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Chemical Constituents and Pharmacological Activities of *Rabdosia japonica* var. *glaucocalyx*

ZHAO BAO XIANG[1,2,*], SAN WEN TONG[1], YUN WANG[1], CONG LIN HE[1] and XIAO HUI LI[2]

[1]College of Bio-Information, Chongqing University of Posts and Telecommunications, Chongqing 400065, P.R. China
[2]College of Pharmacy, Third Military Medical University, Chongqing 400030, P.R. China

*Corresponding author: E-mail: xiangzb@126.com

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Rabdosia japonica var. *glaucocalyx* is a widely growing plant in northeast Asia, such as China, Russia, Korea and Japan, which has been used as folk medicine for the treatment of hepatitis, gastricism, mastitis and coughing in China. Recently, it was reported that the *Rabdosia japonica* var. *glaucocalyx* has other bioactivities such as antitumor, antioxidation, antiinflammatory and antibacteria. The results of toxicological tests indicated that the *Rabdosia japonica* var. *glaucocalyx* is safe to human within the scope of the experimental dose. An attempt has been made to review the chemical constituents and pharmacological activities of *Rabdosia japonica* var. *glaucocalyx*.

Key Words: Review, *Rabdosia japonica* var. *glaucocalyx*, Chemical constituents, Pharmacological activities.

INTRODUCTION

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 and has been used as folk medicine for the treatment of hepatitis, gastricism, mastitis and coughing[1]. Recently, it was reported that the *Rabdosia japonica* var. *glaucocalyx* has other bioactivities such as antitumor, antioxidation, antiinflammatory and antibacteria, *etc.* Results of toxicological tests indicated that the *Rabdosia japonica* var. *glaucocalyx* is safe to human within the scope of the experimental dose[2]. An attempt has been made to review the phytochemical and pharmacological work done on *Rabdosia japonica* var. *glaucocalyx*.

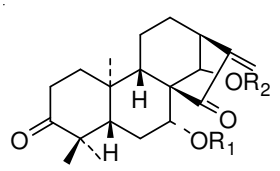
Phytochemical investigations: Phytochemical investigation revealed that diterpenoids, flavonoids and triterpenoids are the major constituents in the whole plant. Meanwhile the diterpenoids have been regarded as the marking composition of *Rabdosia japonica* var. *glaucocalyx*. There were 13 diterpenoids reported so far. These chemical formulae were as follows:

Compounds **1-2** were found in 1981 by Xu *et al.*[3], compound **3** was found in 1988 by Liu *et al.*[4], compounds **4-5** were found in 1992 by Kim *et al.*[5], compounds **6-7** were found in 2008 by Xiang *et al.*[6], compounds **9-13** were found in 2008 by Ding *et al.*[7], compound **8** were found in 2010 by Xue *et al.*[8] and compounds **1-10** were *ent*-kauranoid diterpenoids.

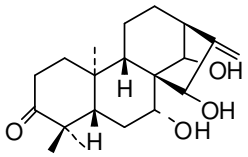
The triterpenoids from *Rabdosia japonica* var. *glaucocalyx* were as follows: ursolic acid, arjunolic acid, eriantic acid B, oleanic acid[9], friedelin, 3β, 28-dihydroxy ursane, 3β-acetyloxy-ursolic acid, 2α,3α-dihydroxy-urs-12-en-28-oic acid, 2α,3α, 23-trihydroxy-urs-12-en-28-oic acid[10], 2α-hydroxyursolic acid[11] and canophyllal[12].

The flavonoids from *Rabdosia japonica* var. *glaucocalyx* were as follows: quercetin, quercetin-3-methyl ether, quercetin-3-O-β-D-glucoside, rutin, apigenin-7-O-β-D-glucoside, luteolin[13], acacetin[11], quercetin-7-O-α-L-rhamnoside, quercetin-3-O-α-L-rhamnoside, acacetin-7-O-β-D-glucoside, chrysoeriol-7-O-β-D-glucoside[14], agastachoside[15], apiginin, luteolin-7-O-β-D-glucoside, luteolin-7-methyl ether[12]. There are some other compounds, such as fructose[16], stigmasterol, stigmasterol-3-O-β-D-glucopyranoside[11], β-sitosterol and β-daucosterol[12].

Pharmacological activities: Liu *et al.*[17] determined the effects of ethanolic extract of *Rabdosia japonica* var. *glaucocalyx* on c-fos gene expression during global myocardial ischemia-reperfusion according the method that 40 Wistar rats were divided into 5 groups: group N as control; group CN as ischemia-reperfusion control and group XH, XM and XL treated with ethanolic extract of *Rabdosia japonica* var. *glaucocalyx* 5, 1 and 0.5 %, respectively prior to ischemia-reperfusion. The isolated rat hearts were perfused in condition of constant temperature and pressure and then the left ventricular myocardiums were extracted for use. The expression of c-fos protein was detected by immunochemical method. The expression of c-fos protein were quantified by using computer



1 $R_1 = R_2 = H$
2 $R_1 = H$ $R_2 = COCH_3$
3 $R_1 = COCH_3$ $R_2 = H$



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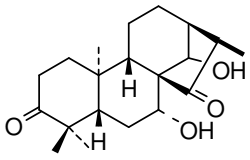

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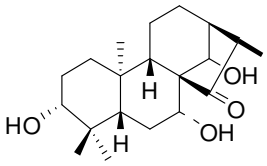

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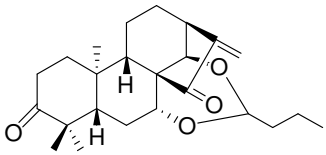

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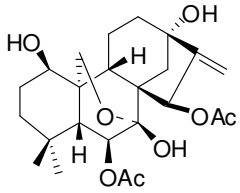

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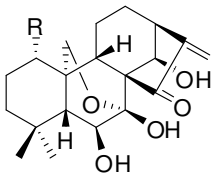
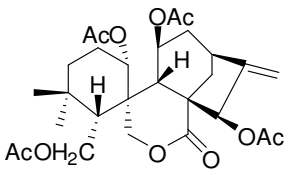


9 R = OAc
10 R = OH



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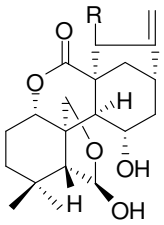

12 R = O
13 R = H/-OH

image analysis system. The result showed that compared with the values of group N, protein expressions relative area of c-fos gene (PERA) were increased significantly in group CN, XH, XM, XL ($p < 0.01$), but decreased significantly in group XH, XM, XL compared with those of group CN ($p < 0.05$). The PERA of c-fos gene in group XM, XL were significantly lower than in group XH ($p < 0.01$) and the PERA of c-fos gene in group XM were lower than in group XL ($p < 0.05$). So the ethanolic extract of *Rabdosia japonica* var. *glaucocalyx* can effectively depress the expression of c-fos gene in myocardium which may account for its protection against myocardial ischemia-reperfusion injury and the middle and the low concentrations of ethanolic extract of *Rabdosia japonica* var. *glaucocalyx* are more effective than the high concentrations.

Zhu *et al.*[18] discussed the protection of total diterpenoids of *Rabdosia japonica* var. *glaucocalyx* against myocardial injury by isotope tracer method, results showed that the low concentration of the total diterpenoids of *Rabdosia japonica* var. *glaucocalyx* can obviously increase normal mice myocardial nutritive blood flow and the high-dosage groups is obviously better than the positive control group, So the total diterpenoids of *Rabdosia japonica* var. *glaucocalyx* can obviously increase mice myocardial blood flow.

Yang *et al.*[16] screened the antitumor activity of *Rabdosia japonica* var. *glaucocalyx*. They found the growth inhibition rate of cyclohexane extract from ethanolic extracts of *Rabdosia japonica* var. *glaucocalyx* at 100 μg/mL to KB cell and the BGC cell is 74.81 and 62.72 %, respectively *in vitro*. Wang *et al.*[19] reported that the glaucocalyxin A (compound **1**) showed significant cytotoxic activity against BEL-7402 and HO-8910 cell. Xiang *et al.*[20,21] tested the cytotoxicity of glaucocalyxin A-X (compound **1-7**) against human tumour cell lines HL-60, 6T-CEM, LOVO and A549 by MTT method. The results showed that glaucocalyxin A-C and glaucocalyxin X (compound **1-3** and compound **7**) exhibited good cytotoxicity but glaucocalyxin D-F showed no activity against the above cancer cell lines with IC_{50} values all higher than 100 μg/mL. They conclude the reason is the presence of the α,β-unsaturated ketone moiety in ring D in the case of glaucocalyxins A, B,C and X, while glaucocalyxins D, E and F have no this group.

Gao *et al.*[22] focused on the effect of glaucocalyxin A induction on apoptosis, the mitochondria- mediated death pathway and the accumulation of reactive oxygen species (ROS) in HL-60 cell. They found glaucocalyxin A could induce a dose-dependent apoptosis in HL-60 cells as characterized by cell morphology, DNA fragmentation, activation of caspase-3, -9 and an increased expression ratio of Bax/Bcl-2. The mitochondrial membrane potential loss and cytochrome c release from mitochondria to cytosol during the induction. Moreover, glaucocalyxin A caused a time- and dose-dependent elevation of intracellular ROS level in HL-60 cells and N-acetyl-L-cysteine (NAC, a well-known antioxidant) could block glaucocalyxin A induced ROS generation and apoptosis. So they inferred that glaucocalyxin A induces apoptosis in HL-60 cells through ROS-dependent mitochondrial dysfunction pathway. Hai *et al.*[23] discussed the effect of glaucocalyxin B

on cell cycle and apoptosis of AGZY cells, they inferred that glaucocalyxin B can block the growth of AGZY cells, block the cells into the G_2/M period and induce the apoptosis.

Wang *et al.*[10] tested the cytotoxic activity of triterpenoids from *Rabdosia japonica* var. *glaucocalyx via* SRB method and Bel-7402, HO-8910, HL-60 cell lines. Results showed that 2α,3α-dihydroxy-urs-12-en-28-oic acid and 2α,3α, 23-trihydroxy-urs-12-en-28-oic acid had good cytotoxic activity, β-daucosterol, β-sitosterol, friedelin and 3β,28-dihydroxy ursane had no cytotoxic activity, oleanolic acid, 3β-acetyloxy-ursolic acid and ursolic acid had some cytotoxic activity.

Zhang *et al.*[24] determined the effect of glaucocalyxin A from *Rabdosia japonica* var. *glaucocalyx* on metabolism of rabbit platelet-activating factor (PAF) and arachidonic acid (AA) by adding glaucocalyxin A to the reaction system of rabbit platelets and using the quantitative biological analysis and radio immunoassay. They found that glaucocalyxin A can inhibit rabbit platelets activating factor formation stimulated by A23187. The inhibition was glaucocalyxin A dosage dependent. Meanwhile glaucocalyxin A also inhibited rabbit platelet TXA_2 formation induced by AA, high concentrations of glaucocalyxin A can increase PGE_2 level, which suggested glaucocalyxin A had weak selective inhibition on TXA_2 synthesis. Which is very important to prevention from arterial thrombosis and atherosclerosis.

Chen *et al.*[25] obtained 4 extracts A, B, C and D from *Rabdosia japonica* var. *glaucocalyx*. Results of *in vitro* experiments showed that A and C tended to enhance the proliferation of mice spleen T-lymphocyte induced by ConA compared to dimethyl sulfoxide solvent of the same concentration. The effect of B and D were concentration-dependant, when B at 1 mg/L and D at 100 mg/L had significant inhibitory effect, So B had better activity. They got four parts B21, B22, B23 and B24 by further extracting B. Compared to dimethyl sulfoxide solvent to the proliferation of mice spleen T-lymphocyte induced by ConA, at the same concentration, B21 and B22 had enhancement effect, while B24 showed inhibitory activity. The results indicated that there was the chemical composition with the function of immune enhancement and immune inhibition in *Rabdosia japonica* var. *glaucocalyx*.

Liu *et al.*[26] discussed the protection of glaucocalyxin A separated from *Rabdosia japonica* var. *glaucocalyx* against DNA damage induced by hydrogen peroxide in human peripheral blood mononuclear cells (PBMCs) and inhibition of lipid peroxidation in rat liver microsome with comet assay and thiobarbituric acid reactive substances determination. Results showed glaucocalyxin A had concentration-dependent protection in DNA damage in human PBMCs induced by 50 μM H_2O_2 but the effect was weaker than quercetin.

Jin *et al.*[27] used pure alcohol, ethyl acetate, chloroform, distilled water and acetone as extractant, respectively to extract fresh leafs of *Rabdosia japonica* var. *glaucocalyx*. Back flow extraction with filter paper or flat dilution was used and the antibacterial activity and the minimum inhibition concentration (MIC) was performed. The result showed that the five kinds of extract have the antimicrobial function, and the four kinds of pathogenic bacteria's MIC order of rank is: pure alcohol extracts < chloroform extracts < acetone extracts < ethyl acetate extracts < distilled water extracts. Wang *et al*.[28] used filter paper assay and the growth rate method to determine the inhibition effect of the extraction of stem and leafs from *Rabdosia japonica* var. *glaucocalyx*. Result showed it had better inhibition effects to gram positive bacteria, while no inhibition activity to gram negative bacteria, but it showed better inhibition effects to fusarium species.

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