Austin Arthritis

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Austin Publishing Group

Research Article

Herbal Informatics Approach for Identification and Validation of Natural Compounds Targeting Gout

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Received: May 25, 2016; **Accepted:** July 05, 2016; **Published:** July 07, 2016

Abstract

Gout is a form of inflammatory arthritis that is caused by deposition of monosodium urate crystals in synovial fluid of joints and other soft tissues. However, the incidence rate of gout is higher in recent decades, it affects 1-2% of the population in western countries. Conventional treatments are not or less effective for patients with such inflammatory condition because of the propensity of these drugs to cause gastrointestinal adverse effects. The present study emphasized the herbal informatics tool for selecting the natural compound to attenuate the symptoms of inflammatory arthritis by inhibiting their disease factors, which includes classical literature surge model followed by the decision matrix and optimization scores to identify the potential leads for discovering its therapeutic potential. Herbals identified by the bioprospection study were validated by molecular docking analysis, which could further help in drug discovery programs to study chemical and biological methods. The purpose of this study is to identify an herbal lead, which could be used to inhibit the inflammatory pathway of gout at *in vitro* and *in vivo* animal models.

Keywords: Herbal informatics; Bioprospection; Gout; Arthritis; Ethnopharmacology; Molecular docking

Introduction

Gout is a progressive inflammatory arthritis, affecting 1-2% of the population in western country in which Indian population contributes approximately 0.75%, where it is more common in men than the females had polyarticular gout [1]. It is characterized by a chronic hyperuricemia condition in which the serum urate levels above ≥ 400μmol/L, and also exceeded the level of physiological saturation threshold [2]. Interactions between Monosodium Urate (MSU) Crystals and cell types including mast cells, endothelial cells, neutrophils, macrophages and synovial fibroblasts are established with clinical manifestations of gout [3].

The one of the most painful form of inflammatory arthritis is acute gout that is characterized by the abrupt onset of severe joint pain, swelling, and erythema. Various risk factors are elevated the concentration serum urate persisting crystal deposition in the joints leading to irreversible joint damage. The inflammatory response is characterized by the initiation of the critical attack, leukocyte recruitment, enlargement and subsequent resolution. The balance between the monocytes and differentiated macrophages plays a key role in modulating the inflammatory response to MSU crystals [4].

There are numerous treatment strategies or allopathic medication such as first line drug (celecoxib), second line drug (glucocorticoid) and third line drug (colchine) for alleviation of the inflammatory pathways of gout, but they are poorly tolerated by the patient due to its long term toxicity like hepatic cell (hepatocytes) damage, gastrointestinal toxicity, and it has not been widely used due to a toxic effect on other organs [5]. Nowadays, Natural products are considered as excellent sources in the management of clinical disorders like aging, arthritis, diabetes. The renewed interest in natural therapeutic methods and the use of herbal therapy has led to a gradually growing interest in natural compounds and the classical methods of plant extract preparations [6]. It has been predicted that about 420,000 plant species exist on earth but only 10% i.e. around 35,000 plants have been explored for their medicinal usage [7]. The World Health Organization (WHO) estimated that medicines prepared from plant source endow with primary healthcare for approximately 3.5 to 4 billion people globally [8].

The present study emphasized the rationale to adopt the In-silicobioprospection model, in order to bio prospect, discover, analyze and authenticate the Herbal Medicine (HM) into Modern Herbal Medicine (MHM), which is based on its ethnopharmacological importance, as testified in ancient literature or otherwise in clinical literature of various countries. Utilizing an herbal informatics approach, leads identified by herbal informatics used for further validation by the molecular docking, which could be useful to discover the potential therapeutic moiety to study at *in vitro* and *in vivo* level.

Methodology

Selection of bioactivity parameters using classical approach

Bioactivity parameters that are mainly responsible for the virulence/ disease factor of the inflammation were selected by Classical bioprospection approach that involves the understanding of the mechanistic aspects or pathophysiology of disorder as exemplified in (Table 1).

Evaluation of relevance factor using keywords hits scoring matrix approach

This step is accomplished by calculating the percentage relevance of the respective parameters using Pub Med as a search engine tool

Citation: Tanwar A, Chawla R, Ansari MM, Thakur P, Chakotiya AS, Dixit B, et al. Herbal Informatics Approach for Identification and Validation of Natural Compounds Targeting Gout. Austin Arthritis. 2016; 1(2): 1008.

Table 1: Rationale for selection of Bioactivity parameters.

S.No	Biactivity parameter	Rationale for selection
1	IL 1 beta [9].	• IL-1 is proinflammatory cytokine play a critical role in the pathogenesis. IL-1 blockade could be used to reduce joint inflammation and prevent progressive joint damage. • Herbal showing IL-1B inhibiting activity *Eclipta Prostata, Ficus Racemosa etc.*
2	IL-6 [10].	• IL-6 plays a pleiotropic role both in terms of activating the inflammatory response and osteoclastogenesis. Significant improvement in signs and symptoms are due to blocking of IL-6 receptor. • Natural compounds showed inhibitoy effect on IL-6 like *Nelumbonucifera, Ocimum sanctum(tulsi), Oxalis Corniculata etc.*
3	TNF-*alpha* [11-13].	• TNF-α spontaneously develops osteoclasts differentiation in the joints with a progressive inflammation, cellular proliferation and bone destruction. • Herbal showing anti- TNF –a activity, *Tridaxprocumbens, Solanum Nigrum, Stevia Rebaudiana, TagetesMinutaetc etc.*
4	Xanthine oxidase [14]	• Enzymes involved in purine catabolism syntethizes uric acid and hydrogen peroxide and accumulate of uric acid cause its precipitation in kidneys and joints (in particular in metatarso-phalangeal joints). • Xanthine oxidase used as therapeutic target for gout
5	AMP Deaminase [15].	• Congenital hyperuricæmia is caused by the presence of an abnormal A.M.P. deaminase. • Inhibition of AMP deaminase, useful in the management of Gout.
6	COX-2 [16].	• Inflammatory gout has increased expression of COX-2. • Inhibition of Cyclooxygenase 2 (COX-2) has emerged as an important for the treatment of gout. • Plants having anti-inflammatory activity *Allium sativum, Berberisaristata etc.*

that rely on Academic Search engine Optimization (ASEO) . ASEO is a basic principle that involves grading of those scholarly objects on the top position that are most expected to be examined [15]. This yield 'N' total hits, out of them initial n=20 presents the sample, which is the representative fraction of the population that is followed by judgments or purposive sampling. In judgments or purposive sampling the hits are deliberately selected or discrete on the basis of relevance. Percentage weightage will be determined by using the following formula and then weightage will be calculated.

Percentage relevance=(Relevant Hits× 100)/20.

Selection of herbal plants using classical bioprospection approach

The classical bioprospection approach accounts for investigation of the following variables based on literature review to devise a logical conclusion, resulted in selection of plants was shown in (Table 2). It includes a) Ethnopharmacological importance; b) Relevance of Herb in traditional medicine; c) Availability factor or cultural acceptability in localized regions; d) Any vedic literature supporting its use; e) Investigations/ prior experience on potential of the herb; f) Indirect indications, if any etc.

Binary coefficient matrix to evaluate the presence/ absence of a parameter in selected plants

This methodology works on the principle of 0-1 binary code of absence/presence of a particular parameter in selected plants from previous step. Based on this, all the plants having more than 04 parameters, reported in PubMed search engine (n= first 20 hits) against 'Bioactivity Parameter + Selected Plant' random search model, were selected. It relates to the fact that only these plants which can support holistic approach should be screened for the next level analysis, in line with the rationale of present study [39].

Weightage matrix based analysis

This step includes evaluation of overall weightage of plants (Scores ≥4 in past venture) by multiplying their binary score with weightage obtained in above step. This is a primary step to screen the plants utilizable to subsequent analysis and removes fake positive results attributed towards investigator's biasness due to 'experience factor'. This step enhances the 'uncertainty factor' required for statistically valuable outcome. This step identifies potential plant leads based on in silico bioprospection approach subjected to fuzzy set membership analysis and optimization to validate the findings [40].

Fuzzy set membership analysis for decision matrix

In this approach, the given mathematical relationship was used to calculate the relevance of the variety/product;

$$\mu s=([(S) - \min(S)])/(\max(S) - \min(S)).$$

where, μS represents the desirability values of members of the fuzzy set S. Min(S) and max(S) are minimum and maximum values, respectively, in the fuzzy set S. [41].

Optimization of decision matrix score

In this approach the numerical value of scores obtained were converted into a leveled score by using a scaled magnitude represented by a symbol.

Molecular docking

To validate the bioprospection model in silico docking simulations of most relevant bioactivity parameter against pre-selected phyto-ligands were carried using Hex 8.0 software. Software's used: Argus Lab (4.0.1), Open Babel (2.4), and Hex (8.0).

Retrieval of 3D structure of COX-2 receptor and preparation of ligand database

The experimental 3D tertiary structure of COX-2 retrieved from RCSB Protein Data Bank as a pdb file (PDB ID- Q05769). Hydrogen atoms were introduced into the enzyme structure using Argus lab (4.0.1) to customize it as the receptor molecule for rigid docking. The predominant phytoconstituent and 2 standard chemotherapeutic inhibitor of COX-2 were retrieved from PUBCHEM. Hydrogen atoms were introduced into the ligand structure using Argus Lab (4.0.1) to customize them for rigid docking. The hydrogenated ligand molecules were then converted into pdb format using Open Babel (2.4) interface as required for rigid docking.

Active site analysis

DoGSiteScorer is a grid-based method which uses a Difference of Gaussian filter to detect potential binding pockets solely based on the 3D structure of the COX 2 -and splits them into sub pockets. Global properties, describing the size, shape and chemical features of the predicted (sub) pockets are calculated. The druggability score is provided for each (sub) pocket, based on a linear combination of the three descriptors describing volume, hydrophobicity and enclosure.

Table 2: Ethnopharmacological properties of herbal compounds for rationale based selection.

S.No.	Herbals	Common name	Ethnopharmacological properties	Phyto-constituents	Traditional uses
1.	*Curcuma Longa* [17]	Turmeric	Anti- rheumatic, Anti-inflammatory, Anti-oxidant	Curcumin, Demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC)	Used for Sprains, swellings, cough, and wounds.
2.	*Azadirachta indica* [18]	Neem	Anti-helminthic, Anti-fungal, Anti-diabetic, Anti-bacterial, Anti-viral, contraceptive, Anti-inflammatory Anti-oxidant and Anti-carcinogenic	Saponins, Anthraquinones, Flavonoids.	Used for Skin diseases, Healthy hair, Detoxifyblood, Balance blood sugar levels, and Sanitizing wounds.
3.	*Mangifera indica* [19]	Mango	Anti-oxidant, Anti-diabetic, Antiviral, Anthelmintic, Anti-allergenic, Antiparasiti	Polyphenolics, Flavonoids, Triterpenoids Bark: Protocatechic acid, Catechin, Mangifera	Tumour, Heat stroke, Miscarriage, Anthrax, Blisters, Wounds in the mouth, Tympanitis,
4.	*Zingiber Officinale* [20]	Ginger	Antioxidant, Anti-inflammatory, Anti-tumour, Anti-microbial, Anti-diabetic.	Gingerol and Zingerone	Nausea, Indigestion, Cold, Flu, Poor circulation, Menstrual cramps etc.
5.	*Withania somnifera* [21]	Ashwagandha	Anti-stress, Anti-tumor, Anti-inflammatory, Anti-arthritic and Anti-oxidant.	Alkaloids: Isopelletierine, Anaferine, Cuseohygrine, Anahygrine, Withanolides, Withaferins, Saponins	Eases stress, Lower blood pressure, Inflammation of joints, Nervous disorders and Epilepsy
6.	*Camellia sinensis* [22]	Green tea	Anti-tumor, Anti-diabetic, Anti-inflammatory	Flavonoids, Catechin, Epigallocatechin Gallate (EGCG), L-theanine, Caffeine, theophylline, Theobromine, and Theanine.	Control bleeding, Heal wounds, Aid digestion, Improve heart Mental health and Regulate body temperature.
7.	*Vitisvinifera* [23]	Grapes	Anti-inflammatory and Anti-sclerotic	Anthocyanins, hydroxycinnamic acids, and Stilbenoids	Cholera, smallpox, nausea, skin and eye infections [21].
8.	*Allium sativum* [24]	Garlic	Anti-Inflammatory, Antibacterial, Antifungal, Antiviral and Anti- rheumatic.	Allicin (diallyl-dithiosulfinate) Diallyldisulphide, vinyldithiins, *S*-allylcysteine, Saponins, flavonoids, Maillard reaction Fatty acid and ethyl linoleate (ELA).	Used for the treatment of Smallpox.
9.	*Syzygium aromaticum* [25]	Cloves	Anti- rheumatic, Antimicrobial and Antioxidant	Gallotannins, Triterpenes, flavonoids, and phenolic acids	Carminative, to increase hydrochloric acid in the stomach and to improve peristalsis
10.	*Piper nigrum* [26]	Black pepper	Anti-inflammatory, Anti-flatulent, Anti-oxidant, antimicrobial, gastro-protective, and antidepressant.	Pyrrolidines, Piperamide, Piperamine, Pipericide, Sarmentosine, Sarmentine, and Trichosta.	Constipation, Insomnia, Oral abscesses, Sunburn, toothaches, Flatulence and Indigestion.
11.	*Tinospora cordifolia* [27]	Giloy	Antineoplastic, Antioxidant, Hepatoprotective, and Hypolipidemic	Alkaloids, diterpenoid lactones, glycosides, sesquiterpenoid, aliphatic compounds, phenolics, polysaccharides, steroids (tinosporine, tinosporide, tinosporaside, cordifolide, cordifol, heptacosanol.	Used for Diabetes, jaundice, high cholesterol, upset stomach, fever, and to boost the immune system.
12.	*Rubiacordifolia* [28]	Manjishta	Anti-inflammatory	Mollugin, Purpurin, Quinonoid, Anthraquinones, Iridoids, Hexapeptides, Rubiprasins, Quinones, and Triterpenoid.	Blood disorders and reduce swelling.
13.	*Garcinia Cambogia* [29]	Malabar tamarind	Anti-inflammatory, Anti-cancer, Antibacterial and Antioxidant	Hydroxycitric acid, Garcinol, Succinic acid, Tartaric acid, Oxy-guttiferone M, Rheediaxanthone A, Isogarcino, Garcinol	Obesity, appetite control, weight loss diets, high triglycerides and high cholesterol
14.	*Gmelina Arborea* [30]	Gamhar	Anti-inflammatory, and Anti-rhuthematic	tyrosol [2-(4-hydroxyphenyl)ethanol], (+)-balanophonin, 8-5′ neolignan, balanophonin, gmelinol, 2,6-dimethoxy-*p*-benzoquinone and 3,4,5-trimethoxyphenol	Pains, burning sensations, and fever.
15.	*Lilium Polyphyllum* [31]	White Lily (Kalihari)	Anti-inflammatory, and Anti-rhuthematic	2,4-D, Glyphosate, fluridone, triclopyr, and imazamox.	Inflammation and swelling.
16.	*Madhuca Indica* [32]	Mahua	Anti-inflammatory, and Anti-rhuthematic	saponin, alkaloid, glucoside, Sapogenin, triterpenoids, steroids, madhucic acid,	Wound Healing, headaches, Itching, pain, and inflammation.
17.	*Mentha arvensis* [33]	Mint (Pudina)	Anti-inflammatory, and Anti-rhuthematic	Menthol, menthone, carvone, limonene, linalool, menthyl acetate, piperitone, and pulegone	Inflammation and swelling.
18.	*Terminalia chebula* [34]	Haritaki	Anti-inflammatory, and Anti-rhuthematic	Tannin, chebulinic acid, ellagic acid, Anthraquinones, polyphenols, terpenes, anthocyanins,flavonoids, alkaloids and glycosides	Digestive diseases, urinary diseases, diabetes, skin Diseases, heart diseases, and fever.
19.	*Hypericum perforatum* [35]	Saint John's wort	Anti-inflammatory, Antidepressant an Anti-Rheuthmatic	Hypericin, Quercetin, Hyperforin, naphthodianthrones, phloroglucinols, flavonoids, pseudohypericin, amentoflavone, Quercetin, chlorogenic acid and essential oils.	Depression anxiety, obsessive-compulsive disorder (OCD), menopausal mood swings, and premenstrual syndrome.

20.	*Peganum harmala* [36]	Harmal seeds	Anti-Rheuthmatic	Alkaloid, harmine, papaverine, Lycoris alkaloids, lycorine and lycoricidinol	Inflammation and swelling.
21.	*Crocus sativus* [37]	Saffron	Anti-inflammatory, and Anti-rhuthematic	Safranal, isophoron, riboflavin, thiamine, 2-phenyl ethanol, utanic acid, and lenolenic.	Used for Painful mensuration, coughs, Asthma, cough, intestinal gas, dry and teeth problem.
22.	*Tephrosia purpurea* [38]	Fabaceae	Anti-inflammatory, anti-oxidant and Anti-rhuthematic	Polyphenols, flavonoids, Quercetin, gallic acid, and allopurinol.	Inflammation, ulcer, urinary disorders and diseases related to liver and heart.

Table 3: Weightage assigned to the Factors based on Average Percentage Relevance.

S.No.	Bioactivity parameter (BAP)	Total number of Hits	Hits Relavant	Percentage (%) Relevance	Weightage score
1.	IL 1 beta	5242	9	45	4.5
2.	IL-6	13141	7	35	3.5
3.	TNF-*alpha*	36569	11	55	5.5
4.	Xanthine oxidase	1769	9	45	4.5
5.	AMP Deaminase	168	5	25	2.5
6.	COX-2	8272	12	60	6

Table 4: Binary matrix and fuzzy set optimization of herbals targeting arthritis.

S.No.	Herbal	Herbal code	Binary score	Weightage score	Fuzzy score
1.	*Curcuma Longa*	Cl	6	26.5	1
2.	*Camellia sinensis*	Cs	6	26.5	1
3.	*Peganum harmala*	Ph	6	26.5	1
4.	*Ocimum sanctum*	Os	5	24	0.7
5.	*ZingiberOfficinale*	Zo	5	24	0.7
6.	*Withania somnifera*	Ws	5	24	0.7
7.	*Vitus vinifera*	Vv	5	24	0.7
8.	*Piper nigrum*	Pn	5	24	0.7
9.	*Punica granatum*	Pg	5	24	0.7
10.	*Rosmarinus officinalis*	Ro	5	24	0.7
11.	*Picrorhiza kurroa*	Pk	5	24	0.7
12.	*Terminalia chebula*	Tc	5	24	0.7
13.	*Hypericum perforatum*	Hp	5	24	0.7

Furthermore, a subset of meaningful descriptors is incorporated to predict the (sub) pocket druggability score (values are between zero and one). The higher the score the more druggable the pocket is estimated to be [42].

Ligand receptor docking (Hex 8.0)

Receptor and Ligand files were imported in the Hex 8.0 software. Graphic settings and Docking parameters were customized as follows and rigid docking was performed. E values of the docking predicted the free energy of docking, which served as the basis for ranking phyto ligands in increasing order of their docking abilities.

The parameters used in the docking process were:

a) Correlation type: Shape and electro

b) FFT mode: 3D fast lite

c) Grid Dimension: 0.6

d) Receptor range: 1800

e) Ligand range: 1800

f) Twist range: 3600

Results

Selection of bioactivity parameters using classical approach

On the basis of the keyword hits scoring analysis, weightage was given to various parameters identified for screening of herbal plants with respect to factors involved in causing gout. as exemplified in (Table 3). Weightage was decided according to the percentage relevance obtained for each parameter. Highest relative percentage relevance was obtained for COX-2 inhibition (i.e. 6), followed by other parameters like TNF- alpha Inhibition (5.5), IL-1beta Inhibition (4.5), Xanthine oxidase Inhibition (4.5), IL-6 inhibition (3.5) and AMP Deaminase inhibition (2.5).

Binary (presence-absence) coefficient matrix

Out of 50 identified herbals, 27 herbals exhibited a binary score of either 4 or more than 4, higher than that of the counterparts, e.g. Ethnopharmacological relevance behind the selection of various herbal plants was also exemplified in (Table 2), *Curcuma Longa, Camellia sinensis, Peganum harmala, Ocimum sanctum, Zingiber Officinale, Withania somnifera, Vitis vinifera, Piper nigrum, Punica granatum, Rosmarinus officinalis, Picrorhiza kurroa, Terminalia*

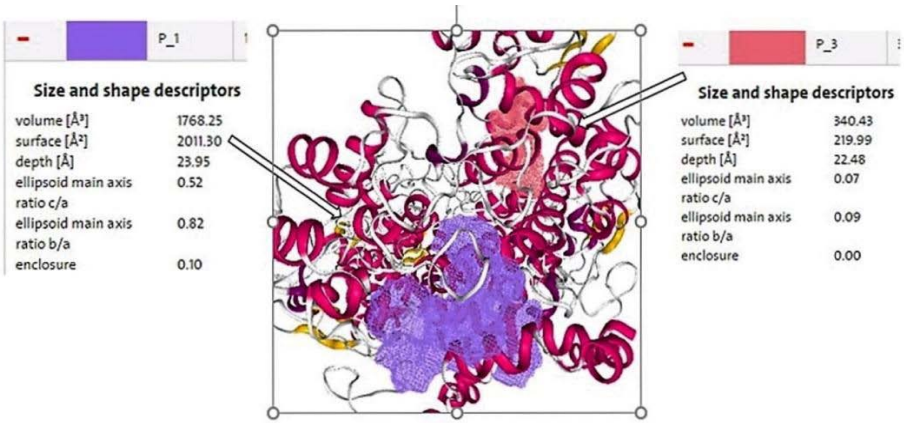

Figure 1: Dog Site Scorer revealed that one pockets P1 of the COX-2 receptor were found to be energetically drugable score (0.67) in comparision with P3 (0.07).

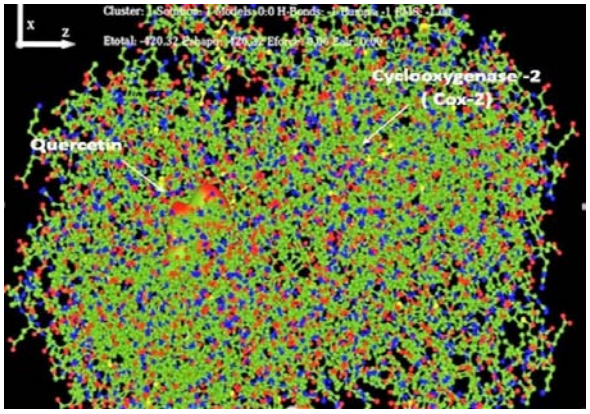

Figure 2: Energy of docking (E value) was calculated using Hex 8.0, revealed predominant phytoconstituents Quercetin (*Vitisvinifera*) found to have high binding energy (-420.32 Kcal/mol).

chebula, Hypericum perforatum, Azadiracha indica, Mangifera indica, Trigonella foenum-graecum, Allium sativum, Syzygium aromaticum, Phyllanthus emblica, Centella asiatica, Harpagophytum procumbens, Tinospora cordifolia, Garcinia Cambogia, Crocus sativus, Swertia chirayita, Malus domestica..

Simple additive weighing matrix

Out of 27 plants selected on the basis of binary coefficient matrix (Binary Matrix score ≥ 4), it was revealed that 13 herbal plants showed immense potential of acting as a therapeutic agent. e.g. *Curcuma Longa,Camellia sinensis, Peganum harmala, Ocimum sanctum, Zingiber Officinale, Withania somnifera, Vitis vinifera, Piper nigrum, Punica granatum, Rosmarinus officinalis, Picrorhiza kurroa, Terminalia chebula, and Hypericum perforatum.*

Fuzzy set optimization

On the basis of decision matrix analysis, 03 herbals like *Curcuma Longa, Camellia sinensis, and Peganum harmala* held the top most position with μS score being 1, relative to the lowest μS score exhibited by Malusdomestica (0.70). Optimized scores were also obtained for the selected plants based on fuzzy set membership analysis as shown in (Table 4).

Molecular docking

Active site analysis: Active site analysis using Dog Site Scorer revealed that one pockets P1 of the COX-2 were found to be energetically favorable for performing molecular docking studies. Out of the pockets present, P1 (0.67) was found to be more druggable based on its linear combination of volume, hydrophobicity and enclosure attributed to its descriptors than the other pockets [P0 (0.41), P3(0.07)] as shown in (Figure 1).

Ligand receptor docking (Hex 8.0): The process of classifying ligands that are most likely to interact with a particular receptor is based on the predicted free energy of binding. Its work on the principle of lowering the value of free energy change (E-value) promotes extemporaneity of binding interaction between the predominant phyto-ligand and targeted receptor as shown in (Figure 2). Energy of docking (E value) was calculated using Hex 8.0 and revealed 21 predominant phytoconstituents including Demethoxycurcumin, Curcumin, Catechin, Epigallocatechin Gallate, Harmalol, Eugenol, Rosmarinic acid, Gingerol, Shogaol, Isopelletierine, Withaferins, Anthocyanins, Luteolol, Piperidines, Pyrrolidines, Luteolin, Borneol, D-Mannitol, Picroside I, Hydroxycinnamic acid, and Quercetin having E value in the range :19.65 to -420.32 kcal/mol. Five phytoligands that are Pyrrolidines (-49.13), Isopelletierine (-56.13), With a ferins (-55.47), Epigallocatechin Gallate (-59.12), and Quercetin (-420.32) exhibit significant ability to inhibit COX-2 as compared to standard chemotherapeutic inhibitor Meloxicam and Colchicine (-18.98 kcal/mol and -18.23 kcal/mol respectively) as exemplified in (Table 5).

Table 5: Predominant phytocompounds and standard inhibitor docking score (E value) targeting COX-2.

S.No.	Herbal	Herbal code	Phytoconstituents	E -value (Kcal/mol)
1.	*Curcuma Longa*	Cl	Curcumin	-46.05
2.	*Camellia sinensis*	Cs	Epigallocatechin Gallate	-59.12
3.	*Peganum harmala*	Ph	Harmalol	-28.19
4.	*Ocimum sanctum*	Os	Anthocyanins	-23.52
5.	*Zingiber officinale*	Zo	Gingerol	-26.32
6.	*Withania somnifera*	Ws	Withaferins	-55.47
7.	*Vitus vinifera*	Vv	Quercetin	-420.32
8.	*Piper nigrum*	Pn	Piperidines	-46.88
9.	*Punica granatum*	Pg	Ellagic acid	-25.80
10.	*Rosmarinus officinalis*	Ro	Rosmarinic acid	-43.47
11.	*Picrorhiza kurroa*	Pk	Picroside I	-29.62
12.	*Terminalia chebula*	Tc	Arjunolic acid	0.7
13.	*Hypericum perforatum*	Hp	Hydroxycinnamic acid	-30.55
14.	Meloxicam	Standard inhibitor		-18.98
15.	Colchicine	Standard inhibitor		-18.23

Discussion

Hyperuricemia can occur due to exaggerated production of uric acid in the joints. Inflammatory gout results from deposition of monosodium urate crystals in joint fluids and other soft tissues. The prevalence rate is higher in metropolitan Indian population [43]. Moreover, due to high incidence of metabolic syndrome in younger population, a *Mathew* and *Danda* epidemiological study showed that 15.8% of the affected patients were below the age of 30 years.

Existing drugs like NSAID for the management of inflammation is not effective because of its serious gastrointestinal side effects, including bleeding and ulceration. Colchicine and corticosteroids has been associated with an increased risk of toxic signs as well serious complications, including bone marrow destruction and liver or kidney cell damage [44]. For the proper management and mitigation of the inflammatory response, natural products are becoming popular as curative remedies for controlling the progression of such inflammatory arthritis [45].

The present study emphasized the classical bioprospection in a rhetorical way by using a holistic mathematical approach to obtain unbiased results. The process involves targeting bioactivity parameters by literature survey, their precedence indexing, score assessment, collection of plants to prepare a large database, on the basis of presence or absence of BAP identification of potent plants and on the basis of scoring and decision matrix calculation of their final weightage [46].

In this study, the binary matrix approach used to identify the herbal compound having all or none principle, thus exterminating the plants, which have scored less than the median cut-off value i.e., > 4. After the first screening step, out of 50 plants, 27 plants filtered out for continuing weightage matrix and the fuzzy set membership analysis, which provide a comprehensively acceptable optimized score [47].

This model considered 13 herbal compounds with comparatively higher percentage relevance as potent therapeutic agents against inflammatory gout, i.e. *Curcuma Longa, Camellia sinensis, Peganum harmala, Ocimum sanctum, Zingiber Officinale, Withania somnifera, Vitis vinifera, Piper nigrum, Punica granatum, Rosmarinus officinalis, Picrorhiza kurroa, Terminalia chebula, and Hypericum perforatum*. The predominant phyto ligands of this herbal lead, Pyrrolidines (-49.13), Isopelletierine (-56.13), Withaferins (-55.47), Epigallocatechin Gallate (-59.12), and Quercetin (-420.32) etc., exhibited significant ability towards the receptor as compared to standard chemotherapeutic inhibitor (Meloxicam, 18.98) when they were docked. This study indicates that the selected herbal compound is beneficial for the treatment of Gout *in vitro* level, which provides the direction for conducting further *in vivo* study for targeting Gout.

Conclusion

The bioprospection study has provided 13 Natural compounds i.e., *Curcuma Longa, Camellia sinensis, Peganum harmala, Ocimum sanctum* etc. with significant therapeutic potential against gout. The study are still warranted so as to provide cross-validation to the in silico herbal informatics at *in vitro* and *in vivo*.

Acknowledgement

The authors are grateful to Vice Chancellor, Jamia Hamdard and Director, INMAS for provision of research facilities and support.

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Austin Arthritis - Volume 1 Issue 2 - 2016
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Citation: Tanwar A, Chawla R, Ansari MM, Thakur P, Chakotiya AS, Dixit B, et al. Herbal Informatics Approach for Identification and Validation of Natural Compounds Targeting Gout. Austin Arthritis. 2016; 1(2): 1008.