The discovery of MicroRNA-Phytochemicals Interaction of diseases caused by viruses using ensemble data mining techniques

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***Abstract*—Currently, viral infection diseases cause high mortality rates all over the world such as Ebola, HIV, H5N1, and COVID-19. Nowadays, gene-based therapeutic or personalized medicines are considered in clinical decisions for treating patients. Furthermore, medicines from natural sources such as plant-derived medicine or herbs are wildly used because of easy accessibility, lessor side effects, safer and cheaper. Therefore, this study aims to identify 1) microRNA-target gene interaction of the genes that involve in anti-virus infection by applying various individual classification techniques and the ensemble technique and 2) the combination of phytochemicals compounds that possibly be potential drugs to treat specific biological pathways related to viral infection using clustering technique named MCODE. Our outcome of the present work is to contribute to the discovery of genetic-based therapy and to identify the phytochemical compounds for increasing the efficacy of the treatment of diseases caused by viruses with minor side effects.**

Keywords—Ebola, HIV, H5N1, microRNA-gene prediction, SVM, Neuron Network, Decision Tree, Ensemble, MCODE, Phytochemicals

I. INTRODUCTION

Viruses cause worldwide infectious diseases morbidity and mortality [1]. The yellow fever virus is the first virus discovered in 1901, Its mutated offspring are found till now [2]. The virus species are divided into many groups based on different classifiers such as nucleic acid structure, symmetry types (helical or icosahedral), and lipid envelope [1]. Among all human pathogens, viruses are found 66%, the rest are bacteria, fungi or helminths [2].

Ebola is a threatening, rare but severe virus when it spreads into the human body causing bleeding inside and outside, destroy the immune system and finally destroy organs. The fruit bats spread the Ebola virus during relocation. Humans are infected through direct contact with blood, secretions, organs or other body fluids of infected persons, dealing with dead bodies or direct patient care, contacting sick animals or infected bats [3].

HIV is a no cure virus infection majoring global public health issue. It destroys the immune functions that can be measured by CD4 cell count. HIV transmission is mainly exchanging of body fluids such as blood, breast milk, and semen from infected people to others [4]. The resistance function in the human body to HIV is rare and varies between individuals. It is reported that some gene mutations affect failing to HIV-1 infection such as HLA, CCR5, and CCL3L1 [4].

H5N1 is an influenza virus causing a potential pandemic threat that destroys the respiratory system in hosts [5]. It can be transmitted from infected poultry to humans and also from the human to human [6].

Virus-human interactions are discovered for long time as the viruses can encode proteins that interfere the immune system which produce variety of responses to viral infection in human body [7]. Various human genes are reported involving in virus-human interaction, IFITM3 associates in anti-viral restriction factor when human is attacked by severe influenza virus [8]–[10]. Besides, it is reported that IRF7 gene acts as transcription factor gene against influenza virus [11], and CPTII and SFPA/B associate in cell homeostasis when human fights to influenza virus [12]–[16].

For HIV disease, TRIM5A, APOBEC3G, and IFITM3 are essential genes discovered as the significant proteins that accelerate disease progression [17], [18], HLAB57 lowers the viral load and slow down T-cell decline [19], [20]. Furthermore, for the Ebola disease, IL10, IL1B involve in resistance processes against the Ebola infection [21]–[23].

MicroRNA regulates gene expression by binding to its target mRNAs then repress protein production [24]. Studies have reported how microRNA plays a crucial role in viral infections by inducing gene mutations that associate with the main biological pathways led to an increase in replication of various viruses such as DENV, VSV, influenza A virus in living cells [25]–[27].

In recent years, there are various reports indicate significant natural products or herbs that have high efficacy in anti-viral treatments. Phytochemicals are plant-derived substances that are used as Chinese and Indian traditional medicine since the ancient time [28]. The extract from bloody geranium (Geranium sanguineum L.) and elderberry can reduce the infectivity of influenza [29]–[31]. Moreover, it is found that flavonoid, alkaloid, lignan, coumarin, terpenes, and terpenoid

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extracting from the phytochemicals in the orthomyxoviridae family have anti-virus properties against influenza virus (H3N2, H5N2, H5N1, and H1N1) [28], [32].

Many shreds of evidence reveal plant-derived based compounds involve the expression of microRNA in various types of diseases. Resveratrol extract induces up and down-regulation of the significant group of microRNAs (miR-141, miR-663, miR-200c, miR-17, miR-21, miR-25, miR-92a-2, miR-103-1, and miR-103-2) that involve in invasiveness, EMT, and metastasis [33]–[36]. Furthermore, the extract from curcumin induces up and downregulation of a significant group of microRNAs (miR-15a, miR-16, miR-186, and miR-21) involving apoptosis and metastasis process [37], [38].

This study aims to apply various data mining techniques both classification and clustering models for the discovery of microRNA-phytochemicals relations of the diseases caused by Ebola, HIV, and H5N1virus. Various biological data resources are used in this study. The Decision Tree, SVM, and Neuron Network models are selected classifiers to predict novel microRNAs interacting with significant genes involving in anti-viral biological processes in the human body. Furthermore, we applied a clustering model named the Molecular Complexed Detection (MCODE) to identify the significant protein modules and then merged up with their phytochemical's interactions. It is expected that this study may provide essential preliminary information of the relations of microRNA, Protein-Protein Interaction (PPI), and phytochemicals compounds for further development of plant-derived based drug discovery in diseases caused by viruses like Ebola, H5N1, and HIV.

II. Methodology

A. Research Framework

In this study, we performed two essential parts which are 1) MicroRNA-target prediction by the ensemble classification techniques and 2) Protein module identification by clustering technique named MCODE. Preliminary, the genes involving the viral biological processes in the human body were gathered from the AMIGO2 [39] repository and the confirmed protein-protein interaction pairs were obtained from the BioGrid [40].

The microRNA-target prediction by the ensemble approach: to construct to input data set, the individual protein from the BioGrid protein list was calculated their microRNA biding scores from the three well-known microRNA-target prediction algorithms (TargetScan [41], MiRanda [42], and miRDB [43]). Each microRNA-protein target pair was labelled as a positive set (labelled as TRUE) when it was found in the mirTarbase [44] repository. Then the input dataset was analyzed by the three classification algorithms which are decision tree, SVM, and Neural Network. Lastly, the final decision was obtained from the majority voting among the three classification algorithms.

The protein module identification by clustering algorithm: the protein-protein interaction pairs obtained from the BioGrid was constructed as the input data set of the clustering algorithm. Then, the MCODE [45] approach was adopted to cluster the significant protein modules. Finally, for each significant protein module was analyzed their enriched biological processes and also their interacting phytochemicals.

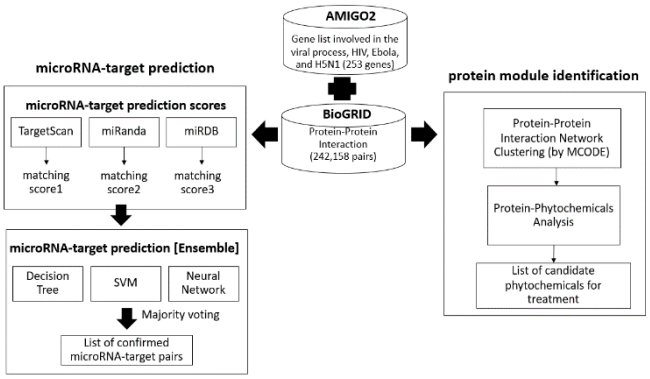

Fig. 1 The research framework

B. Data sources

Initially, a dataset of 293 genes involved in the viral processes in the human body, biological processes related to HIV, Ebola, and H5N1 is extracted from the AmiGo2. A dataset of 242,158 confirmed protein-protein interaction lists is obtained from the BioGRID and it was 32,127 distinct proteins. Next, the two previous data sets were merged up as the list of observed-PPIs to be an initial data set for both the MicroRNA-target prediction and Protein-Protein Interactions clustering.

C. MicroRNA-target Prediction—by the ensamble method

The 32,127 distinct proteins were analyzed as to their microRNA binding partners by the three different tools. Finally, we got three biding scores of 230 microRNA-target biding pairs set as attributes of the data set from TargetScan, miRanda, and miRDB. The positive data set of microRNA-target prediction was labelled referenced by miRTarbase repository. Therefore, the dataset composes of three attributes which are three binding scores and two classes (YES-confirmed binding, NO-not confirmed binding).

The TargetScan, MiRanda, and miRDB were selected to use in this study because they are based on the different microRNA-target binding concepts. It is based on the hypothesis that using different aspects to make a decision, gives higher accuracy and improves the average prediction performance.

TargetScan [41] is an algorithm for predicting microRNA-protein targets by searching for the conserved regions along the gene sequence that match the seed region of each microRNA (8mer, 7mer, and 6mer sites).

MiRanda [42] is an algorithm for finding matching nucleotides along the gene sequence. The score bases on the complementarity of the binding concept (A=U or G≡C) and it allows G=U for wobble pairs.

MiRDB [43] is a service that gives the prediction score by adopting the Support Vector Machine (SVM) to analyze the expression profile data of microRNA and genes.

To perform the ensemble classification, the input data set with class labelling was analyzed by the three different classification algorithms via the RapidMiner software. The Decision tree (DT), Support Vector Machine (SVM), and Neural Network (NN) were finally selected in our ensemble model because they gave the highest accuracy score compare to others. The ten-fold cross-validation is set for each algorithm, each parameter setting of each algorithm as the table I.

After we obtained the results from three classifiers, the ensemble approach was constructed by combining results from three algorithms then make the final decision by the majority voting approach.

TABLE I. PARAMETER SETTING OF CLASSIFIERS

Classifier	*Parameter setting*
DT	criterion = gain ratio, max depth = 20, confidence = 0.25, min gain 0.1, min leaf size = 2, min size of split = 4, number of pre-pruning alternative = 3
SVM	kernel type = dot, kernel catch = 200, C=0.0, convergence epsilon = 0.001, max iteration = 100000
NN	training cycle = 200, learning rate = 0.01, momentum =0.2, error epsilon = 1.0E-5

D. Protein-Protein Interactions Clustering—by MCODE

The significant protein modules were analyzed by a clustering algorithm named Molecular Complex Detection (MCODE) [45]. The observed PPIs data set was submitted to the MCODE to identify the significant protein modules. Subsequently, each protein module was analyzed on its enriched biological processes by the biological enrichment analysis on the STRING [46] database.

E. Protein-Phytochemicals Interaction Analysis

We obtained the list of phytochemical compounds extracting from natural sources from the literature search. There are 42 compounds on the list. Then, the compounds were unified under canonical SMILES code referencing by the PubChem database [47]. Then the Swiss Target Prediction tool [48] was adopted to find their target proteins. The protein-phytochemical interactions were analyzed in each protein module to discover the possible target drugs extracted from normal plants, medicinal plants, or fruits.

F. Inquiry Webpages Construction

Finally, the inquiry webpages displaying the research results were set up for investigators to pose queries. The webpages were created by using PHP language and MySQL database.

III. RESULTS

A. MicroRNA-target Prediction

Our evidence indicates that the neuron network algorithm gives the highest accuracy (88.26%), precision (81.73%), and also recall (77.56%) values. The decision tree gives the lowest performance for all measures. The ensemble approach gives the best performance compare to each classifier. The accuracy of the ensemble approach reaches 88.95%, 80.63% for the precision, and 74.87% for the recall measure.

TABLE II. PARAMETER SETTING OF CLASSIFIERS

Algorithm	*Accuracy*	*Precision*	*Recall*
DT	85.63%	79.00%	70.00%
SVM	86.52%	80.00%	72.00%
NN	88.26%	81.73%	77.56%
Ensemble	88.95%	80.63%	74.87%

B. Phytochemical-protein modules with enriched GO and KEGG pathways

Fig.2 depicts the protein module from cluster#1, the proteins are involved in this module associated with the immune response. Our experiment found that there are various phytochemical compounds targeted to proteins of the module. The evidence depicts the tocopherols interacts with GAPDH, phytoestrogen interacts with RPS6KB1, combretastatin interacts with ABL1, Phenethyl Isothiocyanate interacts with STAT6 and silymarin interacts with PPARG.

This evidence may suggest that tocopherols, phytoestrogen, combretastatin, Phenethyl Isothiocyanate, and silymarin which are extracted from different plant sources possibly be a good combination of natural drugs that target the immune response process in the human body when virus infection. Moreover, it is found that some microRNAs target to specific gene (protein) in a module, this finding suggests that these group of micrRNAs may play important role in specific gene expression effecting to the immune response process and also possibly associate with the efficacy of the phytochemicals drug.

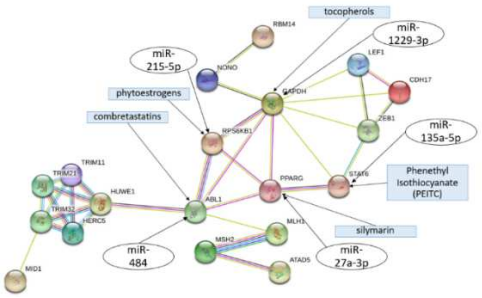

Fig. 2 The protein module involving in the immune response process and its Phytochemicals interaction

Fig. 3 depicts the protein module from cluster#1, the proteins are involved in this module associated in the regulation of apoptotic processes. The findings as fig. 3 indicates that there is various phytochemical compounds target to proteins of the module, CDK5 is targeted by tetrahydrocannabinol, PPARG is targeted by silymarin, TAOK1 is targeted by Alpha carotene, ABL1 is targeted by combretastatins, SMO is targeted by Perillyl Alcohol, GAPDH is targeted by tocopherols, PDPK1 is targeted by gingerol, PRKCQ is targeted by Panax ginseng, and FLT3 is targeted by combretastatins. This evidence suggest that the combination

of these phytochemical compounds possibly be a good combination of drug for targeting on the regulation of apoptotic processes when virus infection. Besides, the expression of a group of specific microRNAs involving in a module possibly associate in the regulation of apoptotic process and also possibly associate with the efficacy of the phytochemicals drug.

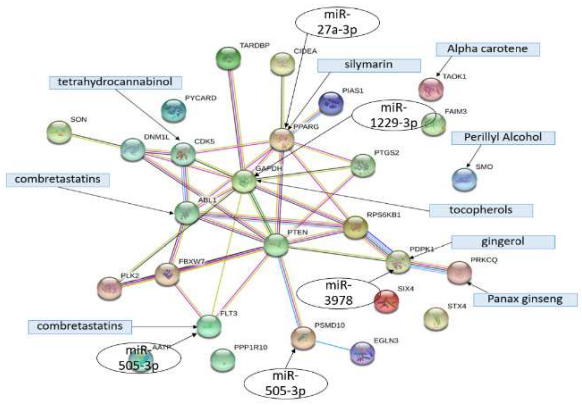

Fig. 3 the protein module involving in the regulation of apoptotic process and its phytochemicals interaction

C. *Inquiry Webpages*

The research results of this study can be searched on the web-based system developed by PHP and MySQL database. The web pages were set up for investigators with inquiries for more information. The discovery reports of this study can be accessed at sit.mfu.ac.th/mfucovid19.

Fig.4 depicts a web page displaying the significant clusters (protein module) from this study. There is information on each cluster including cluster-ID, biological process, observed gene count, false discovery rate (FDR), and proteins involved in this biological process, and phytochemical information.

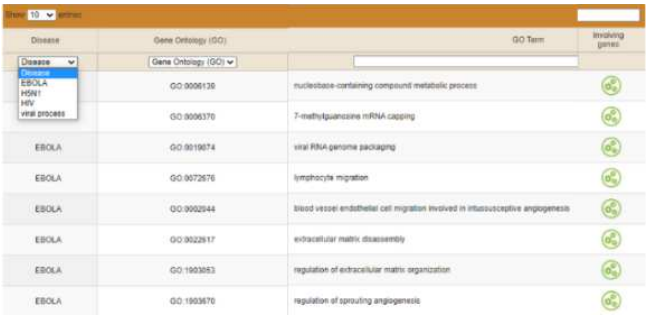

Fig. 4 the diseases caused by viruses with gene ontology and involving genes information

Fig.5 depicts a web page displaying protein modules involving in specific biological processes and false detection rate, and more information such as gene involving the module, protein-phytochemicals interaction.

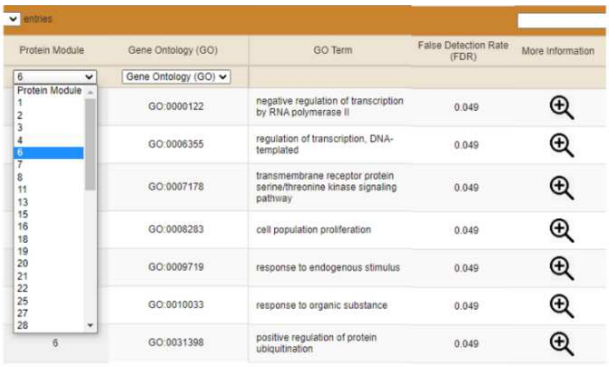

Fig. 5 the significant protein modules with gene ontology, false detection rate, and more information.

Fig. 6 depicts a web page displaying proteins in a specific module with more information such as the phytochemical interactions, sources, chemical information from PubChem and probability score.

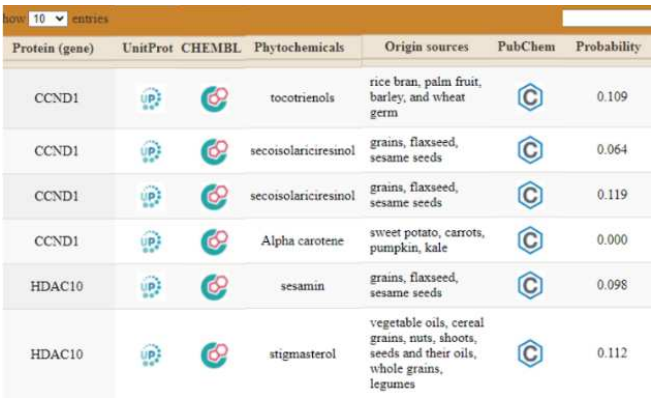

Fig. 6 Protein (gene) involving in the module with phytochemicals interaction information.

IV. Conclusions

The present study applied various data mining techniques in both classification and clustering approaches to identify two essential pieces of the correlated information of microRNA, Protein-Protein Interaction (PPI), and phytochemicals compounds for further development of plant-derived based drug discovery in diseases caused by viruses like Ebola, HN1, and HIV. Firstly, the microRNA-target prediction was analyzed based on an individual decision tree, SVM, and neuron network algorithm. Then the final decision was resolved by the ensemble approach that gives the highest accuracy (88.95%). Secondly, the significant protein modules were identified by the MCODE algorithm, then protein-phytochemicals interactions were analyzed and the enriched biological processes for each protein module were obtained.

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