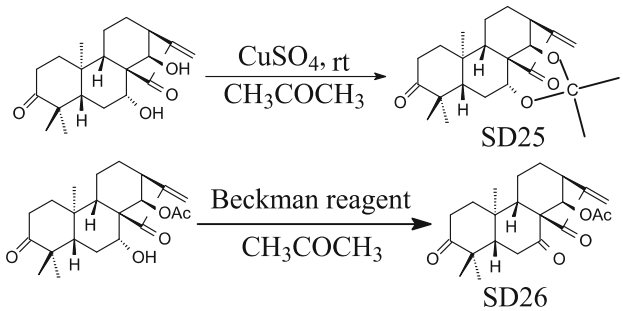


Scheme 3. Synthesis of SD17 – 20 [32].

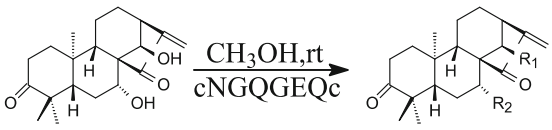
ica gel column chromatography purification to obtain Glaucocalyxin G from the plant.



Scheme 4. Synthesis of SD21 – 24 [33].



Scheme 5. Synthesis of SD25 – 26 [10].

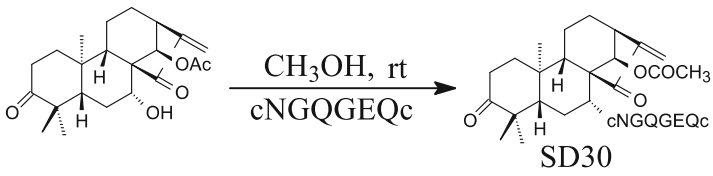


SD27-29

No.	SD27	SD28	SD29
R_1	OH	cNGQGEQc	cNGQGEQc
R_2	cNGQGEQc	OH	cNGQGEQc

cNGQGEQc**:** a low molecular weight peptide

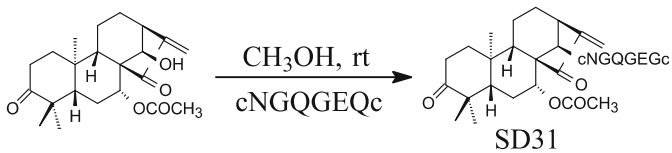
Scheme 6. Synthesis of SD27 – 29 [34].



SD30

Scheme 7. Synthesis of SD30 [35].

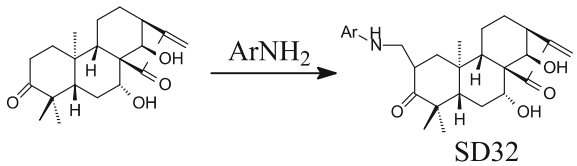
2.5. Synthetic Derivatives



SD31

Scheme 8. Synthesis of SD31 [36].

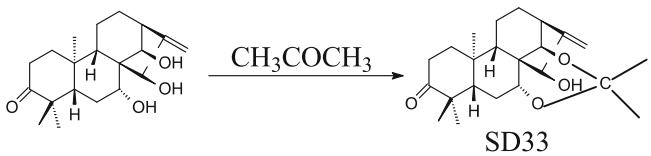
Over 50 synthetic derivatives (SDs) were obtained from diterpenoids of *R. japonica*, especially from compound **1**. The path-



SD32

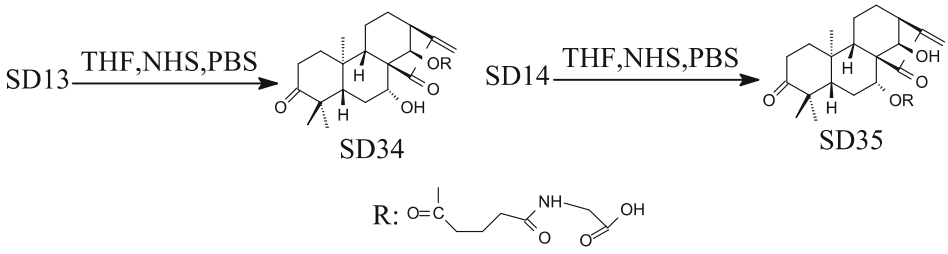
Scheme 9. Synthesis of SD32 [37].

ways of syntheses are presented in Schemes 1 – 13.



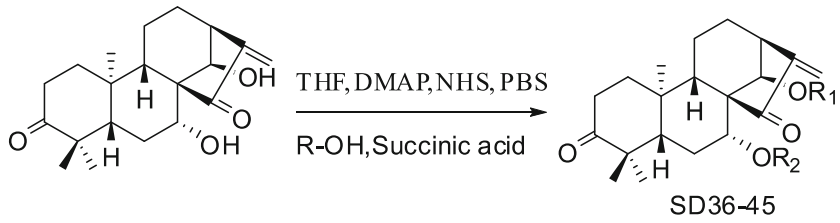
SD33

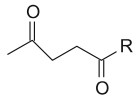
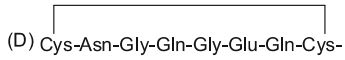
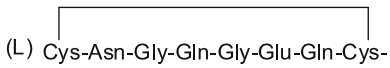
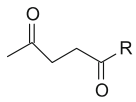
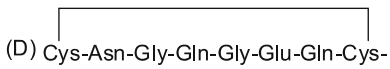
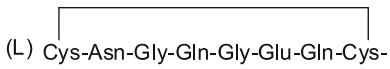
Scheme 10. Synthesis of SD33 [11].



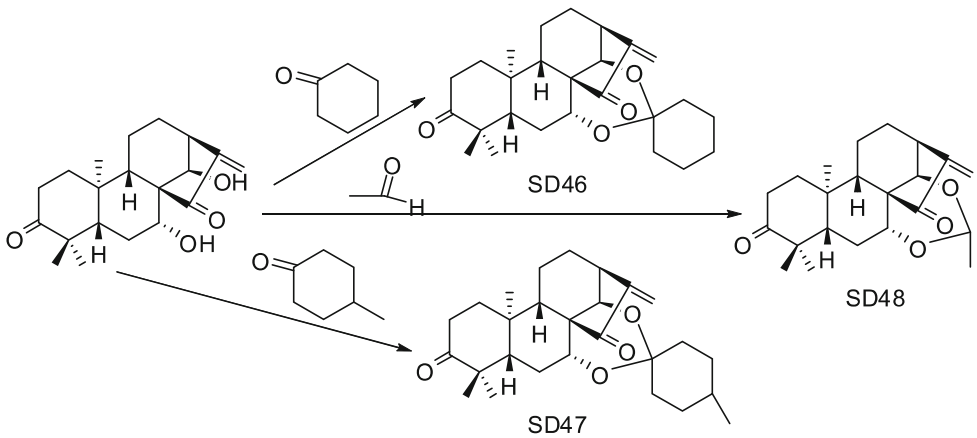
NHS: N-Hydroxysuccinimide; PBS: Phosphate Buffered Saline

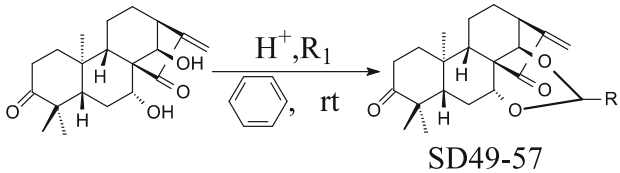
Scheme 11. Synthesis of SD34 – 35 [32].

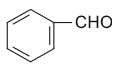
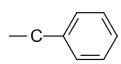
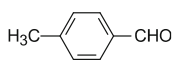
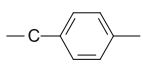


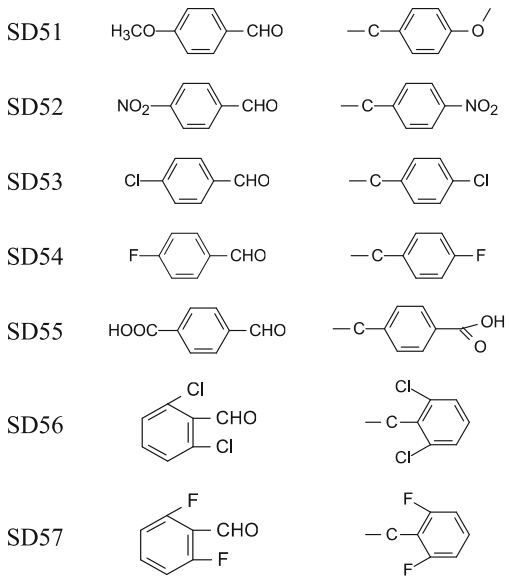
No.	R_1	R_2	R
SD36			Arg-Gly-Asp
SD38			Arg-Gly-Asp-Val
SD40		H	Arg-Gly-Asp-Ser
SD42			
SD44			
SD37			Arg-Gly-Asp
SD39			Arg-Gly-Asp-Val
SD41	H		Arg-Gly-Asp-Ser
SD43			
SD45			

Scheme 12. Synthesis of SD36 – 45 [38, 39].





No.	R_1	R
SD49		
SD50		



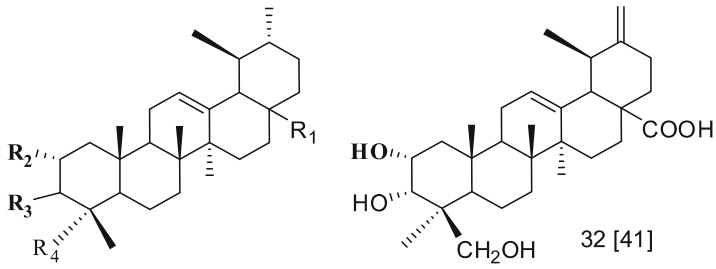
Scheme 13. Synthesis of SD46 – 57 [29].

3. TRITERPENOIDS

There are 16 triterpenoids isolated from *R. japonica* plant so far. All of them belong to pentacyclic triterpenoids and have been also isolated from other plants. These compounds can be subdivided into two groups.

3.1. Ursane Type

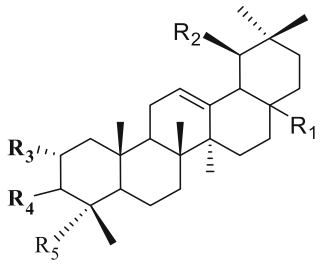
The structures of ursane-type triterpenoids from *R. japonica* are as follows:

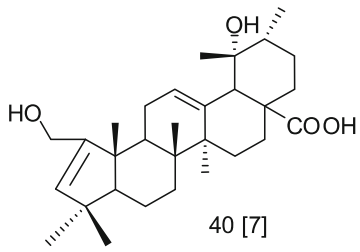


No.	R_1	R_2	R_3	R_4	Ref.
25	COOH	H	β-OH	CH_3	[40]
26	OH	H	α-OH	CH_3	[40]
27	COOH	H	α-OAc	CH_3	[41]
28	COOH	OH	α-OH	CH_3	[40]
29	COOH	OH	β-OH	CH_3	[41]
30	COOH	OH	α-OH	CH_2OH	[40]
31	$COCH_3$	H	β-OH	CH_3	[42]

3.2. Oleanane Type

The structures of oleanane-type triterpenoids from *R. japonica* are as follows:



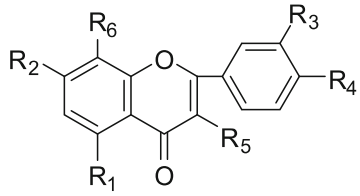


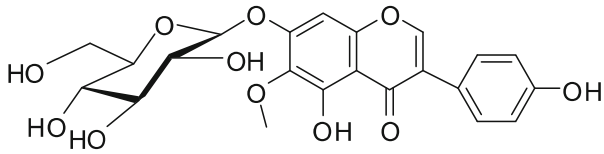
40 [7]

No.	R_1	R_2	R_3	R_4	R_5	Ref.
33	COOH	H	H	β-OH	CH_3	[40]
34	COOH	H	H	α-OAc	CH_3	[41]
35	COOH	H	OH	β-OH	CH_3	[7]
36	COOH	H	OH	β-OH	CH_2OH	[43]
37	COO-glc	OH	OH	β-OH	CH_2OH	[16]
38	CH_3	H	H	=O	CH_3	[44]
39	CHO	H	H	=O	CH_3	[44]

4. FLAVONOIDS

There are 20 flavonoids isolated from *R. japonica* plant, including 19 flavonoids and one isoflavonoid, all of which were also isolated from other plants. The structures of these compounds are as follows:





60 [6]

No.	R_1	R_2	R_3	R_4	R_5	R_6	Ref.
41	OH	OH	H	OH	H	H	[44]
42	OH	OH	OH	OH	H	H	[45]
43	OH	OH	H	OCH_3	H	H	[46]
44	OH	OH	OH	OCH_3	H	H	[7]
45	OH	OH	OH	OH	OH	H	[45]
46	OH	OCH_3	OH	OH	H	H	[44]
47	OH	OH	OH	OH	OCH_3	H	[45]
48	OH	O-glc-6- OAc	H	OCH_3	H	H	[47]
49	OH	O-glc	H	OH	H	H	[45]
50	OH	OH	OH	OH	O-glc	H	[45]
51	OH	OH	OH	OH	O-glc	H	[48]
52	OH	O-glc	OH	OH	H	H	[44]
53	OH	O-rha	OH	OH	OH	H	[49]
54	OH	OH	OH	OH	O-rha	H	[49]
55	OH	O-glc	H	OCH_3	H	H	[49]
56	OH	O-glc	OCH_3	OH	H	H	[49]
57	OH	OH	OH	OH	O-rutinose	H	[49]
58	OH	OH	H	OH	O-rutinose	H	[16]
59	OH	OH	H	OH	H	glc	[7]

5. VOLATILE OIL

There are 41 chemical constituents of the volatile oil isolated from *R. japonica* plant, most of which represent aliphatic compounds and their derivatives. The complete list of these compounds is as follows: hexane (**61**), ethyl-cyclopentane (**62**), 2-methyl-3-ethyl-pentane (**63**), 2-methyl-hexane (**64**), 2,2-dimethyl-hexane (**65**), 2,5-dimethyl-hexane (**66**), 2,2,4-trimethyl-pentane (**67**), 1-ethyl-2-methyl-cyclopentane (**68**), octane (**69**), 1,1,3-trimethyl-oyclohexane (**70**), ethyl acetate (**71**), butanedioic

acid bis(2-methylpropyl) ester (**72**), butanedioic acid methyl-bis(1-methylpropyl) ester (**73**), hexanedioic acid bis(2-methylpropyl) ester (**74**), 1,2-benzenedicarboxylic acid bis(2-methylpropyl) ester (**75**), pentadecanoic acid 14-methyl-methyl ester (**76**), hexadecanoic acid ethyl ester (**77**), (Z,Z,Z),9,12,15-octadecatrienoic acid methyl ester (**78**), linoleic acid ethyl ester (**79**), 9,12-octadecadienoic acid ethyl ester (**80**), octadecanoic acid ethyl ester (**81**), butanedioic acid diethyl ester (**82**), 2,3,3- trimethyl-cyclobutanone (**83**), 6,10-dimethyl-(e)-5,9-undecadien-2-one (**84**), 4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one (**85**), 6,10-dimethyl-2-undecanine (**86**), tetradecanal (**87**), (Z,Z,Z)-9,12,15-octadecatrien-1-ol (**88**), 1-octen-3-ol (**89**), 3,7-dimethyl-1,6-octadien-3-ol (**90**), 1,5-diethenyl-3- methyl-2-methylene-cyclohexane (**91**), 4,11,11-trimethyl-8- methylene-bicyclo-[7,2,0]undec-4-ene (**92**), a-caryophyllene (**93**), 2-ethoxy-propane (**94**), and 3-methyl-pentane (**95**). In addition, there are seven aromatic compounds, including eugenol (**96**), 3-allyl-6-methoxyphenol (**97**), 4-methoxy-6-(2-propenyl)1,3- benzoeioxole (**98**), dibutyl phthalate (**99**), 1,2- benzenedicarboxylic acid bis(2-methylpropyl) ester (**100**), methyl salicylate (**101**) and 2,4-difluoro-1-isocyanato-benzene (**102**) [50].

6. OTHER COMPONENTS

There are nine other compounds, including caffeic acid (**103**) [7], caffeic acid vinyl ester (**104**) [7], palmitic acid (**105**) [41], stigmasterol-9-en-3-ol (**106**) [7], stigmasterol (**107**) [46], β-sitosterol (**108**) [42], daucosterol (**109**) [42], fructose (**110**) [42], stigmasterol-3-*O*-glucoside (**111**) [46]. Finally, there are 26 inorganic elements, including Fe, Cu, Zn, Ni, Cr, Mn, As, Se, Cd, Pb, Hg, Sb, K, Na, P, Ca, Mg, S, Ba, Li, Al, V, Ti, Ce, Y and Yb [51 – 52].

7. FUTURE PERSPECTIVES

Because of good biological activities and safety, the pharmacokinetics [53 – 54], protein binding rate [55], and dosage forms [56 – 59] of some monomers of R. *japonica* plant, in particular glaucocalyxin A, have been studied. *Rabdosia japonica* var. *glaucocalyx* has attracted the attention of chemists, pharmacologists and researchers, invention of new drugs being the ultimate goal. However, no clinical drugs have been created based on this plant thus far, although some diterpenoids from plants of the Labiatae family have become important drugs, such as triptolide, rographolide and tanshinone. Thus, *R. japonica* seems to have a great potential and remains largely unexplored, so that Further study on this plant is very meaningful. Of course, further studies of the plant should also focus on the related derivatives.

Though there were over twenty patents about the extraction techniques and synthetic derivatives of diterpenoids from *R. japonica* so far, but its activity is not sufficient to be drug. Therefore, systematic modification and structure - activity relationship (SAR) studies on *R. japonica* diterpenoids are very important for understanding these interesting compounds and searching for drug candidates. In the present-day studies, most modifications are focused on 7-OH and 14-OH, the esterification reaction being the main means which led to the emergence of about fifty derivatives. So, further studies need to be performed to modify other sites, even the skeleton, obtain more derivatives, and establish more detailed SARs which will be useful for modifying, designing and synthesizing novel analogs of *R. japonica* compounds and searching for drug molecules. There are few glycosides of diterpenoids and triterpenoids from the plant. Thus, research on *R. japonica* var. *glaucocalyx* is still going strong, as was pointed out by Prof. Park [60].

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