A Computational Pharmacology Approach for Rapid Discovery of Drugs and Natural Products Against COVID-19

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Abstract

During outbreaks of emerging infectious diseases, there is an urgent need to propose scientific hypotheses regarding the efficacy and mechanisms of candidate therapeutics. Both vaccine and new drug development require considerable time; therefore, drug repositioning (repurposing existing drugs) strategies hold unique value. However, insufficient clinical data on pathogens and host responses for emerging diseases constrains the formulation of candidate drug hypotheses. At this stage, broad-spectrum antiviral drugs are often attempted based on patients' clinical characteristics. This paper draws inspiration from the heuristic search approach commonly employed in the field of artificial intelligence and proposes a novel method (aCODE). Based on broad-spectrum antiviral drugs that have demonstrated preliminary therapeutic efficacy, the method obtains their host target protein sets, searches for gene module combinations with the highest correlation at the whole-genome scale, and subsequently performs pattern matching and statistical test ranking for candidate compounds (such as approved drugs and natural products). This method can update input drugs based on progress in clinical practice and iteratively output more precise results. The output natural products, traditional Chinese medicine, or food-medicine homologous components can undergo rapid testing in combination with other information, forming an agile R&D testing closed loop. For the second version update of this method and its comparative analysis with literature evidence, please refer to: http://chinaxiv.org/abs/202002.00024.

Full Text

Preamble

aCODE: Agile Discovery of Drugs and Natural Products for Emerging Epidemic COVID-19 Based on Computational Pharmacology

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Abstract

During the outbreak of emerging infectious diseases, there is an urgent need to generate scientific hypotheses regarding the efficacy, mechanisms, and side effects of candidate drugs. Since vaccine and new drug development require considerable time, drug repositioning strategies hold unique value. However, for emerging diseases, clinical data on pathogens and host responses are often insufficient, limiting the formulation of candidate drug hypotheses. During this phase, broad-spectrum antiviral drugs are frequently attempted based on patient clinical characteristics. Drawing inspiration from heuristic search strategies commonly employed in artificial intelligence, this paper proposes a novel method called aCODE (Agile Discovery of Drugs or Natural Products for Emerging Epidemics). Based on broad-spectrum antiviral drugs showing preliminary efficacy signals, the method obtains their host target protein sets, searches for the most highly correlated gene module combinations at the whole-genome scale, and subsequently performs pattern matching and statistical ranking of candidate compounds (such as approved drugs and natural products). This approach can update input drugs as clinical practice progresses, iteratively outputting more precise results. The identified natural products, traditional Chinese medicine components, or food-derived substances can be rapidly tested in combination with other information, forming an agile R&D testing closed loop. For the second version of this method and its comparison with literature evidence, please refer to: http://chinaxiv.org/abs/202002.00024.

Keywords: COVID-19; computational pharmacology; drug repositioning; natural products; network pharmacology

1. Introduction

Major emerging infectious disease outbreaks are characterized by time constraints and limited data. Pathogen-target-based drug discovery requires detailed knowledge of viral structure and function, while clinical efficacy and toxicity validation demands substantial time. Phenotype-based drug repositioning (old drugs for new uses) represents an important alternative approach [1], yet for emerging infectious diseases, obtaining sufficient genomics and phenomics data in the short term is challenging. To address the need for rapidly generating testable drug hypotheses and quantitative evaluation under such extremely limited data conditions, we propose a new method called aCODE (Agile Discovery of Drugs or Natural Products for Emerging Epidemics), inspired by heuristic search strategies commonly used in artificial intelligence (Figure 1 [Figure 1: see original paper]). Based on broad-spectrum antiviral drugs with limited efficacy signals, we obtain their host target protein sets, search for the most highly cor-

related gene module combinations at the whole-genome scale, and subsequently perform pattern matching and statistical ranking of candidate compounds (such as approved drugs and natural products). Using the recent COVID-19 outbreak in China as a case study, we input several drugs reported to show preliminary efficacy signals, computationally rank natural product components, and perform mixed clustering of initial drugs with natural product molecules to understand the potential cellular and molecular mechanisms of candidate compounds. This method can iteratively update the initial drug list as clinical practice progresses, thereby optimizing system accuracy and predictive capability. The output natural products, traditional Chinese medicine components, or food-derived substances can be rapidly tested, forming an agile R&D testing closed loop, and providing scientific support for home-based prevention and protocol testing among large populations when medical resources are limited during outbreaks.

2.1 Identification of Human Gene Modules

In this study, human gene module data were downloaded from the Molecular Signatures Database (MSigDB) (https://www.gsea-msigdb.org/gsea/msigdb/) [2], which includes commonly used gene modules such as GO Biological Process, GO Cellular Component, and GO Molecular Function. These gene module annotations are static collections of all genes involved in specific biological processes. Given that aging is the most universal factor affecting various human diseases and immune function changes, we selected age-related genes as representatives for each module. Using human blood cell DNA methylation data with age information from GSE40279 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE40279) [3], which contains DNA methylation profiles from 656 whole blood samples ranging from 19 to 101 years old, we applied a recently developed algorithm that extracts gene-level DNA methylation features [4-6] to identify aging-related gene sets regulated by DNA methylation. This algorithm (SIMPO) uses a SIMPO score to represent gene-level DNA methylation status.

The SIMPO algorithm is calculated as follows:

$$SimPo\ score = \frac{\bar{x} - \bar{y}}{t(m + n - 2)} \quad (1-1)$$

Where: - $\bar{x}$: average DNA methylation value of all probes in the gene body region - $\bar{y}$: average DNA methylation value of all probes in the gene promoter region - m: number of probes in the gene body region - n: number of probes in the gene promoter region - S_1^2: variance of DNA methylation values for probes in the gene body region - S_2^2: variance of DNA methylation values for probes in the gene promoter region

Subsequently, we calculated differences in gene SIMPO scores between elderly (80 years) and young (<35 years) individuals using t-tests, selecting genes with

P-values < 0.001 as significantly age-associated. The intersection of this age-related gene set with each biological function gene module from MSigDB served as the representative for that module. In this way, we obtained multiple aging-related biological function gene modules.

2.2 Identification of Significantly Associated Gene Modules for Initial Drugs

In the current version, ten drugs listed in Table 1 were used as initial inputs, primarily sourced from the fourth edition of the national guidelines, drugs with cellular evidence [7], and broad-spectrum antivirals.

Table 1. Initial Drug Set - Lopinavir - Ritonavir - Ribavirin - Indinavir - Oseltamivir - Saquinavir - Chloroquine - Carfilzomib - Mycophenolate mofetil - Nelfinavir

Targets for these initial antiviral drugs were collected from the STITCH (chemical association networks) database (http://stitch.embl.de) [8]. To accommodate compounds with fewer targets in STITCH, we selected the top 300 targets by combined score for each compound as candidate targets. Hypergeometric distribution tests were used to calculate the correlation between initial drugs and each functional gene module, selecting the top 200 most significantly associated biological function gene modules (by P-value) as significantly associated modules for initial drugs.

The hypergeometric distribution test formula is:

$$P\text{-Value} = 1 - F(x-1|M,K,N) = 1 - \sum_{i=0}^{x-1} \frac{\binom{K}{i}\binom{M-K}{N-i}}{\binom{M}{N}} \quad (1-2)$$

Where x is the number of intersecting genes between initial drug targets and the functional gene module, M is the total number of genes in the universe, K is the number of initial drug target genes, and N is the number of genes in a particular biological function gene module.

2.3 Prediction of Potential Anti-COVID-19 Drugs

The background drug dataset for screening anti-COVID-19 compounds was collected from the Traditional Chinese Medicine Integrated Database (TCMID) of natural product (traditional Chinese medicine) chemical components (http://www.megabionet.org/tcmid/) [9]. Consistent with the initial anti-COVID-19 drugs, background drug targets were collected from STITCH, selecting the top 300 targets by combined score as candidate targets. We then calculated the correlation between background drugs and each significantly associated gene module for initial drugs using hypergeometric distribution tests. Additionally, based on the P-values from these tests for both initial and background drugs, we obtained correlations through clustering analysis.

3. Results

Using the SIMPO algorithm, we obtained SIMPO scores for each gene in age-related DNA methylation data to represent gene-level DNA methylation status. Through t-tests comparing elderly (80 years) and young (<35 years) individuals, we identified genes with P-values < 0.001 as significantly age-associated. By intersecting these with biological function gene modules from MSigDB, we identified aging-related biological function gene modules.

Next, by combining antiviral initial drug target genes with aging-related biological function gene module data and performing hypergeometric distribution tests, we identified 200 biological function gene modules significantly associated with antiviral initial drugs (Figure 2 [Figure 2: see original paper]). Figure 3 [Figure 3: see original paper] specifically shows the biological function gene modules significantly associated with the antiviral initial drug Ribavirin.

We then screened natural product (traditional Chinese medicine) chemical components for antiviral activity. By combining target genes for these natural product components from STITCH and performing hypergeometric distribution tests, we calculated correlation scores between candidate drugs and each significantly associated gene module for initial drugs. When a compound corresponded to multiple initial drug-associated modules, we accumulated the -log(P-values) (Supplementary Table 1), where P-values were from hypergeometric distribution tests.

The analysis revealed that the initial input drug Ribavirin showed the strongest association with COVID-19 disease-related gene modules (Supplementary Table 1). Furthermore, four natural product components exhibited higher correlation scores than known antiviral initial drugs, including silicon dioxide, 3,4-benzopyrene, apigenin, and fumaric acid. Notably, rutin, apigenin, and kaempferol—ranking highly in correlation scores—frequently appeared in traditional Chinese medicine formulas recommended by the National Health Commission and various Chinese medicine institutions (Table 2), suggesting that this method facilitates the discovery of potential anti-COVID-19 drugs.

Additionally, based on P-values from hypergeometric distribution tests for both initial and candidate drugs, bidirectional drug-gene module clustering allowed observation of similarity in gene module correlations between candidate and initial drugs (Figure 4 [Figure 4: see original paper] and Figure 5 [Figure 5: see original paper]). Natural product compounds clustering closely with known initial drugs were predicted as potential anti-COVID-19 agents with similar mechanisms of action.

4. Discussion

Our results demonstrate that based on limited early-stage treatment experience from emerging infectious diseases, it is feasible to infer and calculate disease characteristics for quantitative analysis of a broader range of candidate drugs.

The essence of our method involves three steps: first, aggregating a set of drugs with preliminary efficacy signals in drug-dimensional space; second, using this information to guide the calculation of correlations between gene modules and the disease in gene-dimensional space with subsequent gene module clustering; and finally, returning to drug space to cluster and rank candidate compounds.

The aCODE method offers several key features: (1) **Agile iterativity**: The initial drug list can be updated iteratively as clinical practice progresses, thereby optimizing system accuracy and predictive capability; (2) **Rapid closed-loop capability**: Output natural products, traditional Chinese medicine components, or food-derived substances can be rapidly tested, forming an agile R&D testing closed loop; and (3) **Mechanistic insight**: The method enables clustering and comparison of cellular and molecular biological mechanisms between candidate and initial drugs, providing scientific support for home-based prevention and protocol testing among large populations when medical resources are limited during outbreaks.

Several aspects of the aCODE method can be continuously improved: (1) **Drug target database updates**: Currently using public STITCH data, future versions could incorporate more refined proprietary drug target databases; (2) **Disease-related gene updates**: Host cell omics data from viral infections could update the disease-related gene module data used here; (3) **Gene module specificity refinement**: Current MsigDB modules primarily derive from Gene Ontology, a hierarchical system. To balance specificity and generality, we selected modules containing 50-500 genes, but future versions could expand or refine this database, prioritizing smaller, more specific modules; and (4) **Integration of additional drug evidence**: As a purely data-driven computational process, when results align with clinical or literature evidence from other sources, Bayesian principles increase confidence in candidates, allowing further investigation of their drug development potential.

Notably, this method serves as a GPS-like tool for rapidly focusing on candidate compounds. For each specific candidate, comprehensive evaluation across multiple dimensions—including efficacy magnitude, direction, toxicity, druggability, and economics—is required. This method only involves computational pharmacological analysis of drugs and candidate compounds and does not provide clinical recommendations for specific candidates.

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Supplementary Table 1. COVID-19 Drugs and Natural Product-Derived Candidate Compounds with Their Molecular Mechanisms

Compound	Significantly Associated Gene Modules (Top 3)
Ribavirin (利巴韦林)	D GSE13485_PRE_VS_POST_YF17D_VACCINATION_PBMC_DN, GSE19888_ADENOSINE_A3R_INH_VS_ACT_WITH_INHIBITOR_PRETREATMENT GSE42724_NAIVE_BCELL_VS_PLASMABLAST_UP
Silicon Dioxide	GO_COFACTOR_METABOLIC_PROCESS, GO_CYTOKINE_ACTIVITY, GO_REGULATION_OF_IMMUNE_EFFECTOR_PROCESS
3,4-Benzopyrene (3,4-苯并芘)	GO_DRUG_METABOLIC_PROCESS, GO_OXIDOREDUCTASE_ACTIVITY_ACTING_ON_PAIRED_DONORS_WITH_INC GO_COFACTOR_METABOLIC_PROCESS
Apigenin	GO_MAMMARY_GLAND_DEVELOPMENT, PID_P53_DOWNSTREAM_PATHWAY, GO_DRUG_METABOLIC_PROCESS
Chloroquine	GO_COFACTOR_METABOLIC_PROCESS, GO_PRODUCTION_OF_MOLECULAR_MEDIATOR_OF_IMMUNE_RESPONSE

Compound	Significantly Associated Gene Modules (Top 3)
Fumaric Acid (富马酸)	GO_PROTEIN_TYROSINE_KINASE_ACTIVITY, GO_ANATOMICAL_STRUCTURE_HOMEOSTASIS, GO_PROTEIN_AUTOPHOSPHORYLATION
Mycophenolate Mofetil (霉酚酸酯)	GO_ENDOPEPTIDASE_ACTIVITY, GO_SERINE_HYDROLASE_ACTIVITY, GO_HUMORAL_IMMUNE_RESPONSE
1-Methoxycanthin-6-One (1-甲氧鸟氨酸-6-一)	MODULE_197, KEGG_ERBB_SIGNALING_PATHWAY, PID_P53_DOWNSTREAM_PATHWAY
Atenolol	GO_PROTEIN_TYROSINE_KINASE_ACTIVITY, GO_PROTEIN_AUTOPHOSPHORYLATION, GO_POSITIVE_REGULATION_OF_PHOSPHATIDYLINOSITOL_3_KINASE_SIGNAL
L-Homocysteine (L-同型半胱氨酸)	GO_DRUG_METABOLIC_PROCESS, GO_COFACTOR_METABOLIC_PROCESS, GO_COLLAGEN_CONTAINING_EXTRACELLULAR_MATRIX
L-Alpha,Gamma-Diaminobutyric Acid (L- , -二氨基丁酸)	GO_PROTEIN_TYROSINE_KINASE_ACTIVITY, GO_PROTEIN_AUTOPHOSPHORYLATION, GO_POSITIVE_REGULATION_OF_PHOSPHATIDYLINOSITOL_3_KINASE_SIGNAL
Baicalein	GO_PEPTIDYL_THREONINE_MODIFICATION, KEGG_ERBB_SIGNALING_PATHWAY, GO_BLOOD_VESSEL_ENDOTHELIAL_CELL_MIGRATION
1,7-Diphenyl-5-Hepten-3-One (1,7-二苯基-5-庚烯-3-一)	REACTOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK, GO_MAMMARY_GLAND_DEVELOPMENT, GSE7509_UNSTIM_VS_FCGRIIB_STIM_DC_DN
Benzyl Salicylate	REACTOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK, GO_MAMMARY_GLAND_DEVELOPMENT, MODULE_24
Creatinine	GO_CYTOKINE_ACTIVITY, GSE7509_UNSTIM_VS_FCGRIIB_STIM_DC_DN
Benzene	GO_DRUG_METABOLIC_PROCESS, PID_P53_DOWNSTREAM_PATHWAY, GO_REGULATION_OF_VASCULATURE_DEVELOPMENT
Palmitoleic Acid	GO_PROTEIN_TYROSINE_KINASE_ACTIVITY, GO_PROTEIN_AUTOPHOSPHORYLATION, GO_OXIDOREDUCTASE_ACTIVITY_ACTING_ON_PAIRED_DONORS_WITH_INC

Compound	Significantly Associated Gene Modules (Top 3)
2-Propenal (2-丙烯醛)	GO_ENDOPEPTIDASE_ACTIVITY, GO_SERINE_HYDROLASE_ACTIVITY, KEGG_ERBB_SIGNALING_PATHWAY
Neoisorutin (新异芦丁)	GO_ENDOPEPTIDASE_ACTIVITY, GO_SERINE_HYDROLASE_ACTIVITY, REACTOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK
Rutin	GO_ENDOPEPTIDASE_ACTIVITY, GO_SERINE_HYDROLASE_ACTIVITY, REACTOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK
Deoxycholic Acid (脱氧胆酸)	GO_OXIDOREDUCTASE_ACTIVITY_ACTING_ON_PAIRED_DONORS_WITH_INC GO_REGULATION_OF_PEPTIDASE_ACTIVITY
Delphinidin (德尔菲尼丁)	REACTOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK, GO_DRUG_METABOLIC_PROCESS, KEGG_ERBB_SIGNALING_PATHWAY
Zerumbone	GO_ENDOCRINE_SYSTEM_DEVELOPMENT, GO_PEPTIDYL_THREONINE_MODIFICATION, ZHOU_INFLAMMATORY_RESPONSE_LPS_UP
Wedelolactone	NABA_SECRETED_FACTORS, GO_CYTOKINE_ACTIVITY, GO_ENDOCRINE_SYSTEM_DEVELOPMENT
Anwulignan (安五脂素)	GO_PHAGOCYTOSIS, GO_CYTOKINE_ACTIVITY, RUAN_RESPONSE_TO_TNF_DN
Macelignan (肉豆蔻木酚素)	GO_PHAGOCYTOSIS, GO_CYTOKINE_ACTIVITY, RUAN_RESPONSE_TO_TNF_DN
Ascorbic Acid (Vitamin C)	GO_COFACTOR_METABOLIC_PROCESS, GO_OXIDOREDUCTASE_ACTIVITY_ACTING_ON_PAIRED_DONORS_WITH_INC MOOTHA_MITOCHONDRIA
Threonine	GO_ANTIGEN_RECEPTOR_MEDIATED_SIGNALING_PATHWAY, GO_IMMUNE_RESPONSE_REGULATING_CELL_SURFACE_RECEPTOR_SIGNALI GO_PEPTIDYL_THREONINE_MODIFICATION
Methylprednisolone	GO_ADAPTIVE_IMMUNE_RESPONSE_BASED_ON_SOMATIC_RECOMBINATION_ GO_LYMPHOCYTE_MEDIATED_IMMUNITY, SMID_BREAST_CANCER_NORMAL_LIKE_UP
Kaempferol	GO_OXIDOREDUCTASE_ACTIVITY_ACTING_ON_PAIRED_DONORS_WITH_INC GO_MAMMARY_GLAND_DEVELOPMENT, GO_BLOOD_VESSEL_ENDOTHELIAL_CELL_MIGRATION
Anthracene	GO_CATALYTIC_ACTIVITY_ACTING_ON_RNA, GO_CATALYTIC_ACTIVITY_ACTING_ON_DNA, GO_DNA_CONFORMATION_CHANGE
Piceatannol	GO_PROTEIN_TYROSINE_KINASE_ACTIVITY, GO_REGULATION_OF_PEPTIDASE_ACTIVITY, GO_NEGATIVE_REGULATION_OF_HYDROLASE_ACTIVITY

Compound	Significantly Associated Gene Modules (Top 3)
Eckol	GO_ENDOCRINE_SYSTEM_DEVELOPMENT, KEGG_ERBB_SIGNALING_PATHWAY, GO_PEPTIDYL_THREONINE_MODIFICATION
3,4,5-Trihydroxybenzoic Acid (3,4,5-三羟基苯甲酸)	GO_REGULATION_OF_PEPTIDASE_ACTIVITY, PID_P53_DOWNSTREAM_PATHWAY, GO_MAMMARY_GLAND_DEVELOPMENT
Gallic Acid (没食子酸)	GO_REGULATION_OF_PEPTIDASE_ACTIVITY, PID_P53_DOWNSTREAM_PATHWAY, GO_MAMMARY_GLAND_DEVELOPMENT
1-Methoxy-4-(1-Propenyl)-Benzene (1-甲氧基-4-(1-丙烯基)-苯)	GO_COFACTOR_METABOLIC_PROCESS, GO_ENDOCRINE_SYSTEM_DEVELOPMENT, KEGG_ERBB_SIGNALING_PATHWAY
Anethole	GO_COFACTOR_METABOLIC_PROCESS, GO_ENDOCRINE_SYSTEM_DEVELOPMENT, KEGG_ERBB_SIGNALING_PATHWAY
Cis-Anethole	GO_COFACTOR_METABOLIC_PROCESS, GO_ENDOCRINE_SYSTEM_DEVELOPMENT, KEGG_ERBB_SIGNALING_PATHWAY
p-Propenyl-Anisole	GO_COFACTOR_METABOLIC_PROCESS, GO_ENDOCRINE_SYSTEM_DEVELOPMENT, KEGG_ERBB_SIGNALING_PATHWAY
Trans-Anethole	GO_COFACTOR_METABOLIC_PROCESS, GO_ENDOCRINE_SYSTEM_DEVELOPMENT, KEGG_ERBB_SIGNALING_PATHWAY
3,3',4',5,5',7-Hexahydroxyflavone (Myricetin)	GO_POSITIVE_REGULATION_OF_PHOSPHATIDYLINOSITOL_3_KINASE_SIGNAL KEGG_ERBB_SIGNALING_PATHWAY, GO_ENDOTHELIAL_CELL_PROLIFERATION
Honokiol	GO_CYSTEINE_TYPE_PEPTIDASE_ACTIVITY, GO_ENDOPEPTIDASE_ACTIVITY, GO_OXIDOREDUCTASE_ACTIVITY_ACTING_ON_PAIRED_DONORS_WITH_INC
Dihydrotestosterone	GO_DNA_BINDING_TRANSCRIPTION_ACTIVATOR_ACTIVITY, REAC-TOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK, GO_POSITIVE_REGULATION_OF_PHOSPHATIDYLINOSITOL_3_KINASE_SIGNAL

Compound	Significantly Associated Gene Modules (Top 3)
4-Methylsulfinyl Butyl Isothiocyanate (Sulforaphane)	KEGG_ERBB_SIGNALING_PATHWAY, MODULE_197, GO_COFACTOR_METABOLIC_PROCESS

Note: Compounds marked with "D" in the "Type" column represent initial input drugs.

Note: Figure translations are in progress. See original paper for figures.