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Research Article

Computer aided screening of natural products in search of lead molecules for design and development of potent anti-inflammatory agents

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Abstract: The aim of this study was to examine correlation between anti-inflammatory activity and molecular properties of the ten selected natural products in search of a lead compound through Molinspiration, Osiris and PASS cheminformatics software. Ten naturally occurring natural products of diverse chemical classes which seem to be promising and potential candidate for the drug development or identification of lead molecules as anti-inflammatory drugs were selected for bioactivity prediction and drug likeness score on the basis of Lipinski's rule of five. Aceclofenac and Hydrocortisone (cortisol) were used as reference standard for comparing the bioactivity score, molecular and pharmacokinetic properties of natural products. All the compounds except AKBA obeyed Lipinski's rule of five. All natural products showed good bioactivity score for drug targets including nuclear receptor ligand and enzyme inhibition and thus expected to have excellent pharmacological activity *in vivo*. All the screened compounds except rosmarinic acid and lovastatin showed Pa values above 0.5 for possible anti-inflammatory activity by PASS software. The majority of the compounds are predicted to have low toxicity potential by Osiris online software. AKBA, celastrol and silybin emerged as potential candidates for the further research as their molecular properties, pharmacokinetic profile and toxicity potential were found to be better than the other tested compounds including standard anti-inflammatory drugs, cortisol and aceclofenac.
Keywords: Anti-inflammatory activity, Lipinski's rule of five, Molinspiration, PASS

INTRODUCTION

Inflammation is a normal protective response of the organism to tissue injury caused by physical trauma, noxious chemical or pathogenic microorganisms. Inflammation is characterized by redness due to increase in blood flow to the affected area, swelling associated with increased vascular permeability and pain as a result of sensitization of primary afferent nerve fibers [1]. Inflammation is an important protective attempt by the body towards irritation, injurious stimuli, infection as well as it initiates the healing process for the tissue [2].

Inflammation is a very common symptom of many chronic diseases such as rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, chronic asthma etc. The worldwide prevalence of inflammatory diseases is on rise in our modern day society especially in elderly population [3]. Many epidemiological studies have shown inflammation to be a major risk factor for various types of cancer. According to one study underlying infections and inflammatory reactions are linked to 15–20% of all cancer deaths [4].

Non steroidal anti-inflammatory drugs (NSAIDs) are commonly used for the management of inflammatory conditions but these drugs cause unwanted gastro intestinal (GI) side effects such as gastric irritation, ulcer etc and are costly [5]. Therefore, a search is on to discover an ideal anti-inflammatory agent which is safe with low or no GI side effects, potent, orally active, relatively inexpensive and highly tolerated and convenient for patients. Natural products isolated from the medicinal plants used in traditional medicine to treat anti-inflammatory conditions seem a viable and logical alternative in search of safe and effective anti-inflammatory agents or discovery of the lead molecules for the development of anti-inflammatory drugs [6].

Medicinal plants and traditional herbal medicines have produced many valuable drugs in the past and are likely to continue to produce lead compounds [7]. Aspirin, morphine, penicillin, quinine etc are some of lead compounds isolated from natural sources and are in clinical use. Natural products such as curcumin, celastrol, resveratrol, boswellic acid, silybin, quercetin, lovastain, gentisein, eugenol and rosmarinic

acid (table 1) isolated from different medicinal plants have been reported to possess significant anti-inflammatory activity in various animal models of inflammation. All these phytochemicals belong to diverse chemical classes (Figure 1) that have been shown to interfere either directly or indirectly with the process of inflammation. These selected natural products are of potential therapeutic interest and offer a great hope in identification of anti-inflammatory agent(s) or bioactive lead compounds that can be developed into modern therapeutic drugs for the treatment of inflammatory diseases. To develop an orally active compound, certain properties of the lead compound should be taken into consideration such as Lipinski's rule of five or Veber's parameters that help pharmaceutical scientists to select the best candidates for drug development and to reject those with a low probability of success [8,9]. Computer based (*in silico*) molecular modeling (bioinformatics and cheminformatics) are quite useful for this purpose, because they are extremely fast and cost efficient and can be applied even when a compound is not physically available [10].

In continuation of our research to find and optimize new anti-inflammatory lead molecules from natural sources, possessing high target selectivity, low toxicity and better pharmacokinetic profile, we have selected ten natural compounds viz. curcumin, celastrol, resveratrol, acetyl keto boswellic acid, silybin, quercetin, lovastain, genistein, eugenol and rosmarinic acid for virtual computer screening. The selected natural products were screened for the molecular properties such as drug likeness and bioactivity score by online Molinspiration software, toxicity was predicted based on Osiris property explorer and PASS (Prediction of Activity Spectra for Substances) computer software program was used to predict their anti-inflammatory activity and other possible biological activities.

Table 1: Biological source and physicochemical properties of selected natural products

Natural product	Plant name (common name)	Family	Chemical class	Molecular formula	Melting pt (^{0}C)
Acetyl-Boswellic acid (AKBA)	*Boswellia serrata* (Salai guggul)	Burseraceae	Triterpene	$C_{32}H_{48}O_5$	298-302
Celastrol	*Tripterygium wilfordii (Regel's Wingnut)*	Celastraceae	Triterpenoid	$C_{29}H_{38}O_4$	180-185
Curcumin	*Curcuma longa* (tumeric)	Zingiberaceae	Curcuminoid	$C_{21}H_{20}O_6$	183
Eugenol	*Syzygium aromaticum* (clove)	Myrtaceae	Monoterpene	$C_{10}H_{12}O_2$	-7.5
Genistein	*Glycine max* (soybean)	Fabaceae	Isoflavone	$C_{15}H_{10}O_5$	297-298
Lovastatin	*Aspergillus terreus* (yeast)	Trichocomaceae	Statin	$C_{24}H_{36}O_5$	174-175
Quercetin	*Allium cepa* (onion)	Amaryllidaceae	Flavonol	$C_{15}H_{10}O_7$	315-316
Resveratol	*Vitis vinifera* (red grapes)	Vitaceae	Stilbenoid	$C_{14}H_{12}O_3$	261-263
Rosmarinic	*Rosmarinus officinalis* (rosemary)	Lamiaceae	Caffeic acid ester	$C_{18}H_{16}O_8$	171-175
Silybin	*Silybum marianum* (milk thistle)	Asteraceae	Flavonolignan	$C_{25}H_{22}O_{10}$	230-233

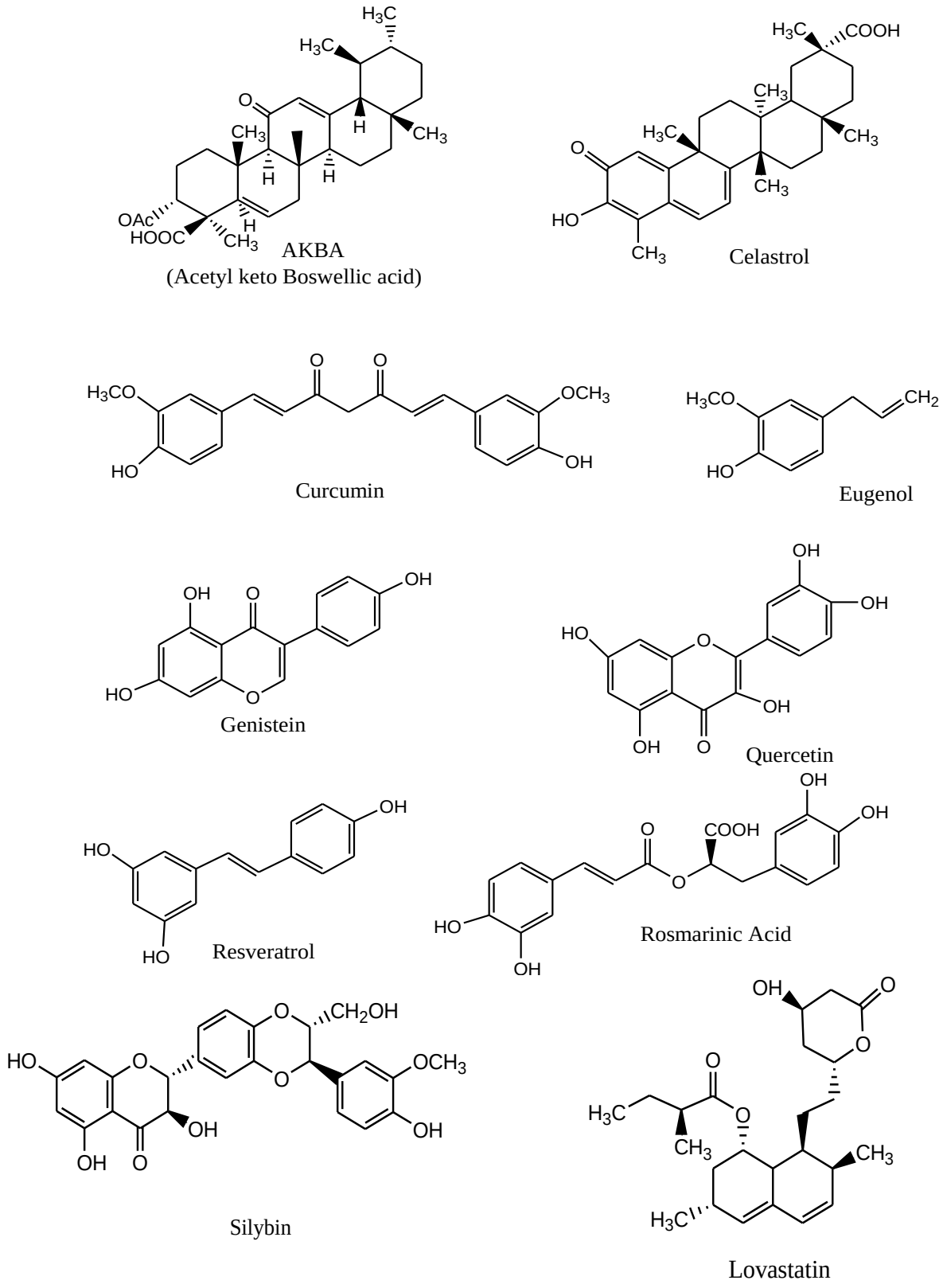

Figure 1: Chemical structures of screened natural products

MATERIALS AND METHODS

ACD labs Chemsketch version 12.0 was used to draw the structures and generation of SMILES notations of all the selected natural products. SMILES notations of the selected compounds were then fed in the online Molinspiration software version 2011.06 (www.molinspiration.com) for calculation of molecular properties (Log P, Topological polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of

rotatable bonds and violations of Lipinski's rule of five etc and prediction of bioactivity score for drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors) [8]. The bioactivity score and drug likeness properties of the natural products were compared with the standard drugs cortisol and aceclofenac. Percentage of absorption (% ABS) was calculated by: % ABS =109-[0.345× TPSA] as per the reported method [11].

The toxicity potential of the natural products was determined by employing an online cheminformatics tool, the Osiris property explorer (www.organicchemistry.org/prog/peo/). It predicts various pharmacokinetic attributes such as toxicity risk assessment, cLogP value, molecular weights, solubility and overall drug-likeness score of the valid structure of molecule, thus helping in evaluation of its overall potential to qualify for a drug. The prediction results are valued and color coded either green or red. Those properties which are shown in red indicate high risks of undesired effects like mutagenicity or effect on reproductive system. Whereas a green color indicates drug-conform behavior and compatibility in vivo.

Anti-inflammatory and other possible biological properties of selected natural products were predicted with the help of PASS computer program [12]. PASS is a computer based program commonly used in drug discovery and development for the prediction of biological activity spectrum of a compound based on its chemical structure including phytoconstituents [13]. It helps in finding and optimizing most probable new leads with required pharmacological activity from the data bases of compounds.

RESULTS AND DISCUSSION

Molinspiration online molecular property calculation toolkit was used to evaluate the drug likeness of natural products in search of the lead anti-inflammatory candidate(s) based on Lipinski's rule of five and the results are presented in the table 2. Drug likeness evaluates whether a particular molecule is similar to the known drug or not. It is a complex balance of various properties and structural features of a compound. Lipinski's rule is widely used to predict drug's pharmacokinetic *in vivo*. According to Lipinski's rule of five [8], a candidate molecule is more likely to be orally bioavailable as long as it does not violate his rules: a) the molecular weight is under 500, b) the calculated octanol/water partition coefficient (log P) is less than 5, c) there are not more than 5 hydrogen bond donors (OH and NH groups), d) there are not more than 10 hydrogen bond acceptors (notably N and O). However, there are some exceptions to this rule as some of orally active drugs such as atorvastatin, cyclosporin do not obey the rule of five. The pharmacokinetic properties such as absorption, distribution, metabolism, excretion and toxicity (ADMET) are dependent on chemical descriptors of the molecule and contribute a lot in the lead identification and in success of drug development process.

Table 2: Drug likeness score for natural products

Compound name	miLog P[a]	TPSA[b]	*n* Atoms	n ON[c]	*n* OHNH[d]	*n* violation	*n* rotb[e]	% ABS[f]	MW[g]
AKBA	6.148	80.68	36	5	1	1	3	81.17	498.70
Celastrol	4.681	74.60	32	4	2	0	1	83.26	436.59
Curcumin	2.303	93.07	27	6	2	0	8	76.89	368.39
Eugenol	2.1	29.46	12	2	1	0	3	98.84	164.20
Genistein	2.268	90.90	20	5	3	0	1	77.64	270.24
Lovastatin	4.345	72.84	29	5	1	0	7	83.87	404.55
Quercetin	1.683	131.35	22	7	5	0	1	63.68	302.24
Resveratrol	2.986	60.68	17	3	3	0	2	88.06	228.25
Rosmarinic acid	1.626	144.52	26	8	5	0	7	59.14	360.32
Silybin	1.465	155.15	35	10	5	0	4	55.47	482.44
Aceclofenac	4.429	75.63	23	5	2	0	7	82.91	354.19
Cortisol	1.617	94.83	26	5	3	0	2	76.29	362.47

[a]Logarithm of partition coefficient between *n*-octanol and water (miLogP); [b]topological polar surface area (TPSA); [c]number of hydrogen bond acceptors (*n*-ON); [d]number of hydrogen bond donors (*n*-OHNH); [e]number of rotatable bonds (*n*-rotb); [f]percentage of absorption (%ABS); [g]molecular weight (MW).

Partition coefficient or Log P is used to measure molecular hydrophobicity and is an important parameter in rational drug design. Log P values of all the natural products except Acetyl Keto Boswellic acid were found to be less than 5. AKBA is expected to have the highest lipophilicity because its log P value is 6.148,

whereas silybin will be the most hydrophilic, log P= 1.465. This implies that these compounds will have good permeability across cell membrane. Molecular weight of all analyzed natural products was found to be <500. This suggests that these molecules can easily be transported, diffuse and absorbed as compared to large molecules. Number of hydrogen bond acceptors (O and N atoms) and number of hydrogen bond donors (NH and OH) in the tested compounds were also in agreement with the Lipinski's rule of five i.e. less than 10 and 5 respectively. Thus it can be predicted that all these natural products except AKBA are likely to be orally active as they did not violate any of the criteria of Lipinski's rule of five. AKBA obeyed four out of five rules but showed one violation for the log P value.

Topological polar surface area (TPSA) is closely related to the hydrogen bonding potential of a molecule and is a very good predictor of drug transport properties such as intestinal absorption, blood brain barrier penetration etc. It is therefore, linked to the bioavailability of drug molecule. TPSA of all natural products was found in the range of 29.46-155.15 and is below the 160 A^0 limit. TPSA of Silybin, Rosmarinic acid and Quercetin (155.15, 144.52 and 133.35 A^0 respectively) was much higher than the rest of the compounds (29.46-93.07 A^0). Molecular flexibility of a drug molecule is measured by number of rotatable bonds and Veber considered it to be a good descriptor of drug's oral bioavailability [9]. Among all the screened compounds, curcumin, lovastain, rosmarinic acid and silybin were most flexible and appropriate as they contain 8, 7, 7 and 4 rotatable bonds respectively. Fortunately, none of the analyzed natural product was found to be rigid as all of them had one or more than one rotatable bond(s). The percentages of absorption for natural products calculated from TPSA, ranged between 55.47-98.84% and indicated moderate to good oral bioavailability.

The predicted bioactivity scores by Molinspiration for the screened natural products and their comparison with the standard drugs are summarized in Table 2. As a general rule, larger is the bioactivity score, higher is the probability that investigated compound will be active. Therefore, a molecule having bioactivity score more than 0.00 is most likely to possess considerable biological activities, while values -0.50 to 0.00 are expected to be moderately active and if score is less than -0.50 it is presumed to be inactive [14].

Table 3: Bioactivity score of the compounds according to Molinspiration cheminformatics software

Compound name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
AKBA	0.12	-0.02	-0.56	0.60	0.23	0.49
Celastrol	-0.12	-0.27	-0.33	0.46	-0.08	0.60
Curcumin	-0.06	-0.20	-0.26	0.02	-0.14	0.08
Eugenol	-0.86	-0.36	-1.14	-0.78	-1.29	-0.41
Genistein	-0.22	-0.54	-0.06	0.23	-0.68	0.13
Lovastatin	0.39	0.25	-0.19	0.67	0.16	0.79
Quercetin	-0.06	-0.19	0.28	0.36	-0.25	0.28
Resveratrol	-0.12	-0.27	-0.33	0.46	-0.08	0.60
Rosmarinic acid	0.17	-0.08	-0.18	0.57	0.15	0.24
Silybin	0.07	-0.05	0.01	0.16	0.02	0.23
Aceclofenac	0.14	0.06	0.13	0.03	-0.01	0.15
Cortisol	0.0	-0.29	-0.85	1.17	0.09	0.63

The results of the present study demonstrated that the investigated compounds are biologically active molecules and will produce the physiological actions by multiple mechanisms after interacting with GPCR ligands, nuclear receptor ligands, and inhibit protease and other enzymes. Though bioactivity score for Enzyme inhibitor is found to be >0.00 for all tested compounds barring eugenol, but the highest score (0.79) was observed for lovastatin closely followed by celastrol and resveratrol (0.60). Bioactivity score of natural products for ion channel modulator activity and kinase inhibiton suggested their moderate interaction with this target. Similar results were obtained for GPCR ligand and only few compounds namely AKBA, lovastatin, rosmarinic acid showed score >0.00, rest of the molecules were either inactive or moderately active towards this drug target. It appeared that nuclear receptor ligand is the mechanism by which these natural products would produce their biological actions as bioactivity score for this target was found to be in the range of 0.02- 0.67. The bioactivity score of AKBA was found to be 0.60 for nuclear receptor ligand. The most promising compounds as per the bioactivity scores were identified to be AKBA, lovastatin and rosmarinic acid

which are predicted to act by more than three mechanisms (table 3). It can be concluded that synthetic or semi synthetic analogs of these compounds can be designed and evaluated for their pharmacological activity as they are expected to be orally and therapeutically active.

Toxicity risks and drug score assessment of selected natural products was predicted by Osiris property explorer and the results are presented in table 4. This online program predicts on the basis of functional group similarity of the investigated compound with the extensively in vitro –and in vivo studied compounds present in its data base. The results are indicated with color codes such as red, green and yellow [15]. Green color suggests low toxic tendency, yellow shows the mild toxicity and red color indicates high probability of toxicity. As can be seen from the results, all compounds except eugenol, genistein, quercetin and resveratrol predicted to be safe and expected to show low or no toxicity regarding mutagenicity, tumerogenicity, irritant effect and effect on reproductive system. Both Eugenol and genistein showed green color for reproductive and irritation effects respectively. Quercetin poses the potential risk of tumerogenicity and mutagenicity while resveratrol might produce toxic effects on reproductive system in addition to be mutagenic. The drug score ranged from 0.11-0.64 and was obtained in the following order; silbyin> lovastatin> rosmarinic acid > curcumin > celastrol, quercetin > AKBA >genistein> resveratrol> eugenol. The greater score for silybin, and lovastatin indicating the importance of functional groups such as hydroxyl, methoxy, ester, and methyl present in them. Solubility for these natural products was also predicted to be within the permissible optimum range.

Table 4: Drug-likeness/scores and toxicity calculations of selected natural products based on Osiris property explorer

Compound	Solubility	Drug-likeness	Drug score	Mutagenic	Tumorigenic	Irritant	Reproductive effect
AKBA	-6.0	-1.72	0.19	Green	Green	Green	Green
Celastrol	-5.02	-1.46	0.30	Green	Green	Green	Green
Curcumin	-3.62	-3.95	0.4	Green	Green	Green	Green
Eugenol	-2.05	-2.78	0.11	Red	Red	Red	Green
Genistein	-2.73	1.16	0.17	Red	Red	Green	Red
Lovastatin	-4.57	1.65	0.57	Green	Green	Green	Green
Quercetin	-2.49	1.6	0.30	Red	Red	Green	Green
Resveratrol	-2.86	-3.25	0.16	Red	Green	Green	Red
Rosmarinic acid	-2.23	-2.07	0.49	Green	Green	Green	Green
Silybin	-3.41	1.64	0.64	Green	Green	Green	Green

PASS computer program was used to predict the anti-inflammatory and other biological activities of selected natural products. This program predicts the activity based on structural activity relationship (SAR) analysis of the training set containing more than 205,000 compounds in its data base. The mean accuracy of prediction is approximately above 90%. PASS application can be used for drug candidates or even to well-known drugs, used for many years. The predicted activity spectrum of a compound estimates as probable activity (Pa) and probable inactivity (Pi) [16] which varies from 0.00 to 1.00. Usual interpretation of prediction results is based on the Pa values. If Pa > 0.7 the chance to find the activity in experiment is high, but in many cases the compound may occur to be the close analogue of known pharmaceutical agents. If 0.5 < Pa < 0.7 the chance to find the activity in experiment is less, but the compound is not so similar to known pharmaceutical agents. If Pa < 0.5 the chance to find the activity in experiment is even less [12, 16]. All the screened compounds except rosmarinic acid and lovastatin showed Pa values above 0.5 for possible anti-inflammatory activity. The highest Pa values (0.876 and 0.845) for anti-inflammatory activity was observed for boswellic acid derivative, AKBA and for celastrol. Pa value of lovastatin was found to be the lowest among all natural products. A total of four compounds had their Pa values>0.7, suggesting these compounds or their analogs could possibly be the lead or ideal drug candidates for anti-inflammatory therapy. Most of these compounds were also found to be active against many other common, chronic and fatal diseases. The Pa values along with other possible biological activities of these natural products are presented in table 5.

Table 5: PASS predicted Anti-inflammatory activity and other possible biological activities of natural compounds

S. No.	Natural product	Pa	Pi	Other predicted biological activities (Pa)
1.	AKBA	0.876	0.005	Hepatoprotective (0.932), Chemopreventive (0.896), antinociceptive (0.810), Diuretic (0.61)
2.	Celastrol	0.845	0.005	Antineoplastic (0.811), Hepatoprotective (0.689), antiarthritic (0.582), antifungal (0.480)
3.	Curcumin	0.709	0.015	Antihypercholesterolemic (0.773), Chemopreventive (0.697), Antioxidant (0.643), anthelminitic (0.439)
4.	Eugenol	0.503	0.056	Antiseptic (0.814), choleretic (0.679), analeptic (0.618), spasmolytic (0.534), antipyretic (0.513)
5.	Genistein	0.648	0.023	Cardioprotectant (0.792), antineoplastic (0.753), hepatoprotective (0.68), antiseptic (0.477)
6.	Lovastatin	0.243	0.091	Antihypercholesterolemic (0.991), vasodilator (0.969), antifungal (0.834), immunosuppressant (0.790)
7.	Quercetin	0.670	0.020	Antineoplastic (0.773), cardioprotective (0.756), skin whitener (0.599), radioprotective (0.567)
8.	Resveratrol	0.562	0.040	Carminative (0.853), antiseptic (0773), vasoprotector (0.759), antineoplastic (0.627), antinociceptive (0.503)
9.	Rosmarinic acid	0.487	0.061	Antidiabetic (0.798), hypolipemic (0.699), Antipsoriatic (0.603), Antithrombotic (0.585)
10.	Silybin	0.716	0.014	Hemostatic (0.967), hepatoprotective (0.948), anti-carcinogenic (0.898), antigout (0.641), firbrinolytic (0.647), expectorant (0.426)

CONCLUSION

The selected natural products are predicted to have desirable molecular properties and pharmacokinetic profile for drug likeness by Molinspiration software. The anti-inflammatory activity of these compounds was also confirmed by PASS- assisted computer program. AKBA, celastrol and silybin emerged as promising anti-inflammatory lead molecules. The toxicity profile of these three compounds by Osiris software was also found to be the lowest. Therefore, further detailed studies are recommended to develop these compounds as orally active anti-inflammatory agents. An attempt should also be made to design, synthesize and study structure activity relationship (SAR) of the synthetic analogs of short listed natural products.

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