Effect of 34 Kinds of Traditional Japanese Herbal Medicines on Prolongation of Cardiac Allograft Survival

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ABSTRACT

Herbal medicines have been used for over 3,000 years in Asian as alternative therapy for their variety effects and have recently become popular in Europe and the United States. In the last 30 years, Japanese herbal medicines were widely used for treatment of diseases after been recognized officially by Japanese government. In this study, we investigated the effect of 34 kinds of traditional Japanese herbal medicines on alloimmune responses in a murine model of cardiac allograft transplantation. CBA mice ($H2^k$) underwent transplantation of a C57BL/6 ($H2^b$) heart and received oral administration of 2 g/kg/d of the 34 kinds of herbal medicines from the day of transplantation until 7 days afterward. Naïve CBA mice rejected B6 cardiac grafts acutely (median survival time [MST], 7 days). CBA transplant recipients given 2 g/kg/d of Sairei-to (TJ-114) and Tokishakuyaku-san (TJ-23) had prolonged C57BL/6 allograft survival indefinitely (both MSTs > 100 days). Moreover, CBA transplant recipients given Seisinrensiin (TJ-111), Tokishigyakukagoshuyushokyoto (TJ-38), Rikkunshito (TJ-43), Maobushisaishinto (TJ-127), Ninjin-yoei-to (TJ-108), Ryokan-kyomi-shinge-nin-to (TJ-119), Inchingorei-san (TJ-117), Hochuekkito (TJ-41), Kihi-to (TJ-65), and Sinbu-to (TJ-30) had also prolonged C57BL/6 allograft survival significantly (MSTs of 28, 22, 16, 14, 14, 13, 12, 9.5, 9 and 9 days, respectively). However, none of other 22 kinds of herbal medicines could prolong the allograft survival. Furthermore, oral administration of 2 g/kg/d of Daikenchuto (TJ-100) induced sudden death (within 1 minute) in CBA mice. In conclusion, 12 kinds of Japanese herbal medicines prolonged allograft survival and one showed toxic effect in mice.

HERBAL MEDICINES have long been used in Japan, China, and Korea as alternative therapy. Recently, treatment with traditional herbal medicines has been establishing a fixed position. Daikenchuto (TJ-100) [1], Hochuekkito (TJ-41) [2], and Hangekobokuto (TJ-16) [3] has been used to shorten postoperative ileus, treat atopic dermatitis, and treat functional dyspepsia, respectively. Also, Tokishakuyaku-san (TJ-23) has been used to treat many gynecologic disorders [4] and even reduced impairments after stroke [5].

Our recent studies in experimental heart transplantation model have shown that oral administration of the commonly used Japanese herbal medicine Inchingorei-san (TJ-117) [6], Sairei-to (TJ-114) [7], and Tokishakuyaku-san (TJ-23) [8] could significantly induce prolongation of murine cardiac allograft survivals and generate regulatory T cell. In the present study, we investigated the effect of 34 kinds of traditional Japanese herbal medicines (Fig 1) on alloimmune responses in murine cardiac allograft transplantation and collected into the list.

METHODS

Heart Transplantation

Male C57BL/6 ($H\text{-}2^b$, B6) and CBA ($H\text{-}2^k$) mice (8 to 12 weeks old) were purchased from Sankyo, Ltd (Tokyo, Japan), housed at the

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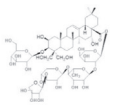
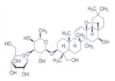
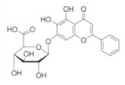
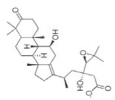
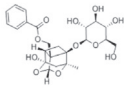
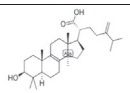
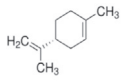
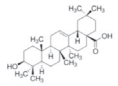
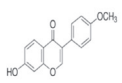
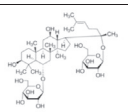
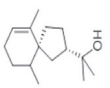
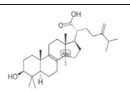
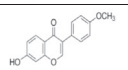
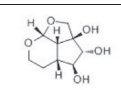
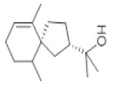
Name of Japanese Herbal Medicine	Main Component	Major Element	Molecular Formula	Chemical Structure
Jumihaidoku-to (TJ-6)	Platycodon root	Platycodin D	C57H92O28	
Saikokaryukotsuborei-to (TJ-12)	Bupleuri radix	Saikosaponin A	C42H68O13	
Orengedoku-to (TJ-15)	Ogon	Baicalin	C21H18O11	
Gorei-san (TJ-17)	Alismatis rhizoma	Alisol B 23-acetate	C28H44O4	
Tokishakuyaku-san (TJ-23)	Paeoniae radix	Paeoniflorin	C23H28O11	
Shinbu-to (TJ-30)	Poria sclerotium	Eburicoic acid	C31H50O3	
Hangebyakujutsutenma-to (TJ-37)	Citrus unshiu peel	(R)-(+)-Limonene	C10H16	
Tokishigyakukagoshuyushokyo-to (TJ-38)	Zizyphi fructus	Oleanolic acid	C30H48O3	
Hochuekki-to (TJ-41)	Astragalus root	Formononetin	C16H12O4	
Rikkunshi-to (TJ-43)	Ginseng radix	Ginsenoside Rx	C42H72O14	
Yokukan-san (TJ-54)	Atractylodis lanceae rhizoma	Hinesol	C15H26O	
Gorin-san (TJ-56)	Poria sclerotium	Eburicoic acid	C31H50O3	
Kihi-to (TJ-65)	Astragalus root	Formononetin	C16H12O4	
Jinsoin (66)	Pinellia tuber	Homogentisic acid	(HO)2C6H3CH2CO2H	
Simotsu-to (TJ-71)	Rehmannia root	Rehmaglutin A	C9H14O5	
Sikunsi-to (TJ-75)	Atractylodis lanceae rhizoma	Hinesol	C15H26O	
Yokukansankachinpihange (TJ-83)	Pinellia tuber	Homogentisic acid	(HO)2C6H3CH2CO2H	

Fig 1. The major elements and their chemical structures of each Japanese herbal medicine.