UNIVERSITI TEKNOLOGI MARA

A TRANSCRIPTOMIC APPROACH IN ELUCIDATING *HELICOBACTER PYLORI* PATHOGENESIS AND OCCURRENCE IN HUMAN AND *PERIPLANETA*

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

Helicobacter pylori (*H. pylori*) is a Gram-negative spiral-shaped bacterium that colonises the human stomach. *H. pylori* infection constitutes an established risk factor in the development of gastritis, peptic ulcer, and gastric cancer. One of the most critical cofactors in *H. pylori* infection is the host immune response. However, the underlying mechanism involved remains poorly understood. Furthermore, the exact route of transmission of *H. pylori* is still unclear and not well documented. Contaminated food caused by cockroaches may contribute to the transmission of *H. pylori* infection. Therefore, the objectives of this study are to investigate the pathogenesis of *H. pylori* infection occurring in human and cockroaches, the variation of the virulence factor between strains isolated from human and cockroaches and to elucidate immune response in human gastric cancer (AGS) and mice model. In this study, a total of one hundred gastric biopsies from patients undergoing endoscopy at Universiti Teknologi MARA (UiTM) Sungai Buloh and cockroaches around the eateries area in Sungai Buloh were collected. The bacterial isolates were subjected to bacteria identification and followed by genotyping using polymerase chain reaction (PCR). Differential expression of virulence genes among both this group of strains was investigated by inoculating the isolated strains into AGS cells. The expression was then measured by using quantitative real-time PCR (qRT-PCR). Simultaneously, the expression of host immune response upon infection with different *H. pylori* strains was conducted using RT^2 Profiler PCR array. In the *in vivo* study, mice comprising of six groups, including a control group of uninfected mice were used. The experimental groups were orogastrically infected with different *H. pylori* strains on days 0, 3, and 5, respectively. The mice were euthanised, and stomachs were harvested after post-infection for microbiology, histology, and molecular analysis. The expression of inflammatory cytokines was conducted using quantitative real-time PCR (qRT-PCR). A total of five *H. pylori* isolates (*H. pylori S3, S5, S7, S33, S38*)from gastric biopsies and ten *H. pylori* isolates (*H. pylori C3, C6, C7, C8, C12, C23, C32, C33, C38, C40*) from cockroaches were obtained in study. The *cagA* gene presence in 80% of the isolates. The expression of *sabA*, *babA*, *ureA,* and *flaA* gene was elevated and showed the highest expression in *H. pylori cagA*$^+$ strain after interaction with the host cells. Nine gene encoding toll-like receptors (TLRs) were significantly elevated in *H. pylori*-infected cells, especially the TLR9 gene that showed the highest expression in the infected cells with *H. pylori cagA*$^+$ strain. The regulation of TLRs activates the signalling of NFκβ gene expression. Moreover, *H. pylori*-infected cells regulate strong Th1 and Th17 immune responses. Th cells secrete higher expression of pro-inflammatory cytokines, including IL1β, IL6, IL8, IL12, IL17α, IL18, IL23, and TNFα in the infected cells. Lower expression of the anti-inflammatory cytokine, IL10 in the infected cells downregulates the JAK-STAT signaling pathway. The level of pro-inflammatory cytokines also elevated in the *H. pylori*-infected mice. The comprehensive data on the differentially expressed gene was successfully generated, and the host immune response involved in the diverse clinical outcome of *H. pylori* infection. The comparative study has also revealed that *H. pylori* strains isolated from humans and cockroaches demonstrated a comparable immune response gene expression profiling. This data could provide new insight into the pathogenesis of *H. pylori* infection in humans and establish the potential role of cockroaches in the transmission of *H. pylori* infection.

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