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Pharmacological activities of mogrosides

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“According to traditional Chinese medicine, *S. grosvenorii* has a cooling nature and sweet taste and possesses heat clearing, lung moistening, phlegm removing and other properties.”

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Siraitia grosvenorii, a perennial vine belonging to the Cucurbitaceae family, is primarily produced in Guangxi, Guangdong and Hunan provinces of China. According to traditional Chinese medicine, *S. grosvenorii* has a cooling nature and sweet taste and possesses heat clearing, lung moistening, phlegm removing and other properties.

Natural products play a relevant role in drug therapy today with a substantial number of agents used in the clinic being either natural or derived from plants. China has numerous ‘extremely efficacious’ fruits. Therefore, these sources may aid in the development of safer and more acceptable drugs. Since 1977, *S. grosvenorii* has been included in the Chinese pharmacopoeia, which records that the fruit has properties of “clearing heat, moistening the lungs, benefiting the throat, restoring the voice and lubricating the bowels to relieve constipation”. It can be used to treat cough due to fever of the lung, sore throat and loss of voice, as well as constipation due to ‘intestinal dryness’. Based on the safety and unique efficacy of *S. grosvenorii*, the Ministry of Health and the State Administration of Traditional Chinese Medicine have listed this fruit as both a food item and medicine.

In terms of nutrients and other constituents, *S. grosvenorii* contains large amounts of flavonoids [1], phenolic acids and terpenoids in addition to its carbohydrate [2], protein, amino acid [3] and vitamin components [4]. These compounds represent the biochemical basis of the various medicinal properties of *S. grosvenorii*.

Apart from its medicinal properties published in the Chinese pharmacopoeia, domestic and international researchers have investigated other effects of *S. grosvenorii*, such as reactive oxygen species (ROS) scavenging [5], anti-inflammatory [6] and anticancer activities [7], as well as the regulation of blood lipid metabolism and improvement of blood glucose metabolism [8], suggesting that *S. grosvenorii* may be an effective candidate for drug discovery. The current predominant lifestyle that consists of a high sugar and high fat diet accompanied by lack of exercise exposes even healthy individuals to an increased risk of developing cancer. Mogrosides are important bioactive components of *S. grosvenorii* fruit and are very sweet and low in calories. In this study, we reviewed literature on the pharmacological activities of *S. grosvenorii* mogrosides to guide more comprehensive studies on the pharmacology of *S. grosvenorii* fruit.

Chemical structure of mogrosides

Mogrosides are the primary active components of *S. grosvenorii* saponins, and are 200–350-times sweeter than sucrose is. Owing to their high sweetness and nontoxic characteristic, mogrosides are widely used in beverages. Mogrol is the precursor of mogrosides in *S. grosvenorii* fruit. With the growth of the fruit, mogrol is transformed into mogrosides by UDP-glycosyltransferases. The glycoside molecule is composed of a mogrol and a glucose group joined by a glycosidic linkage. The differences in the number of glucose groups linked to the C3 and C24 positions on the mogrol structure yield mogroside molecules with major differences in taste. Chen *et al.* used chromatography to determine the triterpenoid saponins in *S. grosvenorii* and found that mature *S. grosvenorii* is rich in mogrosides IV

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and V, which have a particularly sweet taste, whereas the immature fruits are rich in mogrosides IA1 and IIE, which have a bitter taste [9,10]. During the process of ripening, *S. grosvenorii* aponins undergo continuous glycosylation, and in the ripe fruit, mogrosides IA1 and IIE are converted to the extremely sweet mogroside IV and V molecules. However, after oral ingestion, different structures of mogrosides were mostly degraded into mogrol by digestive enzymes and intestinal microflora after single ingestion [11]. Therefore, it can be suggested that mogrol is responsible for the different physiological functions of different structures of mogrosides.

Toxicity studies

The degree of toxicity is an important indicator in drug evaluation, especially in patients with reduced immunity and physical weakness, because drugs with low toxicity cause fewer adverse reactions and lesser discomfort. *S. grosvenorii* mogrosides received the US FDA food safety certification after clearing toxicology and food safety tests, and have been approved for use as food additives. Animal studies have shown no toxic side effects following the administration of *S. grosvenorii* mogrosides at high doses [12,13]. Toxicity studies have shown that mogrosides are nontoxic (a median lethal dose, $LD_{50} > 15 \text{ g}\cdot\text{kg}^{-1}$ is considered nontoxic). The acute toxicity of mogrosides was found to be lower than that of table salt and citric acid (LD_{50} , 3 and $6.73 \text{ g}\cdot\text{kg}^{-1}$, respectively) following oral administration to rats. The results of *Salmonella* reverse mutation tests (Ames mutagenicity test) of mogrosides were negative, indicating that they do not have direct or indirect mutagenicity. Research studies have reported no adverse effects after administration of mogrosides at high doses to dogs via gavage, as determined by hematology tests and the measurement of other biological indicators.

Bioactivity of mogrosides

Hypoglycemic effects

People with diabetes must pay special attention to the sugar content of foods; however, they often find it difficult to resist the temptation of sweet foods. In addition to being very sweet and having low calorie values, *S. grosvenorii* mogrosides lower blood sugar; therefore, they can be used as a sugar alternative for patients with diabetes and for the large population of overweight people. Researchers have investigated the ability of mogrosides to regulate adenosine monophosphate-activated protein kinase (AMPK) [14], a key protein molecule that regulates the energy balance of the body [15]. AMPK consists of an α catalytic subunit and β and γ regulatory subunits and plays an important role in regulating glucose and lipid metabolism within the body [16]. Studies have found that AMPK is closely related to bodyweight and Type 2 diabetes [17]. Drugs targeting AMPK are already being developed for the treatment of metabolic disorders. Numerous hypoglycemic medications lower blood glucose levels by activating the AMPK pathway *in vivo*. AMPK activation inhibits the expression of glucose phosphatase and phosphoenolpyruvate carboxylase genes, thereby inhibiting the gluconeogenesis pathway and reducing blood glucose levels in the body. After digestion of mogrosides in the body, they are metabolized into mogrol [11], which has been found to activate AMPK. Thus, mogrosides lower blood sugar levels in the body by regulating AMPK. These findings demonstrate the efficacy of mogrosides and the mechanisms underlying their hypoglycemic effects.

Blood lipid-lowering effects

Lipid metabolism disorders are common complications associated with diabetes and are primarily manifested as hyperlipidemia and hyperlipoproteinemia [18]. Long-term abnormalities in blood lipid levels can easily induce hyperlipidemia, atherosclerosis and other diseases [19]. In addition, lipid metabolism disorders are characterized by elevated serum total cholesterol and triglyceride levels. Qi *et al.* reported that *S. grosvenorii* mogrosides lowered serum total cholesterol and triglyceride content and improved high-density lipoprotein cholesterol content in diabetic mice, thereby normalizing the blood lipid levels [20]. These findings indicate that mogrosides regulate lipid metabolism and exert a prophylactic effect against diabetes-induced lipid metabolism disorders.

Antioxidant effects

Free radicals, such as free hydroxyl, superoxide anion and peroxide radicals, are the by-products of metabolic processes in the body and can cause harm to the body. Because of their chemical activity, the free radicals produced during metabolic processes can affect intracellular unsaturated fatty acids [21]. An excess of free radicals can increase the levels of lipid peroxidation products and induce changes in the structure and function of the cell membrane. Numerous studies have shown that lipid peroxidation induced by oxygen free radicals is closely related to inflammatory diseases, atherosclerosis, cerebral arterial spasms and other diseases [22]. Therefore, maintaining

the balance of free radicals in the body is important for ensuring good health. *S. grosvenorii* mogrosides increased serum glutathione peroxidase (GSH-Px) and superoxide dismutase activities in diabetic hyperlipidemic mice and significantly reduced serum malondialdehyde levels [23]. Malondialdehyde is an end product of lipid peroxidation and serves as an important indicator in evaluating the strength of lipid peroxidation reactions. These findings indicate that *S. grosvenorii* mogrosides can effectively scavenge reactive oxygen species and reduce lipid peroxidation.

Anti-inflammatory effects

Lipopolysaccharide (LPS) is a major component of the cell wall of Gram-negative bacteria. It can induce inflammatory response and plays an important role in establishing inflammation [24]. To evaluate the anti-inflammatory effects of *S. grosvenorii* mogrosides, Di *et al.* used LPS-induced macrophages (RAW264.7) and phorbol ester-induced ear edema murine models of inflammation [25]. LPS was used to stimulate RAW 264.7 macrophages to induce inflammation. Then, the cells were incubated with varying concentrations of *S. grosvenorii* mogrosides. The results showed that mogrosides significantly inhibited the release of cyclooxygenase-2 and mRNA expression of inducible nitric oxide synthase and IL-6 in murine macrophages in a dose-dependent manner. This indicates that mogrosides exert anti-inflammatory activity by inhibiting the release of inflammatory mediators, such as prostaglandins, IL-6 and NO, by macrophages. Similarly, in a murine ear edema model, phorbol ester-induced inflammation was inhibited by mogrosides. Following administration, there was a reduction in the expression of cyclooxygenase-2 and IL-6 in the murine inflammation model, indicating that mogrosides exerted anti-inflammatory effect by inhibiting the release of inflammatory factors and mediators of inflammation.

Anticarcinogenic activity

Midori *et al.* investigated the antagonistic effects of *S. grosvenorii* mogrosides on different types of carcinogens that induce tumor development in animals [26]. 7,12-Dimethyl benzene[a]anthracene (DMBA) is a chemical carcinogen commonly used in the development of animal tumor models. Once DMBA enters the body, it is oxidized by cytochrome P450; the resulting metabolite induces depurination DNA that leads to DNA mutations and the subsequent development of diseases such as skin cancer, breast cancer and leukemia in animals. The phorbol ester TPA (12-O-tetradecanoylphorbol-13-acetate) is a potent carcinogen that can activate protein kinase C (PKC), which plays a key role in biological signal transduction, cell growth, proliferation, apoptosis, migration and other cellular responses. Abnormalities in PKC pathway are closely related to the development of cancer, and TPA induces tumor formation by activating PKC. Peroxynitrite (ONOO-) cleaves DNA, thereby leading to cell necrosis, and simultaneously mediates tumor cell formation [27]. Therefore, exposure to high doses of TPA, DMBA, ONOO- and other carcinogenic substances induces the transformation of normal cells into tumor cells. Midori *et al.* used carcinogens (TPA, DMBA and ONOO-) to induce carcinogenesis in mice and found that *S. grosvenorii* mogrosides slowed down the transformation of normal cells into skin cancer cells by antagonizing the carcinogens. The above findings suggest that mogrosides have a preventive effect against skin cancer induced by TPA, DMBA, ONOO- and other chemical carcinogens.

Antitumor targeting effect

The dysregulation of cellular signal transduction pathways leads to unrestricted cell proliferation, which is a primary cause of carcinogenesis. Traditional cytotoxic drugs are prone to drug resistance and have strong toxic side effects, poor selectivity and other shortcomings [28]. In contrast, molecular targeting drugs can differentiate between normal and cancer cells and exhibit therapeutic effects with high selectivity and low incidence of toxic side effects. Presently, the discovery of molecular targeting drugs is an important advancement in the development of anticancer drugs. Recent studies have shown that mogrol, a precursor of mogrosides exerts antitumor effects by specifically targeting cancer cells [29].

Signal transducer and activator of transcription 3 (STAT3) is closely associated with the development of various types of tumors [30–33]. In normal cells and tissues, STAT3 activation is brief and strictly regulated. However, various types of human cancers show continuous activation of STAT3, which can lead to the overexpression of genes involved in cell proliferation and apoptosis. On the one hand, this promotes tumor cell proliferation. On the other hand, it can inhibit tumor cell apoptosis, leading to the occurrence and development of tumors. Therefore, STAT3 proteins are important targets for the treatment of tumors. Research has shown that *S. grosvenorii* mogrol inhibits excessive activation of STAT3 [29], which promotes tumor cell apoptosis. The results of experiments in tumor-bearing nude mice indicate that *S. grosvenorii* mogrol has a direct tumor killing activity.

By inhibiting the phosphorylation of STAT3, mogrol blocks the STAT3 signaling pathway [29], which in turn upregulates the expression of p21 and p27 and arrests cell development from the G1 phase to the S phase of the cell cycle. This leads to cell cycle arrest in the G0/G1 phase, thereby contributing to the inhibition of tumor cell proliferation. Furthermore, the antiapoptotic proteins B cell lymphoma-2 (Bcl-2) and Bcl-extra-large protein (Bcl-xl) are downregulated, which promotes tumor cell apoptosis. These findings provide new insights into the anticancer mechanisms of *S. grosvenorii* mogrol.

Conclusion & future perspective

The most interesting characteristics of mogrosides are that they are highly sweet and pharmacologically safe.

In the food product industry, *S. grosvenorii* mogrosides are good sugar substitutes because they are extremely sweet and low in calories. Unlike sugar, mogrosides can effectively reduce the intake of energy substances, thereby meeting the requirements of patients with diabetes and obesity. With the recent increase in demand for low-calorie sugar substitutes, mogrosides will attract increasing attention.

Considerable progress has recently been made in the determination of the pharmacological properties of mogrosides. Mogrosides have shown definite efficacy as anticarcinogens, anti-inflammatory agents, free radical scavengers and glucose- and lipid-lowering agents. They have been recognized to have numerous molecular targets and diverse mechanisms involving complex signaling pathways. However, the relationship between these pathways is unclear and yet to be explored. In addition, the pharmacological activities and underlying mechanisms of mogrosides need to be explored.

Toxicity is a very important aspect in drug evaluation. In terms of safety, currently, there are many reports establishing that *S. grosvenorii* is nontoxic and has no significant adverse effects. Mogrosides were granted 'generally regarded as safe' status to be used as food additives by the FDA. Thus, mogrosides show broad potential for utilization as safe and effective drug candidates.

Recently, there has been progress in the mechanistic understanding of the pharmacology of mogrosides; however, several key aspects still require elucidation. So far, there is limited information on comprehensive pharmacologic evaluation of mogrosides in the human body for long term; in addition, mogrosides are made up of a mixture of cucurbitane-type tetracyclic triterpenoids with high sweetness, which may be degraded and biotransformed in animals after ingestion; however, the physiological functions of the metabolites of mogrosides is not clear. A future study should explore the physiological activity of essential metabolites of mogrosides *in vivo*.

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