Prediction of synergistic effect between multiple compounds related to diabetes mellitus

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Abstract. The medicinal plant contains several active compounds that work synergistically and targets some proteins. In order to obtain an herbal formula that can target two or more proteins from a disease, it is necessary to analyze the effect of compound interactions contained in medicinal plants. In 2015, Li Y et al. introduced a Network Target-based Identification of Multicomponent Synergy (NIMS) method to calculate the synergistic effect between two compounds for rheumatic disease in Traditional Chinese Medicine. However, research on interactions between three or more compounds is also needed to create an effective formula that can work on multiple targets. In this study, we proposed a novel method called One-Against-One NIMS (OAO-NIMS) to predict the synergistic effect of three compounds. Our proposed method was applied to examine compound interactions related to diabetes mellitus disease, and the best combination of three compounds was obtained by Gliquidone, Glipizide, and Mitiglinide with synergy score of 0.425.

1. Introduction
Indonesia is a tropical country with the second largest biodiversity in the world after Brazil. Indonesia has 30 000 types of plants, and 2 500 of them are medicinal plants [1]. One of the traditional medicines (herbs) that has long been used by Indonesian people is Jamu. Jamu is a drug which is made of medicinal plants based on knowledge, skills, beliefs, and experiences [2]. According to Basic Health Research data in 2013 by the Health Research and Development Agency of Ministry of Health, 30.4% of households in Indonesia utilize traditional health services, and 49.0% of them use Jamu [3].

Herbal remedies are used in the prevention and treatment of physical and mental illnesses. In addition, herbal medicine may have more than one pharmacological effect so that it can be applied to treat for more than one disease. Moreover, the medicinal plant contains chemical compounds [4] that can work on multiple targets (target multicomponent-network) as multicomponent drugs. Multicomponent drugs from herbal medicines are made by identifying synergistic combinations of compounds. Therefore, to obtain multicomponent drugs, we need to examine the synergistic effect between pairs of compounds [5]. Synergistic effects can be positive synergy (synergistic), negative synergy (antagonistic), and no synergy (independent) [6].

Synergism between compounds is usually carried out experimentally, which requires a significant cost and a long time. In this case, the computational approach can reduce research costs and time by analyzing the interactions between proteins, such as Protein-Protein Interaction (PPI) network, using the Network target-based Identification of Multicomponent Synergy (NIMS) [7]. NIMS can be utilized to analyze the level of synergy between compounds in multicomponent drugs. In addition, NIMS can also
be applied for high dimensional data with computationally faster execution time by utilizing the information contained in proteins that relate to compounds and diseases. Li Y et al. (2015) used the NIMS method to calculate synergies from Traditional Chinese Medicine recipes for rheumatic diseases [8]. Furthermore, Widhikari (2017) evaluated the synergistic effect of two active compounds from diabetes mellitus type-2 with the data obtained from IJAH web server (http://ijah.apps.cs.ipb.ac.id) [9]. Here, NIMS originally used to evaluate the synergistic effect between two compounds. Therefore, a proper approach to apply NIMS to assess interactions between three or more compounds is needed.

Diabetes mellitus (DM) is a disease characterized by high levels of sugar in the blood. This disease consists of two types, namely DM type-1 and type-2, which are differentiated based on dependency on insulin and non-insulin, respectively. According to Aguiree (2013), DM is the biggest deadly disease in Southeast Asia and the Western Pacific [10]. In Southeast Asia, one in five adults with diabetes lives in this region and one in four live births is affected by hyperglycemia in pregnancy, whereas in Western Pacific one in three adults with diabetes lives in this region and one in three deaths attributable to diabetes happen in this region.

In this study, we proposed a novel approach to measure synergistic effects between multiple compounds by combining NIMS with the one-against-one approach adopted from Support Vector Machine for multiclass [11]. The method was then applied to examine synergistic effects between three active compounds related to DM. As a result, compounds with high synergy score can be utilized as candidates for DM multicomponent drugs after laboratory evaluation and testing.

2. Material and methods

2.1. Datasets

The diabetes mellitus data used in this study is collected from IJAH web server, as follows: (1) Diabetes mellitus, insulin-dependent, 12; (2) Diabetes mellitus, ketosis-prone; (3) Diabetes mellitus, insulin-dependent, 10; (4) Diabetes mellitus, insulin-dependent, 19; (5) Diabetes mellitus, non-insulin-dependent, 5; (6) Diabetes mellitus, neonatal permanent; (7) Diabetes mellitus, non-insulin-dependent; (8) Diabetes mellitus, insulin-dependent, 2; (9) Diabetes mellitus, insulin-dependent, 20; (10) Diabetes mellitus, insulin-dependent, 22; (11) Diabetes mellitus, non-insulin-dependent, 1; (12) Diabetes mellitus, insulin-dependent; and (13) Diabetes mellitus, neonatal, with congenital hypothyroidism.

The number of DM type-1, type-2 and both types in IJAH web server are nine, three, and one, respectively. Those acquired DMs relate to 36 target protein and only 16 proteins that have phenotypes. Furthermore, a manual phenotype search was performed on the OMIM database (https://omim.org) and found phenotype of another two proteins. Out of 18 target proteins, only ten proteins have interactions with 34 compounds. These ten proteins only associated with six types of DM, namely (1) insulin-dependent 12, (6) permanent neonatal, (7) non-insulin-dependent, (8) insulin-dependent 2, (10) insulin-dependent 22 and (12) insulin-dependent.

PPI data was collected from the STRING database (https://string-db.org), and we obtained 18 982 proteins involving more than 8 million interactions. The phenotype data from HPO (https://hpo.jax.org/) and OMIM databases produced 3 494 proteins with 5 838 phenotype interactions. The summary of the data used in this study is shown in Table 1. The data of target protein related to DM in IJAH web server is still relatively small, from 13 DM diseases only obtained 36 target proteins.
Table 1. Dataset used in this study.

| Data type | Source | Number of data |
|-----------|--------|----------------|
| Protein   | IJAH web server (collected March 8th, 2018) | 36 proteins |
| Compound  | IJAH web server (collected March 8th, 2018) | 34 compounds |
| Disease   | IJAH web server (collected March 8th, 2018) | 13 diseases |
| PPI       | STRING ver. 10 | 18,982 proteins with more than 8 million interactions |
| Phenotype | HPO and OMIM | 3,496 proteins interact with 5,838 phenotypes |

2.2. Methods
This study mainly consists of three steps, i.e. data pre-processing, prediction of synergistic effect between compounds with NIMS, and evaluation. Calculation of compound synergies with a combination of NIMS and one-against-one approach method is applied to predict the combination of two and three compounds related to DM. Then, an evaluation is examined to the best five predicted combinations of those compounds.

Data pre-processing. The experimental data was collected from open access databases, and it was composed of compounds, target proteins, diseases, PPIs, and protein phenotypes (Table 1). The data were then pre-processed through selection, merging, standardization of IDs, and data reduction. Data selection was carried out on protein, PPI, and disease data. Phenotype data were combined from OMIM and HPO databases. Standardization IDs for disease and protein data were using UniProt ID (https://www.uniprot.org/).

Prediction of the synergistic effect. The calculation of synergistic effects between two compounds was done using the NIMS method. The NIMS method was proposed by Li S et al. (2010) to determine the relationship between responsive target compounds and proteins in the context of biological networks and specific for a disease [7]. Inputs to the NIMS method are compounds, which will be calculated for obtaining synergy score (SS).

The two elements of NIMS are the topology score (TS) and the agent score (AS). TS is taken from PPI networks and AS is phenotypic similarities between compounds. Illustrations of topology score, agent score, and synergy score are presented in Figure 1. Multiplication between topology scores and agent scores will produce synergy scores using equation (1) [7]. In equation (1-3), SS_{12} is synergy score between compound 1 and 2, TS_{12} is topology score between compound 1 and 2, AS_{12} is agent score from compound 1 and 2, IP_{i} is important score of protein i, \sum_{i=1}^{n}(IP_{i}) is the sum of importance score of protein i from compound 1, and min(d_{ij}) is the minimum distance between protein i from compound 1 and protein j from compound 2.

![Figure 1](image-url)  
Figure 1. Relationship between topology score, agent score and synergy score (Li S et al. 2010).
SS_{1,2} = TS_{1,2} \times AS_{1,2} \tag{1}

TS_{1,2} = \frac{1}{2} \left( \sum_{i=1}^{n} \frac{(IP_{1i} \times \exp(-\min(d_{i,j})))}{\sum_{i=1}^{n} IP_{1i}} + \sum_{i=1}^{n} \left( \frac{(IP_{2j} \times \exp(-\min(d_{j,l})))}{\sum_{j=1}^{n} IP_{2j}} \right) \right) \tag{2}

IP_{1} = \frac{(Degree_{1} + Betweeness_{1} + Closeness_{1})}{3} \tag{3}

TS is obtained based on target proteins and compounds (equation 2). The negative exponential function is used to weight the interaction of two target proteins based on the length of the shortest path [5]. IP1; is an important score target protein of active compound-1 and IP2, is an important score target protein of active compound-2 by integrating three main values in the network, namely degree, betweenness, and closeness (equation 3).

Degree (DC) is the number of connections between a node (target protein) and other target proteins in a network. The higher the degree value, the more edges or other target proteins that are connected to a particular target protein and the higher the tendency of the protein to influence the PPI network. Betweenness (BC) is the shortest path between pairs of target proteins by dividing the length of the path that passes the target by the total length of the path (equation 4). Closeness (CC) is a measure of how close the target protein to other proteins (equation 5) [12]. In equation (4) and (5), \( \sigma_{s,t}(v) \) is the number of shortest paths from node \( s \) to node \( t \) through node \( v \), \( \sigma_{s,t} \) is the shortest paths from node \( s \) to node \( t \), including if node \( v \) is not the source/target, \( d_{g}(v,t) \) is the shortest path from node \( v \) to node \( t \), and \( N \) is the number of nodes.

\[
BC = \sum_{v=1}^{N-1} \frac{\sigma_{s,t}(v)}{\sigma_{s,t}} \tag{4}
\]

\[
CC = \frac{\sum_{v=1}^{N} d_{g}(v,t)}{\sum_{v=1}^{N-1} d_{g}(v,t)} \tag{5}
\]

AS is similarity values between pairs of compounds based on phenotypes that relate to the target protein. The agent score is presented in equation (6), where \( S_{ij} \) is similarity value between phenotype 1 of compound 1 and phenotype 2 of compound 2 using Resnik method (equation 7), and \( N \) is the total number of phenotype pairs which can be obtained using equation (8). In equation (7), the calculation of similarities between proteins is done by taking the biggest score from the most representative information center (IC, equation 9). IC values are obtained by negating the results of logarithms from the weight of least common subsumer (LCS) phenotype protein 1 and protein 2 as shown in equation (10) [9].

\[
AS_{1,2} = \frac{\sum_{i,j} S_{ij}}{N} \tag{6}
\]

\[
S_{ij} = \text{sim}_{\text{resnik}}(P_1, P_2) = c e S(P_1, P_2) \max[I\{C(c)\}] \tag{7}
\]

\[
N = |P^{C1}| \times |P^{C2}| \tag{8}
\]

\[
I\{C(c)\} = -\log(P(c)) \tag{9}
\]

\[
P(c) = LCS(|P^{P1}|, |P^{P2}|) \tag{10}
\]

In this study, synergy score between two compounds is obtained by utilizing NIMS, whereas synergy score between multiple compounds (in this case three compounds) is obtained by our proposed approach One-Against-One NIMS (OAO-NIMS). Suppose there are \( N \) compounds, the synergy scores can be
calculated from all possible compounds is \( K = N(N-1)/2 \) [13]. The resulted synergy score is the lowest score in all possibilities. The flowchart of OAO-NIMS for three compounds is presented in Figure 2.

![Figure 2. Illustration of OAO-NIMS for three compounds.](image)

Evaluation. Synergy scores can be classified into synergistic and independent. The compound combination will be classified as synergistic if it has a synergy score greater than 0 and independent if the synergy score is equal to 0. Top five selected compound combinations will be validated its functions by literature.

3. Results and Discussion

3.1. Data pre-processing

Initially, the protein data that has been collected is converted according to uniprot abbrv, such as from ENSP00000250971 to INS_HUMAN. Then, we did PPI data selection for protein interactions related to DM from 8 million to 35,053 interactions by deleting data other than those related to the targeted protein. Subsequently, the selected phenotype data was merged from OMIM and HPO databases, containing 16 and two proteins associated with DM, respectively. In summary, from 13 types of DM that target 36 proteins, we selected only 18 proteins related to DM. In addition, out of 18 proteins, only ten proteins associate with 34 compounds.

3.2. Synergism between multiple compounds related to diabetes mellitus

From PPI data, which consists of 36 target proteins and 35,053 edges, we obtained interaction scores between proteins. Then, we applied the thresholds from preliminary research, i.e. minimum, maximum, median, average, and mode scores were 160, 999, 909, 761, and 999, respectively to PPI interaction scores. The PPI network using the median threshold, including ten proteins related to DM can be seen in Figure 3.

The PPI network on the NIMS is used to calculate the topology score, which is the level of importance of target protein (IP). The more important a protein is in the PPI, the stronger the effect produced by the compound on a network. IP was calculated using betweenness, closeness, and degree (equation 3), as shown in Table 2. The highest IP is obtained by INS_HUMAN or insulin by 0.347, which is useful to reduce the concentration of glucose in the blood, accelerate glycolysis, and accelerate glycogen synthesis in the liver. The relationship between INS_HUMAN protein and several other proteins shows that the INS_HUMAN protein has more connections and is one of the centers in the PPI network related to diabetes mellitus.
Figure 3. Protein interactions related to diabetes mellitus from IJAH web server.

Table 2. Importance scores and functions from the selected protein target.

| Protein      | CC  | BC  | DC  | IP  | Functions                                                                                                                                                                                                 |
|--------------|-----|-----|-----|-----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| INS_HUMAN    | 0.422 | 0.358 | 0.262 | 0.347 | To reduce the concentration of glucose in the blood, accelerate glycolysis, and accelerate glycogen synthesis in the liver                                                                                             |
| IRS1_HUMAN   | 0.371 | 0.155 | 0.148 | 0.225 | As a mediation and control of cellular processes by insulin                                                                                                                                                     |
| GTR4_HUMAN   | 0.350 | 0.095 | 0.106 | 0.184 | Facilitate glucose transportation                                                                                                                                                                             |
| CCR5_HUMAN   | 0.279 | 0.150 | 0.105 | 0.178 | Receptors for a number of inflammatory CC-chemokines include MIP-1-alpha, MIP-1-beta, and RANTES and then transduce signals by increasing intracellular calcium ion levels. It can play a role in controlling the proliferation or differentiation of granulocytic lineages |
| INSR_HUMAN   | 0.353 | 0.079 | 0.087 | 0.173 | Transducing signal receptors for a number of inflammatory CC-chemokines including CCL3 / MIP-1-alpha, CCL4 / MIP-1-beta, and RANTES by increasing intracellular calcium ion levels.                                          |
| AKT2_HUMAN   | 0.339 | 0.079 | 0.099 | 0.172 | Regulates metabolic processes, proliferation, cell survival, growth and angiogenesis                                                                                                                                                 |
| HNF4A_HUMAN  | 0.296 | 0.091 | 0.084 | 0.157 | Influence on kidney, liver and intestine growth                                                                                                                                                                         |
| TF7L2_HUMAN  | 0.320 | 0.076 | 0.063 | 0.153 | Maintain the epithelial stem-cell compartment of the small intestine                                                                                                                                               |
| IL2RA_HUMAN  | 0.295 | 0.066 | 0.068 | 0.143 | Receptors for interleukin-2, involved in regulating immune tolerance by controlling regulatory T cells (TREGs) activity.                                                                                                    |
| JUN_HUMAN    | 0.358 | 0.055 | 0.009 | 0.141 | Increases NR5A1 activity when phosphorylated by HIPK3, which leads to increased steroidogenic gene expression in the stimulation of the cAMP signaling pathway.                                                          |
After we obtained the IP values, TS values were calculated from the ten target proteins. TS was obtained by multiplying the IP by the minimum of protein distance. TS value equals to 1 when the same protein is in the same pair of compounds so that the minimum distance is 0. When multiplied by the exponential of 0, it will produce TS value 1. The top-10 of compound pair with the highest TS values are shown in Table 3. The highest TS of 1.000 is a combination of Sevoflurane and Desflurane compounds. Moreover, the AS was obtained based on the similarity of phenotype with the target protein. The higher the AS value, the more similar the two compounds. Table 3 also presents the top-10 compound pair with the highest AS. The highest AS of 0.918 is a combination of Glipizide and Maraviro compound. If AS value equals to 0, it is caused by an unknown phenotype in the target protein.

| Compound 1      | Compound 2     | TS    |
|-----------------|----------------|-------|
| Sevoflurane     | Desflurane     | 1.000 |
| Tolbutamide     | Chlorpropamide | 1.000 |
| Tolbutamide     | Glymidine      | 1.000 |
| Glipizide       | Mitiglinide    | 1.000 |
| Chlorpropamide  | Glymidine      | 1.000 |
| Sevoflurane     | Isoflurane     | 0.965 |
| Isoflurane      | Desflurane     | 0.965 |
| Azimilide       | Indapamide     | 0.946 |
| Gliquidone      | Tolbutamide    | 0.868 |
| Gliquidone      | Chlorpropamide | 0.868 |

Synergy scores were obtained from multiplying TS with AS. The higher the score obtained, the higher the synergy between these compounds. Table 4 shows the synergy score from a combination of two compounds. The highest combination of compounds was obtained from Glipizide and Mitiglinide compounds, that associated with the protein ABCC8_HUMAN.

| Compound 1     | Compound 2     | Synergy scores |
|----------------|----------------|----------------|
| Glipizide      | Mitiglinide    | 0.4512         |
| Gliquidone     | Glipizide      | 0.4312         |
| Gliquidone     | Mitiglinide    | 0.4254         |
| Gliquidone     | Glymidine      | 0.4007         |
| Glipizide      | Glymidine      | 0.3516         |
| Mitiglinide    | Glymidine      | 0.3425         |
| M-cresol       | Mitiglinide    | 0.3325         |
| M-cresol       | Glymidine      | 0.3209         |
| Glipizide      | M-cresol       | 0.3173         |
| Azimilide      | Indapamide     | 0.286          |

Additionally, we also applied our proposed method OAO-NIMS to calculate synergy score for multiple compounds. The top-10 synergy scores of three compounds using OAO-NIMS are shown in Table 5. The highest scores were obtained from Glipizide, Gliquidone, and Mitiglinide, which were related to ABCC8_HUMAN protein and diabetes mellitus, neonatal permanent. Synergy scores of a combination of Glipizide, Gliquidone, and Mitiglinide were obtained from the minimum synergistic
score of Glipizide – Gliquidone (0.4312), Glipizide – Mitiglinide (0.4512), and Mitiglinide – Gliquidone (0.4254).

### Table 5. Synergy score between three compounds using OAO-NIMS.

| Compound 1  | Compound 2  | Compound 3  | Synergy score |
|-------------|-------------|-------------|---------------|
| Glipizide   | Gliquidone  | Mitiglinide | 0.4254        |
| Glipizide   | Gliquidone  | Glymidine   | 0.3516        |
| Glipizide   | Mitiglinide | Glymidine   | 0.3425        |
| Gliquidone  | Mitiglinide | Glymidine   | 0.3425        |
| Mitiglinide | M-cresol    | Glymidine   | 0.3209        |
| Glipizide   | Mitiglinide | M-cresol    | 0.3173        |
| Glipizide   | M-cresol    | Glymidine   | 0.3173        |
| Glipizide   | Gliquidone  | M-cresol    | 0.2825        |
| Gliquidone  | Mitiglinide | M-cresol    | 0.2825        |
| Gliquidone  | M-cresol    | Glymidine   | 0.2825        |

3.3. Evaluation

According to the top-10 synergy score between three compounds related to DM, we obtained five significant compounds namely Glipizide, Gliquidone, Mitiglinide, Glymidine, and M-cresol (Table 6). Glipizide and Gliquidone are medications for diabetes mellitus that belong to the sulfonylurea group. Sulfonylureas are often called insulin secretagogues, which work to stimulate insulin secretion from pancreatic cells. Mitiglinide belongs to the meglitinide group, with the same mechanism as sulfonylurea but different in chemical structure. This group closes the ATP-independent channel in the pancreas [14]. Glymidine or glycodyazine are used to lower blood glucose by increasing insulin secretion from the pancreas and increasing peripheral tissue sensitivity to insulin. M-cresol is a compound used for insulin preservatives used in insulin injection [15]. Those prospective compounds are associated with diabetes mellitus, neonatal permanent with ABCC8_HUMAN and INS_HUMAN proteins. ABCC8_HUMAN or ATP-binding cassette sub-family C member 8 with the name Sulfonylurea receptor 1 in diabetes mellitus, neonatal permanent mutation, and cause hyperglycemia in the first month of life. INS_HUMAN or insulin is a protein produced by the pancreas and has a function to control blood sugar levels. INS_HUMAN protein besides influencing diabetes mellitus, neonatal permanent also influencing diabetes mellitus, insulin-dependent, 2.

### Table 6. Significant compounds related to diabetes mellitus.

| Compound    | Protein       | Function                                                                 |
|-------------|---------------|--------------------------------------------------------------------------|
| Glipizide   | ABCC8_HUMAN   | Stimulates insulin secretion from pancreatic cells                       |
| Gliquidone  | ABCC8_HUMAN   | Stimulates insulin secretion from pancreatic cells                       |
| Mitiglinide | ABCC8_HUMAN   | Stimulates insulin secretion from pancreatic cells                       |
| Glymidine   | ABCC8_HUMAN   | Increases insulin secretion from the pancreas and increases peripheral tissue sensitivity to insulin |
| M-cresol    | ABCC8_HUMAN   | Preservative insulin                                                     |
|             | and INS_HUMAN |                                                                           |

4. Conclusion

We proposed a new approach to predict synergistic effect between three or more compounds related to diabetes mellitus by combining NIMS with the one-against-one approach adopted from Support Vector Machine multiclass. Synergy scores were achieved from the multiplication of topology scores and agent
scores. Topology scores were obtained from the PPI network, while agent scores were obtained from the similarity of the target protein phenotype. The best combination of three compounds using OAO-NIMS was achieved by Gliquidone, Glipizide, and Mitiglinide with the minimum synergistic score was 0.425. It is expected that the laboratory tests will be carried out on the combination of selected compounds to confirm the results.

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