DOI: 10.53469/jcmp.2024.06(08).06

Research Progress of the Effects of Fructus Arctii

Jiahui Li[1], Xiong Zhang[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***Fructus Arctii, as a commonly used clinical Chinese medicine, has the effect of evacuating wind-heat, promoting the lungs to penetrate the rash, detoxifying the pharynx and so on. It is widely used in wind-heat cold, cough and phlegm, sore throat and other diseases. In recent years, new results of research on the effects of Fructus Arctii continue to appear at home and abroad, and it is found to have good therapeutic effects in anti-tumor, anti-inflammatory, anti-viral, anti-diabetic and lipid regulation diseases, and the clinical research on its pharmacological effects is also widely carried out. This article summarizes and analyzes the new research progress of Fructus Arctii.***

Keywords: Fructus Arctii, Pharmacological actions, Clinical study**.**

1. Introduction

Fructus Arctii (burdock) is the dried mature fruit of Arctium lappa L., family Asteraceae. Qi is slight, with a bitter taste followed by a slight spiciness and numbness on the tongue. It is attributed to the lung and stomach meridians. Pungent, bitter, and cold in nature. It has the efficacy of dispersing wind and heat, declaring the lungs and penetrating the rash, detoxifying the pharynx and so on. Clinically, it is often used in the treatment of wind-heat cold, cough and phlegm, measles, rubella, sore throat, mumps, erysipelas, carbuncle, and sore [1].

Fructus Arctii has a long history of use in clinical practice with remarkable therapeutic effects. Beginning in the "Materia Medica Tu Jing", also known as the evil deeds, ("Mingyi Bielu"), Dali Zi ("Weisheng Jianyi Formula"), bat thorn ("Compendium of Materia Medica"), Yechatou ("Herbal for Relief of Famines "), there are also different names in different parts of the country. Fructus Arctii contains a variety of active ingredients, including lignans, volatile oils, fatty oils and terpenoids, among which lignin compounds are its main active ingredients, especially Arctigenin (ARG) and Arctiin (ARC) [2].

According to the results of numerous pharmacological studies, Arctigenin have stronger pharmacological activity than Arctiin, and are the most directly effective components of burdock [3]. Burdock has many functions such as anti-tumor, anti-inflammatory, anti-virus, anti diabetes, etc. This article analyzes the pharmacological effects and clinical application progress of burdock, in order to lay a theoretical foundation for further research and utilization of burdock.

2. Manuscript Preparation (Heading 2)

2.1 Antitumor Activity

Malignant tumors are one of the main causes of human death, and modern clinical treatments such as surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy are the main methods of anti-tumor treatment. However, these methods not only kill tumor cells but also increase cardiac toxicity, liver and kidney toxicity, and may lead to drug resistance [4]. The search for novel tumor chemotherapeutic agents of natural origin to achieve better therapeutic effects is of great importance. It has been found that lignin analogs in burdock have shown significant anti-tumor effects [3]. Burdock lignin analogs mainly include Arctigenin and Arctiin. Studies have shown that burdock has therapeutic effects on lung cancer, ovarian cancer, liver cancer, pancreatic cancer and endometrial cancer. ARC is the precursor substance of Arctigenin. Mi Jingyu et al. [5] concluded that ARG is the direct active ingredients in burdock. The anti-tumor effect of burdock glycoside has the characteristics of broad-spectrum, low toxicity, and minimal adverse reactions. ARG has effects on cell cycle arrest, apoptosis induction, direct cytotoxicity, and reversal of multidrug resistance in tumor cells [6]. He Fan et al. [7] studied S180 tumor bearing mice and found that the growth of tumor cells was significantly inhibited by gavage of ARG. They speculated that ATG inhibits tumor angiogenesis by interfering with the VEGF signaling pathway. Wang Huanqin et al. [8] found that ARG could significantly inhibit the proliferation of lung cancer cells H460 and could enhance the sensitivity of H460 cells to cisplatin. Chang Liang et al. [9] found that ARG inhibited the proliferation of hepatocellular carcinoma SMMC-7721 cells, and hypothesized that apoptosis might be induced by activating the endoplasmic reticulum stress response. Zhao Jiao et al. [10] found that ARG were able to inhibit the proliferation, migration and invasion of human ovarian cancer SKOV3 cells, and hypothesized that ARG might be able to inhibit the development of SKOV3 cells by targeting the pentose phosphate pathway through miR-1, affecting the downstream expression of related proteins, and the generation and utilization of glycolytic intermediates. Liu Ruonan et al. [11] found that ARG could inhibit the proliferation of endometrial cancer HEC-1B cells, and also had the effect of promoting apoptosis of HEC-1B cells. Dan Liao et al. [12] found that ARG inhibited the proliferation, invasion and metastasis of cervical cancer cells and induced apoptosis via the FAK/paxillin pathway. Zou Lin et al. [13] found that ARG can promote apoptosis by inhibiting the activation of the TLR4/NF-κB pathway, thus reducing the resistance of K562/A02 cells to adriamycin, which provides a new theoretical basis for ARG as an adjuvant drug in the treatment of leukemia.

2.2 Anti-inflammatory Effect

Inflammation is an important defense mechanism of the body against harmful stimuli, but it can also cause many injuries, such as arthritis, asthma, ischemic stroke, and body dysregulation. Burdock can be widely used to treat inflammatory diseases such as wind heat, cold, lung heat, cough, and acute sore throat. The extract of burdock seed, ARG, can effectively inhibit or inhibit the release of inflammatory factors, and exert anti-inflammatory effects. Its mechanism may be related to regulating immune response, reducing neutrophil and macrophage infiltration, inhibiting active macrophages, lymphocyte proliferation, and so on.

Ulcerative colitis (UC) is a non-invasive, non-specific inflammatory bowel disease of incompletely defined etiology, characterized by continuous, diffuse inflammatory changes in the colorectal mucosa, with lesions mainly confined to the colorectal mucosa and submucosa [14]. ARG can significantly alleviate the reduction of intestinal epithelial cells and the infiltration of neutrophils in colitis mice, thereby alleviating DSS induced colitis [15].

Asthma, also known as bronchial asthma, is characterized by airway hyperresponsiveness, airway inflammation and airway remodeling, and has a long and recurring course that is difficult to recover from, which has a great negative impact on the patient's life and work [16]. ARG inhibits TRAF6 expression and NF-κB phosphorylation by downregulating TLR4, thereby reducing Th2 cytokine IL-4 expression in asthmatic rats, enhancing Th1 shift, alleviating airway inflammation and lung tissue pathological damage in rats, alleviating airway smooth muscle hypertrophy and airway proliferation, and alleviating airway pathological damage [17].

Acute lung injury is a complex clinical syndrome caused by factors such as trauma, sepsis, and infection that damage alveolar epithelial cells and capillary endothelial cells, leading to diffuse interstitial and alveolar edema, and ultimately resulting in acute hypoxic respiratory dysfunction [18]. Zhu Zimor et al. [19] found that ARG could improve LPS-induced impairment of nasal epithelial barrier function through activation of ILARG could improve LPS-induced impairment of nasal epithelial barrier function through activation of the IL-22/JAK1/STAT1 signaling pathway, and suggested that ARG could reduce acute lung injury by alleviating inflammation and promoting the repair of the epithelial barrier of the nasal mucosa.

Acute cerebral infarction occurs mostly in middle-aged and elderly people, with a high incidence rate, as well as a high mortality and disability rate. Its pathogenesis is the insufficiency of blood oxygen in cerebral tissues, the occurrence of oxidative stress and inflammatory reaction, thus inducing the generation of oxygen free radicals and the occurrence and development of pathological processes such as neuronal apoptosis and body acidosis. As is well known, NF-κB can regulate many immune and inflammatory responses, promote the expression of various inflammatory mediators, and participate in the pathogenesis of most inflammatory diseases [20]. Modulation of the expression activity of HMGB1/TLR4/NF-κB and TNF-α/TNFR1/NF-κB signaling pathways ameliorates the inflammatory response and has a critical role in the treatment of acute cerebral infarction [21]. ARG can inhibit the activation of the aforementioned pathways, thereby reducing neuronal damage caused by acute cerebral infarction.

Atopic dermatitis is a skin disease with a high prevalence worldwide and is also one of the common chronic skin diseases. AD patients typically exhibit erythema, dryness, scaling, and lichen like changes, characterized by severe itching, which severely disrupts sleep and impairs quality of life. Local anti-inflammatory treatment for AD is a first-line treatment method. Li Jingmin et al. [22] found that ARC can exert anti-inflammatory effects by reducing the transcription of Th1 and Th2 related cytokines, achieving the effect of improving AD like dermatitis.

2.3 Antiviral Effect

ARC and ARG extracted from burdock have strong efficacy as influenza therapeutic agents, capable of inhibiting viral replication, enhancing immune response, and decreasing the frequency of drug-resistant viruses, and have strong in vitro antiviral activity against Influenza A. In one study, burdock was shown to have significantly lower viral loads in the bronchoalveolar lavage fluid of mice infected with Influenza A than did the combination of burdock and oseltamivir in mice infected with this two drugs alone [23]. The incidence of cross-species transmission of H9N2 viruses to humans has increased significantly in recent years. Serological investigations have shown a high risk of H9N2 seropositivity in humans, indicating that the H9N2 virus has adapted to be able to infect humans [24]. Notably, highly pathogenic avian influenza (e.g., H5N1 and H7N9) has acquired genetic fragments from the H9N2 virus that cause fatal respiratory disease in humans [25]. The pandemic potential of the H9N2 virus poses a serious public health risk. Burdock has antiviral activity against H9N2 virus. Burdock was able to effectively reduce H9N2 virus-induced pro-inflammatory cytokines, such as IL-6 and TNF-α, and significantly inhibited H9N2 virus-mediated expression of COX-2 and PGE, as well as inhibited H9N2 virus-mediated activation of RIG-I/JNK MAPK signaling, which had a potential inhibitory effect on the replication of the H9N2 virus and the inflammatory response mediated by the virus [26]. Zika virus (ZIKV) belongs to the genus of yellow viruses in the family of yellow viruses and is a zoonotic pathogen mainly transmitted by Aedes mosquitoes. After ZIKV infection, most patients have no obvious symptoms or mild symptoms, and may be misdiagnosed as other infectious diseases [27]. Recent studies have found that ZIKV infection can cause serious neurological diseases, such as microcephaly and Guillain Barre syndrome [28]. ZIKV infection can regulate the transcription level of host cells, which is conducive to the sustained infection of the virus. Although the pathogenesis of ZKIV infection is not yet clear, causing cell cycle arrest and inducing cell apoptosis has been recognized as the related mechanisms of ZIKV infection [29]. Experiments have shown that ARG has significant in vitro anti ZIKA activity, which can inhibit the replication of ZIKV in cells, and the inhibitory activity is dose-response [30].

2.4 Antihyperglycemic and Anti-diabetic Nephropathy, Diabetic Retina and Other Pathologies

The hypoglycemic mechanism of burdock seed is to stimulate insulin secretion, promote GLP-1 release, and reduce intestinal absorption of glucose. Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia, and the global morbidity and mortality are increasing year by year. Diabetic nephropathy (DN), also known as diabetic glomerulosclerosis, is one of the serious microvascular complications of diabetes mellitus and an important cause of end-stage renal failure. Li Zhuoheng et al. [31] observed the changes of a series of related indexes (blood indexes, renal fibrosis and glomerular basement membrane changes) after administration of ARG to male mice with DN model and found that burdock glucoside at a dose in the range of 80~320mg/kg has an ameliorative effect on DN, which works by regulating the oxidative stress in the kidneys.

Diabetic retinopathy (DR) is a microvascular complication that refers to a disease in which endothelial damage and increased vascular permeability occur in the retinal microvessels within the eye, leading to hypoxia of the retinal tissue and pathological changes in the retina. With the prevalence of diabetes increasing every year, DR will become one of the most common complications of diabetes in the world. A study showed that ARG and ARC, the main active ingredients in burdock seed, can play a preventive protective role against diabetic retinopathy by inhibiting retinal ganglion cell apoptosis and increasing retinal vascular E/P. The mechanism of action may be through the down-regulation of VEGF, TNF-alpha, and ICAM-1 levels to reduce inflammatory injury under high-glycemic conditions [32]. In another experimental study, it was found to inhibit protein kinase C (PKC) activation and block the elevation of retinal vascular endothelial growth factor (VEGF), thereby inhibiting streptozotocin (STZ)-induced apoptosis in the retina of DR rats, and reducing fasting blood glucose (FBG) levels in the treated group [33].

Liver injury is one of the most frequently occurring organ damage in DM. You Gaofei et al. [34] found that both oxidative stress and inflammatory factor levels were improved and liver injury symptoms were reduced in DM mice after ARG intervention through mouse experiments.

2.5 Regulation of Blood Lipids and Anti-cardiovascular Pathologies

The incidence of ischemic cardiovascular and cerebrovascular diseases based on atherosclerosis is increasing year by year. Studies have shown that elevated low-density lipoprotein (LDL) cholesterol or total serum cholesterol is one of the independent risk factors for coronary heart disease and stroke [35], while high-density lipoprotein (HDL) is an anti-atherosclerotic lipoprotein in the body, which is negatively correlated with the development of coronary heart disease [36]. It has been found that lignin-like compounds, polysaccharides, terpenoids and other active substances in burdock have good lipid-lowering effects. The lipid-lowering pathway of burdock is AMPK pathway. On the one hand, it down-regulates transcription factors such as PPAR-γ, C/EBPα and SREBP-1C in the AMPK pathway, inhibits the expression of lipogenic genes, suppresses adipocyte synthesis as well as lipid synthesis; on the other hand, it inhibits the activity of hormone-sensitive triglyceride lipase (HSL) through activation of the AMPK pathway, increases the phosphorylation of acetyl-coenzyme A carboxylase (ACC), inhibits lipid catabolism and reduce the release of free fatty acids [37].

Myocardial hypertrophy is an important pathophysiologic process in the development of heart failure. Myocardial hypertrophy is characterized by hypertrophy of cardiomyocytes on the one hand and abnormal proliferation of fibers in the interstitium on the other. Zhang Tingting et al. [38] found that ATG inhibited ventricular remodeling and inflammatory responses in CHF rats, and the mechanism of action may be related to the inhibition of the activation of HMGB1/TLR4/NF-κB signaling pathway. Zhu Xinyao et al. [39] found that burdock glucoside could improve glucose and lipid metabolism, insulin sensitivity, myocardial fibrosis and myocardial protection in IR mice. The mechanism may be related to the reduction of myocardial AUF1 expression and the inhibition of excessive activation of myocardial TGF-β1/Smad3 signaling channels.

2.6 Hypotensive and Anti-target Organ Damage Effects

The cause of death in hypertensive patients is not simply elevated blood pressure, but target organ damage caused by hypertension [40]. Therefore, prevention and treatment of target organ damage are equally important as controlling blood pressure. Experimental studies have found that burdock has good antihypertensive and target organ protective effects. Through observing the effects of ARG on blood pressure and target organs in spontaneously hypertensive rats (SHR), it was found that high and medium doses of ARG (100mg/kg, 50mg/kg) can significantly reduce systolic blood pressure, lower left ventricular weight and left ventricular mass index in SHR rats, indicating that burdock glycoside has the effect of reversing left ventricular hypertrophy [41]. The mechanism is that ARG can reduce plasma thromboxane B2 and arterial superoxide anion levels in SHR rats, and improve vascular endothelial function and reduce systolic blood pressure by inhibiting the expression of reduced nicotinamide adenine dinucleotide phosphate oxidase in the aorta, increasing the production of nitric oxide [42].

Hypertensive disease in pregnancy is a unique disease in pregnancy, characterized by hypertension, urinary protein and edema and accompanied by systemic organ damage, posing a serious threat to the health of mothers and infants, and is one of the most important causes of maternal and perinatal mortality [43]. Kong Qi et al. [44] found that ARC could improve PIH vascular endothelial injury by enhancing vascular endothelial cell autophagy and inhibiting NLRP3 inflammatory vesicle activation. It provides a possible and reliable experimental basis for the clinical treatment of PIH with ARC.

2.7 Other Roles

As a natural macromolecular component, burdock crude polysaccharide also has a wide range of biological activities such as anti-tumor, anti-inflammatory and anti-virus. Gong et al. [45] found that burdock crude polysaccharide has good antioxidant activity by testing the scavenging ability of DPPH radicals, hydroxyl radicals and superoxide anion, and the

reducing ability of iron ions.

2.8 Conclusion

In summary, burdock, as a traditional Chinese medicine in China, has been widely and deeply studied by scholars at home and abroad in recent years, and many experimental and clinical studies have confirmed the significant clinical effects of burdock on antitumor, anti-inflammatory, antiviral, antidiabetic, and lipid regulation, and its clinical applications have become more and more extensive. The discovery of more new chemical components in burdock seed, for the clinical use of burdock seed for the treatment of more diseases, is worth exploring in depth.

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