Ancient heart drug activates body's own protective mechanisms in blood vessels

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An ancient heart drug that's inspired the work of herbalists and poets for centuries may treat a condition that plagues millions of overstressed and overweight Americans today.

Since the 13th century, the herb Foxglove has been used to cleanse wounds and its dried leaves were brewed by Native Americans to treat leg swelling caused by heart problems.

In an article published online today in *Molecular Pharmacology*, researchers at the University of Michigan Health System reveal that digoxin, the active ingredient in digitalis, or Foxglove, can enhance the body's own protective mechanism against high blood pressure and heart failure.

High blood pressure can be prevented by reducing salt intake, being active and keeping a healthy weight, but about 1 in 3 Americans has high blood pressure, also called hypertension, which can damage the body in many ways.

Most current treatments prevent excess hormone and stress signals that can lead to high blood pressure and heart failure.

But recent studies have found that the body has the ability to keep excess stimulation in check through production of a family of inhibitors called RGS proteins.

Researchers looked for ways to "re-purpose" old drugs to tap into this protective mechanism which is lost among some individuals with high blood pressure and heart failure.

"We tested several thousand known drugs and bioactive molecules for a potential role in enhancing RGS2 and/or RGS4 expression and function and have identified a novel mechanism for digoxin," says lead study author Benita Sjogren, Ph.D., a research fellow in the Department of Pharmacology at the University of Michigan.

Case histories collected by Dr. William Withering in 1775 determined that Foxglove contained the active ingredient, digoxin, now an important drug for treating patients with congestive heart failure.

This new action of digoxin was found by treating engineered human kidney cells with thousands of known drugs in a high-throughput screen at the U-M Center for Chemical Genomics. Digoxin was then shown to have similar actions in isolated mouse blood vessel cells.

"In addition to test tube studies, low dose digoxin, the active ingredient of digitalis, was able to increase RGS2 levels in the heart and kidney," says senior study author and pharmacologist Rick Neubig, M.D., Ph.D., professor of pharmacology, associate professor of internal medicine, and co-director of the Center for Chemical Genomics at the University of Michigan.

"This new action of digoxin could help explain the fact that low doses seem to improve the survival of heart failure patients. It also suggests new uses for low dose digoxin or other drugs that can activate this protective mechanism," he says.

Neubig's lab at the U-M focuses on the large family of RGS proteins and the role they play in the function of the brain, heart, immunity and

cancer and how they can be exploited in therapeutics.

More information: "Cardiotonic steroids stabilize RGS2 protein levels," *Molecular Pharmacology*, published online before print June 13, 2012, doi: 10.1124/mol.112.079293

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