La adriamicina sensibilizada con quercetina en el tratamiento de la leucemia aguda resistente y resistente al tratamiento

Quercetin Sensitized Adriamycin in the Treatment of Refractory and Resistant Acute Leukemia

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Resumen
Este artículo explora el efecto terapéutico y el mecanismo de la adriamicina sensibilizada con quercetina en el tratamiento de la leucemia aguda resistente y refractaria. Los experimentos in vivo mostraron que el tiempo de supervivencia de los ratones con leucemia T-ALL, mientras que el de los ratones con leucemia T-ALL no irradiada tratados con dosis altas de adriamicina combinada con quercetina fue significativamente prolongado (P <0.05). En comparación con el grupo de adriamicina, la actividad SOD de la adriamicina combinada con el grupo de quercetina aumentó significativamente. Los resultados de la secuenciación del transcriptoma mostraron que la expresión de ighv1-84 e igkv6-14 en adriamicina combinada con el grupo de quercetina y el grupo de quercetina fue menor que la del grupo de adriamicina. En comparación con el grupo de quercetina, la expresión de ms4a1, podx1, MECom, sh3bgr12, bx64 y tdrp en adriamicina combinada con el grupo de quercetina y el grupo de adriamicina fue mayor, pero crabp1 fue menor. Conclusión: la quercetina puede inhibir la proliferación de células leucémicas primarias de manera dependiente del tiempo, la quercetina combinada con adriamicina puede inhibir la proliferación de células leucémicas primarias de manera sinérgica y aditiva, y su efecto inhibidor depende de la concentración y del tiempo. La quercetina combinada con dosis altas de adriamicina puede prolongar significativamente el período de supervivencia de los ratones con leucemia T-ALL no irradiada y reducir el daño de la adriamicina al miocardio.

Palabras clave: leucemia refractaria y resistente; Quercetina; Adriamicina; Leucemia aguda de células

Abstract
This paper explores the therapeutic effect and mechanism of quercetin sensitized adriamycin in the treatment of refractory and resistant acute leukemia. In vivo experiments showed that the survival time of non irradiated T-ALL leukemia mice treated by low-dose adriamycin combined with quercetin was not significantly prolonged, while that of non irradiated T-ALL leukemia mice treated by high-dose adriamycin combined with quercetin was significantly prolonged (P < 0.05). Compared with adriamycin group, the SOD activity of adriamycin combined with quercetin group was significantly increased and MDA content was decreased. The results of transcriptome sequencing showed that the expression of ighv1-84 and igkv6-14 in adriamycin combined with quercetin group and quercetin group was lower than that in adriamycin group. Compared with quercetin group, the expression of ms4a1, podx1, MECom, sh3bgr12, bx64 and tdrp in adriamycin combined with quercetin group and adriamycin group was higher, but crabp1 was lower. Conclusion: Quercetin can inhibit the proliferation of primary leukemic cells in a time-dependent manner, quercetin combined with adriamycin can inhibit the proliferation of primary leukemic cells in a synergistic and additive manner, and its inhibitory effect is concentration and time-dependent. Quercetin combined with high-dose adriamycin can significantly prolong the survival period of non irradiated T-ALL leukemia mice and reduce the damage of adriamycin to the myocardium.

Key words: Refractory and resistant leukemia; Quercetin; Adriamycin; Acute T-cell leukemia

1. Introduction

Acute leukemia (AL) is a malignant clonal disease of hematopoietic stem cells. According to the type of cells involved, it can be generally divided into two categories: acute myeloid leukemia and acute lymphoid leukemia [1]. Clinical diagnosis and treatment developed from single chemotherapy to molecular targeted therapy, hematopoietic stem cell transplantation, cellular immunotherapy and so on. Although great achievements have been made in the treatment of acute leukemia, a considerable number of patients still have multiple unresponsive chemotherapy or early relapse, which is rooted in the drug resistance of chemotherapy, the minor residual disease after remission and the persistence of leukemia stem cells [2-4]. Because of the
limitation of bone marrow donor, high cost of transplantation and serious complications, chemotherapy is still the main treatment for acute leukemia. Anthracycline is one of the most commonly used chemotherapy drugs, which plays an important role in the treatment of acute leukemia. It can kill leukemia cells by inhibiting DNA transcription and replication, RNA synthesis and destroying DNA and protein structure. The dose of anthracycline has a positive correlation with the anti leukemia effect, but with the increase of drug dose, the side effects also increase. The drug resistance reaction of acute leukemia cells to anthracycline drugs also weakened the therapeutic effect of these drugs on acute leukemia [5,6]. It is one of the important ways to improve the prognosis and long-term survival of patients with acute leukemia if we can find the effective way to reverse the drug resistance to anthracycline and reduce the side effects of anthracycline. It has been reported that quercetin has antitumor activity on a variety of tumor cells, including leukemia cells [7-11]. Quercetin has diverse antitumor mechanisms. In addition to its antitumor effect, quercetin can also enhance the chemosensitivity of adriamycin, which can be used in the combined treatment of malignant hematopathy.

2. Materials and methods

2.1 Case data

The refractory drug-resistant acute leukemia (non-APL) patients hospitalized in the Department of Hematology, Affiliated Hospital of Inner Mongolia Medical University from November 2016 to December 2018 were screened according to the following criteria. All patients were ethically reviewed by the Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University. Informed consent of patients: 1 initial treatment of 2 courses of induction chemotherapy ineffective; 2CR16-12 months after recurrence, no treatment for standard chemotherapy regimen; 3≥2 recurrence. Any one of the above three conditions is judged as a case of refractory drug-resistant acute leukemia. Peripheral blood of patients with refractory drug-resistant acute leukemia (non-APL) was collected from a vacuum heparin sodium blood collection tube (5 ml green cap tube).

2.2 Reagents and instruments

Human lymphocyte separation fluid is the product of Tianjin Haoyang company; adriamycin is the product of pirarubicin hydrochloride for injection produced by Shenzhen Wanle Pharmaceutical Co., Ltd., 10 mg / bottle; quercetin is the product of sigma company in Germany; CCK8 is the product of dojindo company in Japan; RNasy mini kit is the product of Qiagen company in Germany; RLT lysate is the product of stemcell company in the United States; Improm IITM reverse transcription is the product of Promega products, SOD and MDA test kits were purchased from Nanjing Jiancheng company. The super clean bench is the product of thermo company in the United States; the carbon dioxide incubator is the product of binder company in Germany; the enzyme labeling instrument is the product of BioTek company in the United States; the desktop centrifuge is the product of Heraeus fresco17 centrifuge company in the United States and centrifuge5810r company in Eppendorf company in Germany; the 7500 real-time PCR instrument and 2720 thermal cycler PCR instrument of ABI company in the United States; the inverted fluorescence microscope is the product of Nikon company in Japan Product.

2.3 Experimental grouping and cell culture

2.3.1 Cell collection and drug concentration determination

The mononuclear cells in the peripheral blood of each patient were separated with Ficoll lymphocyte separation solution, and the cell density was adjusted. 100 μ L cell solution (containing cells (1-1.5) × 104 / cell) was placed in 96 well culture plate. The drug concentrations of adriamycin and quercetin were determined as 6 μ g / ml and 0.5mmol/l by pre-test.

2.3.2 Cell experimental grouping and culture

The concentration of adriamycin was 6, 0.6, 0.06 μ g / ml, quercetin was 0.5mmol/l, 0.25mmol/l. The negative control group (CON) and 7 experimental groups were set up in the experiment: the concentration of 6, 0.6 and 0.06 μ g / ml adriamycin, 0.5mmol/l quercetin, 3, 0.3 and 0.03 μ g / ml adriamycin were combined with 0.25mmol/l quercetin respectively, and the corresponding 7 experimental groups were treated with 7 drug concentrations respectively, each concentration was set with 6 multiple holes, and cultured in a incubator at 37 °C, 5% CO2 and saturated humidity.

2.3.3 CCK8 detection of cell proliferation activity

The 96 well plates were inoculated with cell suspension (200 μ L / well), and three cell culture plates were laid. Place the culture plate in the incubator for pre culture (at 37 °C, 5% CO2). Take out one culture plate and add 20 μ l CCK-8 solution to each hole of the plate at 24, 48 and 72 hours respectively (pay attention not to generate bubbles in the hole, they will affect the reading of OD value). Continue to incubate the culture plate in...
the incubator for 4H. The absorbance at 450 nm of the cells was determined by enzyme labeling. Record values and analyze.

2.4 Animal experiments

C57BL6 mouse female, 6-8 weeks old, purchased from Beijing Academy of military medicine, animal quality certificate No.: scxk - (military) 2012-0004. It is raised in the experimental animal center of Inner Mongolia Medical University without restriction of diet. The feeding conditions meet the requirements of SPF mice feeding. The certificate number of experimental animal feeding facilities is syxk (Mongolia) 2014-004. The process of animal experiment meets the requirements of the ethics committee of Inner Mongolia Medical University on animal experiment. C57BL6 mice were used to construct non irradiated T-ALL leukemia model, and the effects of high dose and low dose adriamycin combined with quercetin on leukemia mice were detected. Two experiments were randomly divided.

3. Results

3.1 Determination of drug concentration

In order to determine the concentration of the drug, the primary leukemic cells in human peripheral blood were isolated and treated with different concentrations of doxorubicin or quercetin respectively to detect their inhibition on the proliferation of leukemic cells. The results showed that the inhibition rate of doxorubicin on leukemic cells was close to 50% at the concentration of 6 μ g / ml (Figure 1a), so this concentration was selected as the experimental concentration of doxorubicin. When quercetin is 0.25mmol/l and 0.5mmol/l, there is no significant difference in the effect of quercetin on leukemic cell proliferation compared with the control group (Fig. 1b), and quercetin has a deep color background. In order not to affect the test results, 0.25mmol/l is selected as the experimental concentration of quercetin.

Figure 1. Determination of drug concentration. A: cells were treated with adriamycin of different concentration, and cell viability was detected by CCK8 after 72 h culture. B: cells were treated with quercetin of different concentrations. Cell viability was detected by CCK8 after 72 h culture. Control was a culture base control group.

3.2 Effect of adriamycin, quercetin and their combination on primary leukemia cells

The peripheral blood of patients was collected for cell experiment in vitro. The results showed that at three different time points (24, 48 and 72 h), different adriamycin concentration groups (6, 0.6 and 0.06 μ g / ml) and adriamycin half dose groups (3, 0.3 and 0.03 μ g / ml) + quercetin concentration group (0.25 mmol / L). After the rank sum test of several groups of independent samples, the comparison between the two groups showed that after α = 0.05/21 = 0.0024 was corrected, there was no statistical significance (P > 0.0024) (Figure 2) in the overall difference of the inhibition rate of proliferation of primary leukemic cells in each drug concentration group; the comparison between the groups of the inhibition rate of proliferation of primary leukemic cells in each drug concentration group showed that the overall difference was statistically significant (P < 0.0024), and the inhibition rate of proliferation of primary leukemic cells was also statistically significant (P < 0.0024) The inhibition of proliferation was concentration and time dependent ($r_{24h}$, $a = 0.995, r_{48h}$, $b = 1.000, r_{72h}$, $c = 0.960$) (Fig. 2).

According to the rank sum test of several groups of independent samples, at 24, 48 and 72 hours, there was a significant difference in the inhibition rate of proliferation of primary leukemic cells among 7 different drug concentrations (adriamycin concentration a, C, E; half dose adriamycin combined with quercetin concentration B, D, f; quercetin concentration g) ($\chi^2 = 117.898, P = 0.000; \chi^2 = 122.792, P = 0.000; \chi^2 = 115.131, P = 0.000$). After the comparison of the two groups, $\alpha = 0.05 / 21 = 0.0024$ (the measurement data that meet the
normality shall be described by means of mean ± standard deviation (d), and the data that do not meet the normality shall be described by means of median (interquartile spacing). In vitro primary leukemia cell drug sensitivity experiment, the comparison of multiple groups of mean shall be described by means of multiple groups of independent sample rank sum test, and the comparison of the two groups shall be conducted by means of two groups of independent sample rank sum test according to the ratio of two Correction of comparison times a (a \textasciitilde= a / comparison times). The statistical significance level was set as bilateral P < 0.05. Among them, 21 contrast times, 0.05 initial p value, 0.0024 is the corrected value calculated, at this time P should be \leq 0.0024. The results showed that the inhibition rates of group A and group B were higher than those of group C, D, e, F and G, the difference was statistically significant (P < 0.0024); the inhibition rates of group C and group D were higher than those of group E and group F, the difference was statistically significant (P < 0.0024); the inhibition rates of group G were higher than those of group E and group F, the difference was statistically significant (P < 0.0024) There was statistical significance (P < 0.0024). The inhibition rate of proliferation of primary leukemia cells was concentration dependent on adriamycin and combination of adriamycin and quercetin (f_{24. a/c}=0.995, f_{48. a/c}=1.000, f_{72. a/c}=0.984, f_{34. b/d}=0.993, f_{48. b/d}=0.999, f_{72. b/d}=0.960).

3.3 Inhibitory effect of half dose adriamycin combined with quercetin and adriamycin on proliferation of primary leukemia cells

According to the rank sum test of several groups of independent samples, a, C, e, B, D; f,g had statistical significance on the overall difference of the inhibition rate of primary leukemia cell proliferation at 24, 48, 72 hours at three different time points (P = 0.000). After comparing the two groups, the inhibition rate of proliferation of primary leukemia cell proliferation at 48 hours was higher than that at 24 hours after adjusting α \textasciitilde= 0.05/3 = 0.017, and the difference was statistically significant (P < 0.017); The inhibition rates of adriamycin, quercetin and adriamycin combined with quercetin were time-dependent (RA = 0.999, RB = 0.996, RC = 0.999, RD = 1.000, re = 0.994, RF = 1.000).

There was no statistical significance (z = -2.746, P = 0.005; Z = -2.462, P = 0.013; Z = -0.947, P = 0.335; Z = -2.707, P = 0.006; Z = -0.474, P = 0.64; Z = -0.162, P = 0.883; Z = -2.95, P = 0.95, P = 0.95, P = 0.95, P = 0.95, P = 0.95; Z = -0.0.95; Z = -0.0.95; Z = 0.162, P = 0.883; Z = -2.883; Z = -2.95, P = 0.95, P = 0.95, P = 0.95, P = 0.95; Z = 0.003; Z = -0.961, P = 0.341; Compared with G, a and B, the inhibition rate of proliferation of primary leukemic cells at 24, 48 and 72 hours was statistically significant (z = -2.192, P = 0.008; Z = -1.461, P = 0.0009; Z = -2.233, P = 0.004; Z = -0.365, P = 0.008; Z = -1.583, P = 0.004; Z = -0.934, P = 0.005). The results showed that there was no significant difference between a and B (P > 0.0024), C and D (P > 0.0024), e and f (P > 0.0024), a and G (P > 0.0024), a, and G (P > 0.0024) There was significant difference in the inhibitory effect of B and G on the proliferation of primary leukemia cells (P < 0.0024). Compared with single drug quercetin, doxorubicin and half dose of doxorubicin combined with half dose of quercetin can better inhibit the proliferation of leukemia cells; quercetin can increase the sensitivity of half dose of doxorubicin to inhibit the proliferation of primary leukemia cells; quercetin at a certain concentration can inhibit the proliferation of primary leukemic cells (Fig. 2).

Figure 2. Comparison of proliferation inhibition rates of primary leukemia cells treated with 3 different different drug concentrations for 24, 48 and 72h. The rate of proliferation inhibition was[(negative control group OD value-experimental group OD value)/negative control group OD value×100%]. a compared with b,c compared with d,e compared with f,P>0.0024.a: adriamycin 6μg/ml, b: adriamycin 3μg/ml+quercetin 0.25 mmol/L, c: adriamycin 0.6μg/ml, d: a drixamycin 0.3 μg/ml + quercetin 0.25 mmol/L, e: adriamycin 0.06μg/ml, f: adriamycin0.03μg/ml+quercetin0.25mmol/l, g: quercetin 0.5mmol/L.
3.4 Effect of different dosage on survival period of leukemia mice

In vivo experiments showed that the survival time of low-dose adriamycin combined with quercetin in non-irradiated T-ALL leukemia mice was not significantly prolonged (Table 1), and that of high-dose adriamycin combined with quercetin in non-irradiated T-ALL leukemia mice was significantly prolonged (P < 0.05) (Table 2). The results of survival curve showed that the high-dose adriamycin combined with quercetin group (median survival time 51D) could significantly improve the survival ability of leukemia mice compared with the high-dose adriamycin group (median survival time 14d) and the adriamycin group (median survival time 29d) (Fig. 3), and there were two mice in quercetin combined with high-dose adriamycin that were still free of disease until 6 months after transplantation of leukemia cells. Leukaemia occurs. Low dose adriamycin combined with quercetin group (median survival time 38d) can improve the survival ability of leukemia mice compared with low dose adriamycin group (median survival time 34d) (Figure 4), but the median survival time is the same as quercetin group.

Table 1. Effect of quercetin combined with low dose adriamycin on survival time of leukemia mice (n=7)

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Mean survival time (d)</th>
<th>Median survival time (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td>Physiological saline0.1ml</td>
<td>35.43±4.78</td>
<td>32</td>
</tr>
<tr>
<td>A</td>
<td>1mg/kg</td>
<td>39.29±7.76</td>
<td>34</td>
</tr>
<tr>
<td>Q</td>
<td>50mg/kg</td>
<td>40±6</td>
<td>38</td>
</tr>
<tr>
<td>A+Q</td>
<td>1 mg/kg+50mg/kg</td>
<td>37±2.56</td>
<td>38</td>
</tr>
</tbody>
</table>

Con: control; A: adriamycin alone; Q: quercetin alone; A + Q: combination

Table 2. Effect of quercetin combined with high dose adriamycin on survival time of leukemia mice (n=7)

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg)</th>
<th>Mean survival time (d)</th>
<th>Median survival time (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
<td>Physiological saline0.1ml</td>
<td>28.86±4.81</td>
<td>26</td>
</tr>
<tr>
<td>A</td>
<td>2mg/kg</td>
<td>13.86±1.07</td>
<td>14</td>
</tr>
<tr>
<td>Q</td>
<td>50mg/kg</td>
<td>31.29±5.02</td>
<td>29</td>
</tr>
<tr>
<td>A+Q</td>
<td>2 mg/kg+50mg/kg</td>
<td>85.00±65.06</td>
<td>51</td>
</tr>
</tbody>
</table>

P < 0.05, compared with any other group. Con: control; A: adriamycin alone; Q: quercetin alone; A + Q: combination

Figure 3. Survival curve of T-ALL leukemia mice treated with high dose quercetin combined with adriamycin. Con: Control, A: adriamycin alone; Q: quercetin alone; A + Q: combination. The median survival time was 26 days for Con, 14 days for A, 29 days for Q, 51 days for A+Q.

Figure 4. Survival curve of T-ALL leukemia mice treated with low dose quercetin combined with adriamycin. Con: Control, A: adriamycin alone; Q: quercetin alone; A + Q: combination. The median survival time was 32 days for Con, 34 days for A, 38 days for Q, 38 days for A+Q.
3.5 Activity of SOD and MDA in myocardial injury

The activity of SOD and MDA in mouse heart showed that the activity of SOD in adriamycin + quercetin group was higher than that in adriamycin group (P = 0.0129 in low dose group compared with low dose + quercetin group; P = 0.0022 in high dose group compared with high dose + quercetin group); the activity of MDA in adriamycin + quercetin group was lower than that in adriamycin group (P < 0.0001 in low dose group compared with low dose + quercetin group; P < 0.0001 in high dose group). For the high dose + quercetin group, P < 0.001) (Figure 5).

![Figure 5. SOD and MDA activity in the heart of mice.](image)

3.6 Comparison of transcriptome expression in different groups of leukemia cells

The results of transcriptome sequencing showed that the expression of ighv1-84 and igkv6-14 in group A + Q and group Q was lower than that in group A. Ms4a1, podx1, MECom, sh3bgrl2, bex4 and tdrp were highly expressed in group A + Q and group A, while crabp1 was low (Fig. 6).

![Figure 6. Transcriptome sequencing results of leukemic cells in different groups.](image)

4. Discussion

Leukemia is a very malignant disease of hematopoietic system [12,13]. Acute leukemia often develops rapidly and has a high mortality rate. Chemotherapy is still the main treatment for acute leukemia. The dose of anthracycline is positively related to the anti leukemic effect, but with the increase of drug dose, its side effects also increase, especially the cumulative effect on the heart; its use will induce acute heart failure, congestive
cardiomyopathy and concealed ventricular dysfunction [14,15]. The drug resistance of acute leukemia cells to anthracycline drugs also weakens the efficacy of these drugs in the treatment of acute leukemia. It is reported that quercetin has antitumor activity on a variety of different tumor cells, including leukemia cells, lymphoma cells, colon cancer cells, ovarian cancer cells, cervical cancer cells, prostate cancer cells and breast cancer cells [16,17]. In our previous study, we found that quercetin can inhibit the proliferation of P388 leukemic cells, which is time-dependent.

Traditionally, the mechanism of reversing drug resistance of tumor cells is mainly based on the experiments of drug-resistant tumor cell lines constructed in vitro, which has great limitations. The main research object of this kind of research is that the leukemia drug-resistant cell line deviates from the clinic, which can not effectively simulate the clinical state of the body, and is not conducive to reveal the nature of drug resistance of the actual clinical refractory tumor cells. Therefore, it is impossible to provide guidance for clinical reversal of drug resistance of leukemic cells and individualized treatment of leukemic patients. Therefore, in this study, peripheral blood leukemic cells from patients with clinically refractory and drug-resistant acute leukemia were used to study the effect of quercetin on adriamycin sensitization in vitro, and the experimental results are closer to the clinical results. The results of this study showed that quercetin, adriamycin, quercetin combined with adriamycin can inhibit the proliferation of primary leukemia cells in a concentration and time-dependent manner, and the inhibitory effect of high-dose adriamycin on leukemia cells was significantly higher than that of quercetin, but there was no significant difference compared with that of half dose adriamycin combined with quercetin The results show that quercetin can effectively enhance the efficiency of half dose adriamycin in inhibiting the proliferation of leukemic cells, and has synergistic and additive effects on the proliferation of primary leukemic cells, and the effect of quercetin on cell proliferation is concentration and time-dependent.

The animal experiments of tumor inhibition in vitro are mainly carried out by immunodeficient mice or mice whose immune system is destroyed by irradiation. However, these two models have great limitations, excluding the influence of the immune system will not be able to simulate the normal state of the body, the experimental results deviate from the clinical. The inhibition of quercetin combined with adriamycin on leukemic cells was studied in a non irradiated acute T-cell leukemia mouse model. The results showed that quercetin could not effectively prolong the survival time of leukemic mice. Compared with high-dose adriamycin, low-dose adriamycin is more effective in prolonging the survival period of mice with leukemia. This result is contrary to the cell level experiment.

At the same time, quercetin combined with adriamycin inhibition results show that high-dose adriamycin can effectively inhibit leukaemia cells. There are two mice in quercetin combined with high-dose adriamycin until six leukaemia cells are transplanted Months later, there were no symptoms of leukemia. The above results show that high-dose adriamycin alone can effectively inhibit leukemic cells, but at the same time bring serious side effects to leukemic body, quercetin can reduce the side effects caused by adriamycin. Furthermore, the molecular mechanism of quercetin reducing adriamycin toxicity and inhibiting the proliferation of leukemic cells was studied by transcriptome sequencing. It was found that the expression of ighv1-84 and igkv6-14 in group A + Q and group Q was lower than that in group A.

Adriamycin is a broad-spectrum anti-tumor drug used in the treatment of acute and chronic leukemia. The dose is positively related to the anti leukemia effect. However, with the increase of drug dose, the side effects are also increased. Among them, the side effects of myocardial injury are the most serious, and the injury mechanism is still unclear. In our previous study, we found that adriamycin treatment of leukemia cell line P388 transplanted into a + B / C nude mice can indeed cause myocardial damage, but combined with quercetin treatment, quercetin can alleviate adriamycin on myocardial damage. It has been found that myocardial injury is related to oxidative stress. In addition, some studies have also found that myocardial injury may have an important correlation with oxidative stress [18,19]. Sod can eliminate superoxide radicals in biological cells through disproportionation reaction, so as to reduce the damage of free radicals to cells. MDA is one of the products of lipid peroxidation, which can aggravate the damage of cell membrane. However, the above experiments are based on the results of immunodeficient mice, and do not involve the role of the immune system in oxidative stress. It was found that quercetin could increase SOD activity and decrease MDA content in the heart of non irradiated leukemia mice. The results suggest that quercetin can effectively prolong the survival period of leukemic mice and reduce the damage of adriamycin to the myocardium. The mechanism may be to improve the survival ability of leukemic mice by effectively reducing the toxicity of adriamycin to myocardial cells.

5.Conclusion

Quercetin can inhibit and kill acute leukemia cells. High dose of doxorubicin can inhibit and kill leukemic cells more effectively, but the side effects of high dose of doxorubicin alone will severely aggravate the leukopenia.
Reference


