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ORIGINAL RESEARCH PAPER

Nature is the best source of anti-inflammatory drugs: indexing natural products for their anti-inflammatory bioactivity

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Abstract

Objectives The aim was to index natural products for less expensive preventive or curative anti-inflammatory therapeutic drugs.

Materials A set of 441 anti-inflammatory drugs representing the active domain and 2892 natural products representing the inactive domain was used to construct a predictive model for bioactivity-indexing purposes.

Method The model for indexing the natural products for potential anti-inflammatory activity was constructed using the iterative stochastic elimination algorithm (ISE). ISE is capable of differentiating between active and inactive anti-inflammatory molecules.

Results By applying the prediction model to a mix set of (active/inactive) substances, we managed to capture 38% of the anti-inflammatory drugs in the top 1% of the screened set of chemicals, yielding enrichment factor of 38. Ten natural products that scored highly as potential anti-inflammatory drug candidates are disclosed. Searching the PubMed revealed that only three molecules (Moupinamide, Capsaicin, and Hypaphorine) out of the ten were tested and reported as anti-inflammatory. The other seven phytochemicals await evaluation for their anti-inflammatory activity in wet lab.

Conclusion The proposed anti-inflammatory model can be utilized for the virtual screening of large chemical databases and for indexing natural products for potential anti-inflammatory activity.

Keywords Anti-inflammatory · Chemoinformatics · Ligand-based modeling · Bioactivity index

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Introduction

Inflammation is critical for the development of many complex diseases and disorders including autoimmune diseases, metabolic syndrome, neurodegenerative diseases, cancers, and cardiovascular diseases [1]. This warrants the increasing interest in looking after anti-inflammatory agents. Many original and review papers have reported the inhibitory effect of plants and isolated natural products on inflammation processes, at least in low-grade inflammation. These included natural polyphenols [2], resveratrol [3], quercetin [4], lycopene [5], aspirin [6], edible plants such as tomato [5], cactus [7], *Citrus grandis* [8], and herbal medicine [9, 10]. In general, there is a strong public need for natural [10, 11] and less expensive preventive and curative anti-inflammatory therapeutics [12].

Extended knowledge regarding inflammation will optimize and hasten the development of innovative therapeutic targets from natural sources, which can be used to manage various chronic inflammation-related diseases. Computer methodologies are utilized here, either to discover new hits or to virtually screen large chemical databases [13–16]. There are two crucial components for constructing predictive models: an optimization method and databases of active and inactive chemicals. Such models employ optimization algorithms—for example, simulated annealing [17], genetic algorithms [18, 19], neural networks [20, 21], support vector machines [22, 23], the k-nearest neighbors algorithm [24, 25], and combinations thereof [25–29]. These computerized techniques assume that the set of active chemicals shares common features that are not easily defined if only a narrow space from the active space is utilized. Thus, using a large number of diverse active molecules helps us draw significant and robust conclusions concerning the properties of the active space. The inactive chemicals should cover the property space of the virtually screened database.

Over the last decade, we have developed a novel algorithm, termed the iterative stochastic elimination (ISE) algorithm, which is designed to scan a multi-dimensional space and identify the best solutions (termed global and local minima). It has been applied to solve bioinformatics problems—for example, positioning protons [30], predicting side chains conformations [31], scanning the conformational space of loops [32], and searching the conformational space of cyclic peptides [33] and loops [34]. Later, it was tailored to solve ligand-based problems, such as picking up discriminative descriptors and optimizing the ranges of descriptors to produce the best solutions for differentiating between active/inactive objects. Models that can index chemicals for their molecular bioactivity [25, 35, 36] and prioritize molecules in large databases [36, 37] have also been constructed. It is worth to assign that the anti-inflammatory drugs may act on different biological targets via various mechanisms of action [38, 39]. However, based on our previous experience [35], the proposed filter-based indexing approach is a useful technique capable to deal well with such complex problems.

Materials and methods

To construct a predictive model, we used a set of 441 anti-inflammatory drugs [presented in SMILES format in the supporting information (SI-Table 1)] to represent the active domain and 2892 natural products to represent the inactive domain. This natural product database was prepared by collecting phytochemicals isolated from more than 800 different plants distributed worldwide and is available for purchase from AnalytiCon Discovery (http://www.ac-discovery.com). The diversity within the set of anti-inflammatory drugs is presented in Fig. 1a, and the diversity within the set of natural products in Fig. 1b. The decision to use a natural product database for the inactive domain is justified, since prediction models utilized for virtual screening should possess the same properties' range as the chemicals in the screened database, and this database was prepared from phytochemicals isolated from plants.

The physico-chemical properties of all of the molecules in both databases were identified with molecular operating environment (MOE) software, version 2009.10. The one-dimensional and two-dimensional descriptors were based on calculated physico-chemical properties, such as molecular weight, log *P*, H-bond donors, H-bond acceptors, solubility, total charge, charge distribution, type and number of atoms, and so forth (http://www.chemcomp.com/journal/descr.htm). For the validation and assessment of the constructed model, the data sets of the active/inactive chemicals were split into two-thirds for the training set and one-third for the test set. The whole set was partitioned into training and test sets with the use of a randomly picking in-house module.

The model for indexing the natural products for potential anti-inflammatory activity was constructed with the iterative stochastic elimination algorithm (ISE). With the use of the ISE algorithm [35, 40] an optimal model capable of differentiating between active and inactive molecules could be attained with filters. The filters were constructed by scanning the multivariable space to search for the best sets of descriptors ("variables") and the best range for each descriptor that could differentiate between active and inactive chemicals. Since descriptors typically interact with each other, changes in the range of one descriptor can affect the best range of another descriptor; therefore, to detect the best set of filters, an optimization process should take into consideration all descriptors of a certain set at the same time. The main steps of the ISE-based modeling process are shown schematically in Fig. 2. For further details regarding ISE and its application for obtaining the best ranges from a set of descriptors, and for the optimization process, see our previous publications [25, 36, 41]. The quality of the prediction model is evaluated by measuring various parameters such as enrichment factor, Matthews correlation coefficient (MCC), ROC curve and the area under ROC curve (AUC).

Results

The iterative stochastic elimination approach was employed to commence an in silico prediction system capable of indexing natural products for their anti-inflammatory bioactivity. This study is based on a set of 441 anti-

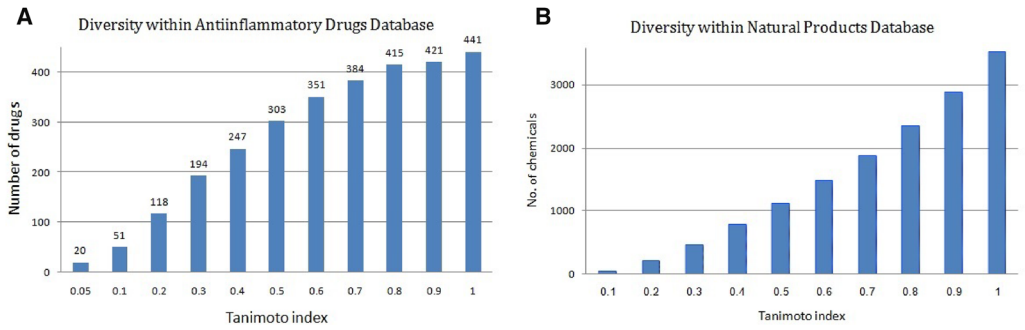

Fig. 1 Diversity within anti-inflammatory drugs (**a**, left side) and natural products database (**b**, right side)

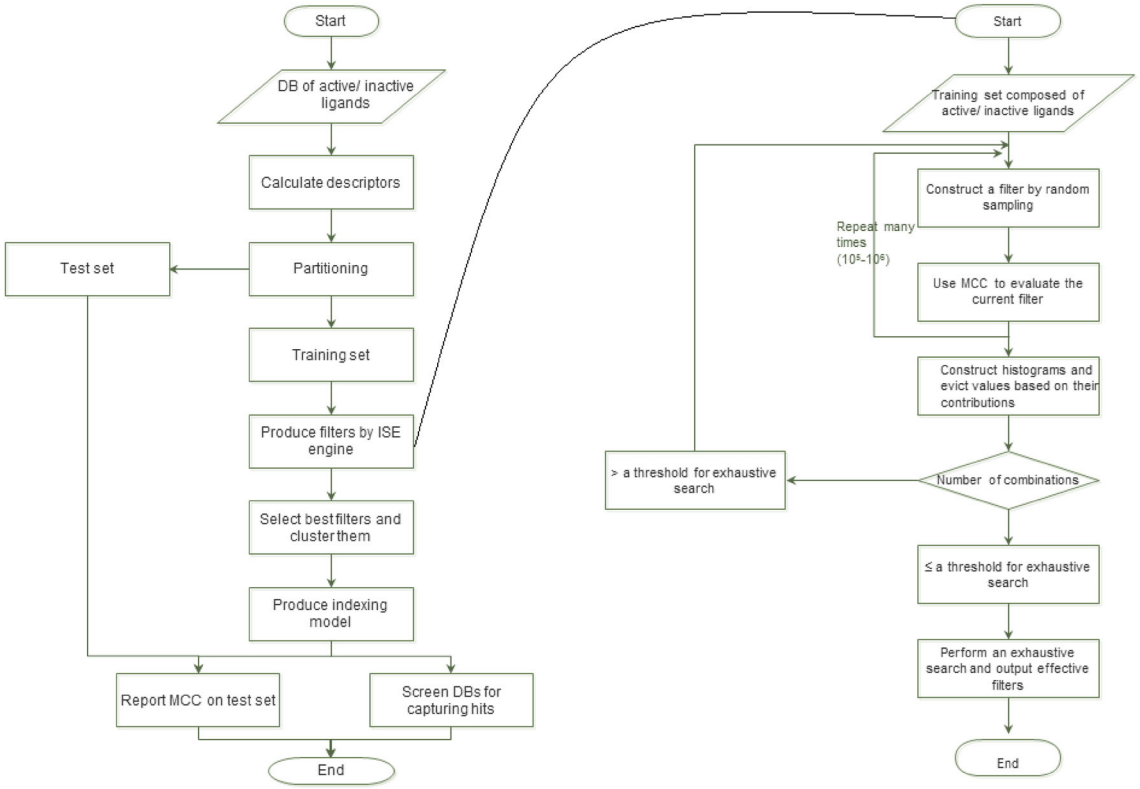

Fig. 2 Flowcharts of the modeling process (left side) and ISE engine (right side)

inflammatory drugs, labeled as the active set, and 2892 natural products, labeled as the inactive set. It is worth noting that a very small fraction of the natural products labeled inactive could, in fact, be active, and the effect of such an assumption on the quality of the prediction model would be insignificant. For highly efficient virtual screening, we had to construct the prediction model using a set of inactive chemicals that possess the same properties' space as those of the items in the screened database. As well, aiming to assure that our active class was not biased by similarities among structures, we checked for diversity among the 441 anti-inflammatory drugs and the 2892 natural products and determined that they were very diverse. More than 87% of the anti-inflammatory drugs had an intermolecular Tanimoto index of similarity < 0.7. As shown in Fig. 3, more than 95% of the anti-inflammatory drugs fall under Lipinski's rule of 5 (ROF) [42], and 88% fall under the Oprea rule for lead-likeness [43]. Figure 4 describes the distribution plots of a few of the physicochemical properties in the anti-inflammatory drugs' database.

Discussion

Fifty-two unique filters (composed of different sets and ranges of descriptors) were produced by applying the ISE algorithm and then utilized to construct the anti-

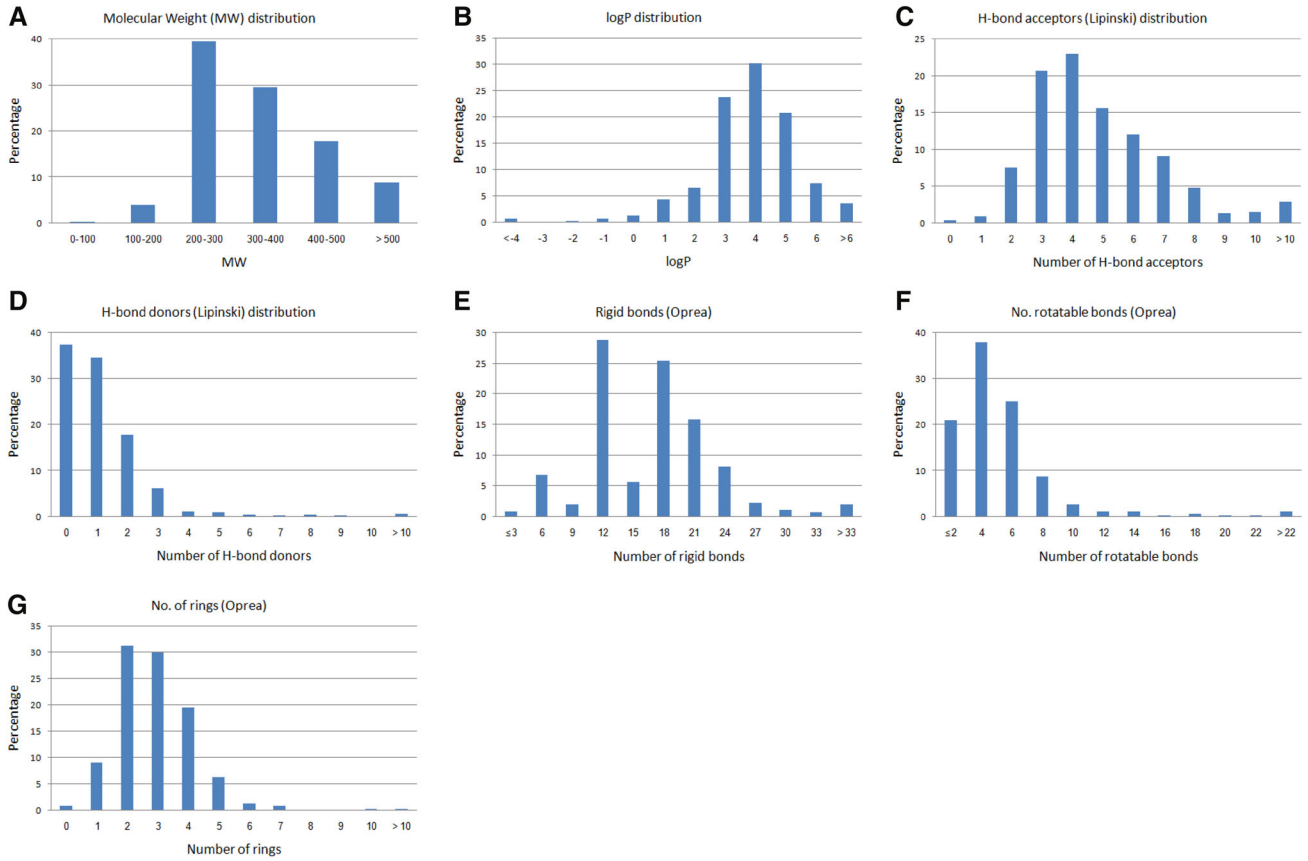

Fig. 3 Physico-chemical properties' distribution of the anti-inflammatory drugs: **a** molecular weight distribution, **b** log *P* values, **c** number of H-bond acceptors [lip_acc], **d** number of H-bond donors [lip_don], **e** number of rigid bonds, **f** number of rotatable bonds, **g** number of aromatic atoms

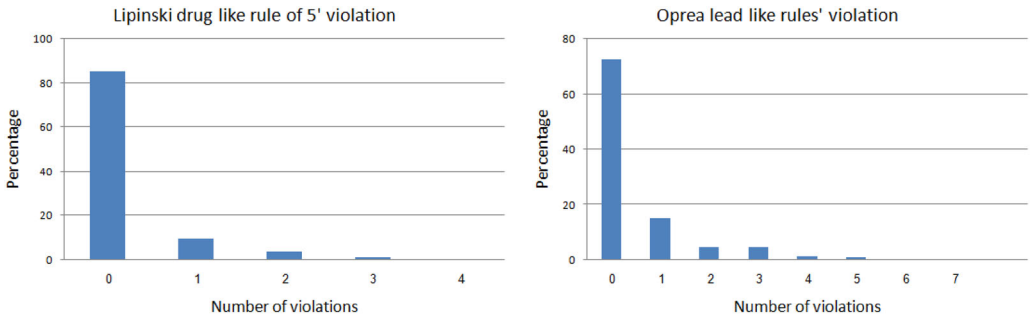

Fig. 4 Violation distribution of anti-inflammatory drugs concerning Lipinski's rules for drug-likeness and Oprea rules for lead-likeness

inflammatory indexing model. Three of these efficient filters are described in Table 1. Filter number 1 in Table 1 has an MCC of 0.60, and it identified successfully nearly 92.95% of the anti-inflammatory drugs (true positives), while only 35.34% of the natural product database was misclassified (proposed as negatives but indexed by the model as positives).

Analysis of the 52 filters in terms of their descriptors revealed their discriminative physico-chemical properties/descriptors. As shown in Table 2, the most dominant descriptors in the best filters used to produce the anti-inflammatory indexing model include, among others, the number of hydrogen bond donors, number of nitrogen atoms, Lipinski druglike, log *P* [GCUT (0/3)], and fractional positive VDW surface area. The number of appearances of the descriptors shown in Table 2 was 4.5–25.9 times higher than expected in case of random selection. Using the WORDLE module, we constructed Fig. 5, which shows the redundancy of the descriptors in a graphical manner. A full list of all the descriptors and their

Table 1 Ranges of descriptors and efficiency ratings for three of the 52 filters used to produce the anti-inflammatory indexing model

Filter 1[a]	Filter 2	Filter 3
MCC = 0.601	MCC = 0.599	MCC = 0.596
TP = 92.95%	TP = 62.27%	TP = 60.68%
TN = 64.66%	TN = 94.43%	TN = 95.26%
chi0v_C (0. to 0.80)	GCUT_PEOE_1 (−2.28 to −0.94)	a_heavy (0. to 4.0)
PEOE_VSA + 2 (0. to 1.0)	GCUT_SLOGP_0 (0. to 2.97)	GCUT_PEOE_0 (0. to 2.96)
PEOE_VSA_POS (0. to 30.95)	PEOE_VSA_POS (0. to 41.27)	GCUT_PEOE_1 (−2.28 to −0.94)
PC+ (0. to 33.80)	Diameter (0. to 78.12)	PEOE_RPC (0. to 6.13)

The definition of the physico-chemical properties of the descriptors' codes and the method, which was utilized by MOE software for their calculation, could be found in http://www.cadaster.eu/sites/cadaster.eu/files/challenge/descr.htm

[a]The filters could be composed of different sets of descriptors and/or ranges (potential lower limit/upper limit) for each descriptor

Table 2 Partial list of the redundancy of descriptors within the set of 52 filters that were used to construct the anti-inflammatory indexing model

Descriptor name	Number of appearances	Dominant more times than random
GCUT_SLOGP_0	29	25.9
a_don	17	15.2
a_nN	13	11.6
PEOE_VSA + 4	13	11.6
PEOE_VSA_FPOS	9	8
BCUT_PEOE_3	8	7.2
SMR_VSA3	8	7.2
GCUT_PEOE_3	7	6.3
GCUT_SMR_3	6	5.4
GCUT_SLOGP_3	5	4.5
Lip_druglike	5	4.5
PEOE_VSA_FNEG	5	4.5
PEOE_VSA_FPPOS	5	4.5
Q_VSA_FPOS	5	4.5
SMR_VSA1	5	4.5

The full list of descriptors is given in the supplemental information (SI-Table 2)

redundancy is given in the supplemental information (SI-Table 2).

The quality of the anti-inflammatory activity-indexing model is described in Figs. 6, 7 and 8. The MBI thresholds (*x*-axis) are plotted against the percentage of true/false positives (left *y*-axis) and against the MCCs (right *y*-axis). Figures 6 and 7 present the enrichment plot and the receiver operating characteristic (ROC) plot of the proposed anti-inflammatory activity-indexing model, respectively. The enrichment plot (Fig. 7) demonstrates how anti-inflammatory drug candidates can be identified if natural products are ranked according to the model's predictions, as opposed to random selection. Note that the enrichment plot of the ISE-based model yields results very close to those of the perfect model in the top fraction. This indicates that the proposed model has a high prioritization power. Using a mix ratio of 1:100 for active:inactive compounds, the proposed model managed to capture 34.5% of the anti-inflammatory drugs in the top 1% of the screened compounds, compared to 100% in the perfect model and 1% in the random model. This means that the enrichment factor in the top percentile was greater than 34-fold.

In the region of MBI ≥ 9.0, the ISE-based model and the perfect model somehow overlap. This means that the proposed model is highly efficient at classifying and picking anti-inflammatory drug candidates from a large pool of inactive natural products. The achieved area under the curve (AUC) was 0.94, indicating a very good prediction model. The database of natural products composed of 2892 phytochemicals was virtually screened using the proposed anti-inflammatory indexing model. We assume

Fig. 5 Number of appearances of descriptors in the 52 filters used to produce the anti-inflammatory indexing model. The picture was constructed using the WORDLE module

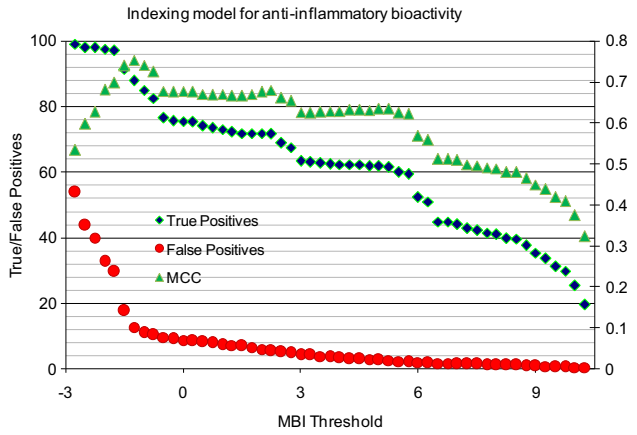

Fig. 6 Indexing model for potential anti-inflammatory bioactivity: true/false positives percentage (left *y*-axis) and MCC (right *y*-axis) plotted against MBI thresholds (*x*-axis)

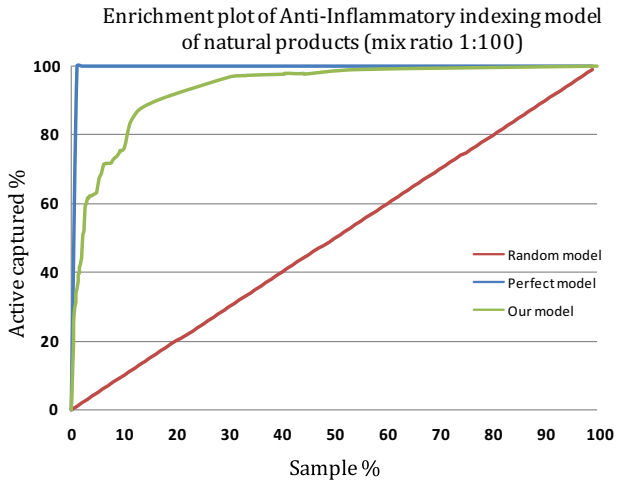

Fig. 7 Enrichment plot of the anti-inflammatory bioactivity-indexing model

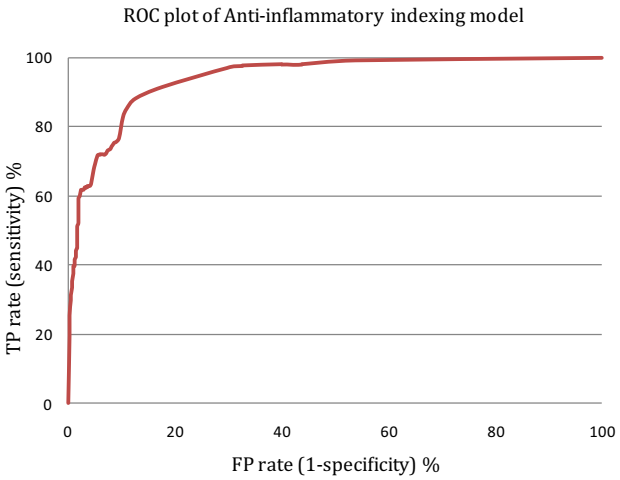

Fig. 8 A receiver operating characteristic (ROC) curve showing the tradeoff between true-positive rate (sensitivity) and false-positive rate (1 − specificity) of the anti-inflammatory bioactivity-indexing model

that few chemicals in the database are anti-inflammatory chemicals and will get high MBI score. The MBI score, as shown in Fig. 6, ranges between −2.75 (lowest score) and 10.25 (highest score).

In Fig. 9, we disclose some of the natural products that were highly indexed (MBI score above 8.0) as potential anti-inflammatory drug candidates. Using threshold of MBI 8.0, the ratio of TP:FP is equal to 35:1. Searching the PubMed revealed that only three molecules (Moupinamide, Capsaicin, and Hypaphorine) out of the ten were tested and reported as anti-inflammatory. Moupinamide (termed also *N-trans*-feruloyltyramine) possesses anti-inflammatory activity via suppression of mRNA expression of inducible nitric oxide synthase [44] and inhibition of COX-I and COX-II enzymes [45]. Capsaicin has shown efficacy in treatment of pruritus [46], nonallergic rhinitis [47] (inflammation of the inner part of the nose) and *H. pylori*-induced gastritis [48]. Few months ago, Sun et al. [49] reported that hypaphorine counteracts inflammation via inhibition of ERK or/and NFkB signaling pathways and can be served as an anti-inflammatory candidate. The other seven phytochemicals await evaluation for their anti-inflammatory activity in wet lab. One molecule (Piperolactam A) from the untested set was reported as a constituent [50] of *Piper betle* Linn that demonstrated anti-inflammatory activity [51].

Conclusions

Using the iterative stochastic elimination algorithm, we have built a highly discriminative and robust model capable of indexing natural products for anti-inflammatory bioactivity. We used a set of 441 anti-inflammatory drugs to represent the active domain and 2892 natural products to represent the inactive domain. The achieved area under the curve (AUC) was 0.94, indicating a highly discriminative and robust model. Some natural products that were scored highly by our ISE-based anti-inflammatory indexing model as anti-inflammatory drug candidates are disclosed. The proposed anti-inflammatory model can be utilized for the

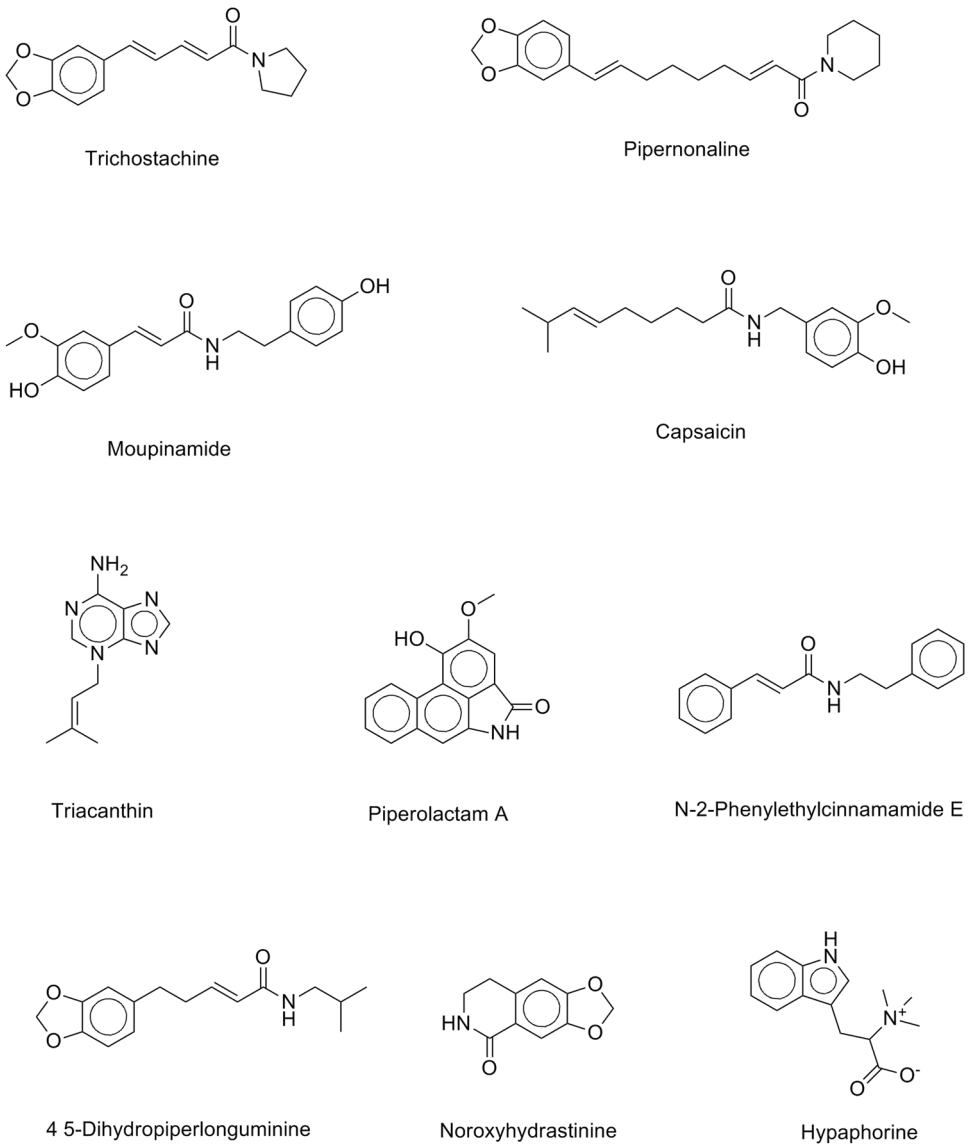

Fig. 9 Some of the natural products that were scored highly as potential anti-inflammatory drug candidates by our ISE-based anti-inflammatory indexing model

virtual screening of large chemical databases and for indexing natural products for potential anti-inflammatory activity.

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