

Research Progress on Antioxidation of Danggui Buxue Decoction

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Abstract:

As a renowned formula for tonifying qi and generating blood in traditional Chinese medicine, Danggui Buxue Decoction has been extensively explored in modern pharmacological research. Studies have revealed its potent antioxidant capacity, which manifests through scavenging oxidative free radicals and modulating the activity of antioxidant enzymes, thereby mitigating oxidative stress processes in the organism. This mechanism demonstrates significant preventive and therapeutic effects against diseases caused by oxidative stress. This article comprehensively reviews current research advancements regarding the antioxidant effects of Danggui Buxue Decoction and its clinical applications in disease management, aiming to provide a theoretical foundation and scientific evidence for its clinical utilization.

Keywords:

Danggui Buxue Decoction, Antioxidant Action, Research Progress

1. Introduction

Free radicals are produced during the physiological processes of all aerobic organisms and are essential for maintaining normal life activities. Under normal physiological conditions, there exists a dynamic equilibrium between the generation and scavenging of free radicals in living organisms. The body maintains this oxidative - antioxidative balance through an antioxidant defense system composed of enzymes such as Superoxide dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPX) [1]. However, when the body is subjected to harmful stimuli, the amount of free radicals in the body either increases or the antioxidant capacity diminishes. This disrupts the oxidative - antioxidative balance, resulting in oxidative stress [2]. As a consequence, an excessive amount of Reactive Oxygen Species (ROS) accumulates, inflicting damage on biological macromolecules like nucleic acids, proteins, and lipids. This, in turn, contributes to the development of various diseases such as atherosclerosis, liver diseases, diabetes, inflammation, cancer, and the aging process [3,4,5]. Therefore, maintaining the redox balance within the body is crucial for good health. Currently, given that some synthetic antioxidants, such as BHT, BHA, and TBHQ, have been proven to be toxic, and with the increasing preference for green and eco - friendly consumption, the exploration of safe and natural antioxidants has become an emerging research focus [6]. Danggui Buxue Tang (DBT), originating

from “Differentiation and Discrimination of Internal and External Injuries” written by Li Dongyuan, is composed of *Angelica sinensis* and *Astragalus membranaceus*. This combination can either invigorate qi to generate blood or strengthen qi to promote blood circulation, thereby exerting a synergistic effect. A multitude of studies have indicated that DBT possesses a wide array of biological activities, covering immunomodulation, hematopoiesis regulation, antioxidation, anti - tumor functions, and the protection of cardiovascular and cerebrovascular systems. Notably, its antioxidant property is particularly remarkable [7,8,9] . Both in - vitro and in - vivo experiments, along with clinical trials, have verified that DBT and its single - herb components can mitigate the oxidative stress process in the body by scavenging oxidative free radicals and regulating the activity of antioxidant enzymes. This effectively helps prevent and treat various diseases [10,11,12]. This article presents a comprehensive review of the antioxidant effects of DBT in treating diabetic nephropathy, premature ovarian failure, and atherosclerosis through scavenging oxidative free radicals and regulating antioxidant enzyme activities. The aim is to offer a theoretical foundation and scientific evidence for the clinical application of this formula.

2. Antioxidant Mechanisms of Danggui Buxue Tang

2.1. Danggui Buxue Tang Scavenges Reactive Oxygen Species and Reduces Oxidative Damage

Reactive oxygen species (ROS) broadly refer to oxygen-derived free radicals and non-radical species, primarily including superoxide anion radicals, hydroxyl radicals, and hydrogen peroxide [13]. Excessive ROS can induce lipid peroxidation, protein oxidation, enzyme inactivation, and DNA damage [14]. Danggui Buxue Decoction (DBT) mitigates oxidative damage by scavenging ROS. Wang employed network pharmacology to construct a drug-component-target-disease network for DBT in treating myocardial injury, identifying key genes and performing pathway enrichment analysis. Their findings suggest that ROS clearance and antioxidant effects may represent one mechanism underlying DBT's therapeutic action in myocardial injury[15]. Yu demonstrated that DBT downregulates myocardial ROS expression, significantly inhibits oxidative stress in hypertrophic cardiomyopathy (HCM) rats, and improves ventricular remodeling and cardiac function[16]. Li established a hypertensive nephropathy rat model via high-salt diet and observed that modified DBT treatment promoted AMPK phosphorylation, enhanced SIRT3 protein expression, reduced hypertension-induced ROS production, decreased inflammatory cytokine synthesis, alleviated renal tissue damage, and improved renal function[17] . Studies report that ROS not only directly disrupt endothelial cell function through oxidative stress but also induce autophagy initiation [18]. Guo created an oxidative stress model in endothelial progenitor cells (EPCs) using H₂O₂, observing elevated ROS levels with impaired proliferation, migration, and angiogenic capacity. DBT intervention reduced intracellular ROS levels, enhanced autophagy under oxidative stress, and restored EPCs' biological functions [19]. Modern pharmacological studies reveal that DBT's flavonoid constituents and ferulic acid [20] exhibit radioprotective effects via free radical scavenging, antioxidant activity, and inhibition of lipid peroxidation, thereby protecting the hematopoietic and immune systems from DNA damage. Kaempferol [21] directly neutralizes oxygen free radicals, reduces ROS levels, and attenuates oxidative stress-induced apoptosis. Isorhamnetin [22] lowers ROS concentrations, ameliorates oxidative stress, and reverses bone metabolism

disorders. The phenolic hydroxyl groups in quercetin's structure exert antioxidant effects by donating hydrogen atoms to neutralize free radicals while being oxidized into stabilized radical forms [23]. Huang established an H₂O₂-induced oxidative stress model in P1G1 normal human melanocytes, demonstrating that quercetin pretreatment significantly reduced intracellular ROS levels via DCFH-DA assay [24]. Saw developed an oxidative stress model in Hep G2-C8 cells, where quercetin pretreatment exhibited potent oxygen radical scavenging activity by DPPH analysis, with DCFH-DA assay and combination index results confirming its ROS-reducing capacity in stressed cells [25].

2.2. Danggui Buxue Tang Enhances Antioxidant Enzyme Activity and Exerts Antioxidant Effects

Within the body's antioxidant enzyme system, superoxide dismutase (SOD) and glutathione peroxidase (GPX) are crucial enzymes that reflect the body's capacity to scavenge free radicals [26]. Catalase (CAT), on the other hand, is a key enzyme in the biological defense system established during the process of biological evolution. SOD catalyzes the conversion of superoxide anions into relatively stable H₂O₂ [27]. Subsequently, GPX and CAT work in concert to scavenge the H₂O₂ generated by SOD, thereby protecting cells from the harmful effects of peroxides [28,29]. DBT exerts its antioxidant effects by regulating both the enzyme-mediated and non-enzyme-dependent antioxidant defense systems. Wang established a rat model of acute myocardial infarction by ligating the left anterior descending coronary artery. Rats in the model group were then treated with low-dose (3 g/kg) and high-dose (6 g/kg) DBT. Compared with the model group, both low- and high-dose DBT treatment significantly decreased the malondialdehyde (MDA) content in myocardial tissue and increased the activities of SOD, CAT, and GPX. Notably, the high-dose group exhibited more pronounced improvements in these indicators, suggesting that DBT protects the myocardium from injury by enhancing the activities of SOD, CAT, and GPX antioxidant enzymes in rats with acute myocardial infarction [30]. Feng fed radiation-damaged rats with DBT at doses of 3.6, 1.8, and 0.9 g/ml for 14 days. The results indicated a significant decrease in MDA content and a marked increase in SOD content, with high-concentration DBT showing a more prominent effect, thus demonstrating its anti-radiation property [31]. Fan demonstrated that DBT could downregulate the elevated MDA level and acetylcholinesterase (Ache) activity in brain tissue induced by sodium nitroprusside. Moreover, DBT improved the learning and memory ability of rats and treated vascular dementia by enhancing the activities of SOD, CAT, and GPX antioxidant enzymes and promoting the release of cholinergic neurotransmitters [32]. Liu measured the levels of GPX, CAT, and SOD in the lung tissue of rats treated with bleomycin and DBT. The findings indicated that DBT alleviated the inhibitory effect of bleomycin on these enzymes, thereby reducing the degree of pulmonary fibrosis [33]. Chen detected the antioxidant and lipid peroxidation indices in the serum and liver-kidney tissues of rats. The results showed that DBT increased the contents of SOD and glutathione (GSH) in the liver-kidney tissues and serum of aging rats while decreasing the MDA level [34]. Similar results were obtained by Guo using a D-galactose-induced aging mouse model, where they measured the SOD activity and MDA content in the serum of aging mice. These findings suggest that DBT can enhance the body's antioxidant capacity by increasing the activity of antioxidant enzymes, reduce oxidative damage, and thus play a role in delaying the aging process [35]. Li added different doses of DBT to the culture medium of *Tetrahymena thermophila*, with sterile distilled water as the control. They

monitored the growth curve of *Tetrahymena thermophila* and measured the gene expression of GPX and thioredoxin reductase (TxnRd2) using Real Time - PCR. The results showed that DBT improved the growth curve of *Tetrahymena thermophila* and promoted the mRNA expression of GPx4 and TxnRd2 genes, suggesting that DBT may affect the lifespan of *Tetrahymena thermophila* by enhancing antioxidant enzyme gene expression and exerting antioxidant effects [36]. Ren found that DBT significantly inhibited the increase in MDA content in red blood cells caused by phenylhydrazine hydrochloride treatment and enhanced the SOD activity of red blood cells. This indicates that DBT has significant antioxidant activity, which can effectively counteract the oxidative damage of phenylhydrazine hydrochloride to mouse red blood cells and mitigate oxidative hemolysis in mice [37]. In a separate study on the ovarian cells of post - menopausal rats, treatment with quercetin increased the mRNA and protein expression levels of the antioxidant - related factor SOD - 1 [38].

3. Applications of Danggui Buxue Tang in Oxidative Stress - Related Diseases

3.1. Application in Diabetic Nephropathy

Mitochondria are recognized as the principal intracellular source of reactive oxygen species (ROS). Under physiological circumstances, the kidneys generate a modest quantity of ROS. Nevertheless, in the context of hyperglycemia, the intrinsic renal cells are unable to effectively modulate the glucose transport rate to maintain intracellular glucose homeostasis. Consequently, the mitochondria within these cells produce an excessive amount of ROS, triggering oxidative stress, which is a pivotal factor in the pathogenesis and progression of diabetic nephropathy (DN) [39]. Accumulating evidence has firmly established that oxidative stress is one of the major etiological factors contributing to the development of DN [40,41]. Clinically, the majority of DN patients exhibit the syndrome characterized by “qi - yin deficiency and renal collateral obstruction.” Hence, the therapeutic approach often centers around “strengthening the spleen to invigorate qi, nourishing yin, and dredging the collaterals.” Danggui Buxue Tang is formulated with *Astragalus membranaceus* and *Angelica sinensis*. *Astragalus membranaceus* exerts its efficacy in strengthening the spleen to replenish qi, nourishing yin and dredging collaterals, as well as promoting diuresis to alleviate edema through multiple mechanisms, including cholesterol reduction and metabolic disorder improvement. *Angelica sinensis*, on the other hand, functions to promote qi circulation, remove blood stasis, soften hardness, and resolve masses by means of its antioxidant properties, free - radical scavenging ability, and improvement of blood perfusion in renal tissues. With a ratio of *Astragalus membranaceus* to *Angelica sinensis* of 5:1, Danggui Buxue Tang has demonstrated its potential in alleviating the early - stage clinical symptoms of DN patients, thereby holding certain positive implications for the treatment of DN [42]. In investigations into the impact of DBT on DN rats, it was observed that DBT could significantly decrease the fasting blood glucose, urea nitrogen, and creatinine levels in diabetic rats. Moreover, it restored the ultrastructural damage in a dose - dependent manner and downregulated the expression of heparanase ($P < 0.05$), indicating that DBT may represent a novel therapeutic option for the prevention and treatment of DN [43]. Jin revealed that DBT might mitigate oxidative stress by rectifying the mitochondrial dysfunction in podocytes of DN rats, reducing ROS expression, and regulating the activation of the TXNIP/NLRP3/GSDMD signaling pathway. This, in turn, plays a

crucial role in renal protection and retarding the disease progression [44,45]. Zhang discovered that DBT could inhibit the activation of the JAK2/STAT3 signaling pathway by suppressing the oxidative stress response under hyperglycemic conditions. This inhibitory effect leads to the exertion of anti-inflammatory activity, ultimately safeguarding the renal tissue of diabetic rats from damage [46]. Ren found that Danggui Buxue Tang could safeguard mesangial cells induced by high-glucose and impede the progression of DM nephropathy. It achieved this by reducing the mRNA and protein expression of the oxidative stress marker (p47phox), upregulating the expression of the endoplasmic reticulum stress marker (XBPs), and modulating both endoplasmic reticulum stress and antioxidant stress. At the protein and gene levels, they also confirmed that Danggui Buxue Tang could counteract the oxidative stress induced by high-glucose, protect mesangial cells by upregulating the expression of nuclear factor-erythroid 2-related factor 2 (Nrf2) under high-glucose conditions, enhancing SOD activity, and decreasing MDA production [47,48]. Li demonstrated that Danggui Buxue Tang could remarkably upregulate the mRNA and protein expression of Nrf2 and HO-1, alleviate oxidative stress, enhance the antioxidant capacity of renal tissues, and mitigate renal pathological damage [49]. Zhang experimentally verified that Danggui Buxue Tang could protect renal tissues by inhibiting the ATF6/CHOP pathway, downregulating the expression of cysteine protease-3 (Caspase-3), and minimizing cell apoptosis triggered by endoplasmic reticulum stress [50]. Shen showed through experiments that Danggui Buxue Tang could relieve endoplasmic reticulum stress and preserve the structure and function of renal tissues by inhibiting the mRNA and protein expression of glucose-regulated protein 78 (GRP78), protein kinase R-like endoplasmic reticulum kinase (PERK), and eukaryotic translation initiation factor 2 α (eIF2 α) in the renal tissues of DN rats [51]. Shuai found that Danggui Buxue Tang could also protect renal tissues by suppressing the expression of the IRE1 α -JNK pathway in renal tissues under high-glucose conditions, thereby reducing the endoplasmic reticulum stress response [52].

3.2. Application in Premature Ovarian Failure

Oxidative stress is widely acknowledged as a major determinant of ovarian aging [53]. It can instigate multiple cell death pathways in mammalian ovarian follicles, such as autophagy, apoptosis, and necrosis, which ultimately lead to diverse degenerative changes in the ovaries and contribute to the development of premature ovarian failure (POF) [54,55]. Therefore, antioxidation represents a critical strategy for delaying the decline of ovarian function. In traditional Chinese medicine, there is no specific term corresponding to POF. Based on its clinical manifestations, it can be categorized into concepts such as “premature cessation of menstruation,” “amenorrhea,” and “obstruction of menstruation” [56]. “Wan’s Gynecology” states, “For women with amenorrhea... it is due to qi depletion and blood exhaustion, resulting in menstrual blockage.” “Huangdi Neijing” mentions, “When a woman is blood-deficient, menstruation does not occur regularly... due to insufficient blood in the uterine cavity, menstruation fails to come.” Menstruation is essentially composed of yin-blood. For women, qi provides the functional impetus, while blood serves as the fundamental substance. Qi and blood are the material basis for women’s physiological processes of menstruation, pregnancy, childbirth, and lactation. When a woman has abundant qi and blood with smooth circulation, her five zang-organs are in harmony, the thoroughfare and conception vessels are unobstructed, and menstruation and pregnancy proceed normally. Conversely, disharmony of qi and blood can lead to an inability to fill the sea of blood, inadequate nourishment of the

internal organs, and disorders in menstruation and pregnancy. Danggui Buxue Tang, a classic formula for replenishing qi and blood, consists of *Astragalus membranaceus* and *Angelica sinensis*. In this formula, *Astragalus membranaceus* is used in a high dosage to vigorously strengthen the qi of the spleen and lungs. Abundant qi promotes blood production. When combined with *Angelica sinensis*, which nourishes blood and regulates the nutritive qi, the formula can ensure the smooth flow of qi and blood and resolve the disease. Animal studies have indicated that *Astragalus membranaceus* can effectively prevent and treat POF by augmenting the content of antioxidant SOD in ovarian tissues, reducing the oxidative stress in the reproductive system, and enhancing the antioxidant capacity of oocytes [57]. Astragaloside can decrease the content of reactive oxygen species (ROS) in the ovaries, delay the activation of mitochondria in oocytes, and protect follicular granulosa cells, thereby ameliorating ovarian function impairment [58]. *Angelica polysaccharide* can activate the AKT/FOXO3 pathway, inhibit oxidative stress in mice, improve the endocrine function of mice with immune - induced POF, and, to some extent, inhibit the development of immune - induced POF [59]. Furthermore, quercetin, kaempferol, and isorhamnetin, the major bioactive components of DBT, possess potent antioxidant activities. Quercetin, an ideal scavenger of peroxide free radicals and an efficient inhibitor of lipid peroxidation [60], can significantly reduce oxidative stress in ovarian tissues and enhance the ovarian antioxidant capacity in a dose - dependent manner by upregulating oxidative - stress - related genes in the ovaries. It also promotes the development of follicles at all stages, the proliferation of granulosa cells, and the estrogen secretion of granulosa cells, thus delaying ovarian aging [61,62,63]. Kaempferol and isorhamnetin can promote the activation of primordial follicles, stimulate the proliferation of granulosa cells, inhibit apoptosis, and mitigate oxidative stress via the PI3K/AKT pathway [64,65].

3.3. Application in Atherosclerosis

Risk factors for atherosclerosis, including a high - fat diet, high - sugar diet, and smoking, can augment the production of mitochondrial ROS, thereby inducing oxidative stress. Oxidative stress, in turn, not only perpetuates the generation of ROS, forming a vicious cycle, but also uncouples mitochondrial oxidative phosphorylation, reducing ATP production. This further impairs mitochondrial function and accelerates the progression of atherosclerosis (AS) [66,67]. Consequently, oxidative stress is considered a contributing factor in the development of AS [68,69]. From the perspective of traditional Chinese medicine, AS can be classified into categories such as “chest impediment,” “dizziness,” “palpitations,” and “kidney impediment.” Blood stasis obstruction and qi - blood deficiency are the key pathological mechanisms underlying the development of AS [70]. Liu in accordance with the theory of qi and blood in traditional Chinese medicine, proposed that qi deficiency is the fundamental cause, while blood stasis is a secondary manifestation of this disease [71]. Qi serves as the driving force for the propulsion and regulation of body fluid and blood circulation. Qi and blood are mutually nourishing and interdependent. When qi is deficient, blood production is compromised. Additionally, deficient qi leads to weakened propulsive force, resulting in poor circulation of blood and body fluids. Over time, the accumulation of phlegm and blood stasis occurs, which further obstructs the circulation of qi and blood, exacerbating blood stasis. Therefore, qi - tonifying therapy is of utmost importance in the treatment of AS. Danggui Buxue Tang is a representative formula for replenishing qi and generating blood in clinical practice. In this formula, *Astragalus membranaceus* is used in a large quantity to

strongly tonify the qi of the lungs and spleen, providing the source for qi and blood generation. It utilizes intangible qi to generate tangible blood. *Angelica sinensis* nourishes blood, regulates the nutritive qi, promotes blood circulation, and relieves pain. The combination of these two herbs enables the generation of blood with abundant qi, balances the qi and blood of the nutritive and defensive systems, and resolves blood stasis. Studies have shown that DBT can significantly decrease the levels of total cholesterol (TC), low - density lipoprotein (LDL), and malondialdehyde (MDA) in experimental AS animals, increase the activity of superoxide dismutase (SOD), and notably reduce the area and thickness of atherosclerotic plaques in the aorta. Its antioxidant effect is likely the primary mechanism underlying its anti - AS activity [72]. Moreover, the antioxidant and free - radical - scavenging properties of *Angelica sinensis* and its component ferulic acid can protect the intima of blood vessels from damage. Le found that *Angelica sinensis* exhibits a protective effect against vascular endothelial damage induced by oxidized low - density lipoprotein (OX - LDL), and its mechanism may be associated with the antioxidant activity of *Angelica sinensis* [73]. Ferulic acid can mitigate damage to vascular endothelial cells and prevent macrophages from undergoing foam cell transformation upon exposure to OX - LDL by scavenging free radicals and enhancing the activity of antioxidant enzymes such as nitric oxide synthase. This contributes to the improvement of AS [74,75]. Quercetin, which possesses anti - inflammatory, antioxidant, blood - pressure - lowering, blood - lipid - lowering, and immunomodulatory effects, can reduce the damage area and plaque size of AS by inhibiting the formation of foam cells [76,77].

4. Conclusions

In summary, when oxidative stress caused by ROS disrupts the body's antioxidant defense system, it can inflict various damages on the body. Excessively accumulated ROS act on biological macromolecules, disrupting cell structures and giving rise to a multitude of diseases such as cardiovascular diseases, neurodegenerative diseases, urinary diseases, skeletal diseases, and the aging process. Moreover, there is an inevitable connection between oxidative stress and mitochondrial damage. Maintaining the balance between oxidation and antioxidation is the key to ensuring the normal operation of the body. Danggui Buxue Tang (DBT) exhibits a strong antioxidant function. It can not only ameliorate atherosclerotic diseases but also regulate the immune system, delay the progression of diabetic nephropathy, and prevent and treat premature ovarian failure. Thus, it has extensive clinical applications. However, the underlying mechanisms of its actions remain to be further explored and investigated.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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