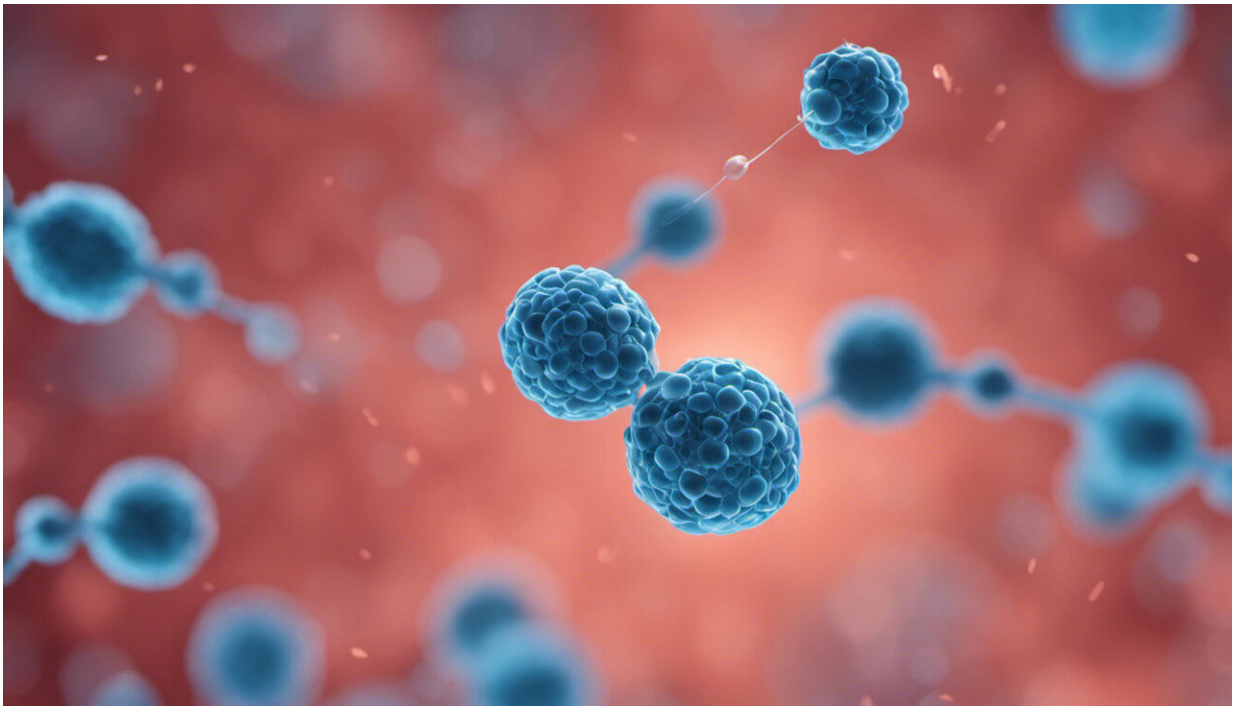
An oral antidiabetic drug shows promise for treating tuberculosis

June 24 2015



Credit: AI-generated image (disclaimer)

The drug metformin, already used in the USA to treat type 2 diabetes, also enhances the body's immune response to tuberculosis, according to A*STAR researchers.

"Metformin is a safe and cheap drug that diabetic patients have been

taking for years and has been shown to have no major adverse effects on non-diabetic individuals," says Amit Singhal, who led the study at the A*STAR Singapore Immunology Network. "Our results suggest that metformin is a leading host-directed therapy candidate that can be combined with current therapeutic and prophylactic treatments to improve tuberculosis control."

Tuberculosis remains one of the most deadly contagious diseases worldwide, infecting an estimated 9 million people in 2013 and killing 1.5 million. It is caused by the bacterium Mycobacterium tuberculosis, which usually attacks the lungs.

Treatments have mainly consisted of antibacterial drugs, but increasing bacterial resistance, even to combinations of up to 18 drugs, has led to a paradigm shift from interventions that directly target the pathogen to strategies that improve the host response. These strategies include therapies such as proper rest and nutrition, which help to reduce inflammation, tissue damage and permanent lung disability—the ultimate cause of death in patients.

In initial cell culture and animal model experiments, the team found that metformin inhibits the growth of Mycobacterium tuberculosis, including multidrug-resistant strains, and enhances the efficacy of conventional anti-tuberculosis drugs such as isoniazid and ethionamide. "This was surprising because metformin has no direct effect on the bacteria per se," says Singhal, who then followed leads in the existing literature linking metformin to the inflammatory response.

He found that mice infected with Mycobacterium tuberculosis and then treated with metformin exhibited less lung tissue damage than untreated controls and had higher levels of immune cells known as T helper cells and cytotoxic T cells. A genome-wide transcriptional analysis further revealed that metformin reduced the expression of genes associated with

inflammation in the mouse lung. Singhal validated these findings with patient data to show that metformin can indeed improve the control and reduce the severity of tuberculosis.

Singhal expects that these results, combined with the verified safety of metformin as a treatment for diabetes, will fast-track its advance to phase II clinical trials and its repurposing for the treatment and prevention of tuberculosis.

"Over 90 per cent of drugs fail during development, leading to high costs of pharmaceutical research and development," says Singhal. "Repurposed drugs can bypass much of the early cost and time needed to bring a drug to market."

More information: "Metformin as adjunct antituberculosis therapy." *Science Translational Medicine* 6, 263ra159 (2014). dx.doi.org/10.1126/scitranslmed.3009885

Provided by Agency for Science, Technology and Research (A*STAR), Singapore