Optimization of Herbal Drugs using Soft Computing Approach

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Abstract

The study presents the results of our investigation into the use of Genetic Algorithms (GA) and Artificial Neural Network (ANN) for identifying near optimal design parameters of compositions of drug systems that are based on soft computing approach for herbal drug design. Herbal medicine has been applied successfully in much clinical practices since long throughout in world. The present study proposes a novel concept using a computational technique to predict bioactivity of herbal drug and designing of new herbal drug for a particular disease. Genetic algorithm investigated the relationship between chemical composition of a widely used herbal medicine in India and its bioactivity effect. The predicted bioactivity with respect to its composition indicates that the proposed computing method is an efficient tool to herbal drug design.

Keywords: Herbal drugs, GA, ANN.

1. INTRODUCTION

In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects [1]. Many traditional medicines are derived from medicinal plants, minerals and organic matter [2]. A number of medicinal plants, traditionally used for over 1000 years named Rasayana are present in herbal preparations of Indian traditional health care systems [3]. In Indian systems of medicine, most practitioners formulate and dispense their own recipes [4]. Major hindrance in amalgamation of herbal medicine in modern medical practices is lack of scientific and clinical data proving their efficacy and safety. There is a need for conducting clinical research in herbal drugs, developing simple bioassays for biological standardization, pharmacological and toxicological evaluation, and developing various animal models for toxicity and safety evaluation [5]. It is also important to establish the active component/s from these plant extracts.

Drug discovery is a complex and costly process, which involves more time for making and testing New Composition Entities (NCE). The average cost of creating NCE in a pharmaceutical company was estimated about $ 1500/ compound [6]. Generally, herbal medicine is not composed of several herbs in appropriate proportion. The constituent of herbs and their proportion of certain herbal medicine are determined according to traditional medical knowledge. Unlike modern drugs in the form of single chemical ingredient, herbal medicine may contain hundreds of chemical compounds. Many researchers believe that synergistic effect of different active ingredients contributes to the therapeutic effect of herbal medicine [7]. Modern clinical trial has proved that herbal drug composed of multiple herbs with multiple compounds in certain proportion has greater efficacy than a single herb. Therefore, modern herbal drug can be produced as a combination of different active components from herbs. However, the complex chemical composition of herbal medicine leads to the lack of appropriate method for identifying active compounds and optimizing the formulation of herbal medicine. The variation of biologic activity of herbal medicine is tightly associated with the variation of their chemical composition. Such relationship between chemical composition and biological activity is regarded as Quantitative Composition–Activity Relationship (QCAR) [8]. By quantitatively analyzing the chemical composition and bioactivity relationship, mathematical model could be established to predict activity of herbal medicine. Moreover, an optimal combination of herbal medicine can be evaluated based on QCAR model, which enables us to integrate different active components to form a more effective herbal drug. In the present study, a soft computing approach has been proposed to model the composition–activity relationship method to predict the bioactivity of herbal drug in designing a new herbal drug for a specific disease.

2. MATERIALS AND METHODS

2.1 Herbal Drugs

Seven plants with reported antidiabetic property are taken for the study. The plants are Aloe Vera [9], Catharanthus roseus [10], Momordica charantia [11], Aegle marmelos [12], Aerva Lanata [13], Phyllanthus emblica [14] and Azadirachta indica [15]. The plant extracts are obtained by sox elation method. Different components are isolated by column chromatography and HPLC method. The biological activities of individual active component are studied in animal models.

2.2 Mathematical Model

QCAR is the correlation between chemical composition and biological activity of the drug system. Suppose 'D' is the herbal drug which is consists of 'n' number of herbs having total weight 'W_d'. Each herbal contains maximum m number of components. Hence the herbal medicine D is a combination of different components, which represents by a row vector [C_1, C_2, C_3… C_m] n. Moreover each component is having separate biological activity, which can be denoted as a column vector says B = [B_1, B_2, …. B_m] ^{T}. The whole matrix is a [n*m] matrix. If a single compositional bioactivity will change the overall bioactivity will change.
Hence B = f (C)

The function may be linear or nonlinear. But generally nonlinear relationship is more appropriate in case of herbal drug.

3. GENETIC ALGORITHMS AND ARTIFICIAL NEURAL NETWORK

The prediction of biological activity of a chemical compound from its compositional features, representing its physico-chemical properties, plays an important role in drug discovery, design and development. Since the biological data is highly non-linear, the machine-learning techniques have been widely used for modeling it. In the present work, genetic algorithm (GA) and artificial neural networks (ANN) are used to develop computational prediction models on a dataset of antidiabetic compounds. The hybrid GA-ANN technique is used for feature selection. The ANN-QCAR prediction models are then developed to link the compositions along with its weight to their reported biological activity.

GAs are general-purpose evolutionary algorithms that can be used for optimization [16]. In a GA, each population member is a potential solution, which is equal to its population size. GAs were first introduced by Holand [17] which is a search algorithm. These are stochastic optimization method and

provide a powerful technology to perform random searches in a large problem space. An introduction and overview of the application of GAs are reported by Venkatasubramanian and Sundaram [18]. The wide range of studies in QSAR has been studied using GAs.

Artificial neural networks (ANNs) have been applied to nonlinear classification and forecasting problems. In an ANN model, a neuron is an elemental processing unit that forms part of a larger network. Neural networks can be applied to form basic types of applications like association, clustering, transformation and modeling. Lots of application of ANN has been applied in structural drug design.

Presently both GA and ANN were applied to predict the bioactivity of the optimized herbal drug. Based on the proposed input data set GA and ANN can be applied to predict the overall bioactivity. The algorithm is shown in figure 1.

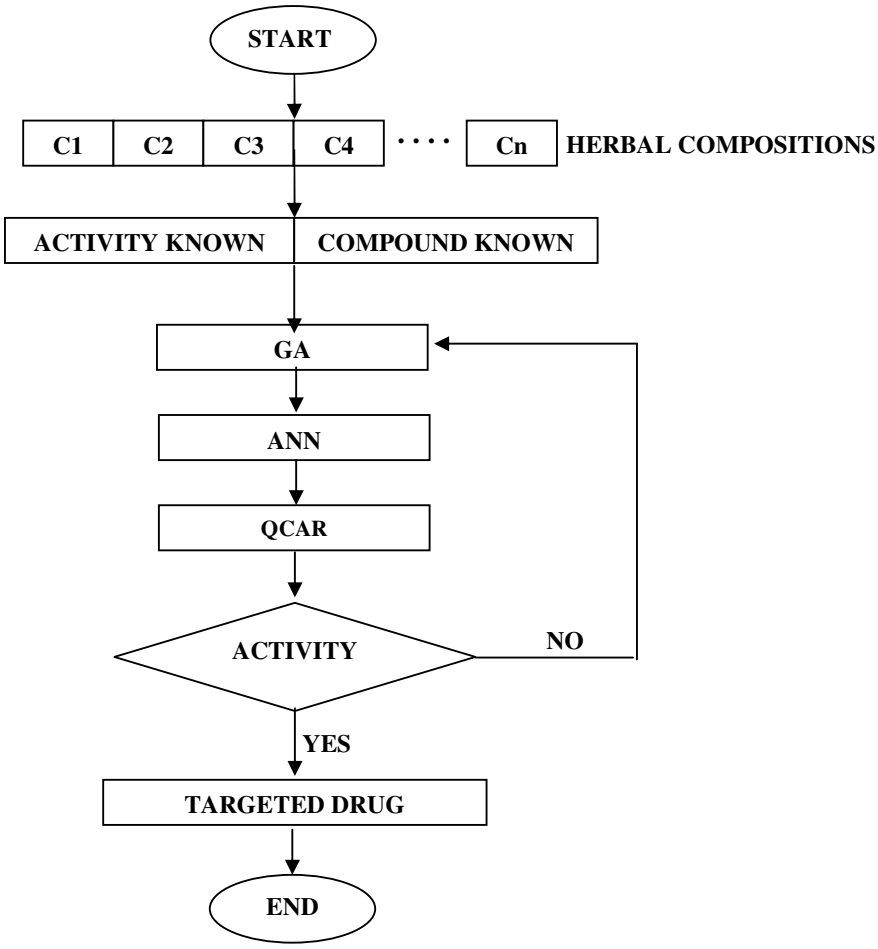

Figure 1 Algorithm for Optimal Composition

4. RESULTS AND DISCUSSIONS

The algorithm was implemented using in house C programme. All calculations were carried out on a computer with a 2.0 GHz Core to Duo processor. The simulation was performed using predictive GA and integrated with ANN having one hidden layer. Table 1 shows the predicted bioactivity of the drug samples. There are 20 no of drug samples having 1 gm weight each. The weight of active compounds of each individual drug is also shown in the table. It is observed that the drug sample no 17 has the highest bioactivity which is the optimized drug. The same has been plotted in figure no 2. The compositions of the drug sample no 17 is the optimized compositions to get the highest bioactivity. The validation of this drug has yet to be done.

Herbal medicine is prevailing from ancient medical philosophy since more than thousands of years. The exact mechanism of action of herbal drug is still a controversial, widespread application of herbal product has proven the availability of herbal drug product, which demands huge workload in sample separation and bio-screening. In most of the cases, some active compositions can be discovered in this way, but the pure compound obtained cannot have the same medicinal effect as the original formulation. On the other hand, because these active components are derived from clinically useful herbal medicines, appropriate combination of active components will improve the hit rate in discovering potential herbal drug. Thus, as suggested new herbal drug should be designed as a combination of several active compositions to ensure the holistic and synergistic effects of herbal medicine. Therefore a feasible way for the production of combined herbal medicine suggests two steps. The first step is rapid and repeatable isolation of active components. The second step is combining these active components in proper ratio for its better efficacy.

In clinical practice, Indian Aurvedic practitioners often modulate the proportion of herbs according to the status of patients. In this way, the chemical composition of herbal medicine is changed. This adjustment happens according to clinical experience of the doctor. In this study, interpretation of created soft computing models can give an insight into the chemical compositions and biological action and allow for narrowing the combinatorial range of active compositions. Such focused screening can reduce the repeated experiments and increase the effectiveness of herbal drug design.

	Major anti-diabetic active components (in gm)						Biological activity
Sample number	C1	C2	C3	C4	C5	C6	Reduction in blood glucose level (%)
1	0.285	0.232	0.000	0.068	0.175	0.240	71.38
2	0.105	0.208	0.111	0.266	0.056	0.254	73.37
3	0.241	0.108	0.000	0.222	0.105	0.324	74.47
4	0.308	0.115	0.117	0.161	0.182	0.117	74.87
5	0.079	0.085	0.299	0.112	0.291	0.134	75.53
6	0.198	0.215	0.000	0.172	0.268	0.147	76.85
7	0.148	0.252	0.210	0.088	0.249	0.053	78.38
8	0.000	0.052	0.289	0.275	0.185	0.199	78.54
9	0.168	0.233	0.000	0.228	0.115	0.256	79.01
10	0.138	0.242	0.085	0.172	0.291	0.092	79.47
11	0.239	0.134	0.221	0.181	0.000	0.225	79.78
12	0.128	0.324	0.000	0.274	0.192	0.082	80.26
13	0.253	0.104	0.288	0.172	0.082	0.101	80.40
14	0.170	0.000	0.150	0.330	0.180	0.170	81.29
15	0.165	0.155	0.175	0.225	0.135	0.145	82.36
16	0.000	0.210	0.200	0.190	0.250	0.150	83.43
17	0.330	0.140	0.180	0.170	0.180	0.000	86.71
18	0.900	0.120	0.150	0.180	0.210	0.250	86.43
19	0.135	0.145	0.155	0.165	0.175	0.225	86.67
20	0.145	0.175	0.180	0.150	0.160	0.190	86.66

Table 1: Predicted bioactivity of individual optimized drugs

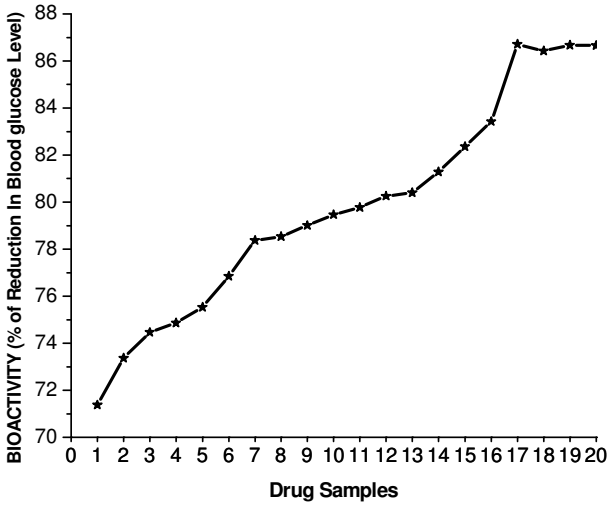

Figure 2: The line symbol graph showing the relation between the drug sample and their maximum bioactivity. The X-axis represents the drug sample number and the Y-axis represents the simulated bioactivities.

5. CONCLUSIONS

The present work is just a preliminary one to study only the concept of drug design using soft computing approach. Further work will be extended for the development of drug, which can reduce, both time and cost. The hybrid soft computing approach can be extended for any kind of diseases. These models can be useful for predicting the biological activity of new untested drug for identifying new active compounds in the traditional drug.

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7. REFERENCES

[1] S. Arumugama, S. Kavimanib, B. Kadalmanic, A.B.A. Ahmedd, M.A. Akbarshac, M.V. Rao. *"Antidiabetic activity of leaf and callus extracts of Aegle marmelos in rabbit".* Science Asia, 34: 317-321, 2008

[2] E. Chan, M. Tan, J. Xin, S. Sudarsanam, D.E. *"Johnson. Interactions between traditional Chinese medicines and Western therapeutics",* 13(1): 50-65, 2010

[3] V.P. Dixit, R. Sinha, R. Tank. *"Effect of Neem seed oil on the blood glucose Concentration of normal and alloxan 4diabetic rats".* Journal of Ethnopharmacology, 17: 95-98, 1986

[4] J. K. Grover, S. Yadav, V. Vats. *"Medicinal plants of India with antidiabetic potential".* J. Ethnopharmacology, 81: 81–100, 2002

[5] P. Heacht. *"High-throughput screening to odds with informatics-driven chemistry".* In current drug discovery, 21-24, 2002

[6] J. Holland. *"Adaptation in Natural and Artificial Systems".* University of Michigan Press (1975)

[7] M.D. Ivorra, M. Paya, A. Villar. *"A Review of natural products and plants as potential antidiabetic drugs".* Journal of Ethnopharmacology, 27: 243–275, 1989

[8] Y. Wang, X. Wang, Y. Cheng. *"A Computational Approach to Botanical Drug Design by Modeling Quantitative Composition–activity Relationship".* Chem Biol Drug Des, 68: 166–172, 2006

[9] E.E. Jarald, E. Sheeja, S. Motwani, K.R. Dutt, R.K Goel. *"Comparative Evaluation of Antihyperglycemic and hyperglycemic Activity of various Parts of Catharanthus roseus Linn".* Research Journal of Medicinal Plant, 2(1): 10-15, 2008

[10] S. Rajasekaran, D. Aathishsekar. *"Therapeutic Evaluation of Aloe vera leaf Gel Extract on Glycoprotein Components in Rats with Streptozotocin Diabetes".* Journal of Pharmacology and Toxicology, 2(4): 380-385, 2007

[11] A.Q. Shamim, W. Asad, V. Sultana. *"The Effect of Phyllanthus emblica Linn on Type – II Diabetes, Triglycerides and Liver - Specific Enzyme".* Pakistan Journal of Nutrition, 8(2): 125-128, 2009

[12] P. Scartezzini, E. Sproni. *"Review on some plants of Indian traditional medicine with antioxidant activity".* J. Ethnopharmacol, 71: 23–43, 2000

[13] S.D. Seth, B. Sharma B. *"Medicinal plants of India".* Indian J. Med. Res, 120: 9–11, 2004

[14] H. Sumida, A.I. Houston, J. M. Mcnamara, D.W.D. Hamilton. *"Genetic Algorithms and Evolution".* J. Theor. Biol, 147: 59-84, 1990

[15] V. Venkatasubramanian, A. Sundaram. *"Genetic algorithms: introduction and applications".* Encyclopedia of Computational Chemistry, John Wiley &Sons, pp. 1115–1127 (1998)

[16] T. Vetrichelvan, M. Jegadeesan. *"Anti-diabetic activity of alcoholic extract of Aerva lanata (L.) Juss. ex Schultes in rats".* Journal of Ethnopharmacology, 80: 103–107, 2002

[17] U. C. S. Yadav, K. Moorthy, N. Z. Baquer. *"Combined treatment of sodium orthovanadate and Momordica charantia fruit extract prevents alterations in lipid profile and lipogenic enzymes in alloxan diabetic rats".* Molecular and Cellular Biochemistry, 268:111–120, 2005

[18] J. Zupan, J.Gasteiger. *"Neural Networks in Chemistry and Drug Design (2nd edn)".* John Wiley & Sons (1999)