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DEREPLICATION OF THE BIOACTIVE POOL IN *Gmelina arborea* Roxb. ROOT *VIA* HYPHENATED GAS CHROMATOGRAPHY COUPLED MASS SPECTROMETRIC SYSTEM

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ABSTRACT

The present investigation was carried out with a focus to explore the biologically active phytoconstituents in *Gmelina arborea* Roxb. root, a widely exploited anti-inflammatory drug material used in most of the traditional, complementary and alternative medical (TCAM) systems. Gas chromatography coupled mass spectrometric (GC-MS) analyses was carried out in the ethanolic extract as part of the dereplication process. The active principles with their retention time, peak area and m/z value of the compounds were detected and the analyses revealed the presence of 23 phytocompounds which were subsequently identified through the interpretation of mass spectra and comparison ofthe chromatogram retention values with the entries in NIST 11 and WILEY 8 databases.

Keywords: *Gmelina arborea*, Root, GC-MS analyses, Dereplication, Anti-inflammatory drug

1. INTRODUCTION

Tropical plants are a rich source of chemically diverse organic molecules with promising biological activities as they synthesize a wide spectrum of unique and structurally diverse secondary metabolites as defense agents against diseases, pests and predators. Hence, they are plausibly the most treasured source of therapeutic agents **[1]**. Nearly half of the plant-based modern medicines come from the tropics, and 74% of

these have been used in native folklore treatments. Thus, tropical plants form the 'world's largest pharmacy' and play a key role in research of leads in modern drug discovery pipeline **[2, 3]**.

Gmelina arborea Roxb. of family, Verbenaceae is a moderately small to large deciduous tree native to tropical and subtropical Asia **[4]**. It is a highly valued medicinal plant used in various traditional, complementary and alternative systems of medicine due to their wider biological potentiality. Being an ingredient of the most famous "Dashamoola" group, its roots are extensively used in most of the anti-inflammatory drug formulations. Moreover, the roots are reported to have demulcent action and used as a tonic to alleviate several inflammatory conditions like rheumatism and gout in folklore medicine **[5]**. Hence, understanding the phytochemical constituents in *G.arborea* root would be beneficial in anti-inflammatory drug development research. Dereplication rather than exhaustive isolation would serve as an ideal strategy in phytochemical research as it would prevent re-isolation and re-characterization of known bioactive compounds and thereby forms an essential step in natural product screening **[6, 7]**. Thus, dereplication not only has significance in the discovery of new therapeutics but also enables the standardization of folklore and traditional medicines **[8, 9]**.

Gas chromatography coupled mass spectrometry (GC-MS) is a hyphenated analytical technique suitable for direct analyses of the chemical constituents in multicomponent mixtures. Thus, it aids in the dereplication process of identifying complex mixture of bioactive pool in medicinal plants. Hence, the present study attempts to examine the phytochemical constituents in *G.arborea* root using GC-MS system.

2. MATERIALS AND METHODS

2.1 Collection of plant material

Fresh roots of *Gmelina arborea* were collected from Payattuvila, Thiruvananthapuram district, Kerala, India. The taxonomical identification of the plant was carried out usingthe Flora of the Presidency of Madras **[10]**. The plant was further authenticated by the Herbarium curator, Department of Botany, University of Kerala, Kariavattom and the voucher specimen (KUBH 10131) was deposited.

2.2 Preparation of plant extract

The collected roots were washed thoroughly and severed into small pieces before shade drying at room temperature for two weeks. The dried material was then milled into coarse powder by mechanical grinder and

stored in air tight bottles until further use. About 10 grams of the powdered root sample was subjected to maceration using magnetic stirrer for 6 hours with 200 ml ethanol as solvent. The extract was concentrated using rotary evaporator under reduced pressure and stored in air-tight containers at refrigerated condition (4 °C) until further use.

2.3 GC-MS Analysis

The analysis of the extract was performed using GC–MS (Model: GC MS- QP2010S, Shimadzu, Japan) equipped with Rxi-5Sil MS fused silica capillary column of 30 m length, 0.25 mm diameter and 0.25µm film thickness. For GC–MS detection, the oven temperature was programmed from 80 °C for 4 minutes and raised to 280 °C for 6 minutes at the rate of 5 °C/min while the injection temperature was set to 260 °C and the column flow rate was 1 ml/min. About one microliter of the sample was injected in a splitless mode (20:0) with a scan range of 50-500 m/z and scan interval of 0.5 seconds. The total running time of GC–MS was 50 min.

2.4 Identification of the components

Interpretation of mass spectrum obtained from GC-MS was conducted using the database of National Institute Standard and technology (NIST 11) and WILEY. The spectrum of the unknown components was compared with that of the known components stored in the NIST11 and WILEY8 libraries. The compounds identified were further confirmed by comparing their retention indices with that of literature data.

3. RESULTS AND DISCUSSION

The GC–MS analysis of ethanolic root extract enabled the identification of major bioactive components in *G. arborea*. The gas chromatogram obtained demonstrates the relative concentrations of various compounds eluted as a function of their retention time **(Figure 1)**. The active principles with their retention time (RT), peak area (%) and base m/z are enumerated in table 1by the ascending order of their retention times.

The GC- MS analysis of *G. arborea* revealed the presence of 23 compounds. Isogmelinol indicated highest peak (38.13%) which is the principal component detected followed by 1-(4,5-diethyl-2-methyl-1-cyclopenten-1-yl)ethanone (23.07%), Methylarboreol (6.74%), Coumaran (6.21%), 4,5-dihydro-2-(2-phenylethenyl)-4,4-oxazoledimethanol (3.41%) and Gamma hydroxyisoeugenol (3.12%). Figures 2, 3, 4, 5, 6 and 7 depicts the obtained mass spectra of Isogmelinol, 1-(4,5-diethyl-2-methyl-1-cyclopenten-1-yl)ethanone, Methylarboreol, Coumaran, 4,5-dihydro-2-(2-phenylethenyl)-4,4-

oxazoledimethanol and Gamma hydroxyiso-eugenol.

Among the identified compounds, the lignan, Isogmelinol is a potent inhibitor of PAF-induced platelet aggregation (IC_{50}: 2.8μM), a characteristic pathophysiological condition in asthma, allergy, inflammation, respiratory and cardiovascular events **[11]**. Gamma hydroxyisoeugenol (Coniferyl alcohol) is one of the monolignols synthesized *via* phenylpropanoid biochemical pathway which on copolymerization with related aromatic compounds forms lignans with potent biological properties. A recent investigation revealed its antimelanogenic activity in theophylline-stimulated mouse B16-4A5 cells with an IC_{50} value of 16.1 μM **[12]**. Other eugenol derivatives including dihydroeugenol, isoeugenol and their glycosides were shown to have potent inhibition against *Escherichia coli, Listeria monocytogenes, Staphylococcus aureus* and *Salmonella enteritidis* **[13]**. Paulownin is another lignan known to have anti-inflammatory,analgesic and hypoglycemic activity **[14]**. Paulownin demonstrates inhibitory activities against *Helicobacter pylori* cystathionine gamma- synthase (HpCGS) with an IC_{50} value of 19 ± 2 μM by non-competitively inhibiting the binding of the substrate, *O*-succinyl-L-homoserine (L-OSHS) to HpCGS **[15]**.

Coumarans are the 2,3-dihydroderivative of benzofuran consisting of a benzene ring fused to a 2,3-dihydrofuran ring. They are reported to have anti-helminthic, anti-inflammatory, anti-diarrhoeal **[16]**, anti-tubercular and anti-HIV activity **[17]**. 2-Benzofuran carboxaldehyde and its derivatives were shown to have antifungal activities of comparable levels with the standard, undecylenic acid when evaluated against the three pathogenic fungi, *Microsporum audouini, Microsporum gypseum,* and *Trichophyton rubrum* **[18]**. Squalene is a triteterpene used in cosmetics as a sunscreen owing to their antibacterial and antioxidant properties **[19, 20]**. It also exhibit anti-inflammatory action *via* lipoxygenase inhibition besides having chemopreventive and immunostimulant properties **[19, 21]**.

Hexadecanoic acid is a straight-chain, 16-carbon, saturated long-chain fatty acid reported to have anti-oxidant **[22]** and anti-cancer properties (IC_{50} value of 0.8 μg mL^{-1} against HCT-116 cells) **[23]**. Besides exerting anti-inflammatory activity *via* competitive inhibition of ester bond hydrolysis in membrane phospholipids by phospholipase A2 as revealed by enzyme kinetics studies **[24]**. Methyl palmitate is a

derivative of hexadecanoic acid. Previous bioactive studies on this fatty acid ester showed that it prevented kupffer cell activation and improved survival rate after orthotopic liver transplantation in the rat **[25]** while, recent *in vivo* studies demonstrated methyl palmitate as an inflammatory cell inhibitor as indicated by reduction in carrageenan-induced paw edema and croton oil induced ear edema in rats. Furthermore, a marked decrease in the neutrophil infiltration and NF-κB expression in liver and lung tissues along with reduced levels of prostaglandin E2 (PGE2), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and myeloperoxidase (MPO) was observed in lipopolysaccharide (LPS)-induced endo-toxemia rat models **[26]**. Two other fatty acid esters identified in the present study include 9-octadecenoic acid methyl ester and linoleic acid methyl ester at RT 31.333 and 31.466 respectively. linoleic acid methyl ester is a more lipid-soluble form of the polyunsaturated omega-6 fatty acid, linoleic acid which is one of two essential fatty acids required for humans. New findings have revealed that the fatty acid could inhibit the viability of human breast cancer cells, MDA-MB-231 and human hepatocarcinoma, SK-HEP-1 cells besides inhibiting the production of lipopolysaccharide/interferon-γ-induced nitric oxide in murine macrophages **[27]**. Their antifungal property was evident from the studies on the effect of fatty acid methyl ester (FAME) fraction from the seeds of *Annona cornifolia* having a major proportion of methyl oleate or 9-octadecenoic acid methyl ester (51.5%), methyl linoleate or linoleic acid methyl ester (19.1%) and methyl palmitate (16.9 %) against the pathogenic fungus, *Paracoccidioides brasiliensis* **[28]**.

Cinnamic acids (phenylacrylic acid) and their derivatives are a group of structurally diverse and low toxic aromatic carboxylic acids with varied pharmacological actions such as anti-depressant **[29]**, antioxidant **[30]**, anti-inflammatory **[31]**, anti-tubercular **[32]**, antitumor **[33]**, hypoglycemic **[34]** and cytoprotective actions in neuroinflammatory diseases **[35]**. Cinnamic acid methyl ester (Methyl cinnamate) is reported to have inhibitory effects on the growth of *Escherichia coli*, *Bacillus subtilis* and *Staphyloccocus aureus* and the fungus, *Candida albicans* **[36]** and is found to inhibit adipocyte differentiation *via* activation of the CaMKK2-AMPK pathway in 3T3-L1 preadipocytes **[37]**. Another naturally occurring phenolic compound is p-vinylguaiacol. Sandwich ELISA and western blot studies revealed that this compound has potent anti-inflammatory effects by dose

dependently inhibiting LPS-induced nitric oxide (NO), prostaglandins (PGE2), inducible NO synthase (iNOS), and cyclooxygenase-2 (COX-2) in RAW264.7 cells, achieved by suppressing the NF-κB and MAPK activation and histone acetylation **[38]**. Furthermore, they are reported to induce the antioxidant enzyme, paraoxonase 1 and enhance the transactivation of Nrf2, a redox-regulated transcription factor primarily involved in cellular stress response and antioxidant defense mechanisms **[39]**.

Apart from the above potentially bioactive anti-inflammatory compounds identified, dereplication in *G.arborea* also revealed prospective compounds including methylarboreol, isojasmone,1-(4,5-diethyl-2-methyl-1- cyclopenten-1-yl)e thanone, 4,5-dihydro-2-(2-phenyl-ethenyl)-4,4 oxazoledimethanol, 1,3-cyclopentanediol, 2-phenethylamino-tetrahydro-pyran-3,4,5-triol, 2-isopropenyl-2-methyl-butanedioic acid whose biological potentiality have not yet been explored. Hence, pharmacological screening of these compounds based on anti-inflammatory assays would enable the identification of new lead compounds of therapeutic value.

Moreover, the identification of isogmelinol (38.13%) and 1-(4, 5-diethyl-2-methyl-1-cyclopenten-1-yl) ethanone (23.07%) as the two principal components in *G. arborea* root enables their use as potential marker compounds in authentication of the drug material. Thus, the present dereplication data would be valuable in standardization of drug formulations based on the plant material besides having potential significance in novel drug discovery research.

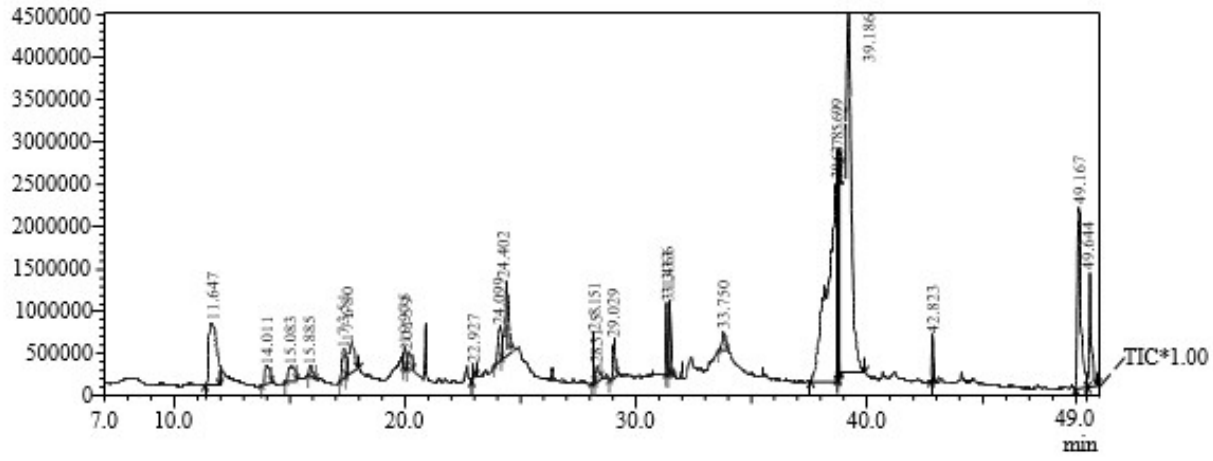

Figure 1: GC-MS Chromatogram of ethanolic root extract of *Gmelina arborea*

Table 1: Phytocomponents identified in the ethanolic root extract of *Gmelina arborea* by GC-MS analysis

Peak	RT	Area%	Name	Basem/z
1	11.647	6.21	Coumaran	120.10
2	14.011	1.00	p-vinylguaiacol	150.05
3	15.083	1.12	1,3-cyclopentanediol	55.05
4	15.885	0.46	Cinnamicacid methyl ester	131.10
5	17.351	1.46	2-benzofurancarboxaldehyde	145.00
6	17.680	2.24	Beta-phenylacrylicacid	147.05
7	19.975	0.59	2-phenethylamino-tetrahydro-pyran-3,4,5-triol	57.05
8	20.159	0.73	Isojasmone	166.05
9	22.927	0.32	Methyl p-methoxycinnamate	161.05
10	24.099	1.72	Dihydroeugenol	137.05
11	24.402	3.12	Gamma-hydroxyisoeugenol	137.05
12	28.151	0.51	Methylpalmitate	74.05
13	28.315	0.52	2-isopropenyl-2-methyl- butanedioicacid	83.05
14	29.029	1.10	Hexadecanoicacid	73.00
15	31.333	0.79	Linoleic acidmethyl ester	67.05
16	31.466	1.02	9-octadecenoic acid (z)- methyl ester	55.05
17	33.750	0.93	Paulownin	149.00
18	38.675	23.07	1-(4,5-diethyl-2-methyl-1-cyclopenten-1-yl)ethanone	151.05
19	38.699	4.31	1,2-benzenedicarboxylic acid	149.00
20	39.186	38.13	Isogmelinol	151.05
21	42.823	0.51	Squalene	69.05
22	49.167	6.74	Methylarboreol	149.00
23	49.644	3.41	4,5-dihydro-2-(2-phenylethenyl)- 4,4-oxazoledimethanol	202.00

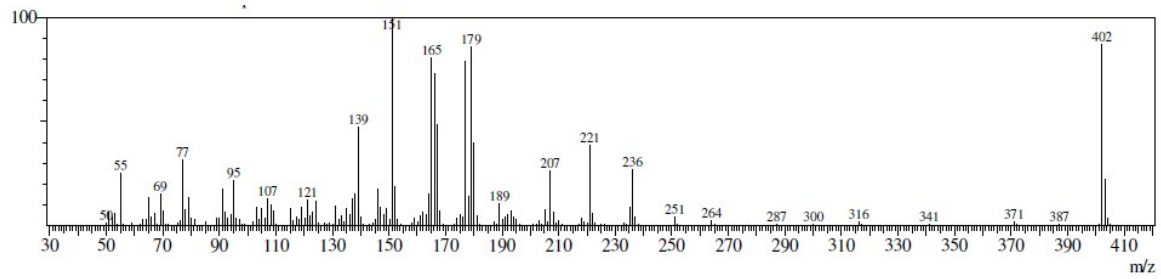

Figure 2: Mass spectrum of Isogmelinol

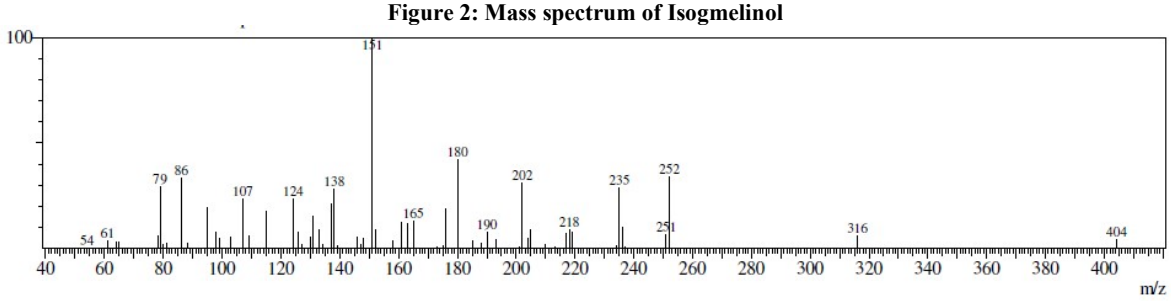

Figure 3: Mass spectrum of 1-(4,5-diethyl-2-methyl-1-cyclopenten-1-yl)-Ethanone

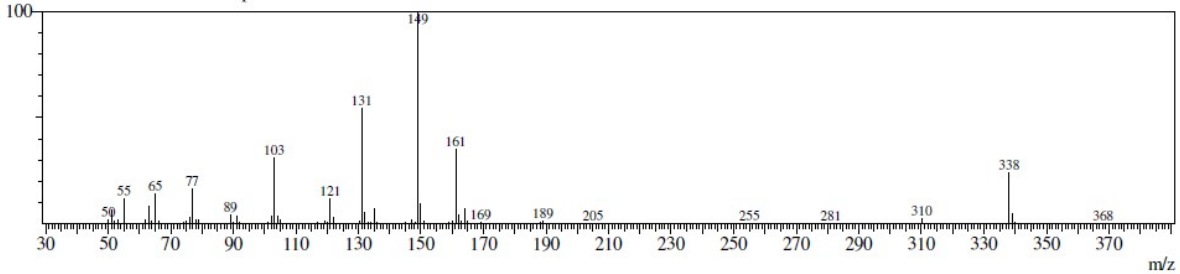

Figure 4: Mass spectrum of Methyl arboreol

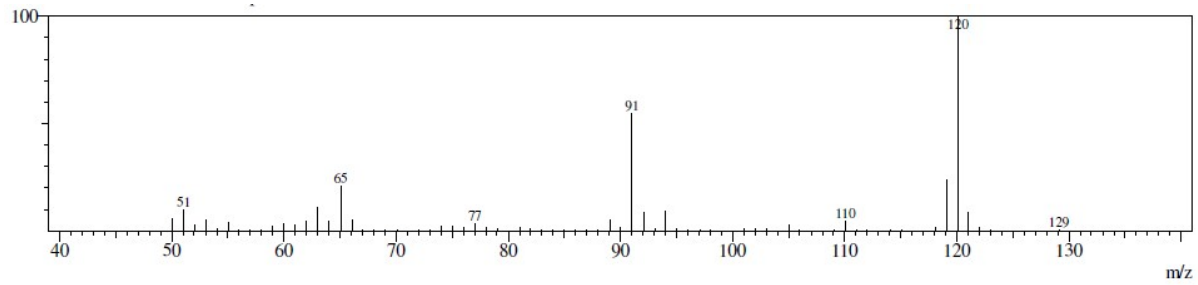

Figure 5: Mass spectrum of Coumaran

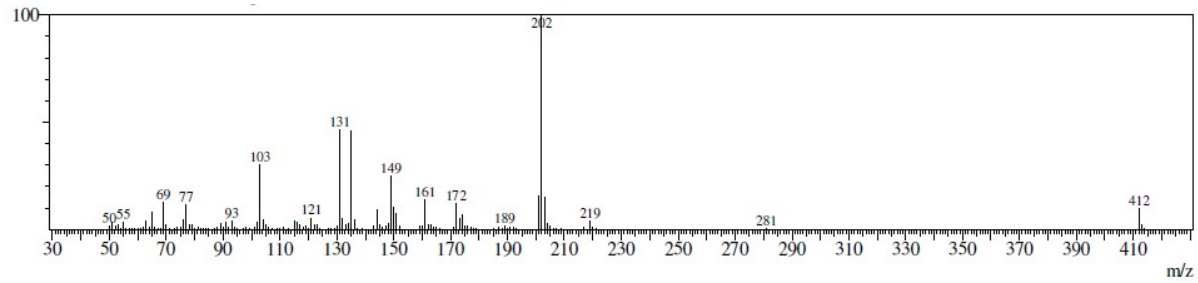

Figure 6: Mass spectrum of 4,5-dihydro-2-(2-phenylethenyl)-4,4-oxazoledimethanol

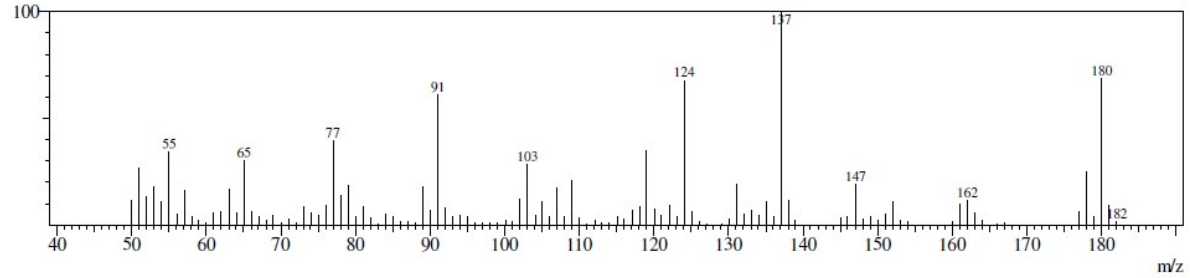

Figure 7: Mass spectrum of Gamma hydroxyisoeugenol

4. CONCLUSION

This is the first report of GC-MS analyses in the roots of *Gmelina arborea*. In the present study, the hyphenated GC- MS system served as an excellent dereplication tool for the identification of major bioactive constituentsin *G.arborea* root extract. The results revealed the presence of phytocompounds such as isogmelinol, paulownin, coumarans, hexadecanoic acid, methyl palmitate, cinnamic acids, p-vinylguaiacol and squalene which would serve as potent lead compounds in anti-inflammatory drug research. Moreover, these findings are vital in understanding drug interactions when used in traditional medical formulations and polyherbal drug preparations, a highly demanding approach in the era of personalized medicine.

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6. Conflict of interests

The authors have declared that no competing interest exists.

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