Mekanisme kardioproteksi mangiferin pada tikus yang diinduksi doksorubisin fokus pada regulasi kalsium intraseluler = Cardioprotection mechanism of mangiferin on doxorubicin induced rats focus on intracellular calcium regulation

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Abstrak

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Latar belakang. Doksorubisin dikenal sebagai antikanker yang sangat poten, namun penggunaanya dibatasi oleh toksisitas terhadap berbagai organ vital, salah satunya jantung. Mekanisme molekuler kardiotoksisitas doksorubisin berhubungan dengan produksi radikal bebas berlebih yang menyebabkan penurunan ekspresi gen-gen yang mengkode protein regulator kalsium intrasel
sehingga terjadi gangguan homeostasis kalsium intrasel yang menyebabkan aktivasi jalur apoptosis intrinsik yang dimediasi caspase, terutama caspase-9 dan caspase-12. Stres oksidatif akibat DOX juga menyebabkan peningkatan produksi sitokin proinflamasi yang berperan dalam terjadinya apoptosis. Mangiferin merupakan salah satu kandidat potensial senyawa kardioprotektor untuk terapi
doksorubisin, akan tetapi mekanisme molekulernya belum diketahui dengan pasti. Penelitian ini bertujuan untuk mengetahui apakah mekanisme molekuler mangiferin berhubungan dengan regulasi kalsium intraseluler.
Metode. Penelitian dilakukan terhadap tikus Sprague Dawley jantan yang diinduksi doksorubisin dengan dosis total 15 mg/kg BB. Pemberian mangiferin dilakukan dengan dosis 30 dan 60 mg/kg BB secara oral selama tujuh minggu.
Parameter yang diamati adalah ekspresi protein regulator Ca2+ intrasel yaitu SERCA2a, parameter apoptosis (caspase-12 dan caspase-9), kadar kalsium sitosol
dan mitokondria, serta parameter inflamasi (TNF-).
Hasil. Induksi doksorubisin menyebabkan penurunan ekspresi SERCA2a, disertai peningkatan ekspresi gen pro-apoptosis yakni caspase-12 dan caspase-9 serta
peningkatan derjat inflamasi dan kerusakan jantung. Pemberian mangiferin menyebabkan peningkatan ekspresi SERCA2a, penurunan ekspresi caspase-12 dan caspase-9 serta penurunan derajat inflamasi.
Kesimpulan. Berdasarkan hasil tersebut, dapat disimpulkan bahwa normalisasi homeostasis kadar kalsium intrasel merupakan bagian dari mekanisme kardioproteksi mangiferin.
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ABSTRACT
Background. Doxorubicin is well known as a potent anticancer agent despite its toxicity on various vital organs, especially the heart. The molecular mechanism of
doxorubicin cardiotoxicity revolves around the overproduction of free radicals which cause downregulation of genes encoding calcium regulatory proteins, leading to disturbance of calcium homeostasis and activation of intrinsic apoptotic pathway mediated by caspases, particularly caspase-12 and caspase-9.
Doxorubicin cardiotoxicity is also accompanied by inflammation that is crucial for apoptosis. Mangiferin is currently studied as cardioprotective agents for

doxorubicin therapy. However, its molecular mechanism has yet been revealed. This study was aimed to determine whether cardioprotective effect of mangiferin is caused by its effect on intracellular calcium regulation.
Method. Male Sprague Dawley rats were induced by doxorubicin with a total dose of 15 mg/kg BW. Mangiferin was given orally at the dose of 30 and 60mg/kg BW for seven weeks. The parameters examined were mRNA expressions levels of calcium regulatory gene (SERCA2a), proapoptotic genes (caspase-9 and caspase-12) and proinflammatory cytokine gene (TNF-), as well as mitochondrial and cytosolic calcium levels.
Result. It was found that doxorubicin caused downregulation of SERCA2a expression and increased the expression of both proapoptotic genes. Interestingly, we found that mangiferin could attenuate those things above by increasing SERCA2a expression as well as decreasing caspase-9 and caspase-12 expressions, while ameliorating inflammation.
Conclusion. Based on this finding, we suggest that the cardioprotective effect of mangiferin is at least in part due to the regulation of intracellular calcium homeostasis.;Background. Doxorubicin is well known as a potent anticancer agent despite its toxicity on various vital organs, especially the heart. The molecular mechanism of doxorubicin cardiotoxicity revolves around the overproduction of free radicals which cause downregulation of genes encoding calcium regulatory proteins, leading to disturbance of calcium homeostasis and activation of intrinsic apoptotic pathway mediated by caspases, particularly caspase-12 and caspase-9. Doxorubicin cardiotoxicity is also accompanied by inflammation that is crucial for apoptosis. Mangiferin is currently studied as cardioprotective agents for doxorubicin therapy. However, its molecular mechanism has yet been revealed. This study was aimed to determine whether cardioprotective effect of mangiferin is caused by its effect on intracellular calcium regulation.
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