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HPLC analysis and subacute effect of *Senna alata* (L.) root and *Xylopia aethiopica* (Dunal) A. Rich seed on steroidal hormones associated with fibroid

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Abstract: Uterine fibroids, influenced by estrogen and progesterone, are common benign tumors in women of reproductive age. This work researched the action of *Senna alata* root and *Xylopia aethiopica* seed on progesterone and estradiol levels in female Wistar rats. Animal studies were conducted by administering 100 and 200 mg/kg doses of each extract to test animals daily for 28 consecutive days, after which blood samples were collected. Serum was analyzed for estradiol and progesterone levels using standard biochemical assays. High-Performance Liquid Chromatography (HPLC) was employed to identify the phytoconstituents in the ethanol extracts of the plants. *S. alata* significantly reduced progesterone levels ($p<0.001$) at both concentrations, while *X. aethiopica* showed marked activity only at 200 mg/kg ($p<0.01$). Estradiol levels remained unchanged with both extracts. HPLC identified bioactive compounds like kaempferol, trans-resveratrol and adenine in *S. alata* roots, and beta-phellandrene, kaempferol and umbelliferone in *X. aethiopica* seeds. These findings suggest hormone regulatory effects of these plants, warranting further research into their efficacy and mechanisms for fibroid management.

Keywords: Estradiol, Fibroid, HPLC, Progesterone, *Senna alata*, *Xylopia aethiopica*.

Introduction

Herbal medicine, the oldest form of healthcare, embodies the collective healing knowledge of countless generations over centuries and has seen a resurgence in modern medical practices, with more than 85% of the worldwide population relying on herbal remedies, as stated by WHO.[1] Since the dawn of humanity, the use of plants has served as a powerful means to treat various ailments. Additionally, many traditional and pharmaceutical drugs are derived directly from natural sources and time-honored therapeutic practices across the globe. Different medical systems and cultures employ herbal treatments for managing fibroids, which are non-cancerous tumors found in the uterus.[2] These tumors are the most common benign growths in women of reproductive age and have increasingly become a notable global health issue in recent years.[3] Although the precise cause of uterine fibroid development remains unclear, a wealth of epidemiological, clinical, as well as experimental research suggests that progesterone and estrogen promote tumor growth.[4] Consequently, these fibroids are uncommon in prepubescent girls, tend to grow more rapidly during reproductive years, become more noticeable during perimenopause, and decrease in size post-menopause.[5] In addition, individuals are at a higher risk of developing uterine fibroids if they consistently have elevated total protein and cholesterol levels.[6] In Nigeria, various regions have traditional natural remedies that are claimed to have long been used to manage fibroids.[7] These herbal treatments are often employed as alternatives to conventional medications and surgical procedures as conventional treatments can lead to several side effects that can reduce their effectiveness and also they are often expensive.[8] Medicinal plants contain numerous phytochemicals with therapeutic properties that are helpful in addressing various disorders of female reproductive system without causing significant adverse effects.[7]

The flower, root, leaves, seed, and bark of *Senna alata* (L.) Roxb (Fabaceae) have reportedly displayed diverse bioactivities.[8] Its roots are claimed to be used traditionally to treat fibroids.[9] *Xylopia aethiopica* (Annonaceae) plant is versatile with medicinal and nutritional applications. Many traditional practitioners utilize its various parts in treating many ailments, including sores, boils, cough, wounds, and cuts.[10] Its seeds are also a major ingredient in recipes claimed to be used to treat fibroid.[9]

The objective of this research therefore was to investigate the effect of ethanol extracts of *Senna alata* root and *Xylopia aethiopica* seed on female Wistar rats, focusing on their subacute

impact on steroidal hormones which are relevant to the development of uterine fibroids. Additionally, the primary phenolic constituents in the extracts were identified with High-Performance Liquid Chromatography.

Materials and methods

Plant material, collection and preparation

Senna alata plant was collected within the school premises of University of Benin, Benin-City on the 19th of August, 2024, while the seeds of *Xylopia aethiopica* was purchased in Benin. A plant taxonomist, Professor Akinnibosun identified the plants as *Senna alata* and *Xylopia aethiopica*. Voucher specimens were deposited at the Herbarium, Department of plant biology and technology, Faculty of Life Sciences, University of Benin, and the voucher numbers UBH-S491 and UBH-X348, respectively given. The plants were dried at room temperature and then 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 a dry mass over a water bath at 60°C and stored in the refrigerator until required.

High Performance Liquid Chromatography (HPLC) procedure

The HPLC analysis was conducted at Bato Chemical Laboratory, Lagos, Nigeria, using a Shimadzu Nexera MX HPLC system. A reverse-phase C18 ubondapak column (100 mm × 4.6 mm, 7 µm) was used with a 70:30 acetonitrile-water mobile phase. The system featured a UV-Vis diode array detector set at 254 nm, with a pump pressure of 15 MPa. Standard solutions established chromatographic peak profiles for comparison. Test samples (5 µL each) were injected at a 2 mL/min flow rate, generating chromatograms for peak area and profile analysis.[11]

Animal handling conditions

Thirty-five non-pregnant female Wistar rats weighing between 100 – 200g were obtained and acclimatized. The animals were placed in separate plastic cages and allowed unrestricted access to dry grower rodent pellet (Chikun feed, Nigeria) and water. They were grouped into seven with each group having five rats each. A proper ventilation was duly 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 under the approval number EC/FP/025/07, and the experimental protocols were also executed in accordance with the approval and recommendations of the Committee, adhering to international standards for animal handling and the established guidelines for the ethical use of animals in research.

Dosing of experimental animals

Twenty-five (25) female Wistar rats were placed in five groups of five rats each. Dosing was done once a day through the oral route with an orogastric tube. Group A was the control group which were allowed free access to food and water only. Groups B and C were treated with 100 and 200 mg/kg doses of *Senna alata* extract, respectively. Groups D and E were treated with 100 and 200 mg/kg doses of *Xylopia aethiopica* extract, respectively. All treatments were given concurrently for a 28-day period. The effect of the extracts on the eating habits of the animals was also 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.[12]

Biochemical assays

On the 29th day, the animals were sacrificed after which their blood was collected and 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 progesterone and estradiol levels of the animals.[13]

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]

Statistical analysis

Data obtained were expressed as mean ± standard error of the mean (S.E.M). A one-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison test was used to assess statistical significance between extract-treated groups and the control. GraphPad Prism (version 7.0.4) was utilized for

data analysis and presentation. Results were deemed statistically significant at P<0.05.

Results and discussion

Effect of plant extracts on food consumption and body weight

A gradual decrease in weight was seen with the groups given the extracts compared with the control, and this was more evident with *S. alata* extract (Table 1). Obesity, a multifaceted condition, constitutes a key risk factor for uterine fibroids, indicating that weight reduction may contribute to diminishing the incidence of fibroids in women.[15] The ability of these extracts to moderate weight gain may be attributed to their bioactive compounds that regulate lipid metabolism and energy expenditure. *S. alata* have been documented to lower blood glucose, triglycerides, serum cholesterol, and leptin, which are key factors in obesity. It also enhances glucose uptake by activating protein kinase B (PKB/Akt), improving metabolic efficiency and preventing excessive fat storage.[9] Similarly, *X. aethiopica* has been reported to exhibit anti-obesity potential by reducing weight gain in a dose-dependent manner while simultaneously lowering blood glucose levels.[16]

Biochemical Assay

Total serum estradiol content

Treatment with *S. alata* root and *X. aethiopica* seed extracts did not result in a significant ($p>0.05$) decrease in the estradiol levels at both concentrations used (Figure 1). Percentage reductions of 15.5 and 3.13% were observed with 100 and 200 mg/kg doses, respectively of *S. alata,* and 30.88 and 15.13% in 100 and 200 mg/kg doses, respectively of *X. aethiopica.* Estradiol exerts its effects through estrogen receptors (ERα and ERβ), particularly ERα, which enhances fibroid cell proliferation.[17] It also stimulates the production of collagen and growth factors that contribute to fibroid expansion.[18] Fibroids not only respond to circulating estrogen but also produce their own estrogen via aromatase-mediated conversion of androgens such as testosterone.[19] A cholesterol-rich environment further enhances estrogenic activity within fibroid tissues.[20] While the extracts did not produce a statistically significant reduction in estradiol levels, their weight reducing/lipid-lowering effects may indirectly impact estrogen metabolism by reducing cholesterol availability for steroidogenesis. By lowering cholesterol, the extracts may reduce the synthesis of these hormones, limiting their proliferative effects.

Total serum progesterone content

Animal treatment with *S. alata* root extract altered progesterone levels at both concentrations resulting in 68.05 and 66.42% reductions in 100 and 200 mg/kg doses ($p<0.001$) respectively (Figure 2). Treatment with *X. aethiopica* seed extract showed 46.81% reduction in progesterone levels at 200 mg/kg dose ($p<0.01$) which was significantly different ($p<0.05$) from 100 mg/kg dose. Progesterone is a steroid hormone that plays a crucial role in regulating pregnancy and menstruation.[2] In addition, progesterone serves as a steroidogenic precursor for various hormones, including estradiol.[21] The ability of *S. alata* root and *X. aethiopica* seed extracts to reduce progesterone levels in this study suggests a potential hormonal regulatory effect.

Increased progesterone levels have been correlated with fibroid progression as it promotes fibroid cell development by activating multiple genetic and epigenetic signaling pathways.[22] 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, a decline in estrogen can consequently lead to decreased progesterone levels.[17]

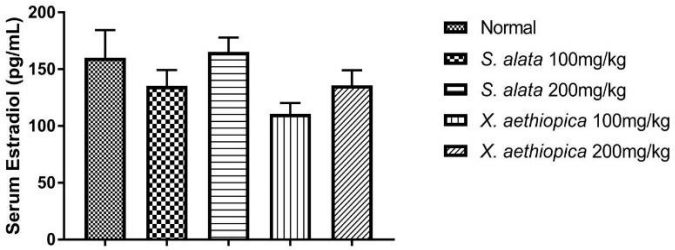

Figure 1: Effect of *S. alata* root and *X. aethiopica* seed extracts on total serum estradiol levels in female Wistar rats

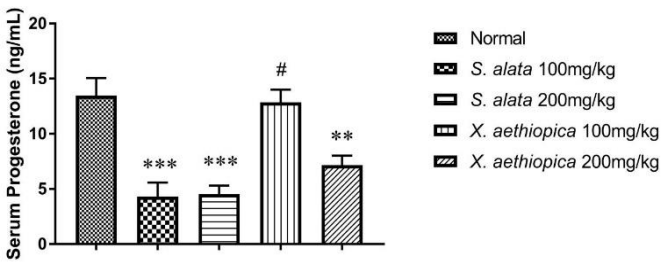

Figure 2: Effect of *S. alata* root and *X. aethiopica* seed extracts on total serum progesterone levels in female Wistar rats. Compared to the normal group **p<0.01, ***p<0.001, compared to 100 and 200 mg/kg *S. alata* #p<0.05

Furthermore, cholesterol acts as a precursor in progesterone synthesis, and the extracts' weight reducing/hypolipidemic properties may contribute to their ability to lower plasma progesterone levels.[20]

HPLC analysis

The HPLC chromatogram of *S. alata* root ethanol extract is presented in Figure 3. This analysis revealed the presence of adenine, kaempferol, chrysoeriol, quercetin, trans-resveratrol, and aloe-emodin as the major constituents. Other compounds present but in lesser amounts include sabiene, sabinene, n-triacontanol and luteolin (Table 2). Also, the identified compounds in *X. aethiopica* include kaempferol, beta-phellandrene, umbelliferone, quercetin, beta-pinene, and eugenol amongst others. (Table 3). The HPLC chromatogram is presented in Figure 4.

Table 1: Change in mean body weights of the rats on different days

Dose (mg/kg)	Change in mean body weights (g) at different days			
	Day 7	Day 14	Day 21	Day 28
Normal	7.60±12.52	4.00±10.18	8.80±10.12	5.00±11.65
S. alata (100mg/kg)	-0.80±10.73	11.40±10.36	-0.20±10.00	-1.00±11.39
S. alata (200mg/kg)	7.00±5.21	-1.40±9.52	5.80±8.43	-9.00±6.69
X. aethiopica (100mg/kg)	4.40±9.34	5.40±10.11	8.40±9.95	-5.4±12.85
X. aethiopica (200mg/kg)	5.40±6.65	4.20±5.14	5.20±3.80	-5.6±7.00

Table 2: HPLC result of S. *alata* root ethanol extract

Component	Retention time (mins)	Concentration (mg/g)
Adenine	3.700	1.72
Chrysoeriol	5.883	0.44
Diomestin	7.233	0.03
Trans-Resveratrol	7.966	0.51
N-Triacontanol	9.116	0.05
Emodin	9.950	0.04
Aloe Emodin	10.500	0.07
3-O-Gentobioside	11.300	0.04
Sabiene	11.850	0.05
Sabinene	12.333	0.03
Quercetin	15.500	0.41
Kaempferol	17.233	1.56
Rhamnetin	19.400	0.04
Apigenin	20.500	0.03
Luteolin	21.416	0.06
Naringenin	23.083	0.04
Apigenin-7-glucoside	25.450	0.04
Luteolin-7-glucoside	27.350	0.05

Table 3: HPLC result of X. *aethiopica* seed ethanol extract

Component	Retention time (mins)	Concentration (mg/g)
Benzoic Acid	0.866	0.09
Camphor	1.366	0.05
Eugenol	2.633	0.15
Beta-Phellandrene	3.700	1.08
Beta-Pinene	5.883	0.23
Umbelliferone	7.966	0.52
Catechin	9.116	0.08
Epicatechin	10.500	0.06
Salicin	11.300	0.04
1,8-Cineole	11.883	0.03
Sabiene	12.816	0.06
Sabinene	13.950	0.03
Quercetin	15.500	0.38
Kaempferol	17.233	1.31
Cinnamic Acid	21.416	0.09
Kaurene	22.566	0.04
Prunasin	24.016	0.03
Crystodigin	24.400	0.03
Digoxin	25.666	0.05
Quercetin-3-0-Glucose	26.483	0.04

The pharmacological activities of *S. alata* and *X. aethiopica* are largely attributed to their secondary metabolites, which include flavonoids, tannins, alkaloids, anthraquinones, and phytosterols.[9,11] Phytosterols, which are plant-derived sterol compounds structurally similar to cholesterol, play a crucial role in regulating lipid metabolism. They compete with cholesterol for absorption in the intestines, thereby reducing serum cholesterol levels,[23] which are relevant in fibroid management. The presence of phytosterols in *S. alata* and *X. aethiopica* suggests that these plants may contribute to fibroid inhibition by reducing systemic cholesterol, thereby limiting estrogen synthesis and fibroid growth. Furthermore, phytosterols have been shown to modulate immune responses and oxidative stress, both of which are implicated in fibroid pathology.[24]

Flavonoids such as quercetin, kaempferol, and chrysoeriol possess strong antioxidant and anti-inflammatory properties. Kaempferol and quercetin, in particular, have been linked to estrogen receptor modulation. Additionally, kaempferol has been found to exhibit anti-cancer activities by promoting apoptosis and inhibiting angiogenesis.[25] Tannins act as hypocholesterolemic and anti-inflammatory agents by binding to lipoproteins, reducing lipid absorption, and modulating immune responses.[26] Umbelliferone exhibits anti-inflammatory and neuroprotective effects,[27] while eugenol has been associated with antioxidant, anticancer, anti-inflammatory and analgesic activities.[28] Beta-phellandrene have been cited for their anti-inflammatory, analgesic and anti-cancer activity[29] while beta-pinene contribute to antimicrobial and cytotoxic properties.[30]

Alkaloids and anthraquinones exhibit anti-proliferative and cytotoxic effects, potentially inhibiting fibroid cell growth and inducing apoptosis. Aloe-emodin has shown potential in suppressing abnormal cell proliferation and has been found to exhibit anti-inflammatory effect.[31] The secondary metabolites of both *S. alata* and *X. aethiopica* exhibit several pharmacological activities that could collectively contribute to a potential anti-fibroid effect. Their anti-inflammatory properties may reduce the chronic inflammation that can promote fibroid growth by decreasing local pro-inflammatory mediators.[32] The anti-tumor and cytotoxic effects suggest that these compounds could inhibit the proliferation of fibroid cells or induce apoptosis in abnormal smooth muscle cells, thereby limiting fibroid expansion.[33] Additionally, the lipid-lowering effects might influence hormonal pathways since lipid metabolites can serve as precursors to steroid hormones that drive fibroid development potentially mitigating hormonal imbalances that favor fibroid growth.[34] Together, these activities indicate a multi-targeted approach where *S. alata and X. aethiopica* metabolites could reduce fibroid progression by modulating inflammation, cell proliferation, and hormone-related mechanisms.

Conclusion

The extracts of *X. aethiopica* seed and *S. alata* root induced significant reduction in progesterone levels but not in estradiol levels. HPLC analysis revealed major bioactive constituents such as kaempferol and adenine in *S. alata* root, as well as beta-phellandrene, kaempferol and umbelliferone in *X. aethiopica* seed. These findings suggest hormone regulatory effects of these plants.

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Conflict of interest

Authors declare no conflict of interest

Authors contributions

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

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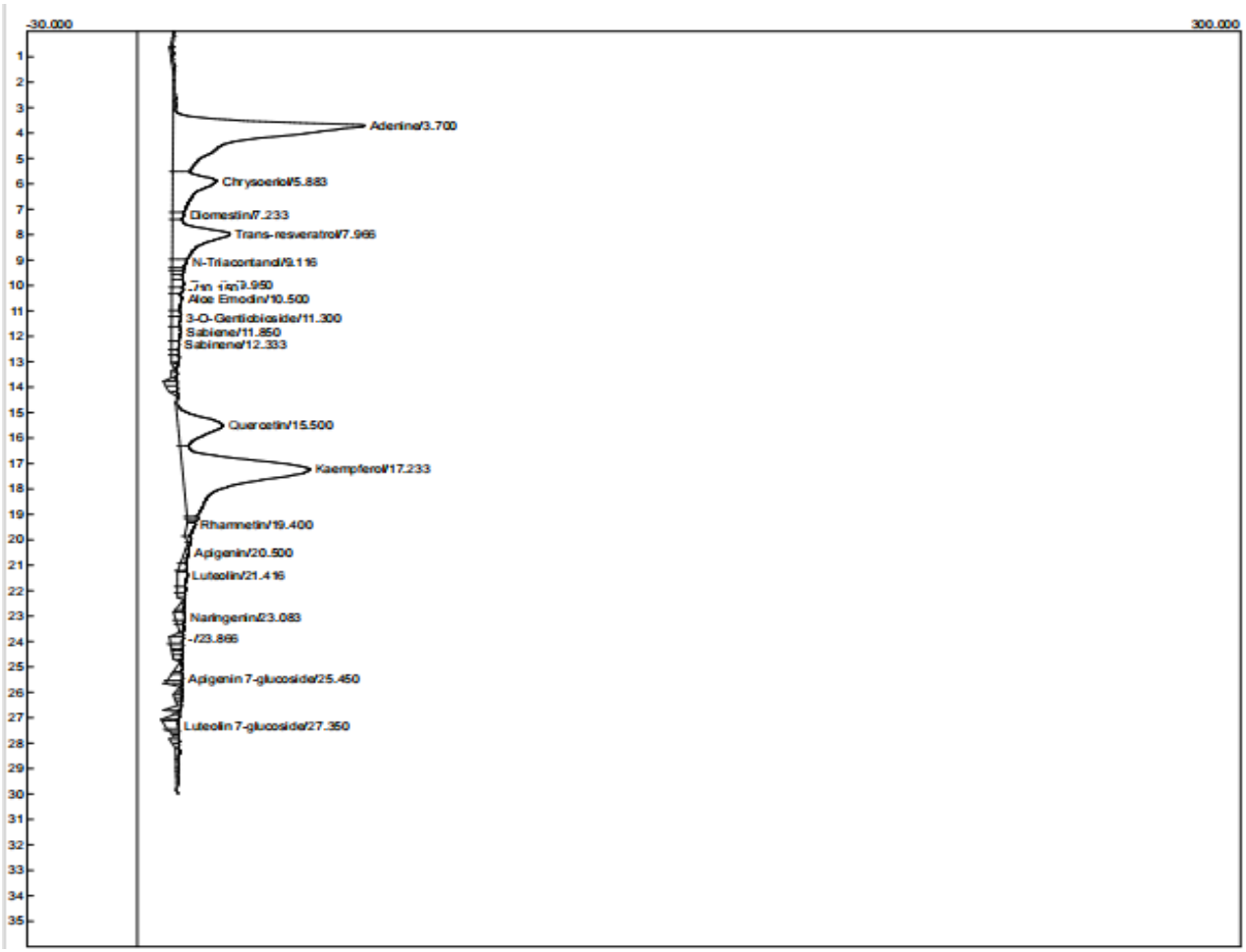

Figure 3: High-performance liquid chromatography chromatogram of *S. alata* root ethanol extract

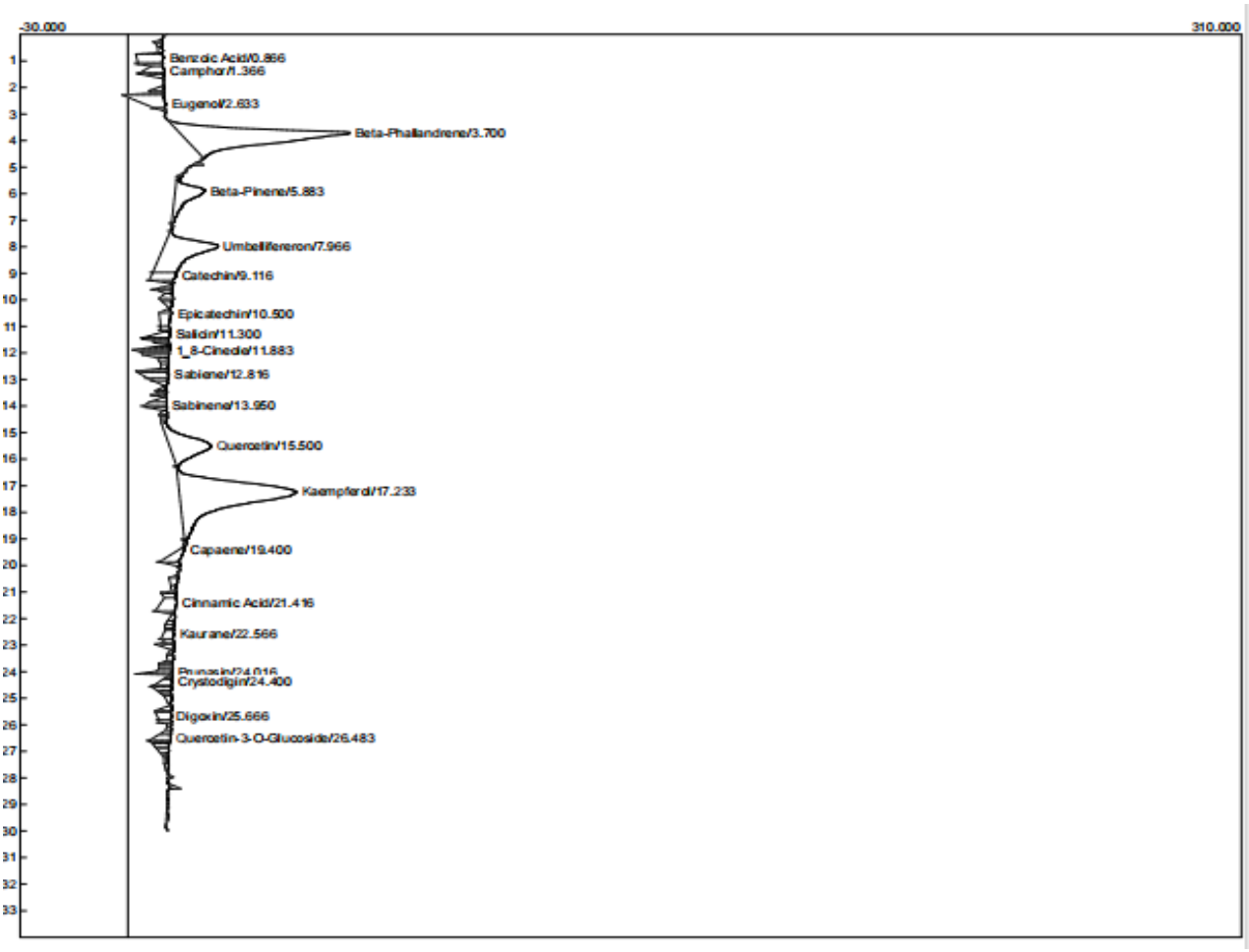

Figure 4: High-performance liquid chromatography chromatogram of *X. aethiopica* seed ethanol extract

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