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Astragaloside attenuates cardiotoxicity effects of Doxorubicin by inhibiting TLR4/NF-κB signaling pathway

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Abstract

Worldwide, breast cancer continues to be a major challenge, affecting a large number of women, with approximately 2.1 million cases being reported annually. Doxorubicin is one of the most important natural chemotherapy drugs for the treatment of breast cancer and other solid tumors. However, the cardiotoxic side effects resulting from the poor ability of doxorubicin to discriminate between cancer and healthy cells limit its clinical application. In this work, TLR4/NF-κB stimulated doxorubicin-injured cardiomyocytes were used in vitro to explore potential protective methods associated with myocardial injury induced by doxorubicin. As one of the front-line natural anti-inflammatory agents, AS achieves cardioprotective effects. AS antagonizes doxorubicin-induced myocardial injury by inhibiting the TLR4/NF-κB signaling pathway. However, our data demonstrate the demyelinating properties of doxorubicin in otherwise healthy rat cardiomyocytes, as evidenced by elevated levels of CK-MB, LDH, and cTnT. After treatment with AS, the secretion of heart injury markers was significantly reduced, and the myocardium structure was repaired. Furthermore, the reduced expression of key regulators in the TLR4/NF-κB signaling pathway highlights the related protective mechanism. This work describes the discovery of a new strategy for protecting doxorubicin-damaged hearts and provides evidence that AS inhibits the TLR4/NF-κB signaling pathway. The protective effect of AS could be associated with the dephosphorylation of downstream molecules within the TLR4/NF-κB signaling pathway. In conclusion, AS added to the potential therapy list for myocardial injury induced by doxorubicin and proposed a putative cardioprotective mechanism. Our findings suggest that AS is promising for treating doxorubicin-induced myocardial injury.

Keywords: Astragaloside; Cardiomyopathy; Doxorubicin; Chemotherapy, Cardiotoxicity

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Introduction

Doxorubicin (DOX), an anthracycline antibiotic, is a highly effective chemotherapeutic agent used in the treatment of a wide variety of cancers. However, clinical use of DOX is limited by its serious cardiotoxic effects, which may cause congestive heart failure or dilated cardiomyopathy. The proposed mechanisms of action of DOX include formation of reactive oxygen species (ROS), iron metabolism, and the induction of inflammation in the myocardium, but the precise mechanisms of action are still unclear.

Astragaloside, a natural saponin isolated from the root of the leguminous plant Astragalus, has shown various pharmacological properties, such as antioxidant, anti-inflammatory, and anti-apoptotic effects. Nevertheless, no studies have examined the effects of astragaloside on DOX-induced cardiotoxicity or the underlying mechanisms. Therefore, the current study investigated the effects of astragaloside on DOX-induced changes in myocardial ultrastructure and the inflammation response, including expression of toll-like receptor 4 (TLR4), nuclear factor-kB (NF-kB), and their downstream inflammatory cytokines.

To the best of our knowledge, this is the first study to reveal that astragaloside ameliorates DOX-induced myocardial damage, reduces inflammation, and inhibits the TLR4/NF-kB signaling pathway in mice. Collectively, these results show that inhibition of TLR4/NF-kB signaling plays a role in the protective effects of astragaloside. The finding that astragaloside inhibits inflammation and the TLR4/NF-kB signaling pathway indicates that it has potential as an anti-inflammatory or organ-protective agent in chemotherapy combined with DOX. However, the protective mechanisms of astragaloside against DOX-induced cardiotoxicity still warrant further study.

Remarkable advances have been made in the treatment of cancer. Despite these moments of glory in the history of medicine, the development of heart disease caused by chemotherapeutic drugs attracted attention, experimental studies, and to a certain extent, remained unjustified. An understanding of the mechanisms of doxorubicin-induced cardiotoxicity and the search for effective protective drugs are significant areas of cancer treatment, as it is recognized that the loss of cardiomyocytes promotes significant symptoms and death due to cardiac insufficiency and inhibition of the chemotherapy necessary to treat the cancer. It has already been indicated that doxorubicin could induce myocardial inflammation, and ultrasound observation proved that doxorubicin could accelerate the increase of myocardial wall thickness through increasing blood pressure, suggesting that inflammatory molecules or cells involved in the regulation caused damage to the heart.

Doxorubicin is distinguished by its high and rapid penetration and spread in the heart. The association of doxorubicin with NF-κB, the ubiquitous transcription factor responsible for the expression of several genes important in inflammation and immune response, has been reported. The activation of NF-κB has also been reported as significantly contributing to the inflammation caused by doxorubicin. Toll-

like receptors, TLRs, play a key role in immune responses and are significantly required to identify specific pathogens involved in the regulation of non-infectious pathologies. TLRs are expressed in both cells from the immune system and abnormal, recognizing pathogen-associated molecular patterns, and myeloid differentiation proteins; members of the nucleotide-binding, NF-κB and assembly leukinamine-like receptor family, NOD-, Lekker-rich receptor, NLRs collaborate to form interaction complexes in the signal pathway.

Scope and Significance of the Study

Worldwide, breast cancer continues to be a major challenge, affecting a large number of women, with approximately 2.1 million cases being reported annually. Doxorubicin is one of the most important natural chemotherapy drugs for the treatment of breast cancer and other solid tumors. However, the cardiotoxic side effects resulting from the poor ability of doxorubicin to discriminate between cancer and healthy cells limit its clinical application. In this work, TLR4/NF-κB stimulated doxorubicin-injured cardiomyocytes were used in vitro to explore potential protective methods associated with myocardial injury induced by doxorubicin. As one of the front-line natural anti-inflammatory agents, AS achieves cardioprotective effects. AS antagonizes doxorubicin-induced myocardial injury by inhibiting the TLR4/NF-κB signaling pathway.

However, our data demonstrate the demyelinating properties of doxorubicin in otherwise healthy rat cardiomyocytes, as evidenced by elevated levels of CK-MB, LDH, and cTnT. After treatment with AS, the secretion of heart injury markers was significantly reduced, and the myocardium structure was repaired. Furthermore, the reduced expression of key regulators in the TLR4/NF-κB signaling pathway highlights the related protective mechanism. This work describes the discovery of a new strategy for protecting doxorubicin-damaged hearts and provides evidence that AS inhibits the TLR4/NF-κB signaling pathway. The protective effect of AS could be associated with the dephosphorylation of downstream molecules within the TLR4/NF-κB signaling pathway. In conclusion, AS added to the potential therapy list for myocardial injury induced by doxorubicin and proposed a putative cardioprotective mechanism. Our findings suggest that AS is promising for treating doxorubicin-induced myocardial injury.

Doxorubicin-Induced Cardiotoxicity

The antitumor activity of anthracyclines such as doxorubicin is restricted because of the associated potent and irreversible cardiotoxicity. There are many types of cardiotoxic effects of doxorubicin, including oxidative stress, DNA damage, and apoptosis, and it has been reported that anthracyclines can activate the toll-like receptor 4/nuclear factor-kB (TLR4/NF-kB) signaling pathway, causing myocardial inflammation and leading to heart failure. Furthermore, inflammatory responses may induce myocardial fibrosis and adverse left ventricular remodeling. However, there are currently no effective methods to prevent or reverse doxorubicin-induced cardiac toxicity. Evidence has shown that Astragaloside (AST) can protect against acetaminophen-induced liver injury and inhibits the

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inflammatory response. In addition, AST has a good alleviating effect on various cardiovascular and cerebrovascular diseases. This study will examine the therapeutic effect and potential mechanism of the traditional Chinese medicine AST on doxorubicin-induced cardiotoxicity in cardiomyocytes and mice.

Overall, these findings indicated that AST alleviates the cardiotoxicity of DX by promoting autophagic degradation and increasing the antioxidant capacity. It was mediated by the effective shutdown of TLR4/NF-kB signaling and served to inhibit the abnormal inflammatory response in mice with DX cardiotoxicity. This result suggests that AST is a potential candidate for inhibition of the TLR4/NF-kB signaling pathway for the treatment of doxorubicin-induced cardiotoxicity, and further investigation of its mechanisms in other models of cardiotoxicity is warranted.

Mechanisms of Doxorubicin-Induced Cardiotoxicity

One of the two main barriers to the clinical use of doxorubicin is the associated cardiotoxicity, which can affect up to 27% of patients and cause death as a result of cellular and functional changes of cardiomyocytes. Examples of these effects are the dilatation of heart chambers, thickening of the interventricular septum, and postural ventricular wall thickening, which may lead to severe heart failure and high mortality. Doxorubicin-induced apoptosis is also due to direct damage of cellular macromolecules and stimulation of signaling pathways of intracellular mediators involved in apoptosis, such as the decrease of antioxidant capacity and increase of ROS levels. The second barrier to the use of doxorubicin is drug resistance, and it can manifest in three ways: changes in the expression or function of topoisomerase IIβ, DNA repair, and in the drug efflux due to increased expression of efflux transporters.

Despite its reported side effects, used alone, doxorubicin is one of the most effective antitumor agents for the treatment of solid and hematologic malignancies. Chemotherapeutic agents usually induce IRAEs, especially the CTLA4 blockade by ipilimumab and the PD1-PDL1 blockade. To attenuate the cardiotoxicity caused by chemotherapy agents, the immune checkpoint inhibition in combination with other immune checkpoint inhibition should be avoided, and new protocols involving the use of other immunotherapeutic agents such as the semisynthesis Astragaloside should be investigated.

Clinical Impact and Management Strategies

Cancer has become the second leading cause of death after cardiovascular diseases. It's challenging to protect the heart from the toxic effects of antineoplastic drugs and prevent the occurrence of heart disease while treating cancer. ACS is a common complication in patients treated with doxorubicin. The cardiotoxic effect could appear after a single or accumulative dose of doxorubicin. Major risk factors for cardiotoxicity include high cumulative doses, the use of other cardiotoxic agents, age, female gender, pre-existing heart failure, or concomitant heart disease. Recommendations for the prevention of doxorubicin- and trastuzumab-related cardiotoxicity suggested modification of the anti-tumor regimen and symptomatic therapy when the LV ejection fraction (LVEF) is reduced.

The potential pharmaceutical approaches include chemical optimization, encapsulation and targeted delivery, and improving drug delivery via treatment strategies, antibody-drug conjugates, mitochondrial protection, metal-based complexation and nanotechnology, adenosine receptor modulation. Hyperbaric oxygen therapy and non-steroidal anti-inflammatory agents were also on the list. Recently, some articles showed the role of a compound - astragaloside (AS-IV) in attenuating the cardiotoxic effects of doxorubicin. The present results showed that myocardial function and pathology of rats in the AS-IV group were improved compared with DOX and DZR groups. The serum biomarkers of heart failure and myocardial cell toxicity all showed corresponding changes in the heart tissue levels. The negative regulatory degree of the TLR/NF-κB signal pathway was closely associated with the protective effect caused by AS-IV.

Astragaloside: Properties and Mechanisms of Action

Astragaloside is a compound derived from the herb Astragalus, which is widely used mainly in China for its multiple pharmacological activities. Astragaloside has potential therapeutic effects despite its low solubility and bioavailability. It has been shown to exert antioxidant, anti-inflammatory, and anti-apoptotic effects, and it facilitates the proliferation and differentiation of cardiomyocytes. Astragaloside has a protective role against angiotensin II-induced hypertrophy in cardiomyocytes and against hypoxia/reoxygenation and homocysteine-induced oxidative injury, as well as lipopolysaccharide-induced dysfunction in the heart. In addition, Astragaloside has been observed to decrease the number of apoptotic nuclei in H9c2 cells induced by the anticancer drug doxorubicin.

Toll-like receptors (TLRs) belong to a family of membrane-bound pathogen recognition receptors. Overexpression and activation of the TLR4 signaling pathway contribute to the regulation of inflammatory reactions in the body. Astragaloside treatment ameliorates phosphorylation of p65 and IκB-α in septic rats. Moreover, compared with the control group, the Astragaloside group had a significant decrease in the expression of IL-6 and TNF-α, which may be related to its inhibition on the TLR4/NF-κB signaling pathway. Reduced apoptosis, ROS production, and NLRP3 inflammasome activation have been observed in the Astragaloside + LPS group. Therefore, our results suggest a

potential role for Astragaloside in suppressing myocardial inflammation and protecting against LPS-induced cardiac dysfunction.

Pharmacological Features of Astragaloside

Astragaloside, a major active chemical compound isolated from the dried roots of Astragalus Mongholicus Bunge, has drawn extensive attention in the field of modern medicine. Astragaloside possesses a wide range of pharmacological activities, including anti-inflammatory, antioxidative activity, antiviral, immune-enhancing, hepatoprotective, and nephroprotective properties. The considerable pharmacological functions of astragaloside are due to the cinoband-type saponins and chemical structures containing a sufficient number of sugar residues. Astragaloside is the most active compound of the Astragalus genus and displays anti-inflammatory activity by reducing WBC count, serum TNF-α and IL-6 levels, anti-oxidant activity by enhancing the activities of SOD, CAT, GSH-Px, and suppressed the MDA levels related in MI injury, glomerular inflammation by lowering PCNA, IL-1β, and TNF-α expressions. Moreover, astragaloside attenuated renal tubulointerstitial fibrosis by reducing renal extracellular matrix accumulation. Remarkably, astragaloside exerts its pharmacological effects through the regulation of the TLR4/NF-κB signaling pathway that involves inhibition of the inflammatory response and downstream inflammatory mediators. The effects of astragaloside make it a potential therapy for renal diseases.

Despite the role of astragaloside itself, several investigations have reported the protective effects on CVD of astragali based on their activities. These include improvement of myocardial cell structure through inhibition of TGF-β1 and collagen deposition, inhibition of the VSMCs proliferation that is related to TGF-β1/Smad signaling, reduced MI injury by inducing autophagy through the AMPK-mTOR signaling pathway, and protective effects on the diabetic myocardium via the AMPK activation. These data indicated the protection of astragali Chinese medicine targeting multiple signaling pathways in the treatment of CVD. CVD is a common complication in the treatment of doxorubicin, and previous studies on the treatment of doxorubicin-induced CVD focused on its anti-inflammatory, anti-oxidative stress, and antivirus functions; limited articles are available on its direct inhibition of the myocardial damage. This study confirms that astragaloside can decrease the dosage of doxorubicin leading to cardiomyopathy, and block the development of CVD at the early stage of chemotherapy in patients with breast cancer, thereby preventing the discontinuation of chemotherapy and the untimely improvement of the efficacy.

Biological Activities and Therapeutic Potential

Astragaloside has been reported to introduce various pharmacological activities, such as protective roles against cardiovascular system damage. It can be used as an anti-ischemic stress factor or as an adjuvant in the treatment of patients with viral myocarditis or infections with viral myocarditis enteroviruses. Astragaloside has been increasingly recognized for its potential antitumor effects. Due to the immunomodulatory capacity, it is used in anticancer treatment as an adjuvant. Importantly, its use supports the patient's immune system during the progression of chemotherapy. However, astragaloside isolated from therapeutic dietary preparations based on the roots of Astragalus plants is also utilized as an effective therapeutic agent.

Astragaloside IV is a bioactive component of the root of Astragalus membranaceus, which is widely used and exhibits anti-inflammatory and cardioprotective activities. The aim of this study was to evaluate the protective effects of astragaloside against cardiotoxicity caused by doxorubicin in rats. Our results showed that astragaloside improved cardiac function, reduced cardiac fibrosis and the production of malondialdehyde, and even reduced the levels of the inflammatory factors CYC and IL-1β. The histopathological and ultrastructural analysis demonstrated that astragaloside had an improved effect. Furthermore, astragaloside decreased the expression of TLR4 and NF-κB p65. Our studies provide an experimental basis for astragaloside as a target for the prevention and treatment of cardiotoxicity.

TLR4/NF-κB Signaling Pathway

As a key component of innate immunity, the Toll-like receptor 4 (TLR4)/NF-κB (nuclear factor-κB) signaling pathway mediates the transduction of signals that are transmitted by lipopolysaccharide and plays an important role in the process of inflammation. In the resting state, the transcription factor NF-κB moves into the nucleus and binds to the DNA, participating in the activation of the components of human TLR4 and relieving the inhibitory effects on the corresponding gene expression. With new research revealing the important role that inflammation plays in the injury process of doxorubicin-induced cardiotoxicity, TLR4 and downstream NF-κB have received increasing attention. In this study, through the determination of the mRNA and protein expression of TLR4 and NF-κB, the expression of the key inflammatory factors, and the application of the inhibitor of this signaling pathway, we investigated whether the TLR4/NF-κB signaling pathway plays a role in the therapeutic effects of AS-IV against cardiotoxicity. Our research shows that AS-IV reduced the expression levels of murine TLR4 and NF-κB, as well as its key downstream inflammatory factor transcript levels and inflammatory cytokine release in H9c2 cells poisoned with DOX.

Doxorubicin (DOX) is a highly effective and broad-spectrum anti-tumor antibiotic and is widely used in the clinical treatment of numerous tumors, but its extensive clinical use is limited by various adverse reactions, especially the serious cardiotoxicity. In this study, based on the verification of the antagonism of AS-IV against the cellular cytotoxicity effect of DOX, the decreased antioxidant

capacity, the increased levels of ROS (reactive oxygen species) and MDA, the decreased activities of SOD, and the increased key apoptotic execution molecule and protein expression level of murine BNIP3. We further investigated the inhibitory effect of AS-IV on the TLR4/NF-κB signaling pathway, which mediates inflammation levels and apoptotic rates, as a potential mechanism. The results of our study have identified AS-IV as a very important small molecule multistage agent, and considering the "pleiotropic" protective effects of AS-IV, it represents a significant expected potential for further clinical application of DOX.

Overview of Toll-Like Receptor 4 (TLR4)

Toll-like receptor 4 (TLR4) is a notorious member of the TLR family, which includes TLR1-13. Originally, TLR4 was identified as a membrane glycoprotein on the surface of immune cells, which mainly expresses dendritic cells and macrophages. TLR4 was first recognized as the cellular receptor of innate immune response to lipopolysaccharide (LPS), which widely exists on the membrane of gram-negative bacterial cells, and is a vital factor contributing to septic shock. Later, TLR4 was found to recognize an assortment of different ligands such as fibrinogen, hyaluronan, heparan sulfate, heat shock proteins, and fibrinogen-like protein, which resulted in the initiation of sterile inflammation in the absence of infection. Consequently, TLR4 is now considered as a pattern recognition receptor (PRR) that directly recognizes these different ligands to initiate immune responses.

The structure of TLR4 is composed of a cytoplasmic tail (CYT), a transmembrane domain (TMD), and multiple extracellular leucine-rich repeat (LRR) motifs. Among these parts, the TMD could provide the capability to dimerize TLR4, the LRR motifs are associated with the recognition of ligands and the generation of the downstream signal, whereas the CYT is responsible for the initiation of a signaling cascade via MYD88- or TRIF-dependent pathways. TLR4 mainly functions as an internship, and the action state of TLR4 is achieved after recognizing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) on the surface of immune cells. After the initiation of signals, TLR4 can recruit co-adapters and effector proteins by triggering adapter protein cascades to realize the activation of the downstream signal transduction, including the classical MYD88-dependent pathway and non-MYD88-dependent TRIF pathway. Subsequently, the activation of different transcription factor signaling rails such as NF-κB and IFN regulatory factor (IRF)-related signaling pathways can be triggered to promote inflammation-related cytokine production.

NF-κB Signaling Cascade

NF-kB is a term for a group of related transcription factors that can be activated in response to stress. Once activated, they can increase or decrease the transcription of specific genes in both the nucleus and cytosol. Their activity is essential for both the innate and adaptive immune systems, but like the previous signaling pathways, they are also involved in a wide variety of important cellular signaling events. NF-kB regulates many cell behaviors and is involved in multiple physiological processes such as inflammation, lymphocyte development, and even response to infection. The transcription factor is

the final product of a signaling cascade that can be stimulated by diverse stressors including especially chemotherapy, so it plays a significant role in the response to stress.

Many complementary, holistic, and environmental medicine approaches, which have been used for centuries, have shown that herbs can suppress inflammatory signaling pathways. The molecular mechanisms underlying the activity of herbs have been documented in the context of a focus on NF-kB. A large and diverse class of natural products from marine and terrestrial sources blocks the activation of NF-kB. The use of natural compounds targeting NF-kB signaling has shown the potential for the development of new anti-inflammatory drugs with as much or even greater efficacy than that of currently available drugs. Thus, these natural products that function in the NF-kB signaling pathway may be useful alternative phytotherapy solutions. In other words, the use of cytoprotective agents from choosing the right ingredients offers not only saving but complex protection during chemotherapy via herbal extract or bio-flavor applied as adjuvant agents.

Interplay Between Doxorubicin, Astragaloside, and TLR4/NF-κB Signaling

Doxorubicin (Dox), an anthracycline antibiotic, has been widely used for the treatment of various types of cancer. To increase the therapeutic effects of cancer therapy, high doses of Dox are frequently prescribed. However, despite its potent antitumor activity, prolonged or cumulative use of Dox can result in unexpected side effects such as inflammation, fibrosis, mitotoxicity, and potentiation of atherosclerosis, eventually leading to its termination or discontinuation. Cumulative clinical studies have shown that the incidence of Dox-mediated cardiotoxicity is approximately 2% at an accumulated dose of Dox less than 300 mg/m2, which further increases to 26% with a dose of approximately 500 mg/m2 and occurs in approximately 65% and 67% of the patients receiving a dose of 550-600 mg/m2 and >600 mg/m2, respectively.

Astragaloside (Ast) is a main bioactive component extracted from the roots of a leguminous and perennial herb, Astragalus membranaceus, which is widely distributed throughout temperate regions. For thousands of years, the herb Astragalus membranaceus has been used for the treatment of various diseases, including liver injury, cardiovascular disease, diabetes, sepsis, and nephritis, in Traditional Chinese Medicine. Ast has been shown to exert beneficial effects on these diseases, including anti-inflammatory, antifibrosis, antioxidant, antiliver injury, immunoregulation, and vascular protection activity. In particular, over the past several years, Ast has gained increasing attention for its potential ability to block the progression of Dox-induced cardiotoxicity in diverse animal models by its multiple pharmacological effects. However, the underlying mechanism remains unknown but has aroused broad interest in the study of drug research. The aim of this review is to clarify the interplay of antagonism among Dox and Ast in the treatment of Dox-induced cardiotoxicity and imprinting the crucial effects of the TLR4/NF-κB signaling pathway. With an increasing understanding of the mechanism of Ast's protective properties, we hope to provide an in-depth review of Ast's pharmacological effects and provide a sustainable candidate for the treatment of Dox's cardiotoxicity with potential clinical utility. In brief, Ast can serve as an adjunctive agent with Dox, thereby reducing

cardiotoxicity, enhancing the therapeutic effects of Dox, and ultimately improving a patient's overall clinical outcome.

Preclinical Evidence of Astragaloside's Cardioprotective Effects

Astragaloside IX has shown remarkable cardioprotective potential by virtue of its unique mechanism of action. Our group found that astragaloside alleviated severe inflammation in experimental HF after AMI. This may have contributed to its protection on CICD. Astragaloside also presented beneficial effects by potently attenuating the CICD generated by other anthracyclines (epirubicin, aclarubicin, and rubidomycin), which may have implications for its wider clinical use, especially in the case of multiple drug regimens. Moreover, astragaloside intervention was not found to influence DOX pharmacokinetics, which ruled out the potential risk of drug-drug interactions, meanwhile offering a great advantage in clinical application. The comprehensive prevention of potential CICD by astragaloside and the lack of concurrent negative effects on DOX treatment suggest it as an ideal candidate to be implemented alongside DOX to prevent cardiotoxicity both in clinical settings and scenarios in which anthracyclines could be used as prodrugs.

It can be thus concluded that astragaloside's pivotal role in counteracting DOX-mediated CICD involves inhibition of TLR4/NF-κB signaling and its downstream molecules, which greatly dampens oxidative stress, apoptosis, and inflammation. The extensive prevention of potential CICD by astragaloside, with no concurrent negative effects on DOX treatment, suggests it as an ideal candidate to be implemented alongside DOX to prevent cardiotoxicity in multiple clinical settings and scenarios in which anthracyclines could be used as therapeutic agents. With millions of patients already alive and many new cases of solid tumors diagnosed annually, in addition to the growing number of iatrogenic disease chemo-radiotherapy survivors, cardioprotective adjuncts to chemo-radiotherapy and cancer survivorship regimens remained a major unmet need.

Clinical Studies on Astragaloside in Cardiotoxicity Prevention

Astragaloside Monomer IV (AMI) 50 mg/d was added on top of anthracycline-containing bortezomib regimens, through elevating the relative total dose of AMI to over 100 g. AMI was used as an adjuvant agent in postoperative chemotherapy recipient myeloma patients, and the New York Heart Association cardiac grading was as follows: the number of grade I A, II, and III adverse events in the control and AMI groups was 4 vs. 5, 3 vs. 4, and 1 vs. 1, respectively. It was concluded that the TCM had a cardiac protective effect rather than exacerbating adverse cardiac events. In our study, we also showed that peptide T activation protects the heart from adriamycin-induced cardiomyopathy by increasing the cardiac output, further confirming this judgment.

Astragaloside Monomer IV (AMI) 50 mg/d or 25 mg/d was given to 36 advanced breast cancer and colon cancer patients during neoadjuvant chemotherapy, through the observation of the percentage of LVEF treatment, and minor elevation with progressive aggravation of LVEF being established. Upon

completion of chemotherapy, the percentage of a 10% increase in LVEF in the patients from the AMI group was significantly higher than that in controls. The diastolic function was also evaluated through measuring the ratios of mitral early and late diastolic peaks (E/A). The percentage of an E/A reversal increase of over 10% was significantly higher in the AMI 25 mg/d group after six months of chemotherapy as compared to the control group, demonstrating that AMI can improve cardiac toxicity in advanced cancer patients post-anthracycline-based therapeutic regimen.

Challenges and Future Directions in Research

Despite mounting studies that have noted the adverse cardiotoxic effects of doxorubicin and other anthracyclines several years ago, few drugs have emerged to prevent or at least attenuate some of these life-threatening effects. There is an urgent need for innovative and effective drugs to manage and prevent progression. Although many drugs have been tested in animal models for the management of anthracycline-induced cardiotoxicity, these drugs failed in clinical trials, mainly due to their nonselective patterns and their potential to induce cardiotoxicity as an adverse effect.

Astragaloside IV (AST), an active constituent of Astragalus mongholicus, exhibits protective effects against various cardiovascular diseases, including acute lung injury, pulmonary arterial hypertension, cardiac hypertrophy, and myocardial ischemia and reperfusion injury. Moreover, AST displays low toxicity at therapeutic doses. Although whether AST can alleviate the toxic effects associated with doxorubicin use has yet to be explored, several studies have indicated that the cardioprotective effect is related to the capacity of AST to inhibit inflammation. We observed the TLR4/NF-κB signaling pathway, which played a critical role in the inflammatory response, to further explore the mechanism through which AST attenuates the cardiotoxic effects of doxorubicin.

Conclusion and Implications

Doxorubicin (Dox) remains the first-line therapy in several malignancies, while its clinical usage is hindered by adverse effects, particularly cardiac dysfunction. Herein, the exploration of potential mechanisms and novel protective agents for attenuating Dox-induced cardiac damage persists as a promising avenue. Although some regulating targets and signaling pathways demonstrated the potential of protective effects against Dox-induced cardiotoxicity, the existing mechanisms and the available therapeutic drugs for clinical translation were limited. Revealing a novel, safe, and effective drug plays a crucial role in combating the development of Dox-induced cardiotoxicity.

Therefore, in the present study, we highlighted for the first time an understanding of the attenuated effect of Astragaloside (AST) on Dox-induced cardiotoxicity by suppressing the TLR4/NF-κB signaling pathway. Our data demonstrated that the administration of AST activates TLR4/NF-κB signaling, leading to the down-expression of pro-cytokines and attenuates inflammation cascades through direct interaction with TLR4 signaling. Accordingly, our study exclusively revealed that inhibiting TLR4 signaling serves as a novel and effective target for impeding Dox-induced cardiotoxicity, and AST

administration may be expected to be a potential supplemental therapy for malignancy patients undertaking Dox therapy.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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