



A genetic algorithmic approach to optimize the compound of natural herbs in the treatment of rheumatoid arthritis-A study

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ABSTRACT

The main objective is to prepare a drug from natural herbs and to optimize the component molecules in the drug using computational algorithms. Natural way of medication is advisable to avoid side effects. A natural drug has been proposed, out of herbs available in hilly regions of Tamilnadu. And Genetic Algorithmic (GA) approach is introduced for optimizing the natural drug prepared from various herbs. A variety of clinical tests like SDAI, CDAI is discussed. These tests are conducted clinically for finding out the activity of the disease. Simulated tests for optimizing the various 10 different combinations based on random weights of the natural drug is conducted. Selecting the best combination based on ACPA is done. This Siddha or Ayurvedic approach will be very useful for RA affected patients, when it is optimized using computer algorithms like GA. Also the various clinical tests for finding the activity of RA disease are studied.

Keywords: Rheumatoid Arthritis, Natural herbs, Drug preparation, Genetic Algorithms, Clinical tests

INTRODUCTION

Rheumatoid Arthritis popularly known as RA is one of the vulnerable disease, similar to cancer. Research has been conducted to identify this disease in early stages and to cure it completely. Symptoms of RA include swell in joints, deformation, joint pain, morning stiffness, grip loss while holding any object, mild fever etc. Some drugs have been invented to control this disease. But most of the drugs contain steroids, causing huge side effects like eye sight loss, kidney disorder, malfunctioning of vital organs, high blood pressure etc. There is a need of a medicine which should cure this disease completely without causing any side effect. Initially the methods and drug preparation processes like HTS, Docking are discussed in this paper. Also, a natural way of curing RA in its early stages is proposed by combining various herbs. And Genetic Algorithm (GA) approach is proposed for optimizing the compound prepared from natural herbs. Clinical test for finding the activity level of the disease can be followed in India. Currently, such tests are recommended by the American College of Rheumatology.

RA is diagnosed in 0.5% to 1.0% of people across the world, especially women aged between 40 to 60 years[1]. Environmental and Genetic factors are the main factors causing RA[2,10]. The specific diagnosis of RA positivity includes reduced Red Blood Corpuscles (RBC) due to sever anemia, thrombocytosis in WBC (White Blood Corpuscles) due to inflammation, high ESR(Erythrocyte Sedimentation Rate) etc.

Alagesaboopathi[3] surveyed about the medicinal plants available in Kumargiri hills of Tamilnadu, India. Some of the species in his survey have the capacity of curing rheumatoid arthritis. Aloe Barberdensis Mill(Lilliaceae) plants juice is used to cure rheumatism. The powder of the plant Calotropis Gigantea, along with cow's milk is used for curing the disease. Cardiospermum Luridium(Sapindacea), also known as Modakathan in Tamil is used to cure rheumatic pains. Ficus Benghalensis latex is applied to the bone joints, externally for curing purpose.

Maran [4] has given some tips on Sidha Medicine. He gave some important tips on curing Rheumatoid Arthritis. Ocimum Sanctum or Ocimum Tenuiflorum also called 'Holy basil or 'Tulsi' in India. Usually it grows up to 55cm height. It is not only a natural medicine, but also an Ayurvedic medicine It cures indigestion problems and also neck, head and skin related diseases. It is also a mind sharpening agent and it reduces stress. Above all it is used with other ingredients to cure Rheumatoid arthritis disease. Zingibe Officinalis which is usually called as ginger is found in almost all the continents. This can be taken regularly with food to cure a variety of diseases.

Muthuraman et al[5], overviewed the properties of Sida Cordifolia Linn and its biological perspectives. He also stated the importance of natural herbs in drug preparation. And this can be used for preparing both allopathic and homeopathic drugs.

Fransen et al[6], described the disease specific measures on RA. He classified the level of RA activity as low, medium, high. Soeken et al[7], reviewed the usage of herbs in preparing drugs for RA. This review was based on randomized clinical trials. They also investigated about the safety and efficiency of such drugs. Sridevi et al[8] performed in-vivo and in-vitro tests and studied about identifying the cytotoxic levels. The authors also investigated about anti-venom property of some medicinal plants. Reddy[9] investigated about the liver of *Mystus Tengia* fish. He analyzed the aggregation of inflammatory cells in its liver. This paper helps in studying about the liver tests[10].

Harish Chander et al[11] utilized a variety of computational approaches for recognizing the micro RNAs. This computational approach is very essential for preparing an effective drug. Valentina et al[12] experimented with Mangrove derived fungi, which is found in mangrove trees and its surroundings. Her investigations proved the anticancer activity of this fungus. Mohan et al[21] suggested a structure guided inhibitor which can be used to discover protein leads. This is used in the treatment of Cancer like diseases.

EXPERIMENTAL SECTION

2.1. High Throughput Screening(HTS)

HTS scenarios are followed in the effective preparation of drugs. HTS is a group of compound analysis, which is usually performed on cell lines, glasswares and microorganisms based on their need.

HTS scenario 1 comprises of the following

- Identifying the reagents, which are complete meaningful candidates
- Docking on the protein structure for identifying the potential of candidates
- Ranking molecules based on highly bounded affinity
- Non Satisfactory candidates are filtered
- The candidate molecules that satisfy the above criteria reaches the optimization stage and have pharmacokinetic properties. Such a reagent undergoes other HTS scenarios and then selected for further stages in the preparation of the drug

2.2. Docking

Docking is a method of predicting orientation of preference of molecule over the other. This forms a stable complex.

2.3. Drug Preparation Process:

Steps in converting prodrug to the drug

Step1: Initial docking is done on the fragment of molecules

Step2: Initially prodrugs are formed.

Step3: Prodrugs with good ADME(Absorption, Distribution, Metabolism, Elimination) are taken to the next stage of conversion into drug

Strategies for synthesizing real molecule in the drug design process:

- i. Inside-out-Strategy
- ii. Outside-in-Strategy

In the proposed drug preparation, the inside out approach is recommended for synthesizing. The following steps are followed in the ongoing process:

- a. Selection of scaffold, which is a temporary supporting structure.
- b. Identify the physicochemical properties of molecules.
- c. Group the fragments on the scaffold
- d. Form a chemically meaningful structure
- e. Ensure the fragments are tightly coupled in the scaffold forming a bioactive molecule

Kinematics[13] explains the physical processes evolving along with the time. It includes various factors like organ growth, drug distribution in the body, chemical reactions etc. Velocity of drug in the body can be identified by the equation, $v = \frac{\partial a}{\partial b}$, where v describes the movement of the drug in the body, a is the distance travelled by the drug from the point of intake to the point where reaches the body and b is the time taken by the drug to react after intake.

Table 1:A sample compound powder comprising of natural herbs for curing RA

Ingredient id	Name in Tamil Language	Botanical Name	Part used
I1.	Vilvam	Aegle Marmelos	Dried Leaf
I2.	Thulsi	Ocimum Sanctum	Dried Leaf
I3.	Aruku	Enicostema Littorale	Dried Leaf
I4.	Nelli	Phyllanthus Emblica	Dried Fruit
I5.	Murungai	Moringa Pteryosperma	Dried Leaf
I6.	Neem	Azadirachta Indica	Dried Leaf
I7.	Vallarai	Centella Asiatica	Dried Leaf
I8.	Kadukai	Terminalia Chebula	Dried Fruit
I9.	Avarambu	Cassia Auriculata	Dried Flower
I10.	Kuppameni	Acalypha Indica	Dried Leaf
I11.	Thuduvilai	Solanum Tricobatum	Dried Leaf, Dried Fruit
I12.	Athi	Ficus Carcia	Dried Fruit
I13.	Mango	Mangifera Indica	Dried Leaf
I14.	Nithyakalyani	Vinca Rosea	Dried Root

Table 1 gives a list of ingredients to be added for preparing a drug which has anti-cancerous properties[4]. This prodrug is prepared by drying all the ingredients in sun. Then I1 through I14 is ground to a powder. This powder can be kept in a glass container or in any porcelain container. This can be kept outside (without refrigeration) for years. One more advantage of this mixture is, it is unaffected by any bacteria or climatic changes. There are many ways of preparing natural drugs, like herbal juice or herbal paste (legiyam) or powdered and dried tablets. When ever needed, the drug can be taken orally usually before food. This natural drug can be given to any person in the initial stages of RA [4]. Other recommended natural herbs for curing RA [4,14,15] are given in Table 2. Some of the natural products are applied externally for pain as well as swell relief. Some are taken orally.

Table 2: Other natural herbs used in the treatment of RA, some externally applied

Botanical Name	Part used
Thespesia Populnea	Milk and Gum
Raphanus Sativus	Root
Neolamarckia Cadamba	Seed
Cardispermum Halicacabum	Leaves
Ocimum Basilicum	Leaf
Pistia	Leaves
Dolonix Elata	Leaves
Vernonia Cinerea	Flower
Anisomeles Malabarica	Leaves
Hiptage Bengalensis	Leaves
Tephrosia Purpurea Pers	Leaves
Vigna Mungo	Root
Madhuca Longifdia	Seed
Wagatea Spicata	Flower, root
Datura alba	Leaves

2.4. Drug Optimization using GA

GA[16] approach is proposed for cell development based on various combinations of the compound comprising of 14 ingredients I1 through I14. A drug is said to be effective if the defective cells are removed and the healthy cells reproduce in more numbers. GA depicts the same. In the presence of the proposed compound, a few cells occur enzymatic resistance and gain the ability of mutation, crossover and reproduction until an optimal solution or a healthy population of cells is obtained. Anti Citrullinated Protein Antibody (ACPA) is present in RA patients. ACPAs are important in diagnosing RA[17].

2.4.1.Steps in GA

Step 1: Form various combinations c_i (random weights) based on ACPA content in natural drug

This is achieved by the formation of Priority Queue each for a particular combination c_i .

Step 2: Calculate the fitness function $f(c_i)$

Step 3: Probability $pi = \frac{f(c_i)}{\sum f(c_i)}$

Step 4: Find Expected count $expected_vi = \frac{f(c_i)}{average(f(c_i))}$

Step 5: Objective function o is calculated as $o_i = \left(1 - \frac{\text{actual_}v_i}{\text{expected_}v_i}\right)^2$

Step 6: Rank the combinations of c_i s having higher objective function

Step 7: Perform Cross over on the c_i s having best o_i s based on threshold, $\tau = \frac{\sum o_i}{oi}$

Step 8: Based on the above steps, choose the best individuals to be inherited to the next generation.

2.5. Approaches for evaluation of RA clinically

There are various tools to measure the RA disease activity. Some of them are given

- CDAI: Clinical Disease Activity Index[18] $CDAI = w + x + y + z$ where w : Swollen 28 Joint Count(SJC), x : Tender 28 Joint count(TJC), y : Patient Global Disease Activity (PGA) and z is Evaluators Global Disease Activity (EGA)
- SDAI: Simplified Disease Activity Index. CDAI test on including CRP test is the SDAI test. This test is recommended by the American College of Rheumatology for measuring the disease activity of RA[19]. C-Reactive Protein (CRP) is a type of protein released by the liver into the blood stream within a particular time after tissue injury[10]. It is measured in milligrams or DeciLitres. American College of Rheumatology has given electronic calculator to measure the index of disease activity of RA. On giving any RA drug, if the percentage of index reduces by 6.5, then it shows good improvement[20]. Table 3 gives the SDAI evaluation measures[19].

Table 3: SDAI evaluation measures

Index Measure	Range
TJC	0-28
SJC	0-28
PGA	0-10
EGA	0-10
CRP	0-10
Total	0-86

2.5.1. Algorithm to calculate SDAI

Let DA: Disease Activity

IF $SDAI \geq 0.0$ and $SDAI \leq 3.3$

Then DA = "Remission"

Else if $SDAI \geq 3.4$ and $SDAI \leq 11.0$

Then DA = "Low"

Else if $SDAI \geq 11.1$ and $SDAI \leq 26.0$

Then DA = "Moderate"

Else if $SDAI \geq 26.1$ and $SDAI \leq 86.0$

Then DA = "High"

RESULTS AND DISCUSSION

Table 4 represents the simulation of the selection process of GA. Table 5 gives Ranked Combinations ready for crossover and mutation for the next generation.

Table 4: GA optimization based on ACPA

Combinations	Random weights	Fitness based on ACPA	Probability	Expected count	Actual count	Objective function
c1	3	18	0.06	0.84	1	0.04
c2	4.5	27	0.09	1.26	1	0.04
c3	2	12	0.04	0.56	1	0.62
c4	1	6	0.02	0.28	1	6.60
c5	4	24	0.08	1.12	1	0.01
c6	5.5	33	0.11	1.54	1	0.12
c7	6	36	0.12	1.68	2	0.04
c8	3	18	0.06	0.84	1	0.04
c9	2	12	0.04	0.56	1	0.62
c10	3	18	0.06	0.84	1	0.04

Table 5: Ranked Combinations

Combinations	Objective function	Rank
c4	6.60	1
c3	0.62	2
c9	0.62	3
c6	0.12	4
c2	0.04	5
c1	0.04	5
c7	0.04	5
c8	0.04	5
c10	0.04	5
c5	0.01	6

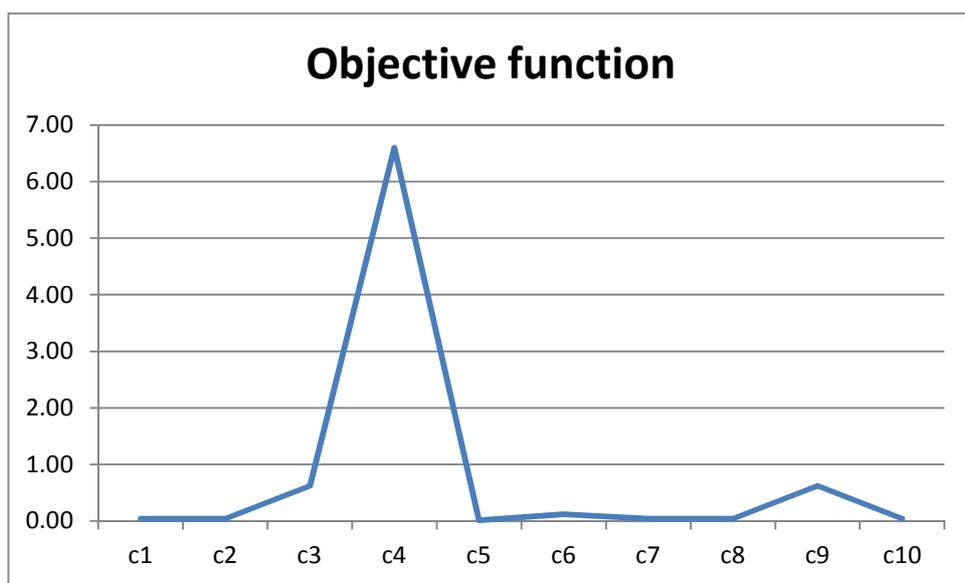


Figure 1: Objective function for various combinations of I1 to I14

Fig 1 shows the combination, c4 has the highest objective value and hence it is recommended for performing crossover to obtain next healthy generation (iteration). Threshold obtained on ranking the combinations for docking is .8. The combinations which are having a value above this threshold are the fittest. Those combinations below this value are trained to become fitter in further iterations after mutation or crossover process. The iteration is continued until a saturated value of fitness reaches.

CONCLUSION

The proposed natural drug optimized with a GA based ACPA approach. It can be given to the RA patients with low level of RA activity. The natural drug can be given to the patients, who are in the early stages of RA, regularly. Long term intake will give better results. This is an initiative to cure RA at its early stages. This paper is will be useful to know about RA and natural way of curing it. The aim behind this article is to create an awareness about the natural drugs available in the treatment of RA. Also a study is conducted on clinical tests, available for evaluating the activeness of the disease.

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