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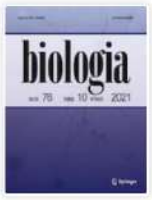


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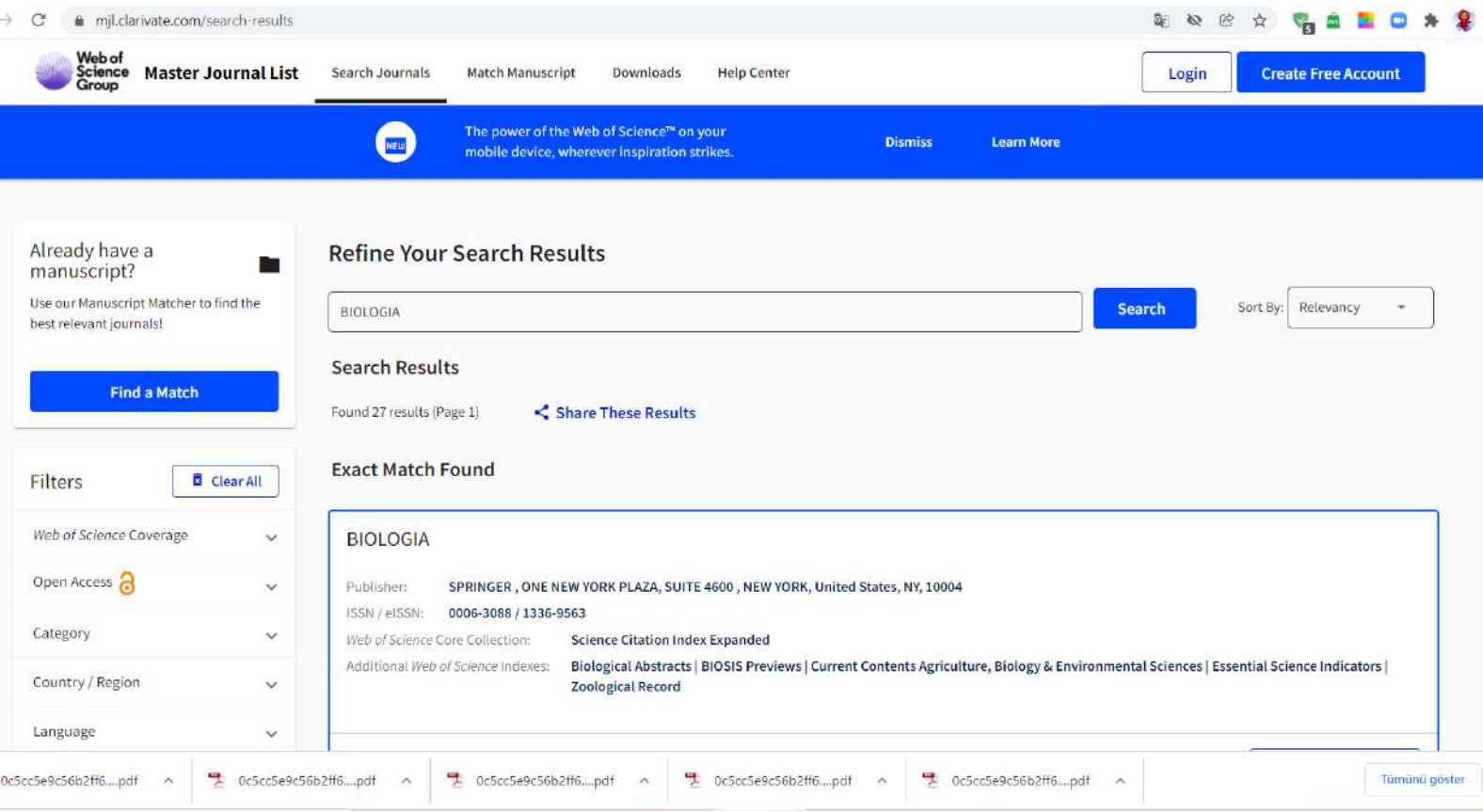
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ORIGINAL ARTICLE

Alterations in aquaporin gene expression level on cyclophosphamide-induced cardiac injury and possible protective role of *Ganoderma lucidum*

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Abstract

This research study was conducted to investigate the cardioprotective activity of alcoholic extract of *Ganoderma lucidum* (GL) against cyclophosphamide (CYP)-induced cardiotoxicity in rats model. Therewithal, the regulation in the expression level of Aquaporin (AQP) water channels in the heart was evaluated. Cardiotoxicity was induced in Wistar rats by administering a single-dose injection of CYP (200 mg/kg, i.p.) on the seventh day of the experimental period. GL (500 mg/kg, gavage) was administered daily for seven days. Cardiac alteration following CYP and GL administration was evaluated using electrocardiographic changes, morphological staining, AQP gene expression and western blot analysis. It was observed that the CYP administration significantly ($p < 0.001$) increased cardiac troponin- I (cTn-I) and elevated the level of creatine kinase isoenzyme MB (CK-MB). Further, rats treated with CYP showed increased expression levels of AQP-3, -4 and − 7 compared to the control group. The treatment with GL significantly ($p < 0.001$) reversed the level of cardiac biomarkers in CYP-induced cardiotoxicity. Potential cardioprotective effect of GL which reduced the severity of cellular damage of the myocardium was supported by histopathological examination. The biochemical, expressional and histopathological reports supported the cardioprotective activity of GL which could be attributed to changes in myocardial edema. To the best knowledge of the authors, this is the first study that reports the cardioprotective role of GL in CYP-induced myocardial edema and the changes in the expression levels of AQP.

Keywords Cyclophosphamide · *Ganoderma lucidum* · Aquaporin · Cardiotoxicity · Edema

Introduction

Cyclophosphamide (CYP) is a cytotoxic and immunosuppressive drug (Iqubal et al. 2019). It is among the potent alkylating agents widely used against rheumatoid arthritis, lupus erythematosus, multiple sclerosis, bone marrow transplant, sarcoma, neuroblastoma, lymphoma, lung cancer, and breast cancer (Shanmugarajan et al. 2008).

However, high doses of CYP cause cardiotoxicity. Phosphoramide mustard and acrolein are two active metabolites of CYP and are metabolized by the liver. Phosphoramide mustard attaches to DNA to suppress the cell division process. Acrolein is a toxic metabolite causing toxicity in the myocardium, cardiofibroblasts, and endothelial cells. CYP exhibits a bimodal mechanism of antitumor activity by itsown cardiotoxic and immunomodulatory feature (Veal et al. 2016; Binotto et al. 2003).

Ganoderma lucidum (GL) has been used in Asian countries to treat wide variety of diseases (Ahmad 2019). GL was reported to be used historically to treat heart diseases such as myocardial infarction, coronary heart disease and arrhythmia in China (Liu et al. 2021). Clinical studies have revealed the beneficial effects of the GL administration as an alternative adjuvant therapy in cancer patients without any obvious toxic outcome (Borchers et al. 2004; Sohretoglu and Huang 2018;

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Saltarelli et al. 2019). GL contains polysaccharides (GPs), proteins, peptides, amino acids and triterpenes that have anti-tumor and immunomodulator functions (Lu et al. 2020). In recent years, GPs have been reported to possess anti-tumor, anti-oxidant, anti-virus, anti-inflammattory, anti-diabetes and neuroprotection effect in various physiological processes (Zhang et al. 2016). GL has beta glucans and polysaccharides that stimulate immunity, as well as ganoderic acid with molecular structures similar to steroids (Xie et al. 2016). However, it's efficiency on cardiotoxicity is still need to be clarified (Xu et al. 2017). Ergosterol peroxide purified from GL has been reported to induce cancer cell death and inhibit cell migration, cell cycle progression, and colony growth of human hepatocellular carcinoma cells (Li et al. 2016).

Aquaporins (AQPs) are proteins enabling the transportation of water, glycerol, CO_2, and NH_3 in different areas of tissues. Due to its selective permeable properties, it has become the target channels in treatment of many diseases. Cardiac AQPs are responsible for water transport in heart muscle, and AQP channels carry out 30 % of the water transport in cardiomyocytes under physiological conditions. The importance of cardiac AQP channels has increased with the determination that cardiac edema significantly alters cardiac functions (Butler et al. 2006).

Many studies have revealed that AQPs are closely associated with biological functions of cancer and expressed in more than 20 human cancer cell types (Dajani et al. 2018). The expression of AQPs is positively correlated with tumor types, grades, proliferation, migration, angiogenesis, or tumor-associated edema and considered to be diagnostic and therapeutic targets in cancer therapy (Verkman 2005; Papadopoulos and Saadoun 2015; Wang et al. 2015). On the other hand, after chemotherapy, which is the most common approach in the treatment of various types of cancer, the mechanism of AQPs in the heart is still unknown. In pathological cases, such as cardiac damage, reduced cardiac lymphatic flow is frequently associated with myocardial edema. Interstitial water accumulation, i.e., edema, occurs in tissues when transcapillary water transport exceeds the flow of the lymphatic system (Verkman 2005; Papadopoulos and Saadoun 2015; Wang et al. 2015; Dajani et al. 2018; Verkerk et al. 2019).

AQP-1 and AQP-4 are water permeable channels, while AQP-3 and AQP-7 provides the passage of glycerol used in energy production in cardiomyocytes (Verkerk et al. 2019). The main AQP of the cardiovascular system is AQP-1 which regulates the water permeability of the heart's capillary networks by mediating the flow of water from the endothelial layer into the bloodstream (Day et al. 2014). It is considered that AQP-1, AQP-3, AQP-4 and AQP-7, which are demonstrated to be present in the heart with several studies, may be a therapeutic target in the improvement of edema after cardiotoxicity (Tie et al. 2017; Verkerk et al. 2019).

The present study investigated whether GL exhibits a therapeutic activity against cardiac hypertrophy and edema. While the protective effects of GL on the cardiovascular system are well known, the relationship between cardiac damage, AQP channels, and GL has not been revealed, yet. Accordingly, this study investigated whether GL treatment and CP-induced cardiotoxcity alters the expression of AQP channel genes in rat heart tissues.

Materials and methods

Experimental animals

Male Wistar rats were used in this experiment (n = 28). The experiment was approved by the Local Ethics Committee of Animal Experiments at Çanakkale Onsekiz Mart University (Protocol number: 2019/08 − 02). All the procedures performed in this study were carried out in accordance with the 1964 Helsinki Declaration standards. In the course of the study, all the rats were kept at 23°-25ºC in a 12 h light/12 h dark cycle (light, 08:00am-08:00pm; dark, 08:00pm-08:00am).

Materials

GL was obtained from Agromycel company in Denizli, Turkey (www.agromantar.com). Extracts from GL were used for the purpose of this study. To this end, solvents with different polarities were exploited. Before extracting, dried plant pieces were put in 10 gr packs of filter paper to be extracted in Soxhlet extractor (Wisd, Wise Therm). 300 mL of solvent was used for 10 g of the plant. After a 12 h extraction, the pieces in filter paper were removed from the device and placed in a drying oven. This solvent-free sample was prepared for extraction in a second round of solvent. The extraction was performed firstly in ethyl alcohol (C_2H_6O, KN: 78, 37 °C) and then in pure water (H_2O, KN: 100 °C). Subsequently, the solvents of the extracts were evaporated at around 56°C by using an evaporator (Spectral, Heidolph, Laborota 4001). The solvents in the extracts were entirely removed in a drying oven (50ºC). The obtained extracts were stored in a refrigerator (0–4ºC). Before the tests, different concentrations of the extracts were prepared by dissolving them in pure water and then sterilized in membrane filters (0,2 μm) (Khan et al. 1988).

CYP (Sigma-C0768) was dissolved in saline solution and intraperitoneally administered in the rats.

Experimental groups

Daily 500 mg/kg of extracts from GL (Zhang et al. 2016) was prepared in 2 mL of saline solution and administered to the

rats by gavage once a day for seven days. On the seventh day of the experiment, only two groups of rats were injected with CYP (200 mg/kg) (Table 1) (Elderbi et al. 2014).

At the end of the 7th day of the experiment, intracardiac blood collected (~4 mL) and hearts were removed under general anesthesia (5 mg/kg xylazine, Rompun®, Bayer, Istanbul, Turkey and 60 mg/kg ketamine hydrochloride, Ketalar®, Eczacibasi, Istanbul, Turkey).

ECG pattern

On the first and seventh days, ECG readings were performed by exciting sedative activity and through anesthesia of extremity derivations (35 Hz; Poly-Spectrum 12-channel ECG-System, Poly-Spectrum-8, Neurosoft, 5, Voronin str., Ivanovo, Russia). To this end, 30 mg/kg of ketamine and 5 mg/kg of xylazine were administered.

Biochemical analysis

The venous blood samples were collected and stored at − 80 °C until analyzed. CK-MB activities (Catalog No: MBS2515061) and cTn-I levels (Catalog No: MBS2104797) in the rat serum samples were determined by using the rat ELISA kit procedures of Sunred Biological Technology (Shanghai, China). Serial dilutions of the standards were prepared according to the kit protocols, serum samples and kit reagents were added to the 96-well plate. The absorbance of the samples and standards were measured spectrophometrically at 450 nm with Multiskan ™ GO Microplate Spectrophotometer, Thermo Scientific ™ reader and concentration of CK-MB and cTn-I levels were calculated according to standards.

mRNA isolation and quantitative RT-PCR analysis

The gene expression levels were evaluated by quantitative RT-PCR (Reverse transcription polymerase chain reaction). Total RNA was isolated from 10 to 30 mg of heart tissue using the kit (Ambion PureLink RNA MiniKit) as described in the manufacturer's protocol. The quality and amount of mRNA were determined according to the 260/280 absorbance rate using the NanoDrop ND-1000 Spectrophotometer. Reverse transcription was performed using a cDNA synthesis kit (HighCapacity cDNA Reverse Transcription Kit). The synthesized cDNA (complementary DNA) samples were used for the RT-PCR analysis. The gene expression levels were analyzed by RT-PCR (ABI StepOne) using Applied Biosystems ™ TaqMan® Gene Expression (Thermo Fisher Scientific, USA). β-actin was used for the normalization of the genes. The gene expressions were determined using Ct values and the fold changes were evaluated by the $2^{-(\Delta\Delta CT)}$ method. The primer IDs for AOP-1, AQP-3, AQP-4, AQP-7, and β-actin are Rn00562834_m1, Rn00581754_m1, Rn01401327_s1, Rn00569727_m1, Rn00667869_m1 respectively (Thermo Fisher).

Histopathologic analysis (hematoxylin & eosin staining)

The cardiac tissue samples taken during the surgical procedure were quickly placed in 10 % neutral buffered formalin. After a 24-48 h fixation, the tissues were embedded in paraffin blocks following routine tissue monitoring procedures. Sections of 4 μm cut out from the paraffin blocks were put on glass slides and then stained with hematoxylin and eosin. The stained preparations were assessed for such criteria as inflammatory cell infiltration, separation of muscle fibers and edema, as depicted in the related literature (Karacavus et al. 2018).

The assessment was performed by using a camera-attached microscope (Olympus CX43). The assessment results were graded as follows: Grade0: No damage, Grade1: Mild damage, Grade2: Moderate damage, Grade3: Severe damage.

Western blot

The heart tissue samples were homogenized by using PROPREP™ protein extraction solution (iNtRONBiotechnology). The protein concentration of the samples was measured with Bradford assay kit (Sigma). The lysates (~15 ug) were eluted by using 4–12 % Bis-Tris SDS-PAGE gel observing the Laemmli protocol (He 2011). Then, the proteins were

Table 1 Experimental groups

Groups (n=7)	Substance	Dose	1.Day————6.Day	7.Day
Control (C)	Saline solutions (S)	2 mL	S	S
CYP	Cyclophosphamide (CYP)	200 mg/kg	S	CYP
GL	*Ganoderma lucidum* (GL) extract	500 mg/kg	GL	GL
CYP+GL	Cyclophosphamide (CYP) and *Ganoderma lucidum* (GL) extract	500 mg/kg + 200 mg/kg	GL	GL+CYP *

*: GL (500 mg/kg) was administered by gavage during the seven days and a single dose of CYP (200 mg/kg) was injected 1 h later on the seventh day of the experiment

transferred to a nitrocellulose membrane by using iBlot® Dry Blotting System (Thermo Fischer). The nitrocellulose membrane was placed on iBind™ Automated Western System (Thermo Fisher) and incubated with anti-mouse AQP-1, -3, -4 and −7, β-actin primary antibodies (Thermo Fisher), and anti-rabbit IgG-HRP (Horseradish Peroxidase)-conjugated secondary antibodies (Thermo Fisher) for 150 min. After this process, the nitrocellulose membrane was scanned with C-DiGit Chemiluminescence Blot Scanner (LI-COR, NE, ABD) by using Western blotting luminol reagents. The densitometric analysis of the bands was carried out by using Image Studio Lite Software 5.0.

Statistical analysis

The obtained data were analyzed with SPSS v20.0 for Windows (Armonk, New York, USA: IBM Corp.) All data were evaluated with the Kolmogorov–Smirnov test and the Shapiro–Wilk test for determining normal distribution. Parametric test were performed for biochemical examinations, ECG, and gene expression. All the groups were compared by One-Way ANOVA test, followed by the posthoc Tukey's test. Nonparametric tests were performed for histopathological examinations, comparison between groups was done using Kruskal-Wallis, Mann-Whitney U-test and Bonferroni correction was performed. A *p*-value of < 0.05 was considered statistically significant. The gene expression levels were evaluated by the $2^{-\Delta\Delta Ct}$ method [ΔΔCt=(Ct Target gene-Ct reference gene)].

Results

Electrocardiography

The ECG readings of all the rats were conducted on the first and seventh day of the research. The QT correction according to Bazzett's formula (QTcB) and the QT correction according to Fridericia formula (QTcF) values were calculated with the RR durations and QT intervals obtained from the records. The Bazett's (QTcB) and the Fridericia (QTcF) formulas as follow; $QTcB = QT/\sqrt{RR}$ and $QTcF = QT/3\sqrt{RR}$. In consideration of the ECG readings on the first day of the study, no statistically significant between-group difference was observed in the QTcB and QTcF data ($p > 0.05$).

The ECG readings obtained on the seventh day of the study, a statistically significant between-group difference was detected in the QTcB and QTcF data ($p < 0.001$). In consideration of the QTcB and QTcF data, the adjusted pairwise comparison yielded a statistically significant increase in the CYP group when compared to the C and GL groups ($p < 0.001$). Although the heart rates in the CYP group were partially higher than those in the control group, they were not statistically significant ($p > 0.05$) (Table 2).

Cardiac enzymes

CTn-I and CK-MB are the specific markers of myocardial damage and important in monitoring cardiotoxicity caused by CYP. Troponin level tends to rise shortly after high-dose CYP administration and is generally indicative of direct myocardial damage. A significant increase in the cardiac CK-MB activity and the cTn-I level was detected in the CYP group in comparison to the control group ($p < 0.001$). Besides, the pretreatment of GL significantly reduced CK-MB activity and cTn-I level in comparison with the CYP treatment ($p < 0.001$) (Fig. 1).

Effects of GL on the expressions of cardiac AQPs in CYP-treated rats

The cardiac AQP-3, -4, -7 levels were found to have significantly increased in the CYP group in comparison to the

Table 2 ECG patterns on the first day of the experiment and the seventh day after the CYP application

Treatment day 1 (n=7)	QTcB (m±SE)	QTcF (m±SE)	Heart rate (beats/min)(m±SE)
C	109.1±0.3	85.2±0.2	263.9±1.6
CYP	106.3±1.3	83.7±0.7	251.1±6.3
GL	105.7±0.7	83.4±0.4	247.9±3.2
CYP+GL	113.3±4.1	83.7±0.1	252.8±8.6
Treatment day 7 (n=7)	QTcB (m±SE)	QTcF (m±SE)	Heart rate (beats/min)(m±SE)
C	102.1±0.5	81.5±0.3	231.3±2.5
CYP	104.3±1.1	82.6±0.6	241.0±5.4
GL	97.4±0.9#	79.0±0.5*	210.7±3.8*
CYP+GL	108.4±2.9	82.0±0.5	243.6±2.8

All results are presented as mean ± standard error (m ± SE) for seven rats in each group. QTcB values for all groups #: compared to CYP $p < 0.05$ and CYP + GL $p < 0.005$; QTcF values for all groups *: compared to C $p < 0.005$, CYP $p < 0.001$, CYP + GL $p < 0.005$; Heart rate values for all groups *: compared to C $p < 0.005$, CYP and CYP + GL $p < 0.001$

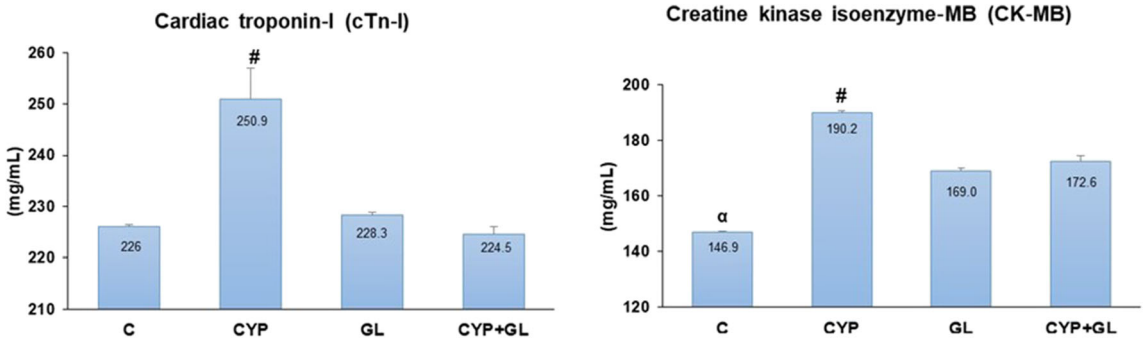


Fig. 1 Effect of GL on cardiac marker enzymes (cTn-I and CK-MB) in CYP-induced cardiotoxicity in rats. #: compared to C, GL, and CYP + GL, $p < 0.001$ α: compared to CYP, GL, and CYP + GL; $p < 0.001$

control group ($p < 0.001$). Besides, the GL pretreatment significantly reduced cardiac AQP-3, -4, -7 levels in comparison with the CYP treatment ($p < 0.001$). The cardiac AQP-3, -4, and − 7 activities in the CYP group were observed to have significantly increased in comparison to the CYP + GL group ($p < 0.001$). That means, the pretreatment of GL significantly reduced cardiac AQP-3, -4, -7 activities in comparison with the CYP treatment ($p < 0.001$) (Fig. 2).

Histopathologic alterations

The C and GL groups exhibited a normal histological appearance. While no statistically significant difference was found between the C and GL groups, a significant difference was detected between these groups and CYP, CYP + GL groups ($p < 0.05$). Inflammatory cell infiltration and edema were observed in the CYP group. Moderate interstitial bleeding and

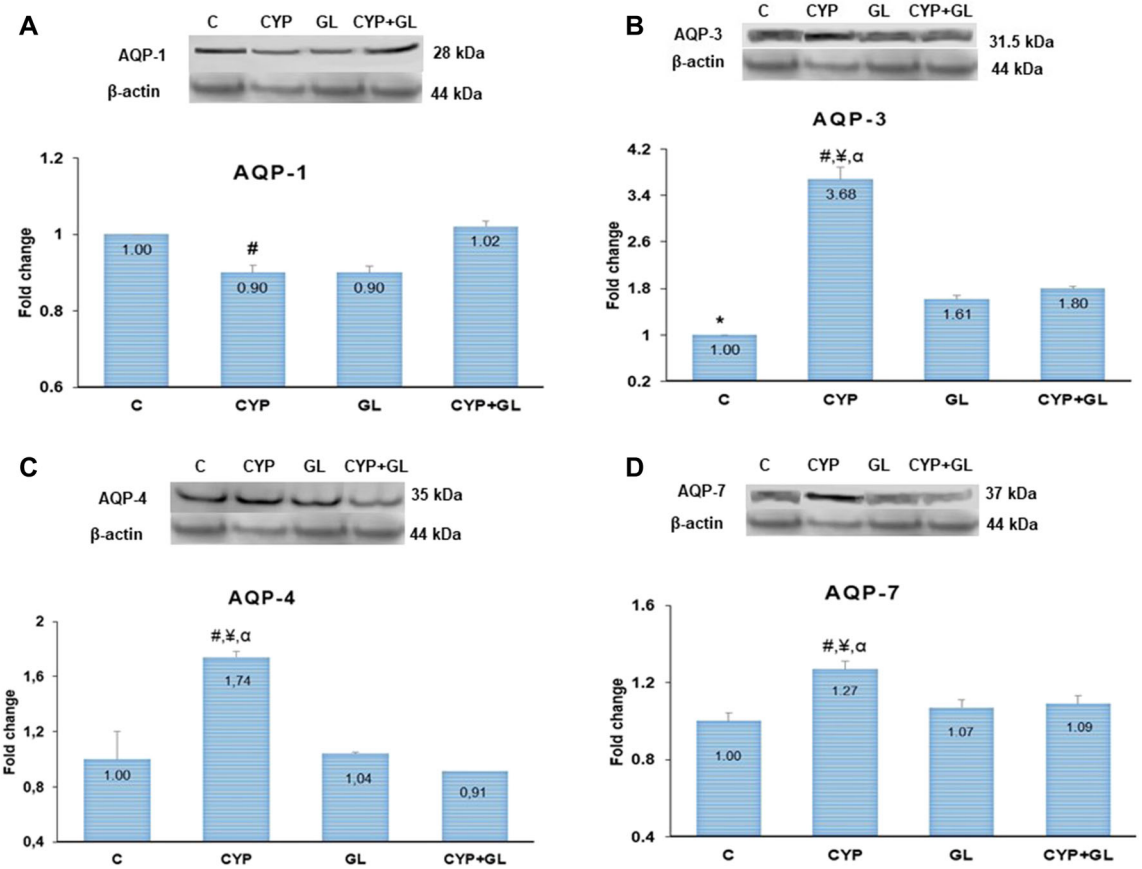


Fig. 2 Between-group differences in the gene expression levels of AQP-1, -3, -4, and − 7. The data were presented as $2^{-(\Delta\Delta CT)}$ relative expression after the mRNA levels were normalized with β-actin. All the results were presented as mean ± standard error for seven rats in each group. (A) Fold change of the AQP-1 #: compared to CYP + GL, $p < 0.05$, (B) Fold change of the AQP-3 #: compared to CYP + GL, $p < 0.001$, ¥: compared to GL, $p < 0.001$, α: compared to C, $p < 0.001$, *: compared to GL, $p < 0.05$, CYP + GL; $p < 0.005$ C) Fold change of the AQP-4 #: compared to CYP + GL, $p < 0.001$, ¥: compared to GL, $p < 0.005$, α: compared to C, $p < 0.001$, D) Fold change of the AQP-7 #: compared to CYP + GL, $p < 0.001$, ¥: compared to GL, $p < 0.001$, α: compared to C, $p < 0.001$

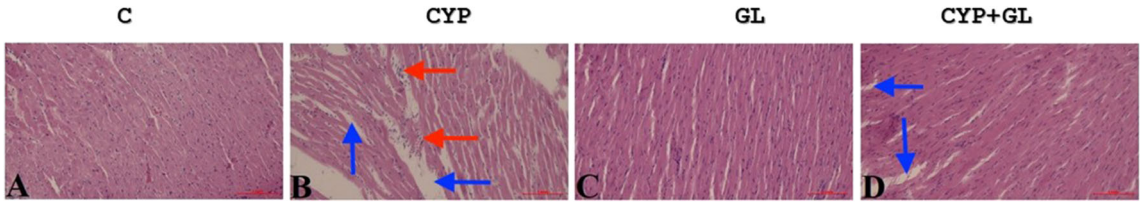


Fig. 3 H&E-stained microscope images of the experimental groups. The images of C, CYP, GL, and CYP + GL groups were labeled as A, B, C, and D, respectively. Red arrows refer to inflammatory cell infiltration areas, while blue arrows to edema areas. The C and GL groups exhibited similar histological appearance, whereas the histological structure of the cardiac tissue in the CYP group was observed to be severely distorted. Mild damages were detected in the CYP + GL group (Magnification, x20)

cell infiltration were identified in the CYP + GL group (Fig. 3; Table 3).

Discussion

The purpose of the present study was to emphasize AQP's role in normal and pathological cardiac function and to research the alterations in myocardial edema under toxicological conditions. For this purpose, the authors investigated edema formation in the heart after the CYP administration and whether GL had the potential to protect these alterations. The experimental design where the rats were injected with non-lethal doses of CYP was created to assess the potentially cardioprotective activities of GL. As a result of the present study conducted by using various analysis, the CYP administration provided statistically significant increases in the expressions of AQP − 3, -4, and − 7, which were significantly reduced after the GL administration. To the best knowledge of the authors, this paper is the first report which deals with the potential cardioprotective role of GL in CYP-induced myocardial edema and the changes in the expression levels of AQP genes.

Table 3 Comparison of histopathologic change scores between all groups

Groups (n=7)	Inflammatory cell filtration	Separation of muscle fibers and edema
Control m±SD	0±0	0±0
bkmedian (min-max)	0(0–0)	0(0–0)
CYP m±SD	2.86±0.4	1.9±0.8
median (min-max)	3.0(2–4)	2(1–3)
GL m±SD	0.3±0.5	0.1±0.4
median (min-max)	0(0–1)	0(0–1)
CYP+GL m±SD	1.1±0.8	0.8±1.2
median (min-max)	1(0–3)	0(0–3)
P	<0.000*	<0.001*

All results are presented as mean ± standard deviation (m ± SD) and median (min-max) for seven rats in each group. *: Mann-Whitney U-test

Many studies report the cardiac effects of CYP, particularly its high-dose administration (Slørdal and Spigset 2006; Floyd et al. 2005). It's reported in many clinical studies, the usage of high doses of CYP may cause serious complications such as cardiotoxicity and cardiomyopathy. As the pathogenesis of high-dose CYP-induced cardiac toxicity, myocyte damage, interstitial hemorrhage and edema may develop following the CYP caused endothelial damage (Katayama et al. 2009). Indeed, cardiotoxic mechanism of CYP or its metabolite leads to oxidative stress, altered calcium homeostasis, inflammation of cardiomyocytes, apoptosis, swelling of cardiomyocytes, nuclear splitting and vacuolization (Temel et al. 2020). Also, histological findings revealed the formation of fibrin, interstitial edema with acute and hemorrhagic pericarditis. Tatlidede et al. (2009) reported oxidative damage caused by chemotherapy and an increase in the number of peroxynitrite radicals in the heart tissue of rats. Elderbi et al. (2014) associated acute cardiotoxicity and cardiomyopathy with CYP (200 mg/kg) administration in rats. In another study, cardiotoxic effects of CYP are listed as dose-related cardiac damage, morphologically characterized necrosis, hemorrhage, and secondary fibrosis (Cetik et al. 2015). Acute heart failure has been reported between 7 and 33 %, and occurred within one week after the > 150 mg/kg intravenous administration of CYP (Dhesi et al. 2013). In this study, we consider that a single dose of CYP (200 mg/kg) administration caused acute heart damage according to the results of CK-MB and cTn-I enzymes.

Polysaccharides of GL were used to investigate their potential cardioprotective roles in doxorubicin-induced cardiotoxicity and it's demonstrated that GL polysaccharides prevent cardiomyocyte death and apoptosis, thereby ameliorating cardiotoxicity (Xu et al. 2017). It has been also reported to exert a substantial effect on the cardiovascular system by reducing blood cholesterol, triglyceride level, and blood pressure (Xie et al. 2016). In a study, GL polysaccharides have provided hypotensive, anti-thrombotic, and hyperlipidemic consequences, improved ECG, reduced chest pain and palpitation (Wachtel-Galor et al. 2004). Similiarly, Saltarelli has evaluated that ethanolic extract of GL has antioxidant capacity and protective effects on damaged DNA (Saltarelli et al. 2019). Liu et al. reported GL spores extract could modify

the gut microbiota and regulate the expression of many proteins related to cardiovascular diseases in rats (Liu et al. 2021). Clinical studies show that GL has no toxic effects (Xu et al. 2017; Liu et al. 2021). The parameters we investigated are biomarkers that alter in the development of cardiotoxicity in the heart. Similar results were obtained in the GL group compared to the control group for all parameters researched in this study. The aim of our study is not only to reveal the cardioprotective effect of GL alone, but to highlight its potential activity as an adjunctive agent to alleviate the edema-like side effect caused by chemotherapy drugs. It has been reported that the combined usage of GL with chemotherapeutic agents may be a useful strategy (Cizmorikowa 2017).

cTn-I, which is a specific marker of myocardial cell damage and chemotherapy-related cardiotoxicity, should be included in the assessment of cardioprotective properties of new drugs (Hasić et al. 2007). Many studies have expressed that CK-MB acts as the diagnostic marker of myocardial injuries (Yıldız et al. 2018). In a study researching the protective activity of GL against doxorubicin-induced cardiotoxicity, oral administration of three different doses of GL extract (500 mg/kg and 1000 mg/kg) 1 h prior to doxorubicin administration considerably reduced the activity of CK-MB (Ahmad 2018). In an experimental study on rats, increased CK-MB, myocardial dysfunction, and oxidative stress were observed in the cardiac tissues of rats to which a high dose of CYP (200 mg/kg) was administered (Asiri 2010). The analysis of the biochemical data in the present study demonstrated significant increase in the cTn-I and CK-MB levels after 200 mg/kg CYP administration. The detection of statistically significant increase in the cTn-I and CK-MB levels in CYP + GL group in comparison with the CYP group we concluded that GL may exhibit cardioprotective properties.

AQP channels provide 1/3 of the total water transport in cardiomyocytes. However, in pathological cases, water transport is mostly performed by AQPs (Rutkovskiy et al. 2013). AQPs play a crucial role in physiology and pathophysiology of body water balance (Verkman 2005; Zhang et al. 2013). AQPs facilitate the movement of water by increasing membrane permeability, increasing water flux in response to osmotic gradients. Maintenance of a normal osmotic environment in the heart involves water and solute movements among cellular, interstitial and vessel compartments. This is mostly affected by changes in blood osmolality under normal conditions, whereas dysfunction of myocardial cell solute transporters and increased capillary leakiness contribute to myocardial edema under pathological conditions. Myocardial edema impairs the contractile function of the heart and is a major contributor to the morbidity and mortality associated with myocardial ischemia and cardiac surgery. Cardiac dysfunction associated with myocardial edema is the principal determinant of clinical outcome (Day et al. 2014; Egan et al. 2006).

The fact that CYP causes myocardial edema in many areas of the heart and that AQP channels have important roles for physiological balance of water and glycerol, reveals the importance of this study. Whether AQPs are essential for (electro) physiological cardiac function has not been fully elucidated yet. Cardiac AQP expressions depend on various factors such as sex, development, and aging. The present study investigated the levels of AQP's sub-types' expressions in rat hearts. It also researched whether GL administered after CYP treatment affected the development of myocardial edema. Previous studies have shown that AQP-4 plays an important role in the development of cerebral edema caused by cytotoxic and vasogenic mechanisms in the brain (Butler et al. 2006). In similar, alterations in the expression profiles of other aquaporin channels, including AQP-4, were examined in the heart in this study.

Motawi et al. carried a research on rats and reported that focal hemorrhage between myocardial bundles and hyalinization of the myocardium with CYP in dose of 200 mg/kg (Motawi et al. 2010). In this research, cardiac tissue histomorphology performed with light microscope and it's revealed that cellular edema, inflammation, significant histological alterations characterized by myofibrillar hypertrophy. The CYP-caused damage was observed in the electrophysiological and biochemical composition. The related literature substantiates these findings. Histopathologic cardiac alterations caused by CYP were found to have a mitigating effect by GL, and a mild damage was detected in the histological structure of cardiac tissue. It's evidenced that GL has a protective activity against CYP-induced cardiotoxicity. However, to the best our knowledge, there was no study examining the changes in gene expression levels of AQP channels related with CYP-induced cardiotoxicity.

It has been reported that the abundance of AQP-1 protein in cardiac tissue reflects the increased numbers of microvasculature in response to hypoxia and might contribute to the interstitial fluid accumulation (Borok and Verkman 2002). However, in our study, we found that AQP-1 expression was not sufficiently upregulated compared to the control group after CYP treatment. Functional studies demonstrate that AQP-1 facilitates water transport in vitro but that osmotic stress does not involve the regulation of cardiac AQP-1 transcript or protein (Butler et al. 2006). In another study, myocardial AQP-1 expression was upregulated in a sheep with chronic anemia in response to a greater interstitial fluid flux (Jonker et al. 2003). AQP-1, -4, and − 7 have been reported to localize in capillary, endothelium, and endocardium. In rats, AQP-1 has been found in isolated atrial and ventricular myocyte membrane, primary cultures of atrial myocytes, and in situ myocytes of frozen atrial and ventricular tissues (Egan et al. 2008).

More advanced studies may clearly reveal AQP-3's role in the heart (Huber et al. 2012). Although AQP-3 is a water

channel, it has been associated with many pathological conditions. Since AQP-3 carries H_2O_2 in addition to water, it may participate in cellular activities including inflammation and cell proliferation. This can lead to cell apoptosis. Since AQP-4 has been shown to play a major role in the development and resolution of cerebral edema caused by cellular and vasogenic mechanisms, AQPs are thought to be involved in clinically relevant cardiac edema (Xiao et al. 2004). In another study, AQPs have shown to be upregulated after myocardial ischemia. AQP-4 is specifically stated to have a pivotal role in the development of cellular edema and myocardial water homeostasis (Papadopoulos and Verkman 2007). AQP-7 has been reported to serve as a glycerol facilitator in cardiomyocytes and glycerol is a substrate for cardiac energy production (Hibuse et al. 2009). Moreover, AQP-3, -7, -9 have been reported to be associated with blood pressure and hypertension (Yadav et al. 2020). Especially AQP-7, a member of the aquaglyceroporin subfamily, has been reported to play a crucial part in cardiac energy balance by facilitating glycerol transport in the heart (Benga 2009). After the administration of toxic doses of CYP to rats in the present study, a statistically significant increase was observed in the expressions of AQP − 3, -4, and − 7, while a significant decrease was detected after the GL administration. Similarly, in a study that performed a mice cardiomyopathy model, it was suggested that oil extracted from GL spores showed cardioprotective properties by reducing the expression levels of the genes containing circ-Foxo3 related to heart failure (Xie et al. 2016).

Limitations

The present study revealed the potential protective effects of ethanol extract of GL in CYP-induced cardiac injury model. On the other hand, more comprehensive research should be established to reveal the scope of the potential protective effects of GL. Elucidation of the mechanism and pharmacokinetics of the active ingredients in GL is essential for their widespread clinical applications. In addition, further researchs should be carried by increasing the scale on dosage to ensure its effectiveness in *in vitro* and *in vivo* conditions. We think that the examination of antioxidant parameters may be useful to reveal cardioprotective effects of GL. However, due to the financial limitations, these predicted parameters could not be considered.

Conclusions

In this study it's revealed that CYP-induced cardiac tissue damage may be decreased with GL which has an antioxidant, anti-inflammatory and antitumor properties moreover, it is essential in monitoring the side effects of chemotheraphy. GL may be considered as an adjuvant agent in development of novel pharmacological formulations. We conclude that perceiving the molecular mechanisms of AQPs may contribute to clinical applications in the diagnosis, prognosis and treatment of many pathological conditions.

Abbreviations CYP, Cyclophosphamide; GL, *Ganoderma lucidum*; AQP, Aquaporin; cTn-I, Cardiac troponin- ; CK-MB, Creatine kinase isoenzyme-MB; GPs, *Ganoderma lucidum* polysaccharides; ECG, Electrocardiography; QT, Distance between the Q and T waves on ECG; RR, distance between two R waves; QTcB, QT correction according to Bazzett's formula; QTcF, QT correction according to Fridericia formula; RT-PCR, Reverse transcription polymerase chain reaction; cDNA, complementary DNA

Author contributions OO, OC and BB designed the research plan. The experimental process was carried out by OC. Western Blot, gene expression, Elisa tests performed by OO and OC. Histopathological examinations were evaluated by BB. The results of the study were evaluated and written by all researchers. Thank you for the GL extraction performed by Ass.Prof.Dr.Neslihan Demir.

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Declarations

Ethical approval The experiment was approved by the Local Ethics Committee of Animal Experiments at Çanakkale Onsekiz Mart University (Protocol number: 2019/08 − 02). All the procedures performed in this study were carried in accordance with the 1964 Helsinki Declaration standards.

Conflict of interest The authors declared no conflicts of interest.

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