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Abstract

More than 10 million Americans, three quarters of them women, suffer some degree of recurrent migraine headaches. Feverfew (*Tanacetum parthenium* (L.) Schultz-Bip.) is a member of the Asteraceae family that is native to Europe. This plant is a perennial flowering aromatic plant common in gardens. It has been widely used as a self-medication of arthritis, fever, and migraine headaches for over 2000 years. Sesquiterpene lactones (SL) are the components responsible for the antimigraine activity of feverfew. In this research, the relationship between SL structural information and their biological activity was studied by using Gaussian 92 program in conjunction with artificial neural networks (ANNs). The molecular orbital parameters of SL were obtained by using Gaussian 92 program. A set of 39 SL molecules was divided into two groups, a training set containing 33 molecules and a testing set containing six molecules. An ANN was trained and tested by using training sets and testing sets on SL's antimigraine activities. The results showed that ANNs successfully predicted the antimigraine activities of SL based on their different structural information.

Introduction

Migraine headaches are highly prevalent disorders, they can be physically and psychologically disabling. More than ten million Americans, three quarters of them women, suffer some degree of recurrent migraine headaches. Migraine can affect any age group but the peak years are ages between 25 and 55. The annual cost of medical care and lost productivity because of migraines in the United States has been estimated to range from $1.2 billion to $17.2 billion (Lipton et al., 1993). It really has become an economic burden on society. Furthermore, reports of migraine in the United States have increased dramatically since 1980, for example, migraines prevalence increased 60% from 1981 to 1989 (Lipton et al., 1997).

Serotonin (5-hydroxytrypamine or 5-HT) is considered to be one of the most important neurotransmitters associated with migraine headaches since recent studies showed that the distribution of 5-HT in the blood of migraine patients differs from that in control subjects. Release of 5-HT from blood platelets can constrict blood vessels and contribute to migraine pain. The antimigraine activity of SL was expressed by the inhibition of serotonin released from platelets by the SL (Marles et al., 1995).

Biological activity of any compound is a direct consequence of its molecular structure, investigations of the relationship between chemical structure and the activity of compound are helpful in understanding the activity of interest and in predicting the activity of new compounds based on knowledge of the chemical structure alone.

This paper discusses one approach which employs self-consistent field-molecular orbital (SCF-MO) quantum mechanical calculations (Clark, 1985) in conjunction with artificial neural networks on prediction of antimigraine activity of SL. The structural information of SL were obtained by using Gaussian 92 program and ANN was trained and tested on the antimigraine activities of 39 SL.

Materials and Methods

Computational studies were performed using Silicon Graphic's R4400 or R4600 computers. There are three main steps used in this research. First, SL structures were obtained directly from Cambridge Structural Database (Cambridge Crystallographic Data Centre, Cambridge, UK) or built by modification of related structures available in this database using some tools in SYBYL 6.2 (Tripos associates, St. Louis, MO, USA). The geometry of lowest energies of each molecule was obtained for the further investigation.

Second, quantum mechanical calculations using the Gaussian 92 program were run on each SL structure to

obtain their structural information, such as eigenenergy and dipole moment. The input for the calculations was an internal coordinate matrix (Z-matrix) of the SL structure with lowest energy. The basis set used was a STO-3G* and POP=REGULAR was used as a keyword to do the regular population analysis. The eigenenergies of the lowest fifteen unoccupied molecular orbitals, the highest fifteen occupied molecular orbitals and the dipole moment of each molecule were chosen from the output file of Gaussian 92.

Finally, ANNs were employed to make the necessary correlation between structual information and the antimigraine activity of SL. The antimigraine activity data of SL were measured as their ability to inhibit the release of serotonin (IC_{50}) and previously reported by Marles and co-workers (1995). IC_{50} is the micromolar concentration of SL that will inhibit the release of serotonin by 50%.

ANNs are computer models that were first developed based on the neural structure of the brain. The brain basically learns from experience. In particular, the most basic element of the human brain is a specific type of cell known as neurons. The power of the human mind comes from the large numbers of these basic components and the multiple connections between them. ANNs are massively parallel computing systems made up of a number of simple, highly interconnected processing elements which process information by determining the value of an output signal based on the values of several input signals. Figure 1 shows a three layer fully connected ANN.

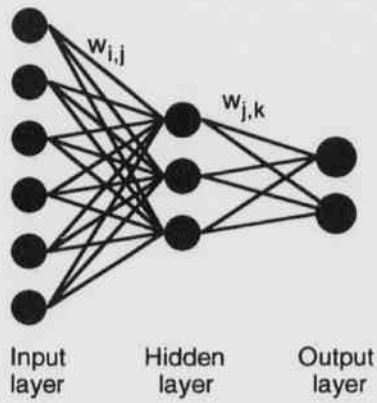

Fig. 1. Architecture of a three layer Artificial Neural Network.

ANN used in this research is error back propagated supervised neural network. It was first developed by McClelland and Rumelhart (McClelland and Rumelhart, 1986). It has been successfully used in our previous studies (Darsey, et.al, 1993; Soman, et al, 1995). As shown in Fig. 1, it has three layers inside of the network: input layer, hidden layer and output layer. Each layer usually includes several processing elements (or neurons, nodes, etc) which are the basic element of neural network. The nodes of the input layer are responsible for the distribution of the input to the next layer of nodes. One hidden layer is placed between the input and output layers.

In this case, 31 nodes which included 30 eigenenergies and 1 dipole moment, were placed in input layer, 12 nodes were used in hidden layer and only 1 node was used in output layer which was antimigraine activity of SL. All these nodes were interconnected through unidirectional connection (weights). Weights are adaptive coefficients that are changed when the network learns. Randomly set weights are used at the beginning and then adjusted by the network so that the next cycle will produce a closer match between the desired and the actual output (Haykin, 1994).

The operations in a processing element started with the computation of the weighted sum of all of the inputs. This weighted sum input, then, was transformed to a working output through a transfer function. The most used transfer function is a sigmoid function. It is used to map the weighted sum of the input values to a reasonable value, before passing the signal into the nodes in next layer. The reasonable values accepted by neural networks are between 0 and 1.

The network learns when it is trained based on a data driven system. Backpropagation network processes the inputs and compares the resulting outputs to the actual outputs. Outputs errors are propagated back through the system, causing the system to readjust the weights. This process runs over and over until continually tweaking the weights.

Once, the network is "taught" how to respond to a set of specific examples, these weights are stored. The network is tested for the accuracy of its predictions of biological activities of SL not included in the training set, using these weight. The dataset which included eigenenergies and dipole moments of 39 SL was divided into two group, one group (training set), which included 33 SL, was used for training the network and another group (testing set), which included six SL, for testing the network prediction. Then, an ANN was trained by using training set to a satisfactory error limit 0.001 and tested by using testing set. This training and testing process were repeated by using different set of training and testing set until all the SL wer predicted once.

Results and Discussion

The basis set used in Gaussian 92 program is STO-3G*, the selection of this basis set is a compromise between qual-

Table 1.

Compound Name	Biological Activity[1] Observed Data	Predicted Data	Error %
Ursiniolide A	5.75	5.68	-1.22
Cinerenin Acetate	5.69	5.71	0.35
Parthenolide	5.52	5.61	1.63
Cinerenin	5.45	5.83	6.97
Cnicin	5.45	5.42	-4.95
Helenalin	5.37	5.19	-3.35
Melampodin A	5.29	5.23	-1.13
Ursiniolide B	5.28	5.32	0.76
Alatolide	5.26	5.22	-0.76
Stizolicin	5.24	5.67	8.21
Centaurepensin	5.22	5.23	0.19
Repin,15-deoxy	5.20	5.23	0.58
Arbusculin B,l β-hydroxy-8β-epoxyangeloyloxy	5.18	5.45	5.21
Santamarin,8β-O-epoxyangelate	5.15	5.14	-0.19
Enhydrin	5.06	5.02	-0.79
Confertiflorin	5.05	5.39	6.73
Repin	5.03	4.91	-2.39
Reynosin,8β-0-2,3-dihydroxy -2-methylbutyrate	5.02	5.01	-0.20
Reynosin,8β-O-epoxyangelate	4.99	5.04	1.00
Salonitenolide	4.99	5.44	9.02
Linifolin A	4.94	4.97	0.61
Santamarin,3,4-cis-α-epoxy-8β-epoxyangeloyloxy	4.75	4.72	-0.63
Glaucolide A	4.68	4.64	-0.85
Grossheinin	4.65	4.57	-1.72
Santamarin,8β-0-(2-hydroxy-ethyl) acrylate	4.75	4.60	0.66
Tatridin B	4.57	4.56	-0.22
Parthenolide, l,10-dihydro-	4.39	4.36	-0.68
Psilostachyin A	4.36	4.29	-1.61
Asperilin	4.24	4.27	0.71
Aromaticin,6α-hydroxy-2, 3-dihydro	4.22	4.16	-1.42
Geigerinin	4.14	4.13	-0.24
Santamarin	4.07	4.09	0.49
Xerantholide	3.99	4.00	0.25
Parthenin	3.89	3.86	-0.77
Vachanic acid,methyl ester	3.70	3.71	0.27
Coronopilin	3.60	3.62	0.56
Burrodin	3.60	3.57	-0.83
Reynosin	3.57	3.54	-0.84
Schkuhriolide	3.56	3.53	-0.84

[1]Biological activity is the Log ($1/IC_{50}$) where IC_{50} is the micromolar concentration of SL that will inhibit the release of serotonin by 50%. Values were taken from Marles et al. (1995).

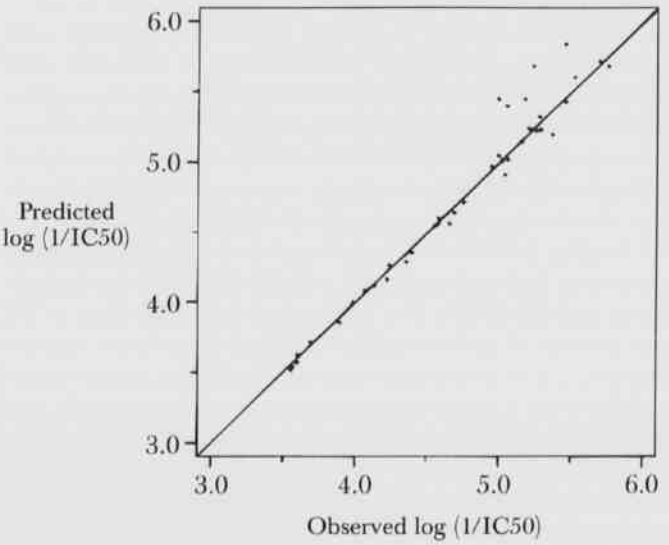

Fig. 2. Correlation between the actual values and the predicted values of biological activities of SL by using ANN.

ity of the results and availability of computer resources. More detailed basis sets such as 6-31G, that could potentially provide higher quality results. However, it produced files larger than the two-gigabyte limit that the computer operating system (IRIX 5.3) could handle.

ANNs analysis of the antimigraine activity of SL was performed as indicated in the methods section, with a training set of 33 SL and a testing set of 6 SL. Several runs were conducted in this manner. The results of this analysis are presented in Table 1, and a plot of predicted versus observed activity is presented in Fig. 2. It can be observed that the percent error for prediction of antimigraine activity of SL ranged from a minimum of -0.19 to a maximum of -9.02. These errors are very low and most of them are probably smaller than experimental error. Figure 2 also showed that ANNs did very well in correlating the structural information and their antimigraine activity of SL since most of the data are in the straight line in this plot.

Conclusions

In this research, we have demonstrated the use of ANNs in mapping quantum mechanical parameters to antimigraine activities of SL. ANNs were found to be very successful in correlating the SL's structure with their antimigraine activity, although they provided very limited information on the particular requirements for maximum activity.

Additional studies on the structure-toxicity relationship studies of the SL using ANNs should be very helpful in identifying or designing SL with high activity and low toxic potential. Also, this method might be applied to map quantum mechanical parameters to other chemical, physical and biological properties of different groups of molecules.

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