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In Silico Anti-Inflammatory Activity Evaluation of Some Bioactive Compound from *Pterocarpus santalinus* L.f. through Molecular Docking Approach

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ABSTRACT

Pterocarpus santalinus (Red Sanders) a highly impressive indigenous deciduous threatened tree species renowned for its characteristic timber of exquisite colour reported to have enormous biological activities and potential health benefits along with its extensive use in furniture. Considering its various health benefits, the present study focused on evaluation of phytochemical constituents of the leaf, bark and heartwood of *P. santalinus* responsible for its anti-inflammatory activity. Phytocompounds were quantified high in heartwood samples collected from natural forests than plantations. Alkaloids and terpenoids were present in both acetone and methanol extracts of leaf, bark and heartwood samples accounts for potential medicinal uses especially its anti- inflammatory activity. GC/MS/MS analysis revealed that the compounds elicited at various retention times found to have various biological properties such as antimicrobial, antioxidant, anti-inflammatory, anti-diabetic and anti-malarial activities. Molecular docking study was aimed to predict the affinity of the compounds namely Viminalol, Protopine, Lupanol, Lup-20(29)-en-3-one and Lup-20(29)-en-3-ol, (3.beta.)- (CAS) of red sanders to bind with anti-inflammatory targeted proteins viz. COX-1, COX-2, NR3C1, S100s, IL1F5 and SPINK5 thereby reduced their functionality towards inflammation. The results proved that red sanders found to have the potential as an anti-inflammatory agent and it can be used in the development of health care products.

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Introduction

The natural plant based remedies are as old as humankind which was evidenced through pre-historic sites and written records and plants are the source of first medicines. Plant based natural medicines are the most widely used medicines for both acute and chronic health issues even with the huge availability of antibiotics and enormous synthetic medicine [1-3]. Over the past 100 years, the development and bulk manufacture of chemically synthesized medicines have revolutionized health care in most parts of the word. In developing countries large population still rely on traditional practitioners and herbal medicines for their primary health care. During the past two decades, use of traditional medicine is not only limited to developing countries, public interest in natural therapies has increased greatly in industrialized countries also with expanding use of ethno botanicals [4]. The growing demand towards plant based natural products has renewed attention in the production of herbal health care formulations, herbal-based cosmetic products, and herbal nutritional supplements. Hence, there is a demand to promote natural products to save the human lives. Pullaiah et al. reported that *Pterocarpus santalinus* is one such tree species in which the bioactive compounds present in it accounts for its potential health benefits [5].

Pterocarpus santalinus L.f. belongs to the family Fabaceae, popularly known as Red Sanders is one of the threatened plants of India. It is an endemic and endangered timber tree species confined to Southern parts of Eastern Ghats. India is one of the countries which has the favourable soil and climatic conditions to grow red sanders. The natural distribution of red sanders occurs almost exclusively in the south eastern parts (Chittoor, Cuddapah and Nellore districts of Seshachalam hill ranges, Kurnool, Nellore and Prakasam) of Andhra Pradesh in the tropical dry deciduous forests and northern parts (North Arcot, and Chengalpet districts) of Tamil Nadu [6]. Red sanders is highly impressive indigenous herb, renowned for its characteristic timber of exquisite colour, beauty and exceptional technical qualities. It is a highly valued tree species for its diverse utility in India and abroad.

Its valuable wavy grained timber is traded as padauk, the wood is also used in traditional and folklore medicines and the red dye obtained from the wood is used as colouring agent for textile, medicine and food. Hence, the natural sources of red sanders were exploited indiscriminately and already included in the endangered category of IUCN red list [7]. Along with its extensive use in furniture, enormous biological activities and potential health benefits of *P. santalinus* have been reported, including antioxidant, anti-diabetic, antimicrobial, anticancer, anti-inflammatory, anti-tumour and protective effects on the liver, gastric mucosa, nervous system, prickly heat, skin diseases, snake

bite, Jaundice and various other ailments were attributed to the bioactive compounds present in it [6].

Significant bioactive compounds identified from *P. santalinus* with promising medicinal uses reported to have more subtle effects on cellular mechanism which reduces the effects of disease instead of preventing deficiency diseases. Stem, bark and leaf extracts of *P.santalinus* showed maximum antimicrobial activity [8, 9]. Considering its various health benefits, the present study focused on the evaluation of phytochemical constituents of the leaf, bark and heartwood of *P. santalinus* responsible for its anti-inflammatory activity.

Inflammatory activity is caused by wound and infection in the tissues because of which the immune cells will release nitric oxide (NO), prostaglandin (PG), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α) in human body [10,11]. Glucocorticoid receptor, NR3C1 is a protein that is expressed constitutively and ubiquitously throughout the body and transcriptional regulator of anti-inflammatory molecules which upon ligand binding enters the nucleus and control diverse biological processes including development, metabolism and inflammation [12]. Activated glucocorticoid receptor up-regulates the expression of anti-inflammatory proteins in the nucleus [13]. Prostaglandin is a major mediator of inflammation process and its excessive production via up-regulation of the COX-2 activity leads to inflammatory mediated diseases including cancer Alzheimer's diseases and acute renal failure [14-18]. Cyclooxygenase (COX) is the first stimulus enzyme involved in the prostaglandin synthetic pathway. COX-1 also causes inflammation though housekeeping enzyme due to its constitutive role in human physiology [19-22].

Inhibition of COX-2 using natural compounds will be a target for inflammation treatment with lesser side effects [23-27]. Selective COX-2 inhibitors using the bioactive compounds isolated from natural resources is preferable to reduce the undesirable side effects of the long term usage of synthetic drugs [28]. Wang et al. reported that the active compound eburicoic acid isolated from *Laetiporus sulphureus* showed significant anti-inflammatory activity. *Platycodi radix* root is widely consumed for ocular inflammation due to high content of saponin [29-32].

Plant based bioactives can also be predicted through molecular docking, an *in silico* approach other than biochemical and chromatographic profiling. The primary purpose of this method is to predict the affinity of a drug candidate (ligand) to bind with the protein and form the most stable complex thereby reduce or block its activity which is responsible for various causative illness. Molecular docking is one of the vital computational methodology and a valuable tool used widely by researchers to underscore the molecular interactions of ligand molecules for drug discovery and development trajectory [33,34]. Hence, in the present study bioactive compounds present in the leaf, bark and heartwood of red sanders having significant biological activities were identified through phytochemical screening, chromatographic analysis and molecular docking studies to confirm the anti-inflammatory activity of red sanders.

Methods

Plant Source

Extensive surveys have been made in Southern states of India viz. Tamil Nadu, Andhra Pradesh and Karnataka for collection of leaf, bark and heartwood samples of *P. santalinus*. Samples were collected from plantations in Tanjore, Karaikudi, Dharmapuri and Thiruvannamalai districts of Tamil Nadu; natural strands in Rajampet, Tirupati and YSR districts of Andhra Pradesh and plantations Bangalore, and Kolar districts of Karnataka. The plant samples were washed thoroughly with tap water and shade dried for a week at room temperature (24 ± 2°C). The dried samples were powdered to get coarse granules using an electric blender and stored in an airtight container for further analysis.

Preparation of Extracts

The powdered plant samples (leaf, bark and heartwood) of *P. santalinus* (50 g) were extracted with 350 ml of acetone and methanol using Soxhlet apparatus at 65-80 °C for 8-10 h to extract the phytocompounds. The solvents of the respective extracts were reduced in rotary vacuum evaporator until complete removal of solvents and the extracts obtained were stored at 4 °C until further use. The stored plant extracts were then dissolved in respective solvents while experimentation to get the working solution of 1 mg/1 mL which has been subjected to qualitative and quantitative analysis.

Qualitative Phytochemical Analysis

Qualitative phytochemical screening of the methanol and acetone extracts of leaf, bark and heartwood samples of *P. santalinus* collected from selected morphologically superior trees was carried out to identify the presence of various secondary metabolites such as Alkaloids, Flavonoids, Tannins, Saponins, Steroids, Phenols, Glycosides, Protein, Carbohydrate and Terpenoids using standard methods [35].

Quantitative Phytochemical Analysis

Estimation of Alkaloids

The total alkaloid content present in the leaf, bark and heartwood of *P. santalinus* was estimated using method described by Karawya et al. Alkaloid present in the sample reacted with bromocresol green and produced yellow colour complex and measured spectrophotometrically at 415 nm [36].

Estimation of Flavonoids

The flavonoid content of bark and heartwood extracts of *P. santalinus* was estimated by the method of Harborne [35]. Flavonoids present in the sample react with vanillin reagent in acidic medium and produced yellow colour which was measured spectrophotometrically.

Estimation of Total Phenols

The total phenolic compound present in the bark and heartwood of *P. santalinus* was estimated Folin-Ciocalteu reagent by the method described by Malick and Singh [37]. Phenols reacted with phosphomolybdic acid in Folin-Ciocalteu reagent in alkaline medium and produced blue coloured complex called molybdenum blue.

Estimation of Saponins

The saponin content present in the leaf, bark and heartwood samples of *P. santalinus* was estimated by the method of Makkar et al. The saponin was quantified based on the colorimetric reaction of vanillin-sulphuric acid with slight modifications [38].

Estimation of Tannins

Tannin like compounds reduce phosphotungstate to molybdic acid in alkaline solution to produce a blue colour complex and the colour intensity is proportional to the concentration of tannin and measured at 700 nm [39].

Estimation of Steroids

Steroids reacted with ferric chloride in the presence of concentrated

sulphuric acid gave pink colour. The intensity of colour developed is directly proportional to the amount of steroids present and it was read at 540 nm in a calorimeter [40].

GC/MS/MS Analysis

The GC-MS/MS analysis was performed using Varian 3800 with Mass spectrum 4000 GC-MS/MS system equipped with a Fused silica capillary column of size 15m x 0.2 mm ID x 1µm linked to an EI detector. Helium gas (99.99% purity) was used as a carrier gas at a constant flow rate of 1ml/min and the sample injected was 1µl; the instrument was set to an initial temperature of 110 ºC, and maintained at this temperature for 2 min. At the end of this period the oven temperature was rose up to 280 ºC, at the rate of an increase of 5 ºC/min, and maintained for 9 min. Injection port temperature was ensured as 250 ºC. The ionization voltage was 70eV. The samples were injected in split mode as 10:1. Mass spectral scan range was set at 45-450 (m/z). Using computer searches on a NIST Ver.2.1 MS data library and comparing the spectrum obtained through GC-MS/MS compounds present in the plants sample were identified.

Identification of Phyto-Compounds

The active components in the extracts were identified by comparing their retention indices and mass spectra patterns with the spectrum of known components stored in the computer library and also with published literatures. Interpretation on mass-spectrum GC-MS/MS was conducted to match the identified components from the plant material using the database of National Institute of Standard and Technology (NIST), Wiley, Mainlib, Replib and Tutorial library sources having more than 62,000 patterns. The name, molecular weight and structure of the components of the test materials were ascertained.

Results

The extract yield was comparatively high in methanol than acetone extracts in all three plant samples viz. leaf, bark and heartwood of red sanders. In leaf samples methanol extract yield was high in samples collected from Thiruvannamalai (14.19 %) district of Tamil Nadu followed by YSR district of Andhra Pradesh (11.12 %). In case of bark samples the yield was high in methanol extract of samples collected from Rajampet, Andhra Pradesh (14.45 %) followed by Thiruvannamalai (14.19 %) district of Tamil, Nadu (12.64%). In case of heartwood the yield was high in methanol extract of samples collected from YSR district of Andhra Pradesh (16.15 %) followed by Rajampet, Andhra Pradesh (12.34 %). Over all the extract yield was high in heartwood, followed by bark and leaf the least (Figure. 1).

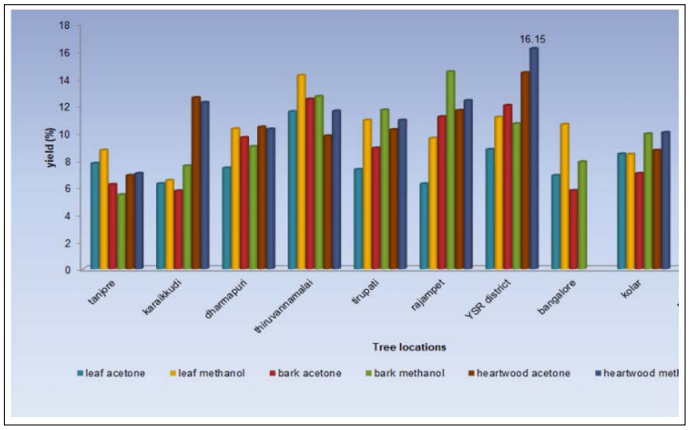

Figure 1: Acetone and Methanol extract Yield of Leaf, Bark and heartwood Samples of Red Sanders

Qualitative Analysis of Leaf, Bark and Heartwood Samples of Red Sanders

Phytochemical screening of methanol and acetone extracts of leaf, bark and heartwood of *P. santalinus* showed the presence of alkaloids, tannins, saponins, phenols and terpenoids. Methanol elicited more phytocompounds than acetone invariably in leaf, bark and heartwood. The samples collected from Karaikudi, Dharmapuri and Thiruvannamalai screened for maximum compounds of 6. Among all plant samples heartwood elicited more compounds followed by bark and leaf the least. Dharmapuri sources found to have tannins in both acetone and methanol extracts of leaf and bark. Alkaloids, terpenoids were present in both acetone and methanol extracts of leaf, bark and heartwood samples of all sources (Table 2).

Table 1: Location details of the samples collected for the study

S. No	Districts	States	Latitude	Longitude	Samples
1	Tanjore	Tamil Nadu	10°41'23.3"N	79°10'12.3"E	Leaf , bark, wood
2	Karaikudi,		10°07’07.7”N	78°50’52.5”E	Leaf , bark, wood
3	Dharmapuri		12°00'22.3"N	78°23'01.3"E	Leaf , bark, wood
4	Thiruvannamalai		12°43'52.5"N	79°14'51.1"E	Leaf , bark, wood
5	Tirupati	Andhra Pradesh	13°45’16.7”N	79°26’53.0”E	Leaf , bark, wood
7	Rajampet		13°43‘19.3"N	79°19‘26.5"E	Leaf , bark, wood
8	YSR district		13°48'26.4"N	79°24'41.7"E	Leaf , bark, wood
9	Bangalore	Karnataka	13°07'46.8"N	77°57'35.4"E	Leaf , bark, wood
10	Kolar		13°07'48.2"N	77°57'35.5"E	Leaf , bark, wood

Table 2: Phytochemicals present in methanol, acetone extracts of *P. santalinus* leaf, bark and heartwood collected from different locations

S.NO	List of particulars	(%) of trees having the phytochemicals					
		leaf		Bark		Heartwood	
		Acetone	Methanol	Acetone	Methanol	Acetone	Methanol
1	Alkaloids	100	100	100	100	100	100
2	Flavonoids	0	0	0	43	44	100
3	Tannins	79	64	43	72	44	44
4	Saponins	14	50	29	22	11	61
5	Steroids	0	7	0	0	0	0
6	Phenols	22	50	35	64	100	100
7	Glycosides	0	0	0	0	0	0
8	Protein	0	0	0	0	33	33
9	Carbohydrates	0	0	0	0	0	0
10	Terpenoids	100	100	100	100	100	100

Quantitative Analysis of Leaf, Bark and Heartwood Samples of Red Sanders

Quantitative analysis of phyto-chemicals in leaf, bark and heartwood extracts of *P. santalinus* showed that among all phytochemicals phenols was quantified high, followed by flavonoids and alkaloids and acetone quantified more than methanol extract samples. Heartwood contains more of phenols, alkaloids compared to bark and leaves. Bark contains more saponin and tannin than leaf and heartwood. Comparatively Tirupati (Andhra Pradesh) samples contain high quantity of alkaloid (101.69 mg/g), flavonoid (135.13 mg/g), tannin (99.33 mg/g) and saponin (118.78 mg/g) than other location samples. Steroids (107.14 mg/g) content were quantified high in YSR district, Andhra Pradesh samples. Phenol (227.47 mg/g) content were quantified high in Dharmapuri samples

Chromatographic Analysis of Leaf, Bark and Heartwood of Red Sanders using GC/MS/MS

GC/MS/MS analysis of the acetone and methanol extract of leaf, bark and heartwood (Fig 2, 3 & 4) showed the presence of various bioactive compounds with medicinal properties by relating their peak retention time, peak area (%), height (%) and mass spectral fragmentation profile with the known compounds described by the National Institute of Standards and Technology (NIST) and Wiley libraries. The GC/MS/MS chromatogram of methanol extracts of leaf, bark and heartwood samples of *P. santalinus* recorded more bioactive compounds in heartwood followed by bark and leaf. Results revealed that 4, 10 and 24 compounds were elicited in leaf, bark and heartwood methanol extract of *P. santalinus* respectively (Table 3, 4 & 5). The phytocompounds 2-Decyl-1H-quinolin-4-one separated at RT 27.649 was quantified high (34.748 %) followed by Gomezine (27. 973 5) in leaf. In bark lupanol was recorded high (22.743 %) followed by 8,13-epoxy-labadan-1,6,7,9-tetraol-11-one, 7-o-acetate(ester) (12.025 %). Maximum of 24 compounds were found in the heartwood of red sanders collected from Dharmapuri (Table 5). In heartwood, 9.beta.-Acetoxy-4-hydroxy-3,4,8-trimethyl-5.alpha.-H-tricyclo[6.3.1.0(1,5)] dodecane was recorded in high quantity (16.992 %). The compounds Viminalol, Protopine, Lup-20(29)-en-3-one, Lup-20(29)-en-3-ol, (3.beta.)- (CAS) identified in heartwood and lupanol in bark samples of red sanders were reported to have anti-inflammatory activity. Hence these compounds were subjected to molecular docking studies for further confirmation through in silico cost effective study.

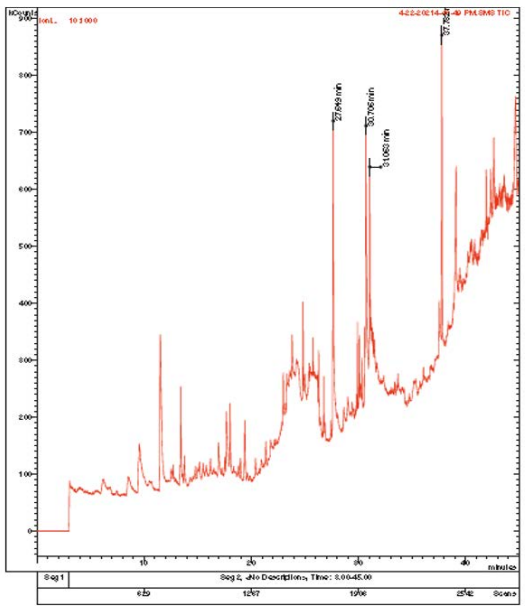

Figure 2: GC/MS/MS Chromatogram of Methanol Extract of Red Sanders Leaf

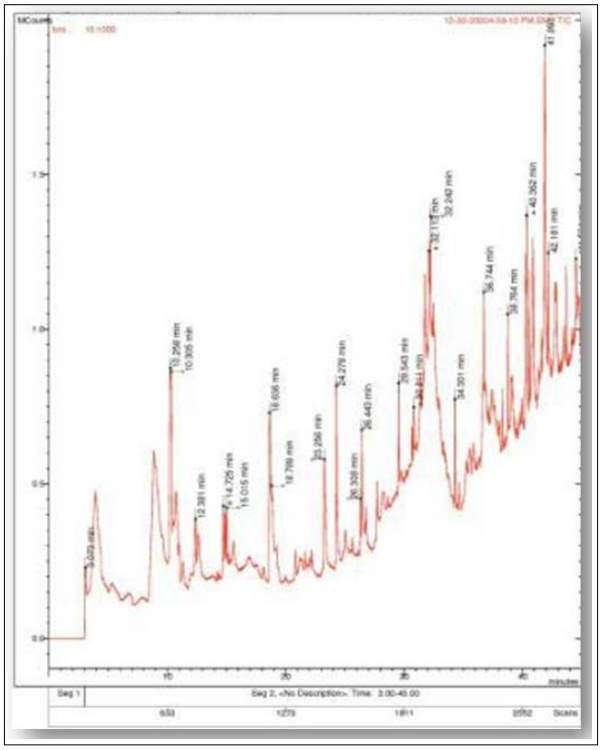

Figure 3: GC/MS/MS Chromatogram of Methanol Extract Red Sanders Bark

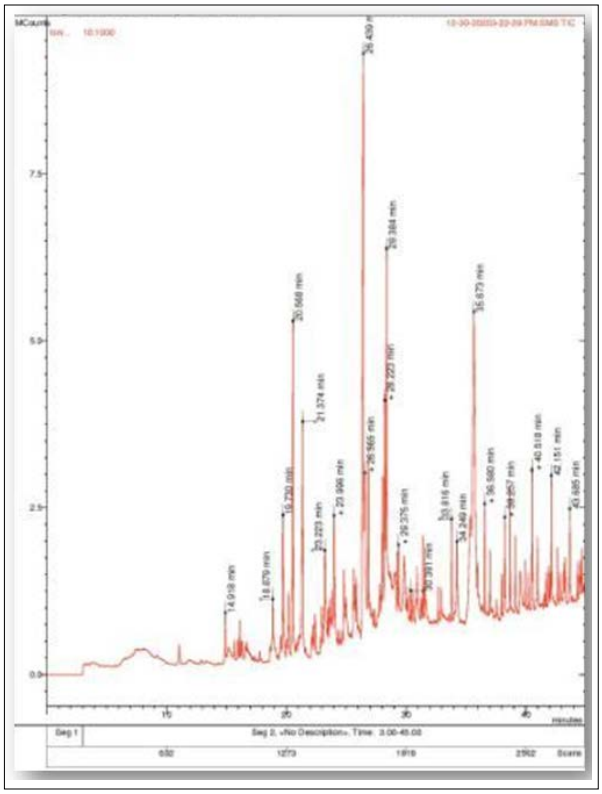

Figure 4: GC/MS/MS Chromatogram of Methanol Extract Red Sanders Heartwood

Table 3. GC/MS/MS analysis of methanol extract of red sanders leaf

Retention time	Compound name	Molecular weight	Molecular formula	Percentage (%)
27.649	2-Decyl-1H-quinolin-4-one	285	$C_{19}H_{27}NO$	34.748
30.705	Gomezine	264	$C_{18}H_{20}N_2$	27.973
31.063	2-(1-Butyl-Pentyl)-3-Methyl-1h-Quinolin-4-One	285	$C_{19}H_{27}NO$	13.570
37.782	(1S,5S,6S)*-5-acetoxybicyclo [4.40]decan-2-one	210	$C_{12}H_{18}O_3$	23.710

Table 4: GC/MS/MS Analysis of Methanol Extract of Bark of Red Sanders

S. No	Retention time	Compound name	Molecular weight	Molecular formula	Percentage (%)
1	37.631	6-o-methyl-(4-deuterium)-.gamma.-tocopherol	381	$C_{29}H_{49}DO_2I$	6.561
2	37.819	(1s,5s,6s)*-5-acetoxybicyclo[4.40]decan-2-one	210	$C_{12}H_{18}O_3$	6.919
3	38.413	lupanol	428	$C_{30}H_{52}O$	22.743
4	38.488	8,13-epoxy-labadan-1,6,7,9-tetraol-11-one, 7-o-acetate(ester)	412	$C_{22}H_{36}O_7$	12.025
6	39.096	13-methoxy-8h-dibenzo[a,g]quinolizin-8-one	275	$C_{18}H_{13}NO_2$	2.052
7	41.753	cholestan-3-one, cyclic 1,2-ethanediyl aetal, (5.beta.)-	430	$C_{29}H_{50}O_2$	3.979
8	42.562	1,3-diphenyldibenzo[g,i]thieno[3'4':3,4] pyrrolo[1,2-a]pyridine-2-(s)	425	$C_{30}H_{19}NS$	2.467
9	44.041	nickel, bis[hapto-3-hapto-4-4,5-diethyl-1,5-dihydro-1,2,2-trimethyl-3- (propen-2'-yl)-2h-1,2,5-azasilaborolin]bis	558	$C_{24}H_{48}B_2N_2Ni_2Si_2$	5.183
10	44.369	9h-purin-6-amine, n,n-dimethyl-9-(trimethylsilyl)-	235	$C_{10}H_{17}N_5Si$	3.318

Table 5: GC/MS/MS Analysis of Methanol Extract of Heartwood of Red Sanders

S.NO	Retention time	Compound name	Molecular weight	Molecular formula	Percentage (%)
1	20.415	Viminalol	426	$C_{30}H_{50}O$	1.502
2	24.835	Piperidine, 1-(1-cyclopenten-1-yl)- (CAS)	151	$C_{10}H_{17}N$	1.449
3	25.634	Pyrrole-3-carboxylic acid, 2,4-diethyl-, ethyl ester (CAS)	195	$C_{11}H_{17}NO_2$	1.217
4	25.727	6A-ALLYL-9-OXO-TRANS-A/B,TRANS-A/C-ECAHYDRO-4H-PYRROLO(3,2,1-IJ) QUINOLINE	219	$C_{14}H_{21}NO$	1.420
5	25.841	Protopine	353	$C_{20}H_{19}NO_5$	2.487
6	26.394	9.beta.-Acetoxy-4-hydroxy-3,4,8-trimethyl-5. alpha.-H-tricyclo[6.3.1.0(1,5)] dodecane	280	$C_{17}H_{28}O_3$	16.992
7	26.529	4a,8b,10b,11a-Tetramethylbicyclo[6.3.0]undec-1-en-5-one	220	$C_{15}H_{24}O$	2.589
8	26.777	Benzo[1,3]dioxol-5-yl-[6-(3,4-dimethoxy-phenyl)-4-methyl-[1,5,2]dioxaz inan-2-yl]-methanone	387	$C_{20}H_{21}NO_7$	2.721
9	27.928	cis- and trans-2,2-Dimethyl-3-(2-methyl-1-propenyl)-1-methoxycyclopropane-1-carbonitrile	179	$C_{11}H_{17}NO$	4.046
10	28.068	Bicyclo[3.2.1]octan-3-one, 6-(2-hydroxyethyl)-, endo- (CAS)	223	$C_{13}H_{21}NO_2$	2.065
11	29.661	3-Methylthioindole	163	C_9H_9NS	2.368
12	29.832	Pyrrole-3-carbonitrile, 2-amino-1-butyl-(1,1-dimethylethyl)-	219	$C_{13}H_{21}N_3$	1.027
13	30.380	Pyrrole-3-carbonitrile, 2-amino-1-butyl-(1,1-dimethylethyl	219	$C_{13}H_{21}N_3$	1.896
14	32.210	Lup-20(29)-en-3-one	424	$C_{30}H_{48}O$	4.275
15	34.000	Taraxasterol	426	$C_{30}H_{50}O$	2.629
16	37.214	Lup-20(29)-en-3-ol, (3.beta.)- (CAS)	426	$C_{30}H_{50}O$	5.181
17	37.873	Acetic acid, pentyl ester (CAS)	410	$C_{30}H_{50}$	6.393

18	38.089	5-Chloro-2,2-dimethyl-2,3,3a,4,5,7a-hexahydro-(3a.alpha.,5.beta.,7a.alpha.)-benzofuran	186	$C_{10}H_{15}ClO$	2.746
19	39.495	9-desoxo-9x-hydroxy-7-keto-ingol-3,8,9,12-tetraacetat	534	$C_{28}H_{38}O_{10}$	12.315
20	39.674	Benz[c]acridine, 5,10-dimethyl-	257	$C_{19}H_{15}N$	1.254
21	41.397	cyclopentadienyl-[hapto-4-(1,4,5,3)-4,5-diethyl-2,2-dimethyl-1-phenyl-3-(propen-2-yl)-1,2-dihydro-1,2,5-phosphasilaborole]cobalt	424	$C_{22}H_{31}BCoPSi$	2.279
22	41.717	2,4a-Oxymethano-1,2,3,4,4a,4b,5,6,7,8,8a,9-dodecahydrophenanthren-9-one, 8-cyanomethyl-2-methoxy-7-methoxycarbonyl-1,1,7-trimethyl-	574	$C_{23}H_{31}NO_5$	2.119
23	42.450	1-Methyl-3-[2-(ethoxycarbonylmethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxyisochromene	428	$C_{24}H_{28}O_7$	7.404
24	43.477	Cobalt, bis(1,3-di-t-butylcyclopentadienyl)-	413	$C_{26}H_{42}Co$	4.688

Table 6: Docking results of compounds from *Pterocarpus santalinus* against protein targets

S. No	Protein (PDB ID)	Ligand	Pubchem ID	Docking Score
1	COX-1(6Y3C)	Viminalol	73170	-3.14
		Lup-20(29)-en-3-ol, (3.beta.)- (CAS)	73040	-4.41
		Protopine	4970	-4.26
2	COX-2(5F1A)	Viminalol	73170	-4.37
		Lup-20(29)-en-3-one	323075	-5.15
		Lup-20(29)-en-3-ol, (3.beta.)- (CAS)	73040	-6.00
		Protopine	4970	-5.81
		lupanol	129649741	-5.37
3	NR3C1(1NHZ)	Viminalol	73170	-6.42
		Lup-20(29)-en-3-one	323075	-6.23
		Lup-20(29)-en-3-ol, (3.beta.)- (CAS)	73040	-8.47
		Protopine	4970	-7.11
		lupanol	129649741	-7.22
4	S100s(2L0P)	Viminalol	73170	-3.85
		Lup-20(29)-en-3-one	323075	-3.12
		Lup-20(29)-en-3-ol, (3.beta.)- (CAS)	73040	-3.36
		Protopine	4970	-1.42
		lupanol	129649741	-3.18
5	IL1F5(4P0J)	Viminalol	73170	-2.48
		Lup-20(29)-en-3-one	323075	-2.36
		Lup-20(29)-en-3-ol, (3.beta.)- (CAS)	73040	-1.82
6	SPINK5(1UVG)	Viminalol	73170	-1.01
		Lup-20(29)-en-3-one	323075	-1.24
		Lup-20(29)-en-3-ol, (3.beta.)- (CAS)	73040	-1.27
		Protopine	4970	0.45
		lupanol	129649741	-0.87

Molecular Docking

In the present study, molecular interaction of the bioactive compounds viz. Viminalol, Protopine, Lupanol, Lup-20(29)-en-3-one, Lup-20(29)-en-3-ol, (3.beta.)- (CAS) having anti-inflammatory activity with 6 anti-inflammatory target proteins namely COX-1, COX-2, NR3C1, S100s, IL1F5 and SPINK5 was carried out on Dell Optiplex 380 Intel (R) Core (TM) i-2400 CPU @ 3.10 GHz processor. Molecular docking studies of the active compounds of heartwood extract of red sanders identified though GC/MS/MS chromatographic technique having promising biological activities revealed that few compounds showed significant docking score

for anti-inflammatory activity. All the bioactive compounds used for molecular docking against NR3C1 (1NHZ), COX-2 (5FIA) and COX-1(6Y3C) showed significant docking scores (Fig 5). Especially Lup-20(29)-en-3-ol, (3.beta.)- (CAS) showed high docking score and can be used as drug against inflammation against NR3C1(1NHZ) and COX-2 (5FIA) efficiently.

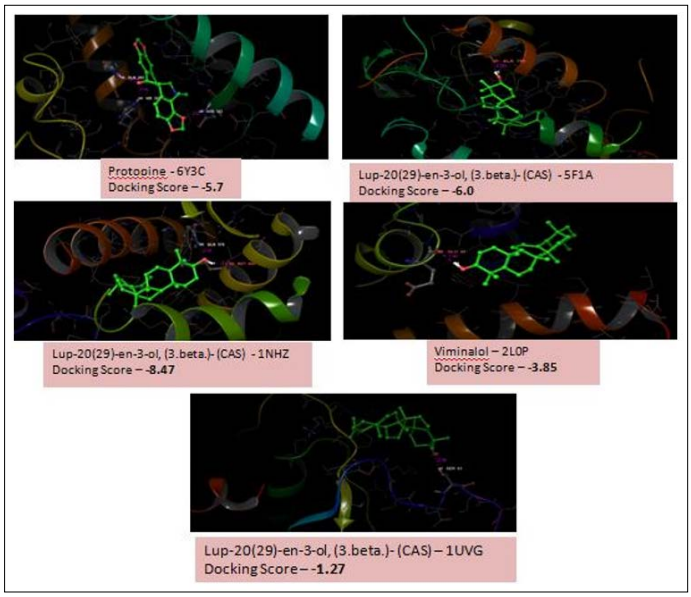

Figure 5: Bonding profile of active compounds on target proteins for anti-inflammatory property

Discussion

During the past few decades interest in natural therapies has increased greatly worldwide with expanding use of ethnobotanicals [4]. Array of efficient nutrient benefits can be extracted in whole plant than the few isolated bioactive constituents from synthetic components. Phytochemicals contained in plants and tree species act as a defence system to combat diseases and benefit consumer health. The thirst towards natural therapies drive us to study the bioprospecting potential of red sanders. Among the three explants of *P. santalinus* used for the study, the extract yield was comparatively high in heartwood followed by bark and leaf. Invariably methanol extracted more of phytochemicals than acetone in all samples.

Senguttuvan et al. reported that methanol extract given higher percentage of yield than petroleum ether, chloroform, ethyl acetate, ethanol and water extracts of leaf and root of medicinal herb, *Hypochaeris radicata* [41]. Comparatively methanol extracted high variety of plant constituents due to its high polarity than other solvents [42]. Truong Dieu-Hien et al. reported that the extraction yield was high (33.2%) when the plant samples were extracted with methanol than ethanol, acetone, chloroform, and dichloromethane showing that the extraction efficiency was high in highly polar solvent [43]. Among the samples collected from various locations situated in Tamil Nadu, Andhra Pradesh and Karnatak the extract yield was recorded high in heartwood sample collected from YSR Districts (16.15 %) of Andhra Pradesh. Plant samples of red sanders collected from natural forest located in all three districts of Andhra Pradesh invariably gave high yield than samples collected from the plantations.

Phytochemical constituents in the medicinal plants possessing various potential biological activities were extensively used in the human treatment, veterinary, agriculture, scientific research and countless other areas [44-46]. Plants and its parts viz. leaf, stem, bark, fruit, root, twig, wood and sap have been used in traditional and as folk medicines by locals to cure several diseases which includes cough, fever, asthma, diarrhoea, indigestion, and skin diseases [47]. Plants reported to have low toxic bioactive organic compounds like alkaloids, tannins, flavonoids, terpenoids, saponins and phenolic compounds with therapeutic potential [48]. Phytochemical screening of methanol and acetone extracts of leaf, bark and heartwood of *P. santalinus* was carried out. It was observed that methanol elicited more of phytocompounds than acetone and among the plant samples heartwood elicited more compounds followed by bark and leaf.

Dharmapuri sources found to have tannins in both acetone and methanol extracts of leaf and bark. Alkaloids, terpenoids were present in acetone and methanol extracts of leaf, bark and heartwood samples of all sources. Arunakumara et al. confirmed the presence of various components, such as carbohydrates, steroids, anthocyanins, saponins, tannins in *P. santalinus*. The presence of flavonoids, glycosides, and phenols were reported in the bark of *P. santalinus*, alkaloids, flavonoids, tannins, phenols, steroids, saponins, glycosides, carbohydrates and terphenoids and carbohydrates, flavonoids, terpenoids, phenolic compounds, alkaloids, saponins, tannins, and glycosides were reported in the heartwood of red sanders [49-52].

A variety of plant ingredients with diverse structures are capable of promoting health benefits. Quantitative analysis of phyto-chemicals in leaf, bark and heartwood extracts of *P. santalinus* showed that among all phytochemicals phenols was quantified high, followed by flavonoids and alkaloids and acetone quantified more than methanol extract samples. Heartwood contains more of phenols, alkaloids compared to bark and leaves. Bark contains more saponin and tannin than leaf and heartwood. Compared to heartwood, bark have large amount of Tannins, phenols, alkaloids and flavonoids. Tannin had more application in industries and biological properties as antioxidants, antiseptics, anticarcinogenic and anti-inflammatory activity. Saponin has been responsible for some biological activities such that insecticidal activity, anthelmintic activity, pesticidal activity, antibacterial, antifungal and antiviral activity [53,54]. In pharmacology, phenol content in plants was mainly targets to treat different diseases [55].

Prolong usage of the drugs against any diseases have been associated with serious and sometimes life threatening side effects which emphasized the research to find out plant based alternative therapeutic regimen with comparative efficacy but with fewer side effects. The natural products with medicinal properties have been used to treat all sorts of inflammatory conditions [56,57]. Keeping this in view chromatographic identification of bioactives with significant biological properties pushed towards GC/MS/MS analysis of leaf, bark and heartwood of red sanders. The compounds elicited at various retention time found to have various biological properties such as antimicrobial, antioxidant, anti-inflammatory, anti-diabetic and anti-malarial activities. The phytocompound Gomezine, a monoterpenoid indole alkaloid elicited at retention time of 30.705 reported to have cytotoxicity and analgesic properties [58,59]. Similarly an alkaloid berberine found in Berberis species, tryptanthrin in Isatis species reported to have anti-inflammatory activity and alkaloid in *Cissampelos pareira* accounts for its immunosuppressive and antioxidant activities [60-62].

The bioactive compound lupanol, natural pentacyclic triterpenoid

identified in the bark of red sanders reported to have anti-inflammatory, anti-arthritic, anti-mutagenic and anti-malarial activity. The compound Viminalol a pentacyclic triterpenoid, Lup-20(29)-en-3-one, Lup-20(29)-en-3-ol, (3.beta.)- (CAS) and Protopine a isoquinoline alkaloid identified though GC/MS/MS analysis reported to have anti-thrombotic, anti-inflammatory, anti-spasmodic, neuroprotective, anti-microbial, anti-bacterial, anti-viral, anti-fungal and anti-parasitic activities. Viminalol isolated from the methanol extract of *Artocarpus communis* roots reported to have antimicrobial activity and antinociceptive and anti-inflammatory [63,64]. Protopine has been found to have diverse biological activities such as anti-inflammation, anti-microbial, anti-angiogenic and anti-tumours activities [65].

Among the phytocompounds identified through GC/M/MS analysis having various promising biological activities five of the compounds, Viminalol, Protopine, lupanol, Lup-20(29)-en-3-one and Lup-20(29)-en-3-ol, (3.beta.)- (CAS) reported to have significant anti-inflammatory activity were selected for molecular docking studies to validate the compounds anti-inflammatory activity against the anti-inflammatory targeted proteins viz. COX-1, COX-2, NR3C1, S100s, IL1F5 and SPINK5 using Dell Optiplex 380 Intel (R) Core (TM) i-2400 CPU @ 3.10 GHz processor suggested that all legand compounds against NR3C1 (1NHZ), COX-2 (5FIA) and COX-1(6Y3C) showed significant docking scores. Docking study to validate anti-inflammatory activity of the bioactives cemented the acanthoic acid a novel pimarane diterpene isolated from Acanthopanax kiusianus through its potential to suppress the COX-1 and COX-2 expressions thereby inhibiting prostaglandin synthesis [66]. COX-2 inhibitory activity of berberine extracted from Berberis species proved that it can be a therapeutic option in treating inflammation [67- 69]. In the present study, Lup-20(29)-en-3-ol, (3.beta.)- (CAS) in leaf, bark and heartwood of red sanders with high docking score proved to use as anti-inflammatory drug against COX-2 (5FIA) efficiently.

Conclusion

Pterocarpus santalinus is a native tree species of India endemic to Rayalaseema region of Andhra Pradesh for high value timber and furniture. It also contains many potent phytochemicals for use in pharmaceuticals and cosmetics industries in addition to its timber and industrial uses. The presence of alkaloids and terpenoids in leaf, bark and heartwood of *P. santalinus* projected it as a promising source of naturally occurring antioxidants especially accounts for its anti-inflammatory activity. This study affirms that the presence of phytocompounds with significant biological activities accounts for the effectiveness of red sanders in treating inflammation. Molecular docking studies highlighted the probable mechanism by which red sanders is expected to elicit anti-inflammatory effects which assures its natural therapeutic use in healing inflammation without side effects.

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