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Subacute effect of *Momordica charantia* plant, *Tetrapleura tetraptera* fruit and *Allium cepa* bulb on steroidal hormones

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Abstract: Fibroids are hormone-dependent tumors influenced by elevated levels of estradiol and progesterone. The search for natural alternatives to conventional treatments has led to the investigation of plant-based therapies. This study evaluates the phytochemical composition and effect of *Momordica charantia* L. (Cucurbitaceae) plant, *Tetrapleura tetraptera* (Schum. & Thonn.) Taub. (Mimosaceae) fruit and *Allium cepa* L. (Amaryllidaceae) bulb on serum cholesterol, estradiol, and progesterone implicated in fibroid growth. Animal studies were conducted by administering 100 and 200 mg/kg doses of each plant extract to Wistar rats over 28 days, after which blood samples were collected. Serum was analyzed for changes in cholesterol, estradiol, and progesterone levels using standard biochemical assays. High-Performance Liquid Chromatography was employed to identify the phytoconstituents in the ethanol extracts of the plants. The results showed that *A. cepa* significantly lowered serum cholesterol levels ($p < 0.05$), while *M. charantia* and *T. tetraptera* did not produce statistically significant reductions. None of the plant extracts caused a significant decrease in estradiol levels, however, *A. cepa* and *T. tetraptera* significantly reduced serum progesterone levels, suggesting potential anti-fibroid activity. Phytochemical analysis confirmed the presence of bioactive compounds that may contribute to these effects. These findings suggest that the tested plant extracts, particularly *A. cepa* and *T. tetraptera*, may have potential in managing fibroid growth through hormonal modulation. However, studies are necessary to validate their efficacy for fibroid treatment.

Keywords: *Allium cepa*, Fibroid, HPLC, *Momordica charantia*, *Tetrapleura tetraptera*, Steroidal hormones

Introduction

Herbal medicine, the most ancient form of healthcare practice, represents the cumulative therapeutic experiences of many generations spanning centuries. It has regained prominence in contemporary medical practice, with over 85% of the global population utilizing phyto-therapeutic remedies, as reported by WHO.[1] Since the inception of humanity, the utilization of herbs and plants has provided an efficacious remedy for the cure of ailments. Furthermore, numerous conventional and pharmaceutical medications are directly sourced from nature and traditional therapies globally.[2]

Various medical systems and cultures utilize herbal medicines for the management of fibroids which are benign tumors located in the uterus. They are the most prevalent benign tumors in women of reproductive age[3] and have emerged as a significant global concern over the years. While the exact cause of uterine fibroid formation is still unknown, epidemiological, clinical, and experimental studies have provided substantial evidence that estrogen and progesterone stimulate the growth of the tumor.[3] For this reason, they are rare in prepubertal females, typically exhibit accelerated growth during reproductive age and become more evident during perimenopause but diminish following menopause.[4]

Furthermore, a person is more likely to develop uterine fibroids if her total protein and cholesterol levels are consistently raised.[5] In Nigeria, many regions possess diverse natural remedies that have historically been utilized for the therapy of fibroids. These herbal formulations are frequently utilized as substitutes for pharmacological therapy and surgical interventions.[6] Conventional medications or therapies often result in many side effects that diminish drug efficacy coupled with their high cost; thus, the utilization of medicinal plants is crucial.[7] Medicinal plants have diverse phytochemicals with medicinal qualities beneficial for treating some illnesses of the female reproductive system, without inducing any significant negative effects.[8] Some herbal remedies for management of fibroid are derived from extracts of plants such as *M. charantia*, *T. teraptera* and *A. cepa*.[6,8,9]

Momordica charantia L. (Cucurbitaceae) is rich in triterpenoids and exhibits diverse biological benefits which include antidiabetic, antibacterial, antiviral, anti-inflammatory and antitumor properties.[10] *Tetrapleura tetraptera* (Schumach. & Thonn.) Taub. (Mimosaceae) has been reported to possess antibacterial, antioxidant, antiviral, antidiabetic, anti-inflammatory, antiparasitic, antiprotozoal and antiproliferative effects.[2] *Allium cepa* L. (Amaryllidaceae) is traditionally utilized for the treatment of ailments such as colds, coughs, diuretics, metabolic disorders, skin diseases, insect bites, pneumonia, ear disorders, urinary system disorders, sexual dysfunction, and as a wound healer.[11]

The major phenolic constituents of the extracts of these three plants were identified using High-Performance Liquid Chromatography (HPLC). The aim of this study was to evaluate the subacute effect of the ethanol extracts of *M. charantia* plant, *T. tetraptera* fruit and *A. cepa* bulb on female reproductive hormones, and total cholesterol which are implicated in uterine fibroid growth, using female Wistar rats.

Materials and methods

Plant material, collection and preparation

Tetrapleura teraptera fruit and *M. charantia* plant were collected from within University of Benin premises, while *A. cepa* bulb was bought from a market in Benin City, Nigeria, on 30th August, 2024. The plants were identified by a plant taxonomist; Professor Henry Akinnibosun as fruits of *T. tetraptera*, *M. charantia* plant and bulb of *A. cepa*. Voucher specimens of each plant were deposited at the Herbarium of the Department of Plant Biology and Biotechnology, Faculty of Life Sciences, University of Benin, and given voucher numbers UBH-T472, UBH-M617 and UBH-A375, respectively. The plants were dried at room temperature and pulverised using a milling machine. The pulverised powder was exhaustively extracted with 99.5% absolute ethanol using Soxhlet extraction method. The extracts were reduced to dryness with a water bath and stored in the fridge until required.

Animal handling conditions

Thirty-five Wistar rats weighing between 100 – 200 g were obtained from and acclimatized at the animal house of Pharmacology Department, Faculty of Pharmacy, University of Benin. They were grouped into seven with each group having five rats each. Proper ventilation was ensured and wood shavings provided as bedding material to collect urine and feces. Ethical consent for the utilization of laboratory animals was secured from the Ethics Committee, Faculty of Pharmacy, University of Benin, Nigeria under the approval number EC/FP/025/07. The University of Benin Ethical Committee's recommendations adhere to international standards for animal handling and was followed.

Dosing of experimental animals

This was carried out following the method described in literature.[12] Female Wistar rats were placed in seven groups of five rats each. Group A was the control group where animals were allowed free access to food and water only. Groups B and C were treated with 100 and 200 mg/kg of *M. charantia* plant extract orally, respectively. Groups D and E were treated with 100 and 200 mg/kg of *T. tetraptera* fruit extract, respectively and groups F and G treated with 100 and 200 mg/kg of *A. cepa* bulb extract respectively. This was done daily for 28 days. The effect of the extracts on the eating habits of the animals was determined based on their body weights throughout the course of the experiment which were taken on days 0, 7, 14, 21, and 28 and the doses of the extracts given were adjusted according to the newly calculated weights.

Biochemical assays

On day 29, the animals were sacrificed by anesthetizing them in a chloroform saturated chamber after which their blood was collected through cardiac puncture and transferred into plain bottles where they were allowed to sit at room temperature for 45 minutes before being centrifuged at 3400 rpm for 10 minutes and serum stored at -25°C. The serum obtained following centrifugation of the blood samples collected was then used to determine the total serum cholesterol, progesterone and estradiol content of the animals.[13]

Determination of Total Cholesterol Content

Cholesterol levels were measured using a semi-automated chemistry analyzer coupled with the AGAPPE test kit. The analyzer was set up so as to measure the cholesterol levels of the samples according to the instruction manual.[14]

Determination of serum estradiol and progesterone levels

This was carried out using the Microplate Reader (Mindray MR-96A). E_2 AccuBind ELISA Kit was used for serum estradiol analysis while progesterone ELISA Kit was used for serum progesterone analysis. The instructions in the manufacturers' manuals were followed. The concentration of estradiol and progesterone in the samples were extrapolated from dose response curves.[14]

High Performance Liquid Chromatography (HPLC) analysis

The HPLC analysis was carried out at Bato Chemical Laboratory in Lagos, Nigeria, using a Shimadzu Nexera MX multiplex system. The chromatography was performed on a μBondapak C_{18} reverse-phase column with a dimension of 100 mm length, 4.6 mm internal diameter, and 7 μm thickness. The mobile phase consisted of acetonitrile and water, with a flow rate of 0.08 mL/min for water and 5 mL/min for acetonitrile. The HPLC system was equipped with a UV-Vis diode array detector set at 254 nm within the UV-visible spectrum. The pump pressure used was 15 MPa. Initially, standard analyte profiles were injected into the HPLC, producing a chromatogram with specific peak areas and profiles. These data were used to define a reference window in the HPLC for the test sample analysis. Next, aliquots of the extracted test samples were injected into the equipment to generate the corresponding chromatogram with its own peak area and profile.[15]

Data analysis

Results were expressed as mean ± standard error of mean (S.E.M). A one-way analysis of variance was performed to compare the extract treatment groups with the control group, followed by the Tukey-Kramer multiple comparison test. Data analysis and visualization were carried out with GraphPad Prism version 7.04.

Results and discussion

Effect of the extracts of *M. charantia* plant, *T. tetrapleura* fruit and *A. cepa* bulb on food consumption and body weight of the rats

The extracts had effect on the eating habits and weights of the animals which was mostly observed with *M. charantia* plant and *T. tetraptera* fruit extract when compared to the normal group (Table 1). Obesity, a multifaceted condition marked by excessive fat accumulation, is linked to various adverse health consequences.[11] It can cause systemic energy metabolism disorders and elevate the risk of digestive, respiratory, endocrine, cardiovascular, and psychiatric disorders.[16] It is typically defined by modifications in the lipid profile, including an increase in low-density lipoproteins, triglycerides and cholesterol, and a reduction in high-density lipoproteins.[17] Moreover, obesity constitutes a key risk factor for uterine fibroids,[18] indicating that weight reduction may contribute to diminishing the incidence of fibroids in women.

The extract of *M. charantia* plant exhibited weight-reducing properties in the rats likely as a result of its hypolipidemic action.[10] *T. tetraptera* fruit extract also resulted in weight reduction in experimental animals, aligning with previous findings regarding its anti-obesity and hypolipidemic properties.[19] *A. cepa* bulb extract at 200 mg/kg, on day 28, showed significant body weight reduction, which conforms with previous research demonstrating its anti-obesity properties.[11] It has been proposed that *M. charantia* reduces visceral fat storage likely by downregulating the expression of essential lipogenic proteins and genes in adipose tissues.[16] Recent studies suggest that *M. charantia* extract influences gut microbiota, leading to the production of acetate, propionate, and butyrate, which regulate hepatic lipid and glucose metabolism through AMPK-dependent pathways involving PPAR-γ.[10] The cholesterol-lowering effect of *T. tetraptera* is partly attributed to its saponin content, which binds to bile acids and prevents their reabsorption, facilitating weight loss and reducing cardiovascular risk.[20] The phytochemicals in *A. cepa*, particularly quercetin, play a role in modulating lipid metabolism and inhibiting adipogenesis [11].

Biochemical Assay
Total serum cholesterol content

Cholesterol serves as a precursor in the synthesis of steroid hormones.[21] There was a significant reduction [34.85% ($P \leq 0.05$)] in serum cholesterol in the group administered 200 mg/kg dose of the ethanol extract of *A. cepa* bulb compared to the normal group (Figure 1). 100 mg/kg of *M. charantia* plant extract was significantly more active than 200 mg/kg with 29.12% reduction in cholesterol content ($P \leq 0.05$). Simultaneous administration of 100 and 200 mg/kg doses of *T. tetraptera* fruit extract gave 14.65 and 27.78% reduction in serum cholesterol levels respectively compared to the normal group. The effect of these plants may be attributed to their ability to regulate fat-metabolizing kinases such as AMPKs and influence the expression of downstream target genes involved in mitochondrial fuel oxidation. These pathways impact adipocyte differentiation[22] and enhance lipid metabolism and utilization in energy-demanding tissues. *T. tetraptera* fruit demonstrated insignificant cholesterol-lowering properties in this study but other published research indicates that the dried fruit extract effectively reduces serum total cholesterol, LDL cholesterol, and triglycerides while increasing HDL cholesterol levels in hypercholesterolemic rats compared to untreated controls.[19]

Studies reveal that *A. Cepa* bulb extract's high quercetin and isoquercetin content contribute to reducing total cholesterol, triglycerides, and LDL cholesterol while increasing HDL cholesterol levels in hyperlipidemic Sprague-Dawley rats [11]. Several mechanisms have been proposed for the hypolipidemic effect of *A. cepa* bulb extract, including activation of AMPK, upregulation of LDL receptors, reduced cholesterol absorption, suppression of malic enzyme and HMG-CoA reductase activity, enhanced fecal cholesterol elimination, decreased lipogenesis and lipid peroxidation as well as modulation of fatty acid metabolism.[11]

Total serum estradiol content

Serum estradiol was reduced to varying levels by the extracts though none were significant compared to the normal (Figure 2). 200mg/kg of *M. charantia* gave the highest reduction of 42.43%. Administering 100 mg/kg dose of *M. charantia* plant extract and 100 and 200mg/kg doses of *T. tetraptera* fruit extract resulted in reduction of 4.94, 36.38 and 26.44%, respectively compared to the normal group.

Estradiol is the most potent form of estrogen found in the human body.[23] Estrogen is known to enhance the expression of various growth factor genes, collagens, and estrogen receptors, which are believed to contribute to the development of fibroids.[24] As a result, reducing estradiol levels in the bloodstream may be an important strategy in managing uterine fibroids. Research suggests that decrease in estrogen levels by medicinal plants may stem from the plant's inhibitory effect on pituitary gonadotropins as well as its direct toxic impact on follicular and theca cells.[25] Studies have shown that *T. tetraptera* extract decreases follicle-stimulating and luteinizing hormone levels.[25] These gonadotropic hormones play an important part in regulating the synthesis of female sex hormones, including estrogen, within the ovaries. Additionally, luteinizing hormone promotes the secretion of testosterone from the ovarian follicles, which is subsequently converted to estrogen by the enzyme aromatase.[26] Furthermore, the extracts' roles in reducing plasma estradiol could be attributed to their cholesterol-lowering properties, as cholesterol is a key precursor in estrogen synthesis.[21] From our studies, *A. cepa* bulb extract showed an insignificant alteration of estrogen levels compared to the normal which is inconsistent with other research that indicate *A. cepa* enhances estrogenic activity.[27]

Total serum progesterone

Progesterone plays a crucial role in regulating pregnancy and menstruation. Additionally, it serves as a steroidogenic precursor for various gonadal and non-gonadal hormones, including aldosterone, cortisol, estradiol, and testosterone.[3] Treatment with 200 and 100 mg/kg doses of *T. tetraptera* fruit and *A. cepa* bulb extracts, respectively, produced significant reductions ($P \leq 0.05$) in serum progesterone levels of 52.01 and 59.14%. respectively compared to the normal group (Figure 3).

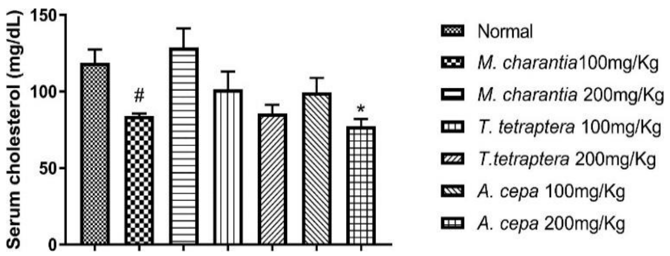

Figure 1: Effect of the ethanol extract of *M. charantia* plant, *T. tetraptera* fruit and *A. Cepa* bulb on total serum cholesterol in female Wistar rats after 28 days. *P < 0.05, compared with normal group. #P < 0.05 compared with 200 mg/kg

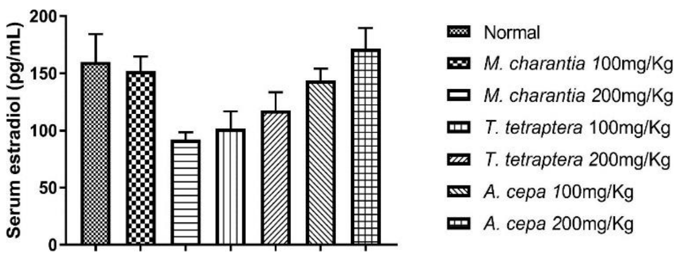

Figure 2: Effect of the ethanol extract of *M. charantia* plant, *T. tetraptera* fruit and *A. cepa* bulb on total serum estradiol in female Wistar rats after 28 days

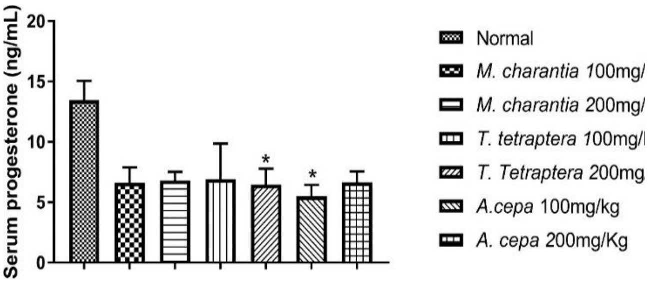

Figure 3: Effect of the ethanol extract of *M. charantia* plant, *T. tetraptera* fruit and *A. Cepa* bulb on total serum progesterone in female Wistar rats after 28 days. *P<0.05, compared with normal group

M. charantia plant extract was also seen to decrease progesterone levels by 50.82 and 49.48%, respectively ($P \geq 0.05$) at 100 and 200 mg/kg. Progesterone signaling is fundamental in uterine fibroid development, as it promotes fibroid cell formation by activating multiple genetic and epigenetic signaling pathways.[28] Therefore, reducing progesterone levels may help shrink uterine fibroids and alleviate their related symptoms. Plant chemicals' ability to lower progesterone may be linked to their effect on lowering plasma estrogen (β-estradiol). Since progesterone levels increase following ovulation due to corpus luteum formation, a process influenced by rising plasma estrogen levels,[29] a decline in estrogen can consequently lead to decreased progesterone levels. Furthermore, cholesterol acts as a precursor in progesterone synthesis,[14] and the extracts' hypolipidemic properties may contribute to their ability to lower plasma progesterone levels.

Table 1: Change in mean body weights of the rats

Dose (mg/kg)	Change in mean body weights (g) at different days				
	Day 0	Day 7	Day 14	Day 21	Day 28
Normal rats	116.00±20.61	7.60±21.54	4.00±15.33	10.80±16.67	4.40±14.1
M. charantia (100 mg/kg)	102.80±10.45	2.20±8.50	12.80±8.28	3.00±6.84	1.60±7.26
M. charantia (200 mg/kg)	147.20±14.87	6.60±14.20	-1.00±10.56	9.80±10.75	-4.40±10.71
T. tetraptera (100 mg/kg)	150.60±10.12	-8.00±9.58	-0.4±10.29	12.60±10.53	-5.40±10.39
T. teraptera (200 mg/kg)	107.80±12.08	5.80±10.40	6.60±10.26	3.80±10.63	-2.20±9.10
A. cepa (100 mg/kg)	114.80±11.00	2.00±9.81	11.80±10.52	6.20±11.27	1.20±13.43
A. cepa (200 mg/kg)	126.20±6.42	0.20±6.38	16.00±7.50	6.40±6.08	-1.00±5.31

HPLC analyses of the extracts

HPLC analysis of *M. charantia* whole plant extract identified major constituents like momordicinin, momordicine, momordicine II, charantin, quercetin and kaempferol. Other minor constituents with less concentrations like caffeic acid, catechin, epicatechin, apigenin, gallocatechin, vincosamide, luteolin, ferulic acid, naringenin, kuguacin A, kuguacin J, biochanin A and karavilagenin A were also observed (Table 2, Figure 4). Various saponins have been isolated from *M. charantia*. Saponins have been shown to reduce visceral fat mass and blood glucose levels, enhance oxidation in hepatic and adipose tissues, and as well significantly lower blood triglycerides.[10] *M. charantia* is also recognized for its high phytosterol content, which is linked to cholesterol reduction. Phytosterols have been associated with several therapeutic effects, including anticancer, anti-atherosclerotic and anti-inflammatory activities.[30] Preclinical studies suggest that momordicine exhibits anti-inflammatory and antifibrotic properties, acting through mechanisms such as inhibition of inflammatory pathways and induction of apoptosis. Its antioxidant effect is attributed to flavonoids such as quercetin and kaempferol, which are key components of the plant.[10]

Umbelliferone, aridanin, echinocystic acid, piperazine, ferulic acid and naringenin have been previously reported to be found in *T. tetraptera* fruit extract.[33] Minor constituents present are isoliquiritigenin, butein, hentriacontane and octodrine (Table 3, Figure 5). Umbelliferone exerts multiple effects, including reducing oxidative stress, inflammation, and apoptosis.[31] Previous research has shown that inflammatory cytokine levels are elevated in uterine fibroids, influencing cell proliferation, fibrotic changes, and extracellular matrix remodeling.[32] Consequently, plants with antioxidant, apoptotic and anti-inflammatory properties may offer therapeutic potential for managing uterine fibroids.

HPLC analysis of *A. cepa* bulb extract identified the major constituents present as quercetin, kaempferol, aurone, capaenes, thiosulfinate, and chalcone. Minor constituents include fructan, flavon, flavonol, cysteine, glutathione, pectin, and prostaglandins (Table 4, Figure 6). Antioxidant effect of *A. cepa* has been attributed to some flavonoids, such as quercetin and kaempferol, which are key components of the plant.[11] Oxidative stress is influenced by various inter-connected pathways, such as angiogenesis, hypoxia, and dietary factors, and this has been linked to fibroid development.[13] As a result, antioxidants are considered promising therapeutic agents for managing fibroids. Additionally, quercetin has been reported to reduce serum estradiol. It has also been suggested that kaempferol might regulate a suitable level of estrogenic activity in the body and as such, is expected to have potential beneficial effects in preventing estrogen imbalance diseases.[34]

Table 2: HPLC result of *M. charantia* plant ethanol extract

S/N	Component	Retention time (mins)	Concentration (mg/g)
1.	Momordicinin	1.266	0.81
2.	Momordicine	2.516	1.81
3.	Momordicine II	4.450	0.51
4.	Momordicilin	5.466	0.21
5.	Caffeic Acid	6.483	0.14
6.	Catechin	7.333	0.04
7.	Epicatechin	7.950	0.05
8.	Gallocatechin	8.783	0.07
9.	Vincosamide	9.350	0.05
10.	Quercetin	11.050	6.39
11.	Kaempferol	12.166	2.54
12.	Charantin	13.700	2.22
13.	Apigenin	16.250	0.07
14.	Luteolin	17.616	0.34
15.	Ferulic Acid	18.900	0.04
16.	Naringenin	19.683	0.07
17.	Kuguacin A	21.133	0.04
18.	Kuguacin J	22.766	0.06
19.	Biochanin A	23.750	0.07
20.	Karavilagenin A	24.850	0.09

Table 3: HPLC result of *T. tetraptera* fruit ethanol extract[33]

S/N	Component	Retention time (mins)	Concentration (mg/g)
1.	Ferulic acid	1.350	0.25
2.	Echinocystic acid	1.650	0.34
3.	Umbelliferone	1.983	6.85
4.	Piperazine	3.166	0.66
5.	Aridanin	4.016	0.25
6.	Octodrine	4.733	0.01
7.	Hentriacontane	6.350	0.09
8.	Naringenin	7.350	0.29
9.	Butein	8.616	0.05
10.	Isoliquiritigenin	9.616	0.03

Table 4: HPLC result of *A. cepa* bulb ethanol extract

S/N	Component	Retention time (mins)	Concentration (mg/g)
1.	Aurone	1.266	0.40
2.	Chalcone	4.450	0.24
3.	Fructan	5.816	0.09
4.	Flavone	6.483	0.10
5.	Flavonol	7.333	0.05
6.	Cysteine	7.950	0.09
7.	Glutathione	8.816	0.07
8.	Pectin	9.350	0.06
9.	Quercetin	11.050	4.27
10.	Kaempferol	12.166	0.53
11.	Capaenes	13.700	0.30
12.	Thiosulfinate	17.616	0.29
13.	Prostaglandins	20.250	0.10

Conclusion

A. cepa extract reduced cholesterol content significantly. *M. charantia* and *T. tetraptera* showed estradiol-lowering effect, but not to a statistically significant level. *T. tetraptera* and *A. cepa* reduced serum progesterone levels significantly. Additionally, the extracts were shown to have major phytoconstituents such as quercetin and kaempferol in *M. charantia* and *A. cepa*, and umbelliferone in *T. tetraptera*, which play major roles in the bioactivity of the plants. These results reveal the steroidal hormone lowering ability of these plants, making them ideal candidates for investigation as antifibroid plant drug agents.

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Conflict of interest

Authors declare no conflict of interest

Authors contributions

ROI designed the study, ROI and TJA administered the extracts, TJA performed the statistical analysis and data interpretation, ROI wrote the paper, and the final manuscript was proofread and approved by both authors.

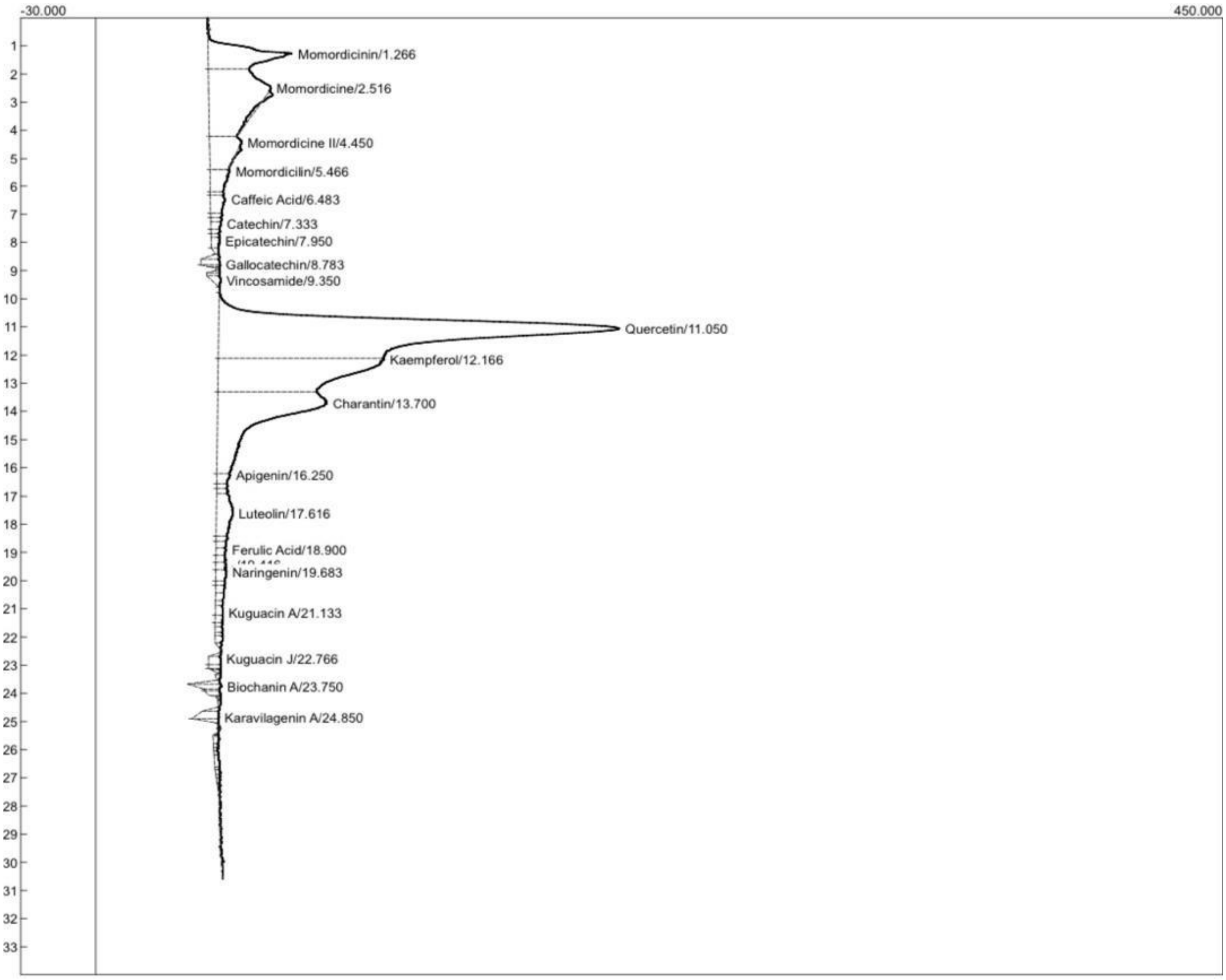

Figure 4: HPLC chromatogram of *M. charantia* whole plant ethanol extract

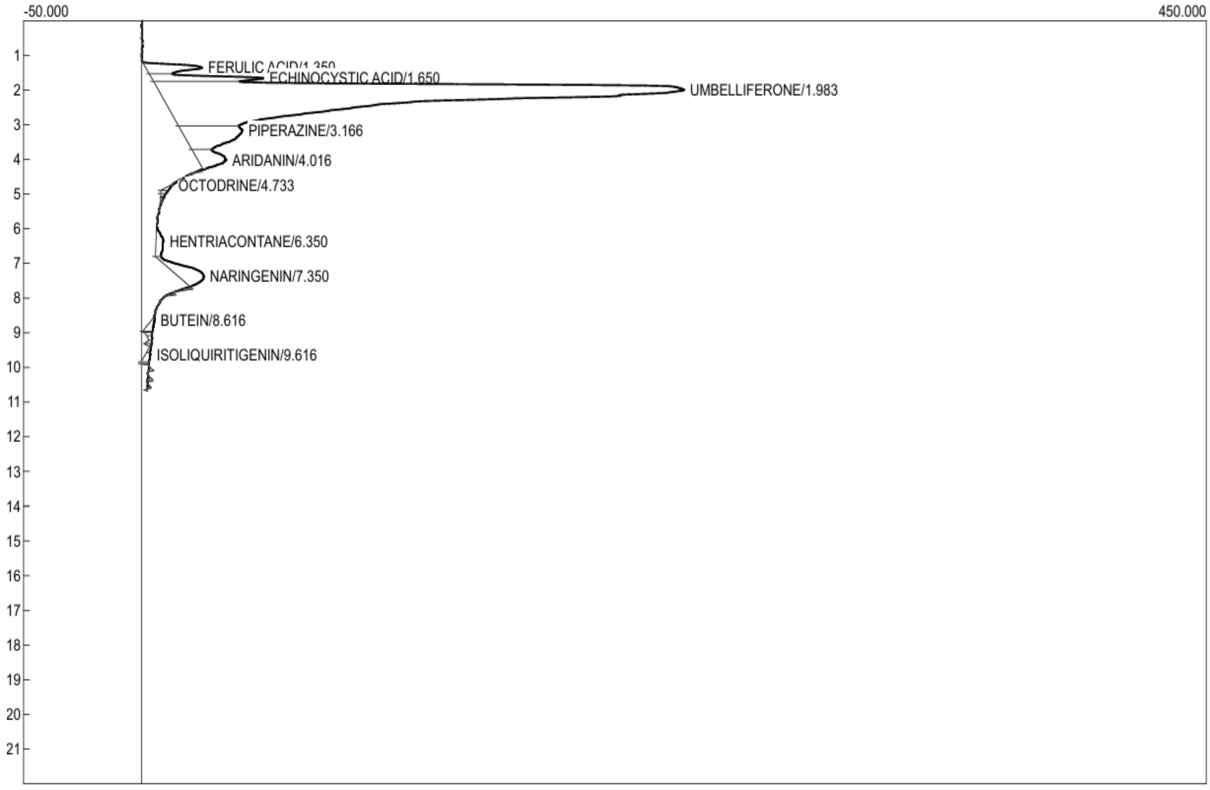

Figure 5: HPLC chromatogram of compounds in ethanol extract of *T. tetraptera* fruit

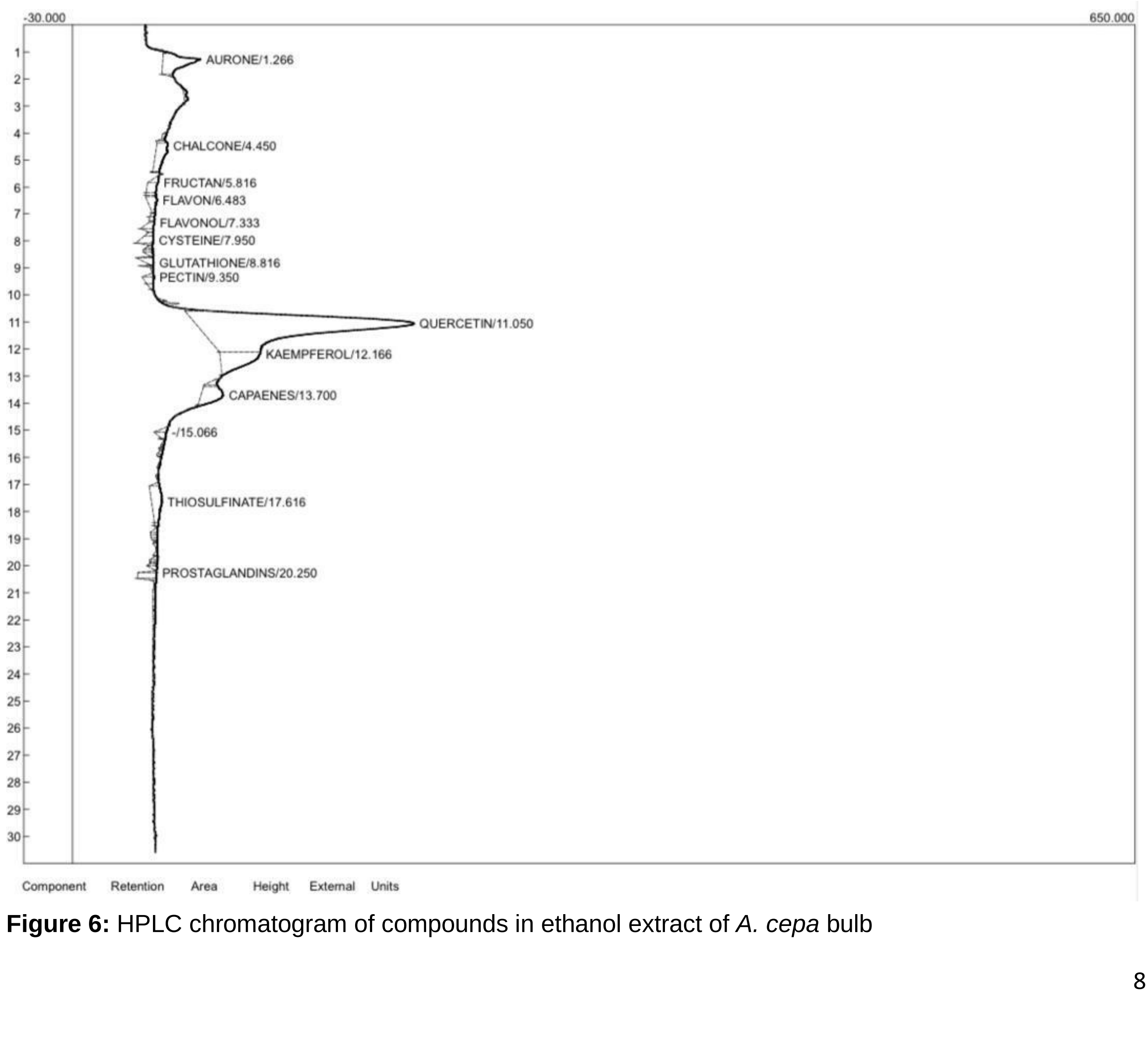

Figure 6: HPLC chromatogram of compounds in ethanol extract of *A. cepa* bulb

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