Trop J Nat Prod Res, May 2024; 8(5):7154-7160 ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Effect of Methanol Fraction of *Aspidopterys indica* Aerial Parts on DOCA Salt-Induced Hypertension and HR-LC-MS Assisted Phytochemical Profiling

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ARTICLE INFO

Article history:
Received 26 March 2024
Revised 22 April 2024
Accepted 30 April 2024
Published online 01 June 2024

ABSTRACT

Aspidopterys indica (Willd.) W. Theob. (Malpighiaceae) has been used as traditional remedy for hypertension and skin diseases. The current study aims to provide a comprehensive profile of bioactive metabolites in *A. indica* aerial parts and its effect against deoxycortisone acetate (DOCA) salt-induced hypertension in Wistar rats. Powdered aerial parts of *A. indica* were extracted by ultrasonication using methanol as solvent. The methanol extract was fractionated by silica gel vacuum liquid chromatography to obtain n-hexane fraction and methanol fraction designated as AIMF. The phytochemical constituents of AIMF were analysed using High Resolution-Liquid Chromatography-Mass Spectrometry (HR-LC-MS) performed in an LC-ESI-Q-TOF-MS system (Agilent Technologies 6550 i-Funnel). Mass analysis was conducted using the ESI-positive ionization mode. Hypertension was induced in uninephrectomised rats by injecting DOCA (25 mg/kg bw) in 1% NaCl into drinking water. Hypertensive rats were then treated with AIMF (200 mg/kg and 400 mg/kg, p.o) once daily for one week. HR-LC-MS analysis identified 52 compounds in AIMF with beta-D-gentiobiosylcrocetin, maritimetin, kaempferol-4'-glucoside-7-rhamnoside, quercetin, rutin, and isoamyl nitrite as the major compounds. AIMF at 400 mg/kg resulted in a significant reduction in the mean systolic and diastolic blood pressure in hypertensive rats with concomitant reduction in renal function parameters (urea, uric acid, and creatinine) and liver function enzymes (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase), as well as an increase in antioxidant enzymes particularly superoxide dismutase (SOD). The key metabolites of AIMF especially those with vasodilatory effect may be responsible for its antihypertensive effect, and play a role in the renoprotective and hepatoprotective effects.

Keywords: *Aspidopterys indica*, HR-LC-MS, Phytochemical, DOCA-Salt, Hypertension

Introduction

Hypertension or high blood pressure is a significant risk factor for various cardiovascular diseases, chronic kidney disease, and cognitive impairment.[1] The kidney is prone to the toxic effect of drugs due to its physiologic functions of filtration, concentration, and elimination of various metabolic substances. Several medications are currently being used in the management of hypertension, including calcium channel blockers, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, and diuretics.[2,3] Overall, the management of hypertension is complex whether through conventional medications or herbal remedies. Healthcare professionals must carefully consider the individual patient's needs, preferences, and health status when determining the most appropriate treatment approach and addressing any potential complications or clinical problems that may arise. Natural substances derived from plants have significantly contributed to the discovery of medicines against many diseases.

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Citation: Pulla UC and Sunitha K. Effect of Methanol Fraction of *Aspidopterys indica* Aerial Parts on DOCA Salt-Induced Hypertension and HR-LC-MS Assisted Phytochemical Profiling. Trop J Nat Prod Res. 2024; 8(5):7154-7160. https://doi.org/10.26538/tjnpr/v8i5.16

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

One reason for the growing interest in herbal medicines is the recognition that herbal medicines often contain a plethora of compounds that can have synergistic effects, offering a more holistic approach to the management of various disease conditions.[4, 5]

Despite the complexities involved, the ongoing exploration of plant metabolites holds great promise for discovering new bioactive compounds. Continued advancements in methodology and interdisciplinary collaboration will further enhance our understanding of the intricate chemistry of plants. Overall, the adoption of LC-MS methods for phytochemical profiling has revolutionized the study of plant metabolism, enabling researchers to explore the chemical diversity of plants in unprecedented detail. This approach holds great promise for discovering bioactive compounds with potential applications in various fields, including medicine, agriculture, and natural product research.[6-9]

Aerial parts of *Aspidopterys indica* are traditionally used for the management of hypotensive,[10] and were reported to have potent antioxidant activity.[11] Catechin and isoorientin which are known for their antioxidant activity are among the compounds isolated from the plant.[12] There are few reports on the phytochemical studies of *A. indica*, thus, this comprehensive exploration can lay the foundation and provide valuable insights into the chemical composition of *Aspidopterys indica* and its potential role in hypertension management.

Materials and Methods

Plant collection and Identification

Aspidopterys indica aerial parts were collected in February 2020 from Kinnerasani Wildlife Sanctuary in Bhadradri Kothagudem district of

Telangana, India. An herbarium specimen was deposited at the Botanical Survey of India (BSI) herbarium with voucher reference number BSI/DRC/2019-2020/Tech./838.[11]

Extraction and fractionation

A. indica aerial parts were cleaned, shade-dried, coarsely pulverized, and extracted by ultrasonication using methanol at 40 kHz for 45 min at 40°C. The extract was filtered, and then concentrated *in vacuo*. The concentrated extract was kept at room temperature in a desiccator for complete drying. A suspension of the dried methanol extract was prepared, and adsorbed onto silica gel. The adsorbed extract was loaded on a previously packed silica gel column, and the column was eluted with n-hexane at a moderate pressure of 20 - 70 mm Hg. Solvents were gradually added until the resulting fraction became colourless. The process was repeated with methanol and the fractions collected were concentrated at 40-45ºC in a rotary evaporator. The fractions were stored in a desiccator until further analysis.[12]

High Resolution-Liquid Chromatography Mass Spectrometry (HR-LC-MS) Analysis

HR-LCMS (ModelG6550A from Agilent Technologies) with a mass resolution of 0.01% was used to identify and characterize the phytoconstituents present in the methanol fraction of *A. indica* aerial parts. The mass was scanned through a m/z range of 150 to 1000 Daltons. The gas chromatography source parameter was maintained at 250°C with a gas flow rate of 13 psi/min. The auxiliary collection speed was 100 µL/min, the ejection speed was 100 µL/min, the collection position offset was 0.0 mm, the waiting time after the collection was 2.0 s, and the sample wash factor was 5.0.[13] Table 1 shows the eluting solvent composition used for the HR-LC-MS analysis.

Acute oral toxicity study

The acute oral toxicity of the methanol fraction of *A. indica* was evaluated using the OECD 425 guidelines as previously reported.[14, 15]

Evaluation of antihypertensive activity

Ethical approval

The study protocols were designed in accordance with ethical standards and compliance with Institutional Animal Ethic Committee (IAEC) guidelines with reference number (1447/PO/Re/S/11/CPCSEA-31/A).

Induction of hypertension and treatment with plant fraction

The deoxycorticosterone acetate (DOCA)-induced hypertensive model was used to investigate the antihypertensive activity of the methanol fraction of *Aspidopterys indica* aerial parts. The DOCA-induced hypertensive model provides valuable insights into the pathophysiology of hypertension and its associated cardiovascular complications. Adult Wistar rats underwent surgical extraction of one kidney, followed by administration of the synthetic mineralocorticoid derivative, deoxycorticosterone acetate (DOCA) in combination with a high-salt diet. This combination is known to induce hypertension by causing sodium imbalance and hypervolemia. Anesthetized rats underwent nephrectomy, where one kidney was surgically removed along with the connection of the renal artery and vein to the ureter. This procedure mimics conditions of reduced kidney function and may exacerbate the effects of DOCA administration and high salt intake. Following nephrectomy, the animals were treated with different doses (200 mg/kg and 400 mg/kg) of AIMF once daily per oral for seven days. Additionally, the animals received 1% sodium chloride solution in their drinking water and subcutaneous injections of normal saline containing DOCA (25 mg/kg bw) twice per week for five weeks. This regimen was aimed at inducing hypertension in the rats by causing sodium imbalance and hypervolemia.[16] the animal grouping and treatment protocol are presented in Table 2.

Blood pressure measurement

The weekly mean heart rate was calculated using the tail-cuff method to assess how the animals responded to the treatment.[17] After five weeks of treatment, animals were anesthetized with thiopental sodium (45 mg/kg bw, i.p.), the hearts were removed and blood samples were collected for biochemical analysis.

Evaluation of biochemical parameters

Blood samples were collected from the retro-orbital plexus. Serum was separated from the collected blood by centrifugation at 2000 rpm for 5 minutes. The Reitman and Frankel methods were used to determine the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) in the serum.[18] The kinetic Jaffe method was used to measure the plasma concentrations of urea and creatinine.[19] The dioxide method[20] and Urease PAP method were used to calculate the plasma concentration of uric acid.[21] Homogenates were prepared from iced cardiac tissue using a mixture of 16 mL of phosphate buffer pH 7.5 and 4 g of tissue. The homogenization process involves mixing at 20,000 rpm for 15 min at -40ºC and then at -50ºC until freezing. Antioxidant components such as Glutathione (GSH), Catalase (CAT), and Superoxide Dismutase (SOD) were estimated using specific methodologies. The Ellman method was employed for GSH estimation,[22] the spectrophotometric method was used for CAT estimation,[23] while SOD was estimated using the Fridovich method.[24] The Malate Dehydrogenase (MDH) method was used to obtain accurate measurements related to metabolic activity or cellular health assessment in cardiac tissue.[25]

Table 1: Eluting solvent composition

S/N	Channel	Ch.1Solv.	Name 1	Ch.2 Solv.	Selected	Used	Percent
1	A	100.0% Water V.01	0.1% FA in water	100.0% Water V.02	Ch.2	Yes	95.00%
2	B	100.0% Acetonitrile V.02	90% ACN +10% H_20 + 0.1% FA	100.0% Acetonitrile V.02	Ch.1	Yes	5.00%

ACN = Acetonitrile, FA = Formic acid

Table 2: Grouping of animals

Group	Treatment
G1	UNTZD Control
G2	UNTZD + DOCA
G3	UNTD + DOCA + Captopril (30 mg/kg)
G4	UNTD + DOCA + AIMF (200 mg/kg)
G5	UNTD + DOCA + AIMF (400 mg/kg)

AIMF = *Aspidopterys indica* methanol fraction, DOCA = Deoxycortisone acetate; UNTZD- Uninephrectomized

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) and Duncan's multiple range test (DMRT) with SPSS version 10.0 software. The level of significance was set at $P < 0.05$.

Results and Discussion

Compounds identified from the HR-LC-MS analysis of AIMF

HR-LCMS technique was used to identify the chemical constituents in the methanol fraction of *A. indica* (AIMF) based on their retention time, m/z, and metabolites category. Data were reported in ESI positive mode as shown in Table 3. The chromatogram and MS data of major

compounds are shown in Figure 1 and Figure 2, respectively. Out of the 52 compounds identified, few has been shown to be biological active. For example, beta-D-Gentiobiosyl crocetin has vasodilatory effect,[26] 23-Acetoxysoladulcidine has antiproliferative, antibacterial, antiviral, insecticidal, and antimetastatic effects,[27] Sphinganine affects cell signaling,[28] Phytosphingosine and Maritimetin possess antioxidant properties,[29,30], Kaempferol-4'-glucoside-7-rhamnoside has anticancer activity,[31] Quercetin has anti-inflammatory, antihypertensive, vasodilatory, antiobesity, antihypercholesterolemic, and antiatherosclerotic activities,[32] Rutin has shown antidepressant, anticonvulsant, anti- alzheimer, and antiarthritic properties,[33] Isocarbostyril possess antitumour properties,[34] 3-Phenoxypropionic acid has nematocidal activity,[35] and Isoamyl nitrite has been shown to have vasodilatory effect.[36]

Acute oral toxic effect of AIMF

An acute toxic effect of AIMF was evaluated by single oral administration of AIMF at 2000 mg/kg dose. There was no mortality in the animals, and no physical and behavioural signs of toxicity were observed in the treated animals over a 14 day observation period.

Effect of AIMF on blood pressure

AIMF significantly reduced systolic and diastolic blood pressure in a concentration-dependant manner (Tables 4 and 5). Systolic and diastolic blood pressure in G2 (DOCA-treated group) was significantly higher compared to G1-control group, while the G5 - AIMF (400 mg/kg) treated group showed a significant reduction of elevated systolic and diastolic blood pressure in the hypertensive rats.

Effect of AIMF on renal function markers

The effect of *Aspidopterys indica* aerial parts methanol fraction (AIMF) on renal function marker is presented in Figure 3. Following treatment with DOCA salt, there was a considerable damage to the kidneys and an increase in blood pressure due to significantly higher levels of renal function enzymes. In the present study, oral treatment of hypertensive rats with AIMF (400 mg/kg) demonstrated a remarkable recovery of kidney damage and showed a considerable decrease in the serum levels of urea (31.23 ± 1.22 mg/dL), uric acid (2.12 ± 1.29 mg/dL) and creatinine (1.93 ± 0.87 mg/dL).

Table 3: Phytochemicals identified from HR-LC-MS analysis of methanol fraction of *Aspidopterys indica* aerial parts

S/N	Compound name	Formula	RT (min)	m/z	Mass
1	Bornyl butyrate	$C_{14}H_{24}O_2$	26.694	247.1653	224.176
2	Beta-D-Gentiobiosyl crocetin	$C_{32}H_{44}O_{14}$	18.735	653.281	652.2734
3	23-Acetoxysoladulcidine	$C_{29}H_{47}NO_4$	15.575	496.3385	473.3496
4	Sphinganine	$C_{18}H_{39}NO_2$	12.413	302.3044	301.2937
5	Armillarin	$C_{24}H_{30}O_6$	12.262	415.2	414.2031
6	Sphinganine	$C_{18}H_{39}NO_2$	12.101	302.3047	301.2973
7	Armillarin	$C_{24}H_{30}O_6$	11.908	415.2106	414.2032
8	Sphinganine	$C_{18}H_{39}NO_2$	11.78	302.3045	301.2972
9	Secodemethylclausenamide	$C_{17}H_{19}NO_3$	11.486	286.1429	285.1356
10	Secodemethylclausenamide	$C_{17}H_{19}NO_3$	11.145	286.143	285.1357
11	Phytosphingosine	$C_{18}H_{39}NO_3$	10.782	318.2992	317.2919
12	Phytosphingosine	$C_{18}H_{39}NO_3$	10.413	318.2991	317.2919
13	5,7-Alpha-Dihydro1,4,4,7a-tetramethyl-4*H*-indene	$C_{13}H_{18}$	6.605	175.1473	174.14
14	Edulan I	$C_{13}H_{20}O$	6.554	193.1578	192.1505
15	Maritimetin	$C_{15}H_{10}O_6$	6.535	287.054	286.0467
16	Maritimetin	$C_{15}H_{15}O_6$	6.23	287.0541	286.0468
17	Hexyl 2-furoate	$C_{11}H_{16}O_3$	6.158	197.1164	196.1093
18	Kaempferol 4'-glucoside 7-rhamnoside	$C_{27}H_{30}O_{15}$	6.154	595.1644	594.1571
19	Myricetin 7-rhamnoside	$C_{21}H_{20}O_{12}$	6.006	465.101	464.0936
20	Quercetin	$C_{15}H_{10}O_7$	5.93	303.0488	302.0416
21	Maritimetin	$C_{15}H_{10}O_6$	5.93	287.0539	286.0466
22	(5-Alpha,8beta,9beta)-5,9-Epoxy-3,6-megastigmadien-8-ol	$C_{13}H_{20}O_2$	5.781	209.1527	208.1455
23	Rutin	$C_{27}H_{30}O_{16}$	5.701	611.1588	610.1515
24	Quercetin	$C_{15}H_{10}O_7$	5.613	303.0489	302.0417
25	7-Hydroxy-6-(methoxyacetyl)-2,2-dimethyl-2H-1-benzopyran	$C_{14}H_{16}O_4$	5.376	249.1111	248.1037
26	2-Phenylethyl 3-methyl butanoate	$C_{13}H_{18}O_2$	4.698	207.137	206.1297
27	1-(beta-D-Glucopyranosyloxy)-3-octanone	$C_{14}H_{26}O_7$	4.441	307.1753	306.1679
28	3-Hydroxycoumarin	$C_9H_6O_3$	4.431	163.0379	162.0307
29	5-Methyl-2,5-di-1-pyrrolidinyl-2-cyclopenten-1-one	$C_{14}H_{22}N_2O$	4.208	235.1792	234.172
30	3-Hydroxycoumarin	$C_9H_6O_3$	4.145	163.0379	162.0306
31	5-Methyl-2,5-di-1-pyrrolidinyl-2-cyclopenten-1-one	$C_{14}H_{22}N_2O$	3.935	235.1795	234.1722

32	Procyanidin B7	$C_{30}H_{26}O_{12}$	3.906	579.1482	578.141
33	Isocarbostyril	C_9H_7NO	3.833	146.059	145.0517
34	Doxylamine	$C_{17}H_{22}N_2O$	3.675	293.1598	270.1704
35	Indoleacrylic acid	$C_{11}H_9NO_2$	3.597	188.0699	187.0626
36	Isocarbostyril	C_9H_7NO	3.596	146.0591	145.0518
37	6-Methylquinoline	$C_{10}H_9N$	3.348	144.0797	143.0725
38	Indoleacrylic acid	$C_{11}H_9\ NO_2$	3.277	188.0699	187.0626
39	3-Hydroxy-carbofuran	$C_{12}H_{15}NO_4$	3.162	238.1062	237.0989
40	3-Phenoxypropionic acid	$C_9H_{10}O_3$	3.02	167.0692	166.0619
41	Isoamyl nitrite	$C_5H_{11}NO_2$	2.941	118.0856	117.0783
42	Isoamyl nitrite	$C_5H_{11}NO_2$	2.027	118.0856	117.0783
43	Retronecine	$C_8H_{13}NO_2$	1.807	156.1009	155.0937
44	Isoamyl nitrite	$C_5H_{11}NO_2$	1.729	118.0858	117.0775
45	Retronecine	$C_8H_{13}\ NO_2$	1.505	156.101	155.0938
46	(2R,3R,4R)-2-Amino-4-hydroxy-3-methyl pentanoic acid	$C_6H_{13}NO_3$	1.425	148.0959	147.0885
47	Isoamyl nitrite	$C_5H_{11}NO_2$	1.424	118.0857	117.0784
48	Retronecine	$C_8H_{13}NO_2$	1.207	156.1009	155.0937
49	6-Deoxyfagomine	$C_6H_{13}NO_2$	1.207	132.1012	131.094
50	(2R,3R,4R)-2-Amino-4-hydroxy-3-methyl pentanoic acid	$C_6H_{13}NO_3$	1.132	148.0959	147.0887
51	Isoamyl nitrite	$C_5H_{11}NO_2$	1.129	118.0857	117.0784
52	8-Hydroxy-2-chlorodibenzofuran	$C_{12}H_7ClO_2$	0.921	241.0035	218.0139

RT = Retention time, m/z = mass-to-charge ratio

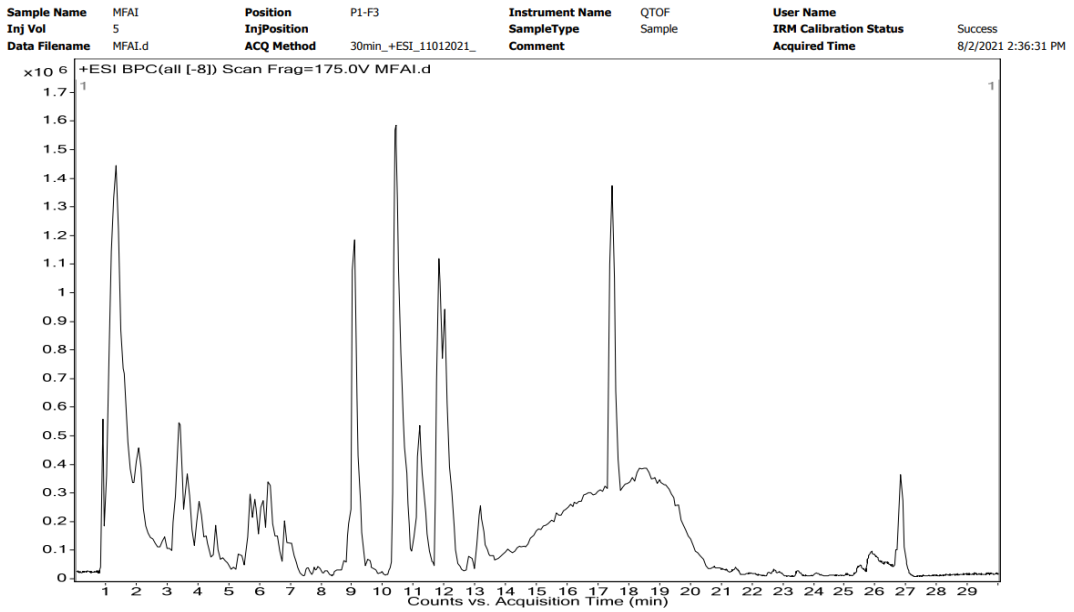

Figure 1: LC-MS Chromatogram of *Aspidopterys indica* methanol fraction

Effect of AIMF on hepatic function markers

The effect of AIMF on serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) is shown in Figure 4. Compared to the control group, DOCA-treated groups had significant elevation in the serum levels of these marker enzymes. G4 and G5 groups administered orally with AIMF (200 and 400 mg/kg, respectively) showed an effective and significant ($p < 0.001$) decrease in the elevated levels of these enzymes. AST, ALT, and ALP levels in G4 were 101.21 ± 1.34 IU/L, 45.21 ± 0.56 IU/L, and 121.23 ± 1.78 IU/L, respectively, while G5 had serum levels of AST, ALT, and ALP of 78.23 ± 0.98 IU/L, 38.28 ± 0.78 IU/L, and 112.56 ± 0.56 IU/L, respectively.

Effect of AIMF on antioxidant enzymes

Figure 5 presents the effect of *Aspidopterys indica* aerial parts methanol fraction (AIMF) on antioxidant enzymes. DOCA treatment disrupted the liver and kidney tissues, resulting in an increased oxidative stress, marked by a significant reduction in superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) levels and an increase in malate dehydrogenase (MDH) levels. Treatment with AIMF (Group 5) resulted in a considerable protection from alteration in the level of SOD and a reduction of MDH levels (Figure 5).

Table 4: Effect of AIMF on systolic blood pressure in uninephrectomized DOCA-Salt hypertensive rats

Group	Systolic Blood Pressure (mm Hg)	
	0th Week	5th Week
G1	126.12 ± 0.23	128.21 ± 1.21
G2	130.43 ± 1.23	218.12 ± 1.34##
G3	121.23 ± 1.23	131.34 ± 1.34***
G4	128.23 ± 1.34	189.32 ± 1.67*
G5	131.32 ± 0.23	169.21 ± 1.23*

Values are Mean ± SEM (n = 6). *P < 0.05 and #P < 0.05 = Significant, **P < 0.01 and ##P < 0.05 =
Highly significant. AIMF = *Aspidopterys indica* methanol fraction, DOCA = Deoxycortisone acetate

Table 5: Effect of AIMF on diastolic blood pressure in uninephrectomized DOCA-Salt hypertensive rats

Group	Diastolic Blood Pressure (mm Hg)	
	0th Week	5th week
G1	86.12 ± 1.34	85.21 ± 1.43
G2	88.76 ± 1.23	174.23 ± 0.23##
G3	87.23 ± 0.23	87.23 ± 1.34***
G4	81.34 ± 0.34	155.23 ± 0.78*
G5	83.45 ± 0.34	145.32 ± 0.45*

Values are Mean ± SEM (n = 6). *P < 0.05 and #P < 0.05 = Significant, **P < 0.01 and ##P < 0.05 = Highly significant. AIMF = *Aspidopterys indica* methanol fraction, DOCA = Deoxycortisone acetate

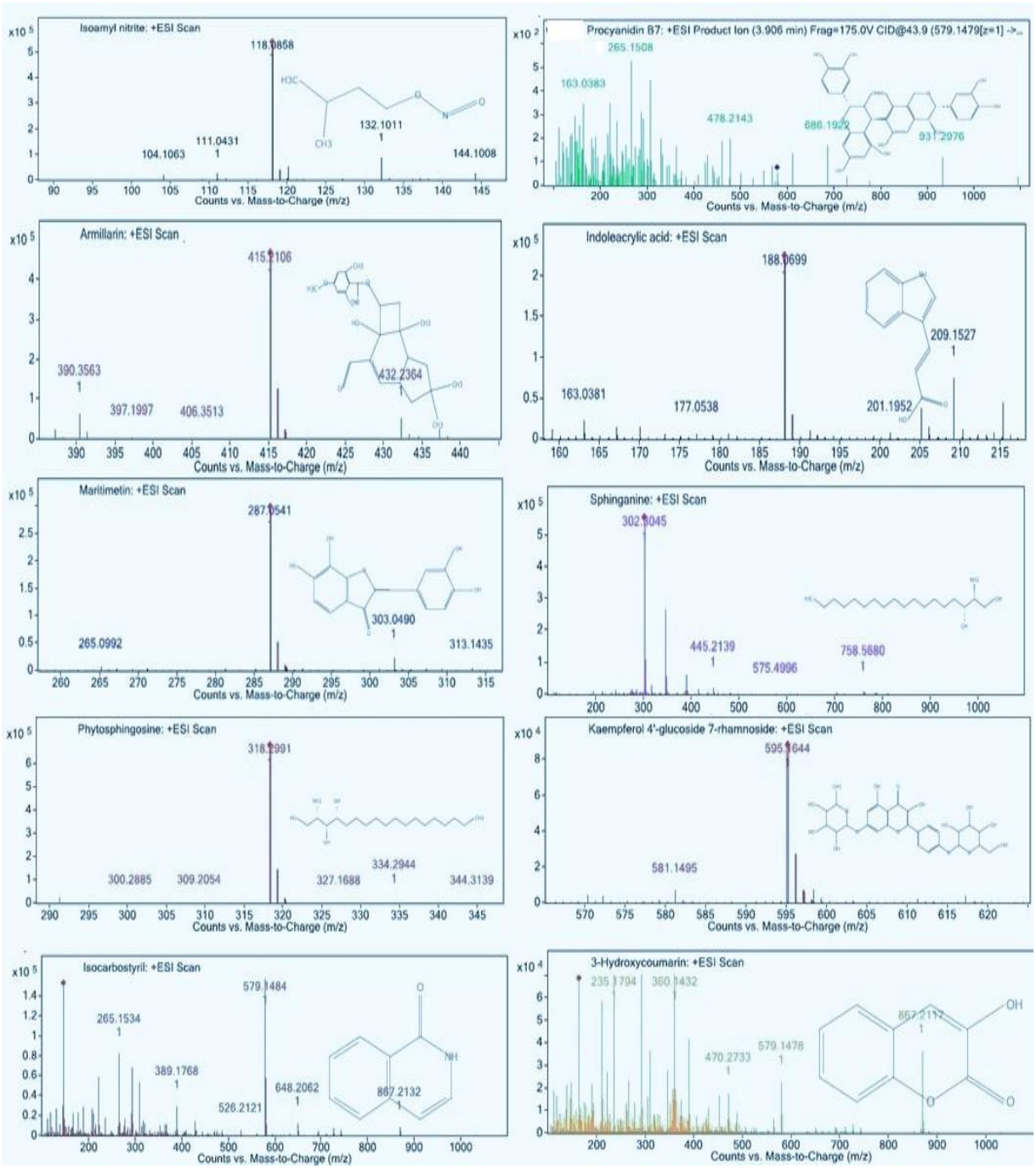

Figure 2: Major phytochemical constituents of methanol fraction of *Aspidopterys indica* aerial parts

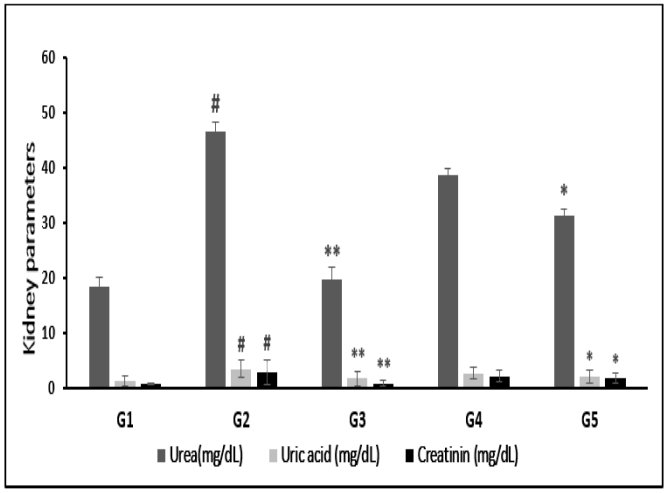

Figure 3: Effect of AIMF on Serum Urea, Uric acid, and Creatinine in uninephrectomized DOCA-salt hypertensive rats
Values are Mean ± SEM (n = 6). *P < 0.05 and #P < 0.05 = Significant, **P < 0.01 and ##P < 0.05 = Highly significant. AIMF = *Aspidopterys indica* methanol fraction, DOCA = Deoxycortisone acetate

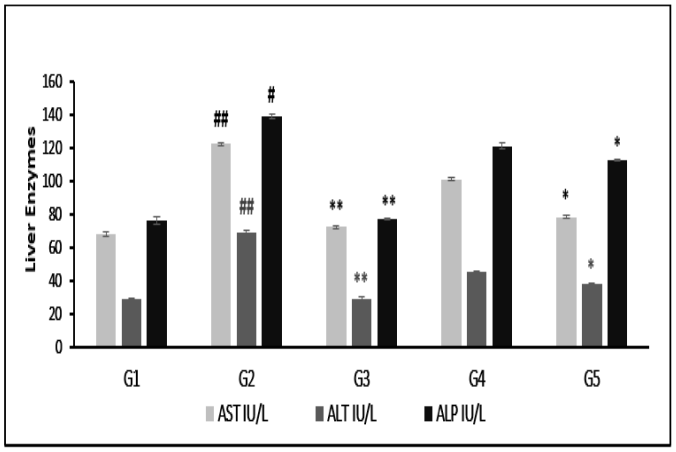

Figure 4: Effect of AIMF on serum AST, ALT, ALP in uninephrectomized DOCA-salt hypertensive rats
Values are Mean ± SEM (n = 6). *P < 0.05 and #P < 0.05 = Significant, **P < 0.01 and ##P < 0.05 = Highly significant. AIMF = *Aspidopterys indica* methanol fraction, DOCA = Deoxycortisone acetate

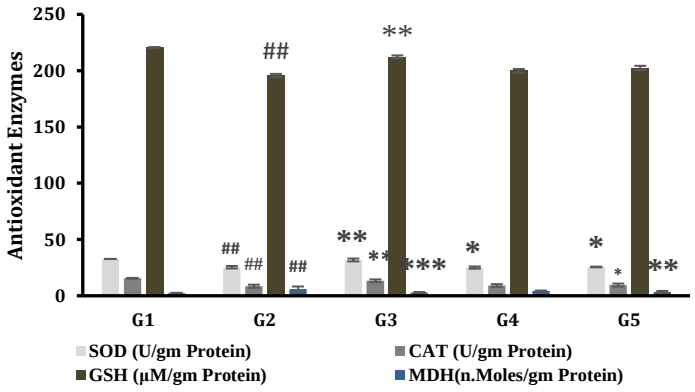

Figure 5: Effect of AIMF on antioxidant enzymes in uninephrectomized DOCA-salt hypertensive rats
Values are Mean ± SEM (n = 6). *P < 0.05 and #P < 0.05 = Significant, **P < 0.01 and ##P < 0.05 = Highly significant. AIMF = *Aspidopterys indica* methanol fraction, DOCA = Deoxycortisone acetate

Conclusion

In summary, the study suggests that the methanol fraction of *Aspidopterys indica* aerial parts contain bioactive phytoconstituents that may help protect against renal damage, increase antioxidant enzyme levels, and exhibit antihypertensive effects. Of the two doses tested, 400 mg/kg body weight showed a higher significant blood pressure lowering effect. This study shows that the presence of key metabolites in AIMF may be responsible for the observed antihypertensive effect. However, further study is required to elucidate their possible mechanisms of action and potential therapeutic applications.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgments

The authors thank GITAM University and SAIF, Mumbai for providing the facility for this study.

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