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AIP BASE- A COMPREHENSIVE DATABASE ON ANTI-INFLAMMATORY PLANTS

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ABSTRACT: The inflammatory process involves a series of events that can be elicited by numerous stimuli, e.g. infectious agents, ischemia, antigen-antibody interactions, chemical, thermal or mechanical injury. The response is accompanied by the clinical signs of erythema, oedema, hyperalgesia and pain inflammatory responses.(1) The greatest disadvantage of the presently available potent synthetic drugs lies in their toxicity and reappearance of symptoms after discontinuation of treatment. The research of screening and development of drugs for the anti-inflammatory activity is therefore, an unending problem and there is need of finding out anti-inflammatory drugs from indigenous plants. Hence to meet the needs we have developed an anti-inflammatory plant database systems which records plants related information. The data on anti-inflammatory medicinal plants and phytochemicals responsible for their anti-inflammatory activity and emphasized the role of information derived from various systems of traditional medicine and its utility for drug discovery purposes.

Keywords: Medicinal plants, Rheumatoid arthritis, plant database, anti-inflammatory plants, phytochemicals

Database : http://btistnau.in/Anti-inflammatory/index.php

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1.INTRODUCTION

An inflammatory counter is a physiological process aiming to restore tissue- homeostasis. The uncontrolled, unresolved inflammation will make the tissue distortion which will lead to pathogenesis of chronic inflammatory and autoimmune diseases, including arthritis, asthma, atherosclerosis, diabetes, and cancer. Generally, the anti-inflammatory diseases are long-term disorder which gives rise to swelling of joints and other tissues. [1]. Traditional medicinal herbs have served as a potential source of alternative medicine for different diseases, especially for millions of people in developing countries. According to WHO, nearly eighty percent of people in world still depend upon herbal medicines [2, 3]. Naturopathic or standard treatment approaches are taking place side by side in a personalized way in most parts of the world today, even in developed countries. Chemical substances derived from animals, plants and microbes have been used to treat human disease since the dawn of medicine. The investigation of natural products as source of novel human therapeutics reached its peak in pharmaceutical industry in the period 1970–1980, which resulted in a pharmaceutical landscape heavily influenced by non-synthetic molecules [4, 5]. A substantial number of plant compounds have been discovered in higher plant. The plant-derived natural compounds that have become indispensable for modern pharmacotherapy can be found in the field of anti-cancer agents, e.g., paclitaxel and its derivatives from yew (Taxus) species, vincristine and vinblastine from Madagascar periwinkle (*Catharanthus roseus* (L.) *G. Don*), and camptothecin and its analogs initially discovered in the Chinese tree *Camptotheca acuminata Decne*. [2,3]. Further notable examples include the *cholinesterase* inhibitor galanthamine that has been approved for the treatment of Alzheimer's disease and was initially discovered in *Galanthus nivalis L*. [6], and the important antimalarial and potential anti-cancer agent artemisinin originally derived from the traditional Chinese herb *Artemisia annua L*. [7,8] AIP Base, provides an extensive collection of medicinal plant having anti-inflammatory effects. AIP Base provides, detailed information on plant information which includes plant profile, plant part used, common name, tamil name, detailed phytochemical properties on druggability properties, physicochemical properties, ADMET properties, three-dimensional structure of phytochemicals which can be used for molecular docking, anti-inflammatory target information, medicinal usage of the plants and its references. The database was collected and maintained in MySQL relation database which were all tabulated.

2. MATERIALS AND METHODS

Curated list of Anti-inflammatory plants

The data on anti-inflammatory plants were explored from various literature sources. 204 anti-inflammatory plants were curated having the anti-inflammatory properties. The information collected for plants include plant profile, plant part used, common name, Tamil name, Plant image, other medicinal usage of the plants. Data were collected from various literature sources and from published articles.

Phytochemical composition of anti-inflammatory plants

After compiling the comprehensive list of medicinal plants, the literature mining was done to collect the information on phytochemicals. Database search was carried out to collect information on phytochemicals. 405 phytochemicals possessing anti-inflammatory property were collected.

Database Architecture and Implementation

Anti-inflammatory web based platform is manually curated database running on Apache web server Xammp server with the application program PHP.[9] The data for the anti-inflammatory database were collected from literature. Unique key is used to maintain non-redundancy in the database. The database table were maintained in MySQL relational database [10] by which the tables are related in database. The tables include Plant profile, disease type, statistics, anti-inflammatory targets as shown in the figure. Unique key is used to maintain the non-redundancy records in the database.

Types of Arthritis

The information on various types of arthritis, description and their symptoms were compiled based on literature survey and from published articles.

3. RESULTS AND DISCUSSION

Database search

To retrieve the data of the traditional medicinal plants we have made our web browser more user friendly so as to make the data easily available for the researchers. Users can search the information either by the type of arthritis or by the plant compound names. Five different disease types were mentioned in the database individually. Apart from these more than 200 plant profiles are given the web page. These plant profile contains information in an orderly manner. plant profiles contain the name of the plant name which includes the scientific name, common name and Tamil name. It also contains the plants medicinal uses and chemical constituents .(Figure 2) In the search option all the information including the ligand properties, anti-inflammatory properties plant profiles and the disease types are provided individually. Also, all the information is in PDF format which makes the user more comfortable to collect all the required data. For example, if a user requires the details of phytochemical compound the user can search either using the compound name or the type of the disease (Figure 1).

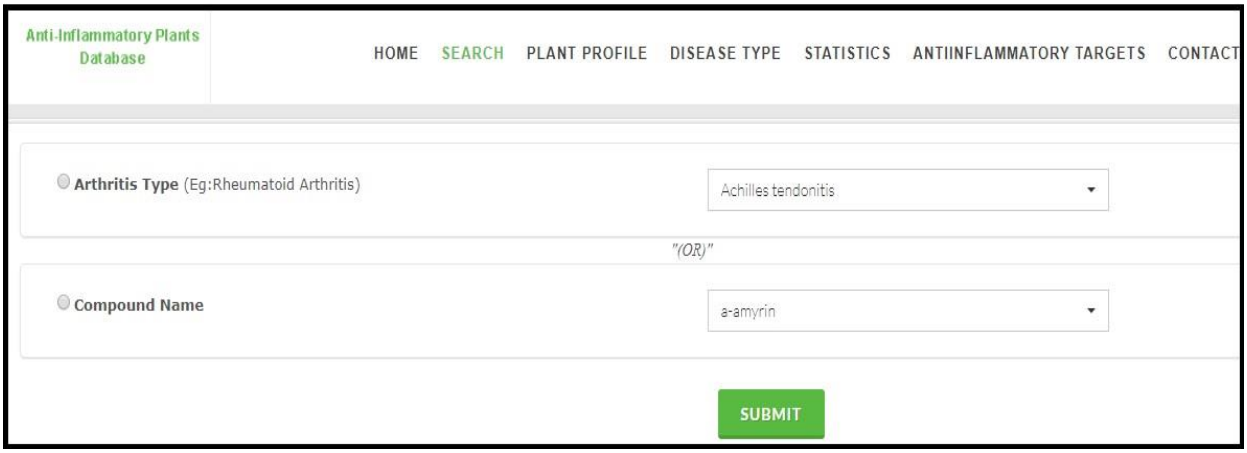

Figure 1: User friendly database web browser

Similarly, users can find and easily visit other pages by just getting clicked on the links provided. Effective browsing options were also introduced into the browser. Hence all the user could obtain all the required information. The users can download the data in the database using the link provided for further studies.

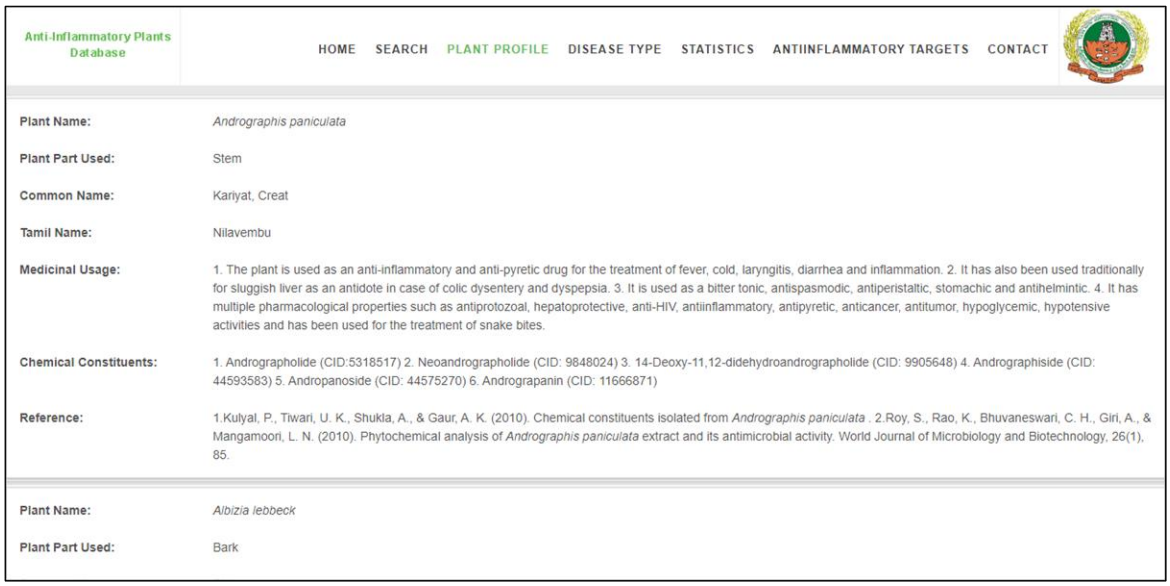

Figure 2: Plant Profile

Plant Phytochemical Formulations

More than 400 phytochemicals were studied. Their ligand properties were analysed and statistical analysis was also carried out. All the phytochemicals were calculated for their molecular weight, heavy atoms, rotatable bonds that are present in the phytochemical compounds, hydrogen bond acceptors. Physico chemical properties were also calculated which includes different categories like lipophilicity, log P values, water solubility, pharmacokinetics, druglikeness,(11) and its medicinal chemistry [12]. The physio chemical properties of five varied categories were checked for 402 compounds. The list of all ligands used for this study is given in Table 1.

Table 1

A-amyrin	Cephaeline	Helenalin	Picrinine
Abrin	Ceryl alcohol	Hentriacontane	Pinitol
Acetic acid	Chamissonolide	Hentriacontanol	Piperidine
Acetyl boswellic acid	Chelerythrine	Hirsuteine	Piperine
Adenine	Chlorogenic acid	Hirsutine	Plumbagin
Ageconyflavone a	Cholin	Holafebrine	Proanthocyanidin
Ajmalicine	Chrysin	Holantosines a	Prococenei
Akkuamigine	Cineole	Holantosines b	Prococene ii
Akuamicine	Cis-isoeugenol	Holarrhimine	Procyanidin
Alamarine	Citral	Homocapsaicin	Procyanidins
Alangimarckine	Citric acid	Homodihydrocapsaicin	Prodelphinidine b6
Alangimaridine	Citronellol	Ibericin	Protopine
Alanine	Coulambamine	Indirbin	Pseudo-tropine
Alizarin,1-methyl ether	Conarrhimine	Irehline	Psoralen
Allantoin	Conduritol	Ishwarane	Psychotrine
Allicin	Conessidine	Ishwarol	Pteropodine
Alliin	Connessimine	Ishwarone	Pterpstilbene
Allocryptopine	Connesine	Isocephaeline	Punicalagin
Alpha - asarone	Conimine	Isoconnessimine	Quebrachitol
Alpha glucal	Coptisine	Isofucosterol	Quercetin
Alpha-humulene	Coroglaucigenin	Isoleucine	Quercetin 3-glucoside
Alstonin	Corotoxigenin	Isomitraphylline	Quercetin,3-7 Diglucoside
Andrograpanin	Corynantheine	Isoorientin	Quercetin-3-rutinoside
Andrographiside	Corynoxeine	Isopteropodine	Resveratol
Andrographolide	Coumarin	Isoquercitin	Rhamnetin
Andropanoside	Coumestan	Isotubulosine	Rhein
Anethole	Cucurbitacin b	Isovitexin	Rhynchophylline
Ankorine	Cucurbitacin d	Jatrorrhizine	Riddelline
Anthocyanin	Curcumin	Kaemferol	Rubiadin
Apigenin	Cyclomahanimbine	Kurchine	Rutin
A-pinene	Cynaropicrin	Kurcholessine	Salicylic acid

Aristolic acid	Cysteine	Lanosterol	S-allyl l-cysteine
Aristoloamide	Damnacanthal	L-arabinose	Salsoline
Aristolochene	Daucosterol	Lawsone	Sanguinarine
Aristolochic acid	D-camphor	Ledol	Sarmentine
Arnifolin	D-cymarose	Leonotinin	Sarmentosine
Aronttianamide	Dehydrotylophorine	Leucoanthocyanidin	Savinin
Ascorbic acid	Demethoxycurcumin	Leucocyanidin	Scopoletin
A-selinene	Demethyl-tylophorinine	Leucodelphinidin	Sedanenolide
Asiatic acid	Demethylwedelolactone	Limonene	Senecionine
Asiaticoside	Deoxytubulosine	Linalool	Seneciphylline
Aspartic acid	D-galactose	Linolenic acid	Sesamin
A-spinasterol	D-glucose	Loganic acid	Shogaol
Astragalin	Diallylsulphide	L-oleandrose	Sitosterols
A-terpinene	Dihydrocheilantifoline	Lupenone	Skimmianine
Azadirachtin	Dihydrohelenalin	Lupeol	Somniferine
Baicalein	Dillenetin	Lupeol acetate	Soranjidiol
Balanitine-4	Diosgenin	Lutein	Speciophylline
Balanitine-5	Dipentene	Luteolin	Spinasterol
Balanitine-6	Dotriacontanoic acid	Luteolin-7-glucoside	Stearic acid
Balanitoside	Dotriacontanol	Lyaloside	Stigmast-4-en-3-one
B-amyrin	D-quercitol	Lycopene	Stigmasterol
Benzoic-acid	D-sermentose	Lycopsamine	Stigmasterolglucoside
Berberine	Dulcitol	Lysine	Strictosidines
Bergapten	Ecdysterone	Macelignan	Tannin
Bergaptol	Echinatine	Madasiatic acids	Taraxastane
Beta-asarone	Echitamine	Mahanimbicine	Taraxasterol
Beta carotene	Epigallocatechin 3-galate(egcg)	Mahanimbine	Tartaric acid
Beta-caryophyllene	Elemicine	Mahanine	Tetrahydroalstonine
Beta-copaene	Ellagic acid	Methionine	Thymol
Betain	Embelin	Methoxynepetaefol	Thymol methyl ether
Beta sitosterol	Embodin	Methyl aristolochate	Thymoquinone
Betulin	Emetine	Methyl piperate	Trans-b-farnesene
Betulinic acid	Encecaline	Mitraphylline	Trans-isoeugenol
Bharatamine	Encecanescins	Mollugin	Trans-p-coumaryl

			alcohol
Bibenzyls	Epicatechin	Myricetin	Trans-p-coumaryldiacetate
Bicyclomahanimbine	Epicatechin 3-gallate	Myristic acid	Trans-p-hydroxycinnamaldehyde
Biflavanoid	Epi-friedelinol	Naringenin	Triacanthin
Bisabolene	Epigallocatechin	N-butyl phthalide	Triacontan-1-ol
Bis-demethoxycurcumin	Epigallocatechingallate	Negundoin c	Trianthenol
Bismurrayafoline e	Episterol	Neoandrographolide	Trichodesmine
Boeravinone a	Erythrodiol	Nepetaefolin	Tridecane
Boeravinone c	Euchrestine b	Nepetaefolinol	Trigonelline
Boeravinone d	Eugenol	Nicotine	Triterpenoids
Boeravinone e	Euglobaliic	Nicotinic acid	Tropine
Boeravinone f	Euglobal-t1	Nimbolide	Tryptophan
B-pinene	Farnesene	Nonacosane	Tubulosine
Brachyamide b	Ferulic acid	Nonane	Tylophorine
Brachystamide b	Ficusin a	Nordamnacanthal	Tylophorinicine
Brassicasterol	Ficusin b	Nordihydrocapsaicin	Tylophorinidine
Bromelain	Fisetinidol	O-acetylethanolamine	Tylophorinine
Cadinene	Flavopiridol	Octacosanol	Tyrosine
Caffeic acid	Formic acid	Octane	Undecane
Caffeine	Formononetin	Oleanane	Ursane
Calactin	Friedelin	Oleanolic acid	Ursolic acid
Calotropin	Fucosterol	Oleic acid	Uscharidin
Campesterol	Fumaric acid	Orientin	Uscharin
Camphene	Gamma-fegarine	Oxalic acid	Uzarigenin
Capric acid	Gamma terpinene	Oxyanthraquinone	Valine
Capsaicin	Garcinol	Oxyberberine	Vanillic acid
Capsanthin	Geraniol	Palmitic acid	Venoterpine
Capsorubin	Geranyl acetate	Palmitoleic acid	Verbenol
Carotene	Germacrene d	P-cymene	Verbenone
Carvocrol	Glucose	Pectin	Vitamin a
Carovene	Glycine	Pellitorine	Vitamin b1
Caryophyllene beta	Glycyrrhizin	Pentatriacontane	Vitamin b2

Caryophyllene oxide	Guggulsterones	Phellendrene	Vitamin c
Catechin	Guineensine	Phenyl alanine	Vitamin k1
Harman	Harpagoside	P-hydroxycinnamate	Vitexin
Physcion	Wedelolactone	Withanolide	Yakuchinone-a
Z-13-docosenamide	Zeaxanthin		

Statistical Analysis

About 44 physico-chemical properties belonging to five major categories such as Lipophilicity, Water Solubility, Pharmacokinetics, Druglikeness, Medicinal Chemistry [10, 11] were analysed for 402 compounds. In this section we discuss five properties of these compounds which includes Molecular Weight, Rotatable bonds, H bond acceptors, Heavy atoms and Log P values (Table 2).

Table 2: Physio chemical properties which has five different categories

Physico – Chemical properties	
	Heavy atoms
	Aromatic heavy atoms
	Rotatable bonds
	H-bond acceptors
	H-bond donors
	MR
	TPSA
	iLOGP
	XLOGP3
	WLOGP
	MLOGP
	Silicos-IT Log P
Lipophilicity	Consensus Log P
	ESOL Log S
	ESOL Solubility (mg/ml)
	ESOL Solubility (mol/l)
	ESOL Class
	Ali Log S
	Ali Solubility (mg/ml)
Water Solubility	Ali Solubility (mol/l)

	Ali Class
	Silicos-IT LogSw
	Silicos-IT Solubility (mg/ml)
	Silicos-IT Solubility (mol/l)
	Silicos-IT class
	GI absorption
	BBB permeant
	Pgp substrate
	CYP1A2 inhibitor
	CYP2C19 inhibitor
	CYP2C9 inhibitor
	CYP2D6 inhibitor
	CYP3A4 inhibitor
Pharmacokinetics	log Kp (cm/s)
	Lipinski #violations
	Ghose #violations
	Veber #violations
	Egan #violations
	Muegge #violations
Druglikeness	Bioavailability Score
	PAINS #alerts
	Brenk #alerts
	Leadlikeness #violations
Medicinal Chemistry	Synthetic Accessibility

Molecular Weight (MW)

In the analysis of MW, about 90% (approx.) of the compounds had less than 500 Daltons. Maximum of 61 and 58 compounds were found in the MW range of 151-200 and 301-350 respectively. Maximum and minimum MW was observed with Tannin (1701.2 Da) and Formic Acid (46.03 Da), respectively (Figure 3).

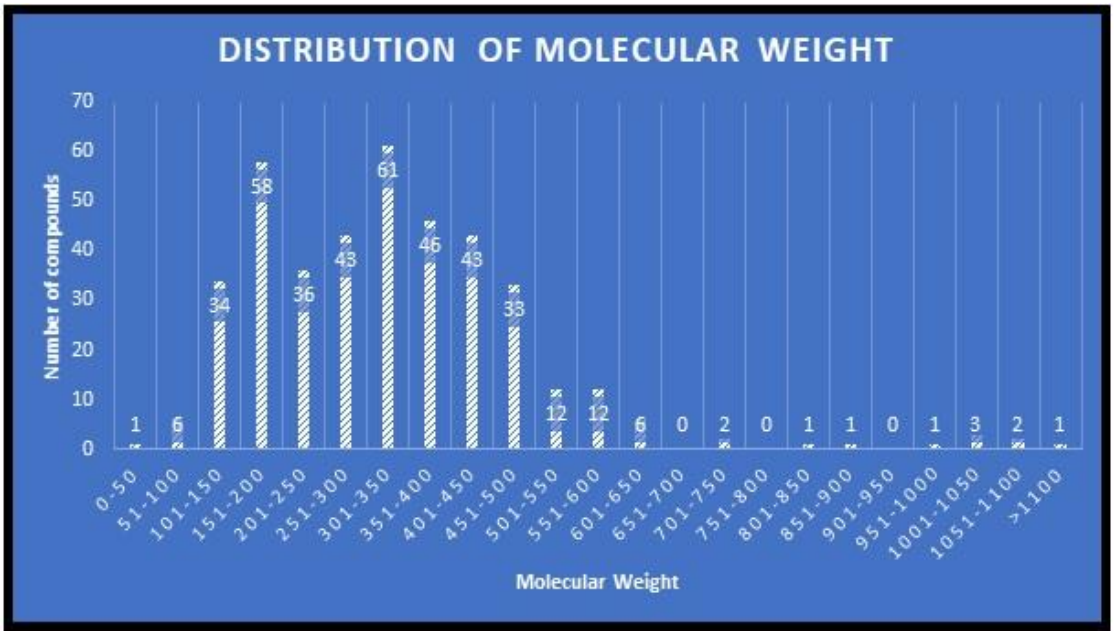

Figure 3: Analysis of the molecular weight of the compounds.

Heavy Atoms

Maximum number of compounds (97% approx.) had less than 50 numbers of heavy atoms. Greater than 76 heavy atoms was found in two compounds such as Punicalagin (78 heavy atoms) and Tannin (122) (Figure 4).

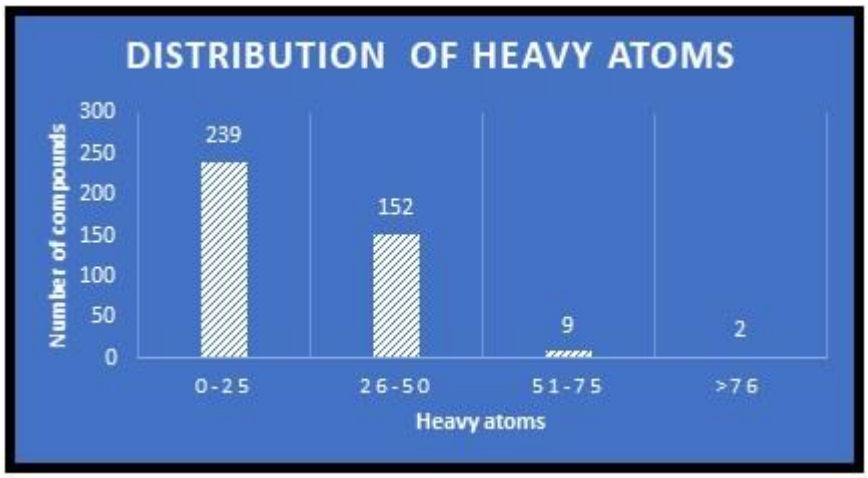

Figure 4: Analysis of compounds for heavy atoms.

Rotatable bonds

About 80% of the compounds had less than 5 rotatable bonds in the present analysis. Below is the graph which shows the number of compounds vs rotatable bonds (at 5 interval). Only 15 compounds tend to have greater than 15 rotatable bonds. Tannin and Pentatriacontane had 31 and 32 rotatable bonds respectively (Figure 5).

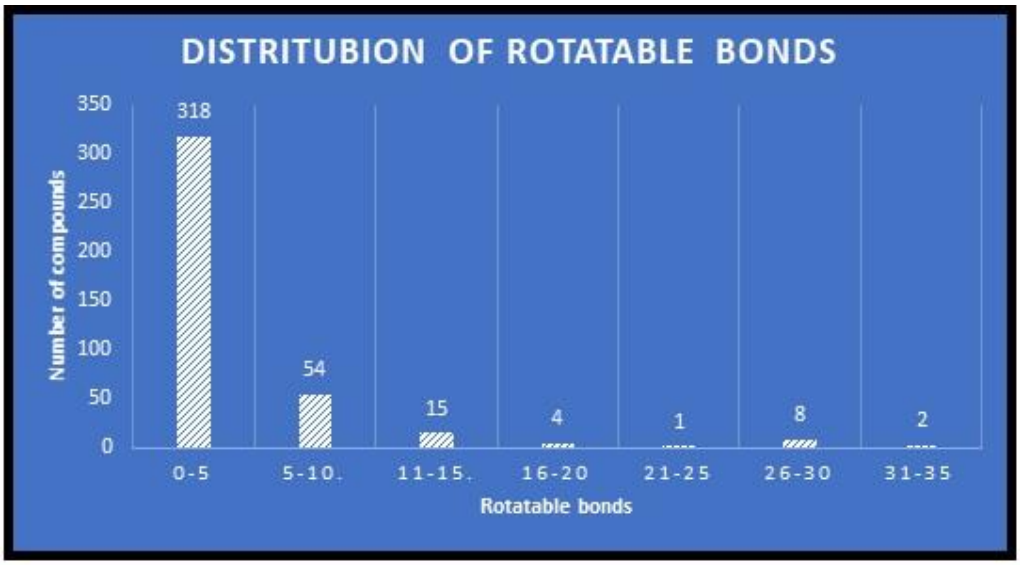

Figure 5: Analysis of phytochemical compounds for rotatable bonds.

Hydrogen bond acceptors

As per Lipinski's rule, druggable compounds should have 10 hydrogen bond acceptors. In this study, 93% (approx.) compounds obey Lipinski's rule of five and possess 10 hydrogen bond acceptors (Figure 6). Furthermore, as observed with previous properties tannin showed the presence of 46 hydrogen bond acceptors.

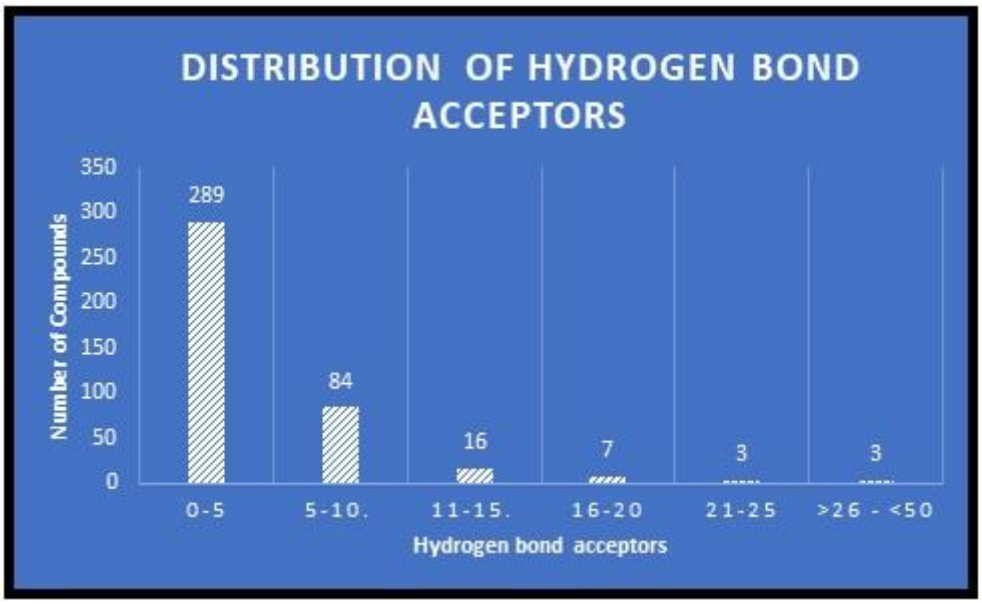

Figure 6: To analyze the distribution of Hydrogen bond acceptors that are present in the compounds

Log P values

Highest and lowest log P was observed with compounds Pentatriacontane (13.33) and Bromelain (-9.35) respectively. 83% (approx.) of the compounds have less log P value (Figure 7)

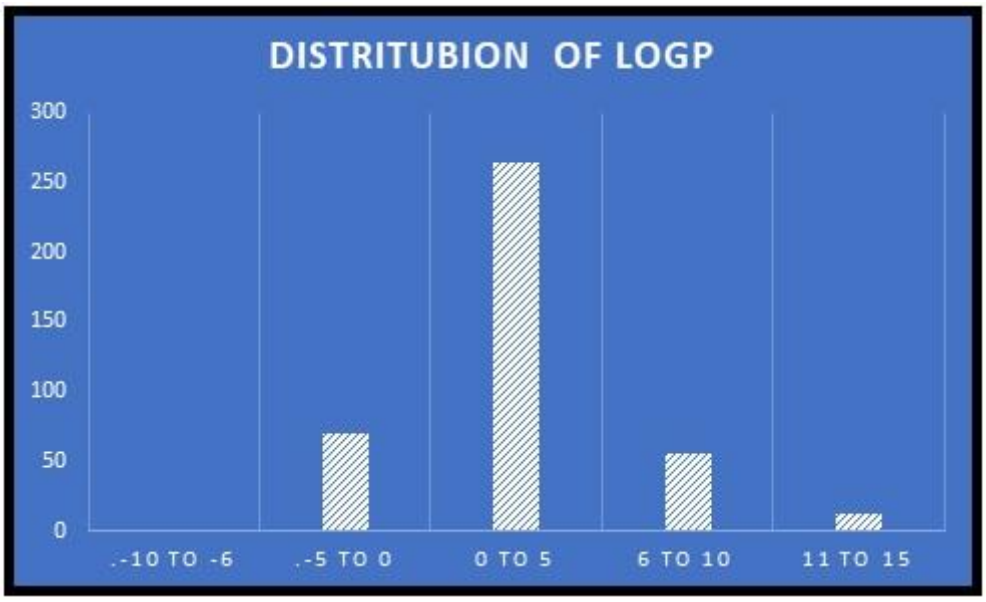

Figure 7: To analyse the distribution of log P values

Anti-inflammatory Targets

AIPBase includes a comprehensive list of three dimensional structure of anti-inflammatory targets. The protein targets were downloaded in pdb format from Protein databank (13) For the non availability of the three dimensional structure in protein databank, the structure was modelled by computational modeling using Discovery studio 2.0 (14) and I Tasser (15).

DISCUSSION

World Health Organization (WHO) defines medicinal plants as plants which possess compounds that can be used for the therapeutic purposes as well as producing useful drugs from the metabolites. According to the WHO, medicinal plants are being used by the people in developing countries to treat various diseases, and these products' market continue to grow [16] which gives a good sign of economic importance of medicinal plants. Based on the previous report, 15% out of 300,000 plant species in the world have been studied for the pharmacological activity. Interestingly, about 25% of modern medicines have been developed from the natural resources such as medicinal plants. Inflammation is a response of tissue to cell injury due to pathogens, damaged tissues, or irritants which initiates the chemical signals to heal the afflicted tissue. Inflammation can be classified into two types known as acute and chronic inflammation [17,18]. Positive vascular response to inflammation in the early stage (acute inflammation) can be clearly seen at the affected tissue as it becomes reddened due to the increase of blood flow and swollen due to edema fluid [19,20] Three main processes that involve during the vascular response to acute inflammation are changes in vessel caliber and blood flow, the increase in vascular permeability, and fluid exudate formation. It is important to understand that an uncontrolled inflammation may contribute to many chronic illnesses [21,22] More than 400 phytochemicals were obtained. Their ligand properties were analysed and statistical analysis was also carried out. All the phytochemicals was checked for their molecular

weight, heavy atoms, rotatable bonds that are present in the phytochemical compounds, hydrogen bond acceptors. Physico chemical properties were also checked which includes different categories like lipophilicity, log P values, water solubility, pharmacokinetics, druglikeness, and its medicinal chemistry. The physio chemical properties of five varied categories were checked for nearly 402 compounds. From the statistical analysis more than 76 heavy atoms was found in two compounds such as Punicalagin (78 heavy atoms) and Tannin (122) in the case of heavy atoms, Maximum and minimum MW was observed with Tannin (1701.2 Da) and Formic Acid (46.03 Da).). Only 15 compounds tend to have greater than 15 rotatable bonds. Tannin and Pentatriacontane had 31 and 32 rotatable bonds. In this study, 93% (approx.) compounds obey Lipinski's rule of five and possess 10 hydrogen bond acceptors. Highest and lowest log P was observed with compounds Pentatriacontane (13.33) and Bromelain (-9.35) respectively. 83% (approx.) of the compounds have less log P value. Traditional medicines used for the treatment of anti inflammatory disorders are used in various tribal/rural cultures worldwide. At present, investigation of anti-inflammatory activity of traditional medicine has led to the development and studies of many herbal remedies employed for such purpose. The information that has been obtained from various sources is helpful in preserving folk indigenous knowledge as well as discovery of potential compounds having promising anti-arthritic activity. The information gathered from the data provides the information on toxicity profile and mechanism of action of tested extracts.

4. CONCLUSION

Plants are one of the most important sources of medicines. Since ancient time's medicinal plants have been used to treat different ailments due to their accessibility, availability, inherited practice, economic feasibility, and perceived efficacy. This study will help the recent and future researchers in more research work on these valuable medicinal plants.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

There is no conflict of financial interest or any other interest.

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