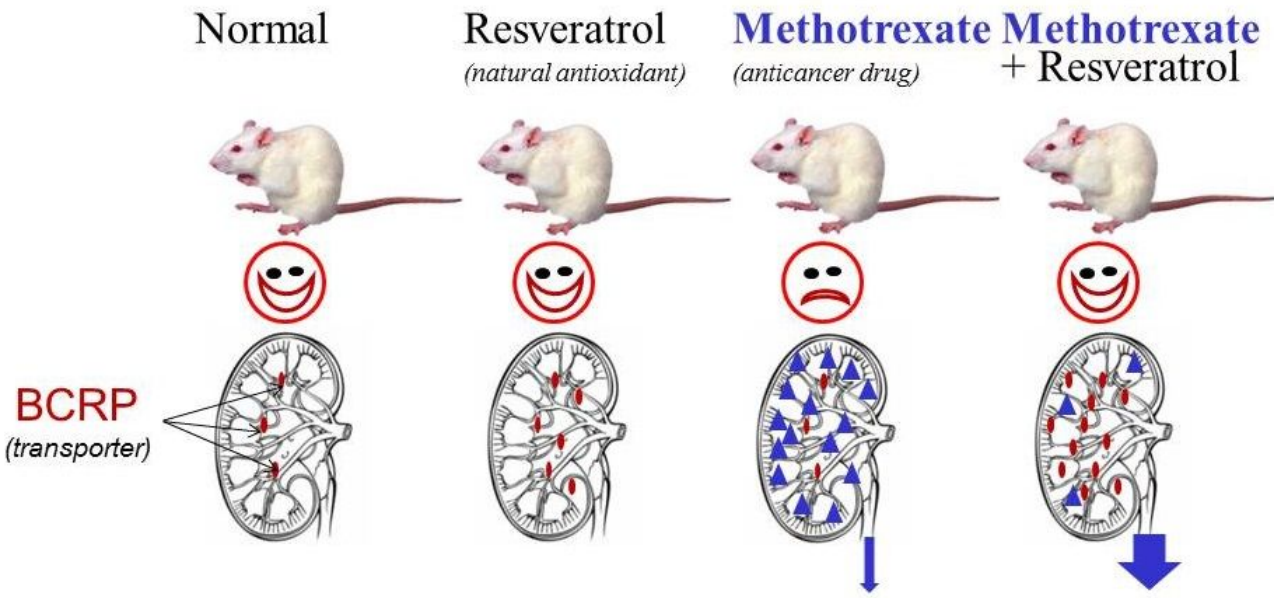
Product of red grapes protects kidney from anticancer toxicity by increasing its extruding protein

Cancer chemotherapy is a double-edged tool. At one side, increasing anticancer dose may cure cancer but can cause severe toxic effects to vital organs. At the other side, decreasing the dose can protect vital organs from the drug side effects, but result in failure of cancer treatment. Methotrexate is one of the well-known anticancer drugs that are also effectively used to treat immune-mediated disorders. Unfortunately, chemotherapy with methotrexate was reported to cause severe damage to the kidneys, which might result in renal failure and death of the patient. Our scientific attention has been drawn to find an adjuvant drug that can protect the kidney from methotrexate-induced damage without decreasing its dose. Resveratrol is a natural antioxidant found in the skin of red grapes, as well as in other plants, produced as a protective defense mechanism against infection. In humans, resveratrol was reported to have a lot of benefits in protecting different organs, in addition to its possible anticancer effect.



Illustrative figure shows four groups of rats receiving different treatments; natural antioxidant of plant origin (resveratrol), the anticancer drug methotrexate, both drugs together and neither of them (normal). The presence of one of the kidney extruding proteins; BCRP, is increased after resveratrol treatment, helping more of methotrexate to get into the urine, and protecting the kidney from methotrexate toxicity.

To study the possible protective effect of resveratrol on the kidney, a rat model of toxicity with methotrexate was used. In a group of rats receiving methotrexate, renal toxicity was confirmed by

kidney function tests and examination of kidney tissue sections under the microscope. Methotrexate toxicity also induced markers of programmed cell death in kidney tissues (apoptosis). In another group of rats, where resveratrol was given with methotrexate, there was much improvement in kidney function tests and microscopic picture, as well as markers of apoptosis, than in rats receiving methotrexate alone. We supposed that the means by which resveratrol protect the kidney might be through increasing the presence of one of the transporter proteins that help in extruding methotrexate from the kidney into the urine.

Breast cancer resistance protein (BCRP) is one of the major kidney transporters that participate in urinary excretion of both methotrexate and resveratrol. The transporter was so named because it was first discovered in human breast cancer cells and acted by extruding the anticancer drugs from these cells, giving them resistance against chemotherapy. By staining kidney tissue sections with antibodies specific to BCRP and calculating the percent of cells having the transporter under microscope, we found that the rats receiving resveratrol alone had more transporters in their kidney than those who did not receive it. Interestingly, rats receiving methotrexate alone did not have higher levels of BCRP in their kidneys, but when methotrexate was given in combination with resveratrol in other rat group; it increased the protein much more, even than if resveratrol was given alone. We also tested the effect of resveratrol on the transport activity of methotrexate, using membranes prepared such that it has the human form of the transporter protein and act functionally similar to it. We found that resveratrol decreased the transport of methotrexate, as expected for two drugs competing to be transported by the same transporter.

However, the transport of both drugs, when given in concentrations similar to that reached in therapeutic situations, did not reach the maximum capacity of BCRP transporter activity. We concluded that resveratrol could protect the kidney from methotrexate toxicity, at least partially, by increasing the presence of BCRP protein that helps in extruding methotrexate in urine. Still, resveratrol might increase methotrexate effect on cancer cells by inhibiting its extrusion through the same protein. We, thus, recommended resveratrol as an adjuvant kidney protector during methotrexate chemotherapy after testing it on humans.

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