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RESEARCH ARTICLE

Acetate Kinase (AcK) is Essential for Microbial Growth and Betel-derived Compounds Potentially Target AcK, PhoP and MDR Proteins in *M. tuberculosis*, *V. cholerae* and Pathogenic *E. coli*: An *in silico* and *in vitro* Study

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Abstract: ***Background*:** *Mycobacterium tuberculosis*, *Vibrio cholerae*, and pathogenic *Escherichia coli* are global concerns for public health. The emergence of multi-drug resistant (MDR) strains of these pathogens is creating additional challenges in controlling infections caused by these deadly bacteria. Recently, we reported that Acetate kinase (AcK) could be a broad-spectrum novel target in several bacteria including these pathogens.

***Methods*:** Here, using *in silico* and *in vitro* approaches we show that (i) AcK is an essential protein in pathogenic bacteria; (ii) natural compounds Chlorogenic acid and Pinoresinol from *Piper betel* and Piperidine derivative compound 6-oxopiperidine-3-carboxylic acid inhibit the growth of pathogenic *E. coli* and *M. tuberculosis* by targeting AcK with equal or higher efficacy than the currently used antibiotics; (iii) molecular modeling and docking studies show interactions between inhibitors and AcK that correlate with the experimental results; (iv) these compounds are highly effective even on MDR strains of these pathogens; (v) further, the compounds may also target bacterial two-component system proteins that help bacteria in expressing the genes related to drug resistance and virulence; and (vi) finally, all the tested compounds are predicted to have drug-like properties.

***Results and Conclusion*:** Suggesting that, these *Piper betel* derived compounds may be further tested for developing a novel class of broad-spectrum drugs against various common and MDR pathogens.

Keywords: Infectious disease, Multi-drug resistant, Natural compounds, *Piper betel*, Tuberculosis, ACK.

1. INTRODUCTION

M. tuberculosis, pathogenic *E. coli*, and *V. cholerae* are deadly human pathogenic bacteria that cause tuberculosis (TB), food poisoning, and cholera, respectively. Although, several drugs have been introduced to control these pathogens, infections from these bacteria frequently remain uncontrolled and epidemics are reported globally due to emerging multi-drug resistance (MDR) of these pathogens [1-3]. Hence, there is a need to develop promising next-generation drugs that can counter these ever-evolving pathogens.

In our previous reports, we showed that natural compounds from *Piper betel* are effective against these pathogens. Piperdardine inhibited pathogenic *E. coli* O157:H7 growth like ampicillin [4]. Piperdardine at 60 mM concentration exhibited a similar anti-*Vibrio* effect as 100 mg/ml of Chloramphenicol [5]. We also reported that Pinoresinaol, Guineensine, Dehydropipernonaline, Piperrolein-B, Eugenyl acetate and Chlorogenic acid from *Piper betel* may have target specificity in *V. cholerae* [5]. Similarly, Acetate kinase (AcK) could be a common target in *C. pseudotuberculosis*, *Y. pestis*, *M. tuberculosis*, *C. diphtheriae*, *C. ulcerans*, and *E. coli* that may be targeted by *Piper betel* compounds [5].

For the generation of Adenosine triphosphate (ATP) from the excess of acetyl-CoA, the enzymes acetate kinase (AcK) and phosphotransacetylase (PTA) form an important

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