On searching antimicrobial agents among natural products: Fighting against Superbug

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Our research focused on finding natural antibiotic compounds based on traditional medicine formulas by applying various machine learning algorithms. By further investigation if some of our predicted antibiotics can be used in clinical practice it would be of great scientific and social significance.

Antibiotic resistance is a major public health threat and there is an urgent need for new antibiotics. Traditional herbal medicine systems, such as Jamu, Unani, and Traditional Chinese Medicine, have been used for finding new antibiotics by applying machine learning algorithms. In total, we predicted 42 potential plant candidates and 201 candidate metabolites as potential natural antibiotics. We published 4 journal papers (with IF > 4) and two IEEE conference papers using the results of this research. With this KAKENHI money we also conducted some other related researches.

Systems Biology

Natural antibiotics Traditional medicines Machine learning Jamu formulas TCM formulas

様　式　Ｃ－１９、Ｆ－１９－１（共通）

１．研究開始当初の背景

Antimicrobial agents are drugs that can kill microorganisms or stop their growth. The antimicrobials can be grouped into several types depending on the microorganisms they act against, such as Antibacterials, Antifungals, Antivirals, Antiparasitics etc. For example, antibiotics are used against bacteria. Widespread overdose and irresponsible usage of antibiotics in clinical practicees for both human and livestock has resulted in resistance of bacteria to antimicrobial agents. Such multidrug-resistant (MDR) bacteria are recently called as Superbugs. MDR bacteria poses global problems with the threat of the reoccurrence of a situation of the pre-antibiotic era and increased cost of healthcare services, and jeopardizes the healthcare gain achieved by the research of last hundred year. Therefore, presently a key scientific question is to develop new drugs that can combat MDR bacteria or other pathogenic microorganisms. Our project focused on finding new antibiotics by utilizing traditional medicine formulas.

２．研究の目的

Antimicrobials work based on multiple mechanisms mechanism such as by targeting the cell wall of bacteria (e.g.beta-lactam antibiotics), by inhibiting protein biosynthesis(e.g. inhibitors of 30S subunit Aminoglycosides),by hindering DNA replication (e.g. by Quinilones) and by causing disruption in important metabolic pathways (e.g. Folic acid metabolism). Also bacteria develop resistance against drugs using multiple mechanisms. One such mechanism is changing its outer membrane permeability and thus preventing the antimicrobials entering the cell or pumping out antimicrobials from inside the cell. Another mechanism is the modification of target molecules. Generally, Antimicrobial agents interact with target molecule in a quite specific way and therefore, minor alteration of the target molecule can have important effect on antibiotic binding thus making the drug ineffective. Such situation may occur on various locations on various target molecules but gradually depending on the drug used and the functional mechanism of the drug. Yet another resistant mechanism is inactivating an antimicrobial drug by chemically modifying it with some enzyme/s.

Based on the above discussion it can be suggested that to treat infection caused by drug resistant bacteria multiple drugs are necessary such that at least one of them can act with a mechanism against which the target bacteria/microorganisms have not developed resistance. But multiple drugs cause lots of side effects. Traditional medicines are known to have no or less side effects. Therefore, good combination of multiple antibiotic drugs derived from natural products might be a good solution to combat superbugs. The purpose of the research was to find natural antibiotics. The proposed research work searched candidate antimicrobial drugs from among huge number of natural products by employing computational approaches and algorithms involving structural similarity calculations and network of metabolites and formulas of traditional medicines.

３．研究の方法

Chemoinformatics approaches were applied incorporating information regarding natural products together with formulas of traditional medicines. We developed classification models for identifying antibacterial natural compounds using data from KNApSAcK database. Also, we developed models to classify formulas of Jamu, Unani and Traditional Chinese Medicines (TCM). We applied various machine learning algorithms such as Lasso regression, Random Forest and XGBoost, deep learning to Jamu and TCM formulas aiming to finding natural antibiotic plants and compounds. For Jamu, we achieved an accuracy of 91.10% using the Random Forest model. For Unani, we achieved an accuracy of 83% using a multilayer perceptron model with SMOTE preprocessing. For analyzing TCM data, we introduced a novel graph based approach to link TCM syndromes with efficacies of modern medicines.

４．研究成果

Based on our research on the proposed topic, we published following four papers in journals.

Gao, P., Nasution, A. K., Yang, S., Chen, Z., Ono, N., Kanaya, S., & Altaf-Ul-Amin, M. D. (2023). On Finding Natural Antibiotics based on TCM Formulae. Methods. https://doi.org/10.1016/j.ymeth.2023.04.001

Nasution, A. K., Wijaya, S. H., Gao, P., Islam, R. M., Huang, M., Ono, N., ... & Altaf-Ul-Amin, M.

(2022). Prediction of Potential Natural Antibiotics Plants Based on Jamu Formula Using Random Forest Classifier. *Antibiotics*, *11*(9), 1199. https://doi.org/10.3390/antibiotics11091199

Bozlul Karim, M., Kanaya, S., & Altaf-Ul-Amin, M. "Antibacterial Activity Prediction of Plant Secondary Metabolites Based on a Combined Approach of Graph Clustering and Deep Neural Network" (2022). Molecular Informatics. https://doi.org/10.1002/minf.202100247

Wijaya, S. H., Nasution, A. K., Batubara, I., Gao, P., Huang, M., Ono, N., ... & Altaf-Ul-Amin, M. (2023). Deep Learning Approach for Predicting the Therapeutic Usages of Unani Formulas towards Finding Essential Compounds. *Life*, *13*(2), 439. https://doi.org/10.3390/life13020439

Also, we published the following two conference papers:

Nasution, Ahmad Kamal, Sony Hartono Wijaya, Ming Huang, Naoaki Ono, Shigehiko Kanaya, and Md Altaf Ul-Amin. "Prediction of Potential Natural Antibiotics based on Jamu Formula Using Machine Learning Approach." In *2022 IEEE 22nd International Conference on Bioinformatics and Bioengineering (BIBE)*, pp. 204-209. IEEE, 2022.

Nasution, Ahmad Kamal, Naoaki Ono, Shigehiko Kanaya, and Md Altaf Ul-Amin. "Investigating Potential Natural Antibiotics Plants Based on Unani Formula Using Supervised Network Analysis and Machine Learning Approach." In *2023 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, pp. 3111-3117. IEEE, 2023.

In total, we predicted 42 potential plant candidates and 201 candidate metabolites as potential natural antibiotics. Many of these candidates have been validated based on published literature mentioning their antibacterial properties. Some others are structurally similar to known antibiotics. Our findings suggest that machine learning methods can be used to effectively predict potential natural antibiotic candidates utilizing traditional herbal medicines. This approach has the potential to accelerate the development of new antibiotics to combat antibiotic-resistant pathogens.

By further investigation if some of our predicted antibiotics can be used in clinical practice it would be of great scientific and social significance.

With this KAKENHI money we also conducted some other related researches.

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On Finding Natural Antibiotics based on TCM Formulae	2023
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