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Effects of three different formulae of Gamisoyosan on lipid accumulation induced by oleic acid in HepG2 cells

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ABSTRACT

Background: Gamisoyosan (GSS) is an herbal formula which has been used to treat women's diseases for several hundred years in Korea. GSS is one of the three most common prescriptions among women and is used to treat menopausal symptoms. Fatty liver disease is also common in postmenopausal women and can precede more severe diseases, such as steatohepatitis. The present study compared the effects of GSS on fatty liver using three different formulae, Dongui-Bogam (KIOM A), Korean Pharmacopeia (KIOM B) and Korean National Health Insurance (KIOM C).

Methods: In oleic acid-induced HepG2 fatty liver cells, cellular lipid accumulation, triglycerides and total cholesterol were measured after treatment with three GSS formulae and simvastatin as a positive control. To investigate the phytoestrogen activity of GSS, MCF-7 cells were treated with GSS, and hormone levels were quantified. Also, qualitative analysis was performed with UPLC.

Results: All types of GSS decreased cellular lipid accumulation. KIOM A was slightly less effective than the other two GSS formulae. KIOM B and KIOM C decreased cellular triglycerides more effectively than simvastatin, but KIOM A did not affect cellular triglycerides. Cellular total cholesterol was decreased by all GSS and simvastatin. GSS showed phytoestrogen activity in MCF-7 cells. From the UPLC analysis data, geniposide, paeoniflorin and glycyrrhizin were detected from three GSS formulae.

Conclusion: These results suggest that all GSS formulae have a beneficial effect on fatty liver disease during menopause and that differences of formula have no effect on the efficacy of the prescription.

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1. Introduction

Gamisoyosan (GSS), a traditional herbal formula comprising 12 different herbal medicines, has been used in Korea to treat

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dysmenorrhea, insomnia, and anxiety. GSS is an herbal formula which has been used to treat women's diseases for several hundred years in Korea. GSS is one of the three major women's prescriptions and is used to treat women's menopausal symptoms. GSS has emerged as the most commonly used formula for treating menopausal symptoms in Korea, Japan, and China.¹

Hormone balance in menopause is important for each individual. During menopause, the function of the ovaries ceases, causing hormone imbalances such as estrogen deficiency and follicle stimulation hormone (FSH) increase. Because of these hormone imbalances, menopausal symptoms including hot flashes, vaginal and urinary symptoms, and sweating can be induced.

According to oriental medicine, menopause symptoms may be caused by energy deficiency in the kidney or liver.²⁻⁴ Especially for women, the liver's role is crucial to maintain regular blood flow and good menstrual condition, because the liver makes blood and emotion flow smoothly. In clinical application, GSS is one of the Chinese medicine formulations frequently used for management of menopausal symptoms.³ Because GSS has the ability to promote liver qi (氣) and modulate vital energy flow and blood flow, it has been frequently prescribed to patients who are easily fatigued and are inclined to have psychoneurotic symptoms including irritability and anxiety.² For example, according to a visual analogue scale score-based investigation, GSS relieved both vasomotor and psychological symptoms in patients with psychological symptoms.⁵ GSS reduced sleep disturbance, headache and dizziness in peri- and postmenopausal women.⁶

Dysfunctional lipid metabolism can lead to several metabolic diseases, including visceral obesity, hypertension, hyperlipidemia and type 2 diabetes. Due to estrogen actions that positively regulate lipid metabolism and lead to the accumulation of subcutaneous fat rather than central fat, premenopausal women are protected from these metabolic diseases.⁷ Loss of estrogen following menopause worsens lipid metabolism and is associated with an increased risk for these metabolic diseases, which can promote the development of other serious diseases, including atherosclerosis, cardiac infarction, apoplexy and fatty liver.^{8,9} Nonalcoholic fatty liver disease (NAFLD) is a type of fatty liver disease that is caused without significant alcohol consumption. NAFLD occurs when fat builds up excessively in the liver; a higher prevalence of NAFLD is observed following menopause. Several studies have shown an association between menopause and NAFLD.^{10,11} Furthermore, NAFLD is twice as common in postmenopausal women compared to premenopausal women.¹² The protective effect of estrogen against the development and progression of NAFLD has been suggested by studies using hormonal replacement therapy (HRT) on postmenopausal women.¹³ In addition, NAFLD can progress from simple steatosis to nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocarcinoma, which are associated with cardiovascular and liver-related mortality. NASH was worsened by estrogen deficiency, and this effect was ameliorated after estrogen therapy in ovariectomized (OVX) mice.¹⁴ Although GSS has been used for the treatment of menopausal symptoms, there are no reports about its effects on fatty liver disease during menopause. Therefore, we investigated the

effects of GSS on fatty liver induced by oleic acid (OA) in HepG2 cells.

Phytoestrogens are naturally occurring plant substances that show estrogen-like activities in the body. A wide variety of food contains phytoestrogens such as coumestans, isoflavones and lignans.^{15,16} Because of their similar conformation to estrogen, phytoestrogens bind to the mammalian Estrogen Receptor (ER) and exert the agonist or antagonist effects of estrogens via the ER in animals and humans. There are some reports that phytoestrogens have protective effects against several diseases, including cardiovascular disease, osteoporosis, menopausal symptoms, and hyperlipidemia.^{17,18}

In this study, three different formulae of GSS, Donguibogam (KIOM A), Korean Pharmacopeia (KIOM B) and Korean National Health Insurance herbal medicine (KIOM C) were used. Among these three formulae, KIOM B and KIOM C have been mainly used for treatment of menopausal symptoms in clinical settings. KIOM A is the original recipe from Donguibogam. The three formulae have different ingredients and dosages. KIOM C has the same composition as KIOM B except for the excipient. We also wanted to know whether there were any differences in effects between these three formulae. In this report, we describe a comparative study of three different formulae of GSS regarding fatty liver improvement and phytoestrogen activity. Further, to investigate the chemical change in the compositions of GSS formulae, we analyzed the indicator components by Ultra Performance Liquid Chromatography (UPLC) qualitative analysis.

2. Methods

2.1. General Procedures

Geniposide was purchased from Sigma-aldrich (St. Louis, MO, USA), paeoniflorin was purchased from Wako Chemical (Osaka, Japan), nodakenin was purchased from Chemfacs (Wuhan, China) and glycyrrhizin was purchased from Ministry of Food and Drug Safety (Osong, Korea). All chemical compounds were identified with purities of $\geq 98\%$. The stock solutions of four chemicals were prepared at concentrations of 0.1 mg/mL in 80% methanol (MeOH) and 20% distilled water. The mixed standard working solutions were diluted with methanol to get a final concentration of 0.025 mg/mL. The working solutions were stored at $+4^{\circ}\text{C}$ prior to analysis. Analytical grade acetonitrile (ACN), MeOH and water were purchased from J. T. Baker (Philipsburg, NJ, USA). Extra pure grade formic acid was purchased from Sigma-Aldrich (St. Louis, MO, USA). UPLC was performed on Agilent UPLC system equipped with a quaternary pump (G4220B), autosampler (G4228A), DAD (G4212A) and column oven (G1316A). The instrument control and data processing were carried out by an Agilent ChemStation software system (Agilent, Santa Clara, CA, USA).

2.2. Materials and Extracts of GSS formula

Among the three formulae of GSS, KIOM A and KIOM B were purchased from the Baekje medicinal herb store. KIOM

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