

Research Progress on Chemical Composition and Pharmacological Action of *Exocarpium Citri Grandis*

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Abstract. *Exocarpium Citri Grandis* is a famous genuine regional drug in Guangdong province, which contains flavonoids, volatile oils, polysaccharides, curmarins and other effective components. In vivo and in vitro experiments have proved that it has many pharmacological actions, such as expelling phlegm and relieving cough, anti-inflammation, anti-oxidation, lowering blood glucose and lipids, protecting myocardium and so on. In order to better control the quality of tangerine and explore its potential pharmacological action, this paper reviews the research progress of *Exocarpium Citri Grandis* from two aspects of chemical composition and pharmacological action at home and abroad in recent years, and its applications in clinic and food industry are prospected.

Keywords: *Exocarpium Citri Grandis*; Chemical composition, Pharmacological action, Research progress.

1. Introduction

Exocarpium Citri Grandis (ECG) is the unripe or nearly ripe dried outer peel of the *Citrus grandis* *Tomentosa* or pomelo of Rutaceae family. It is also known as "light seven claws" and "light five claws". ECG is mostly in the shape of a folded heptagon or a flattened pentagon, with a single piece in the shape of a willow leaf. The intact ones have a diameter of 15-28 cm and a thickness of 0.2-0.5 cm after flattening. The outer skin is yellow-green, densely covered with tomentum, with wrinkles and small oil chambers, the inner skin is yellow-white or light yellow-brown, with vein lines. The aroma is aromatic and the taste is bitter and slightly pungent. It has a long history of being a famous genuine regional drug in Guangdong. It has the ability to regulate qi-flowing for harmonizing stomach and eliminate dampness and phlegm. It is often used for coughs and phlegm, food stagnation and excessive drinking, vomit and flatulence.

In order to provide new ideas and theoretical support for the research and development of ECG, this paper reviews the chemical components and pharmacological effects of ECG.

2. Chemical components

The chemical components contained in ECG are numerous, including volatile oils, polysaccharides, flavonoids and coumarins.

2.1 Flavonoids

The main active ingredients of ECG are flavonoids, the most important of which are naringin and rhoifolin, the sum of which accounts for more than 84% of the total flavonoids in ECG. It has antioxidant, anti-inflammatory, anti-cancer, liver protection, regulation of cardiovascular and cerebrovascular diseases and fat metabolism effects [3-7]. Liu Qundi et al. attributed several flavonoids such as naringin, rhoifolin, naringenin and apigenin by HPLC-DAD-MS/MS analysis. Li Jihua, on the other hand, used HPLC to simultaneously measure the contents of naringin, naringenin, rhoifolin, and narirutin in ECG from different origin, and found that the content of rhoifolin in *Citrus grandis Tomentosa* was much higher than that of ordinary pomelo, while the other compounds had no significant difference in content, so rhoifolin can be used as one of the identification features of *Citrus grandis Tomentosa*. In addition, Han Hanbing et al. determined that the content and total amount of flavonoids in ECG fruit showed different trends with increasing fruit-age. Therefore, it is

important to consider the percentage and total amount of flavonoids in ECG fruit to ensure quality and increase yield as much as possible. With the optimisation of the HPLC conditions, a new chromatographic fingerprint method has been established, which can simultaneously determine naringin, rhoifolin, meranzin hydrate and isoimperatorin in ECG. This new method can be used for rapid identification and quality evaluation of ECG [11,12].

2.2 Volatile oils

Volatile oils are widely found in Chinese herbs and the main components include aliphatic, aromatic, terpenes and sulfur- and nitrogen-containing compounds. The volatile oil constituents of 36 species of ECG fruit were identified by GPC-GC/MS, mainly β -laurelene, γ -terpinene and germacrene-D. A comparison with the volatile oil constituents of their flowers and leaves showed that there were significant differences in the corresponding constituents. Gas chromatography-mass spectrometry (GC/MS) technique was applied to analyse the volatile oil composition of ECG from different origin. It was found that the volatile oils from Luchuan and Nanning were less different from those from Huazhou, while the differences from Baise were larger, which may be related to different growing environments and soil conditions.

A total of 81 compounds were identified by GC/MS analysis of the volatile oil components extracted from the three methods of steam distillation, headspace solid-phase microextraction (HS-SPME) and solvent extraction. Terpenoids were the main components, including germacrene-D, limonene, 2,6,8,10,14-hexadecapentaene, 2,6,11,15-tetramethyl-, (E,E,E)-, and trans-caryophyllene. Comparison of these three methods revealed that HS-SPME is better and can be used for the rapid extraction of volatile components of medicinal plants.

2.3 Polysaccharides

The main polysaccharides found in ECG are pectin, D-xylose, D-galactose, D-mannose and L-arabinose. Hou Xiujuan et al. used response surface analysis to optimize the application of microwave extraction technology in the extraction of ECG polysaccharides. The results show that this technique is suitable for the extraction of polysaccharides from the plant and can effectively protect the useful components of herbs. Lv Anwen et al. found that ECG polysaccharides could scavenge excess free radicals produced in the body and improve the antioxidant capacity of immunosuppressed mice. In addition, ECG polysaccharides also has anti-fatigue, ameliorates Alzheimer's disease in mice, anti-inflammatory, antitussive and expectorant effects [16,19,20].

2.4 Other components

In recent years, there are also studies on the coumarin components in ECG. Niu Yan et al. used silica gel, Sephadex LH-20 column chromatography and preparative HPLC to isolate 12 coumarin compounds from ECG, including 6-prenyloxy-7-methoxy-coumarin, 5-hydroxy-8-(3'-methyl-2'-butenyl) furocoumarin, isoimperatorin, isoimperatorin, meranzin and so on. Among them, the content of coumarin and isoimperatorin are higher. Studies have shown that coumarins have good antiviral and anti-HIV, antioxidant, antitumour and antibacterial activities. Therefore, coumarins may also be the active substances that can exert ECG medicinal effects, but little research has been done in this direction.

3. Pharmacological action

3.1 Antitussive and expectorant effects

There are many pharmacological studies that have reported the antitussive and expectorant effects of ECG. Jiang et al. found that 70% ethanolic extract of ECG had a significant inhibitory effect on ammonia-stimulated cough in mice, and also significantly promoted the excretion of phenol red from the airway of mice, achieving the effect of resolving phlegm and relieving cough. Previous studies

have also shown that ECG polysaccharides significantly prolonged the latency period of ammonia-stimulated cough and reduced the number of coughs in mice within 2 minutes. In addition, naringin in ECG had therapeutic effects in a guinea pig model of ovalbumin-induced cough-variant asthma. Dong Jing et al. observed the effect of active components of ECG on the proliferation of guinea pig tracheal smooth muscle cells by MTT method, and found that naringin and Meranzin hydrate may be the main active components of the expectorant effect of ECG. Jiao Chunwei et al. found that ECG-Cordyceps *militaris* could significantly reduce the number of coughs in mouse cough inducing models, and could regulate the level of serum inflammatory factors in coughing mice, with good cough suppressant activity. Through network pharmacology analysis of its antitussive mechanism, it is found that the antitussive activity of ECG is the result of comprehensive effects on multiple targets and pathways through various active ingredients such as apigenin, β -sitosterol and naringenin.

In clinical practice, it was found that the Ju-Hong Tan-Ke liquid with ECG as the main medicinal material can effectively improve the cough and expectoration symptoms of acute bronchitis in children. The main pharmacodynamic material basis of the liquid was investigated by means of network pharmacology, and it was found that naringin is the main active ingredient in the cough and phlegm relieving effect of ECG. Its metabolite is naringenin, which has anti-inflammatory, antioxidant, anti-tumour and proliferation inhibiting properties. MUC5AC is one of the most important airway mucins associated with various respiratory diseases, and naringenin can inhibit the synergistic activity of MAPKs-AP-1 and IKKs-I κ B-NF- κ B signaling pathways, thereby attenuating the secretion of MUC5AC in A549 cells induced by epidermal growth factor. Naringin can also produce antitussive effect by inhibiting the electrical discharge of rapidly adapting receptors (RARs), as well as modulating the mucus and plasma components of sputum, resulting in expectorant effects.

3.2 Anti-inflammatory effect

The current anti-inflammatory effects of ECG are mainly focused on its flavonoids. Zhu et al. perfused PM2.5 in the trachea of mice and fed them with total flavonoids of ECG. The early stage of inflammation caused by PM2.5 is the release of associated cytokines and inflammatory factors caused by macrophages phagocytosing PM2.5 particles. Total flavonoids significantly inhibited the production of tumour necrosis factor (TNF- α), IL-1 β , IL-6 and IL-18, indicating that TFECCG attenuated PM2.5-induced lung inflammation by inhibiting the release of inflammatory factors. In addition, total flavonoids significantly reduced leukocyte infiltration by down-regulating white blood cells, lymphocytes, neutrophils and monocytes, thereby reducing lung inflammation.

RAW264.7 mouse macrophages were stimulated with lipopolysaccharide to establish an in vitro inflammation model, and it was found that the flavonoids of ECG have the anti-inflammatory effect, and its specific mechanism may be related to the MAPK and NF- κ B signaling pathways. By inhibiting the phosphorylation of some key proteins to inhibit the activation of signaling pathways, thereby regulating the mRNA transcription and protein expression of inflammatory factors, and ultimately play a role in regulating cellular inflammation.

Previous studies have also shown that the ECG polysaccharides can significantly inhibit the swelling of the auricles of mice caused by xylene and has the anti-inflammatory effects. It also has a significant anti-inflammatory effect on the inflammatory response of ammonia-stimulated rabbits and chronic pharyngitis patients[35].

3.3 Antioxidant effect

Yao Lehui found that ECG polysaccharide has significant antioxidant properties, with significant scavenging effect on hydroxyl radicals, DPPH and superoxide anion radicals, and also has good reducing ability. The three methods of DPPH, ABTS and FRAP were used to determine the antioxidant activity of the crude extract, ethyl acetate extraction, and macroporous resin adsorption samples of the ECG flavonoids. The results showed that the total antioxidant capacity had a significant dose-effect relationship and had a strong inhibitory effect on reactive nitrogen radicals, which was similar to the previous study of Hou Xiujuan. In addition, the macroporous resin method can

effectively increase the mass fraction of flavonoids in the crude extract of ECG, and obtain better antioxidant effect.

In order to obtain the active ingredients with significant antioxidant capacity in ECG, the scavenging of DPPH free radicals in vitro was used as the activity screening model to test the scavenging activity of extracts obtained by ECG with different polar solvents. Thin-layer chromatography was used to separate and study the free radical scavenging activity of the obtained products. Finally, it was identified that hesperidin and naringin had obvious scavenging effects on DPPH free radicals, and the scavenging rate increased with the increase of the concentration, and further research on the development of food antioxidants or functional food additives can be carried out in the future.

In addition, ECG extract has strong antioxidant effect of oil, which can delay the induction period of oxidative rancidity of sunflower seed oil and peanut oil, and vitamin C and citric acid can enhance the antioxidant effect of ECG extract.

3.4 Hypoglycaemic and hypolipidemic effects

α -glucosidase can regulate blood glucose by regulating the metabolic process of polysaccharides and is closely related to various diseases such as diabetes and hyperlipidemia. By inhibiting the activity of α -glucosidase, the absorption of glucose in the intestinal tract is inhibited, thus effectively reducing the postprandial blood glucose peak and regulating the body's blood glucose level, which is a treatment method for type II diabetes. However, the current α -glucosidase inhibitors have side effects such as abdominal pain, borborygmus, flatulence. Therefore, scientists hope to find drugs with less toxic side effects from natural active ingredients. Jiang Cuicui et al. found that naringenin in ECG has a strong inhibitory effect on α -glucosidase activity, and its inhibitory effect is dose-dependent and time-dependent, and is better than acarbose. Therefore, ECG can be considered as a natural α -glucosidase inhibitor, providing a new idea for the subsequent development of hypoglycaemic drugs from ECG.

The research on the hypoglycaemic and hypolipidemic effects of ECG active ingredients shows that the total flavonoids and naringin can inhibit the activity of α -glucosidase. Further animal experiments in vivo showed that total flavonoids and naringin of ECG significantly increased serum insulin and high-density lipoprotein cholesterol levels in diabetic mice, while lowering total cholesterol, total triglycerides and low-density lipoprotein cholesterol levels, alleviating dyslipidemia and protecting the liver and kidney. In addition, ECG may also achieve its lipid-regulating effect by regulating the expression of PXR/CYP3A4 through apigenin, meranzin hydrate and naringin .

3.5 Myocardial protective effect

Diabetic cardiomyopathy (DCM) is a specific cardiomyopathy that cannot be attributed to hypertension, coronary heart disease and other cardiovascular diseases.

Current studies have found that naringenin, naringenin and apigenin[43-45] contained in ECG can block various aspects of the occurrence and development of DCM through a variety of signalling mechanisms and have potential clinical research value. Guo Runmin et al. found that high glucose and inflammation can induce the activation of p38 mitogen-activated protein kinase. The intervention of ECG can inhibit the activation of p38 MAPK in DCM cardiomyocytes and alleviate the symptoms of myocardial remodeling in diabetic rats. At the same time, the myocardial interstitial fibrosis and myocardial inflammation are relieved, and the cardioprotective effect is achieved. TGF- β 1 is one of regulatory factor involved in diabetic myocardial fibrosis. By establishing a DCM animal model and a cardiac fibroblast proliferation model, Yang Cheng et al. found that ECG could inhibit the TGF- β 1/Smad signaling pathway in DCM cardiomyocytes and regulate the downstream MMPs/TIMPs pathways to improve myocardial collagen degradation, inhibit the process of myocardial fibrosis and reduce myocardial injury.

3.6 Other effects

ECG is also used to improve cellular immunity, prevent and treat alcoholic and non-alcoholic fatty liver, and as an antibacterial agent. Dong Hongpo et al. found that ECG polysaccharides significantly increased the spleen and thymus indices and the phagocytic index of peritoneal macrophages in normal mice, and increased serum haemolysin levels, promoting the conversion rate of T lymphocytes and enhancing cellular immunity. In addition, ECG can inhibit the accumulation of inducible nitric oxide synthase by elevating the expression of caveolin-1 in hepatocytes, thus exerting an anti-alcoholic fatty liver effect. The aqueous extract of ECG can also improve liver fat pathological changes and hepatocyte apoptosis by regulating the expression levels of alanine aminotransferase, aspartate aminotransferase and alcohol dehydrogenase to protect against acute liver injury. Zhang Xuqian also found that the total flavonoids of ECG can prevent and treat alcoholic fatty liver through comprehensive effects of protecting cells from damage, anti-oxidative stress, and participating in the regulation of enzymes related to fat metabolism. At the same time, ECG flavonoids also have antibacterial effects and act as a quorum sensing inhibitor to overcome the resistance and side effects of antibacterial drugs.

4. Summary

ECG is a precious traditional Chinese medicine. This paper has explored the progress of the research on the chemical composition and pharmacological action of ECG. At present, the research on the chemical components mainly focuses on flavonoids, volatile oils and polysaccharides. There are few researches on coumarins and there is a lack of systematic and comprehensive research. It is suggested that the differences and trends in the chemical composition of the herbs from different origins, parts and development periods can be further explored to provide a scientific basis for the comprehensive development, utilization and quality control of ECG. In addition, the research on the pharmacology of ECG is relatively superficial, and future research on the mechanism of action and signalling pathways can be strengthened to lay the foundation for better clinical application. At the same time, the antioxidant effect of ECG can be further developed and utilized in the food industry.

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