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A NOVEL EXTRACTION AND LC–MS/MS-QTOF BASED METABOLITE PROFILING COUPLED WITH ADMET AND PASS SERVER PREDICTION UNVEILS ANTI-HIV LEADS FROM *OCIMUM TENUIFLORUM* L.

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ABSTRACT: The present study aimed to identify potential anti-HIV phytoconstituents from *Ocimum tenuiflorum* through a novel extraction strategy combined with LC–MS/QTOF-based phytochemical profiling, ADMET and PASS server predictions, HIV target proteins to elucidate bioactive compounds with promising antiviral potential. The LC-MS analysis of the extract revealed the presence of 17 compounds, including flavanones, isoflavones, phenolics, terpenoids, coumarins, and thiazole derivatives. ADMET analysis indicated that most of these phytoconstituents exhibited favourable drug-likeness properties and belonged to toxicity classes IV, V, or VI, suggesting that they are non-toxic and potentially safe for therapeutic use. PASS server predictions revealed that the compounds possess significant HIV integrase-inhibitory activity.

INTRODUCTION: The genus *Ocimum* (family: *Lamiaceae*) comprises approximately 150 species, many of which are well known for their aromatic constituents and diverse pharmacological activities [1, 2]. The plant was named *Ocimum tenuiflorum* by the Swedish botanist Carl Linnaeus in his work "*Manlissa plantarum*" in 1771. It has a synonym *Ocimum sanctum*, which is used in many publications and often used interchangeably. The Royal Botanical Gardens, Kew and the Missouri Botanical Gardens also provide Taxonomic information supporting the name *Ocimum tenuiflorum*.

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Ocimum tenuiflorum L., displays considerable interspecific and inter-cultivar variation, with plants exhibiting green, red, or blackish-red pigmentation in their leaves and stems [3-6]. *O. tenuiflorum has* been reported for its pharmacological properties and the species *Ocimum* holds a prominent place in traditional medical systems such as Ayurveda, Siddha, Unani, and various ethnomedicinal practices, where they are used intreating respiratory ailments, fevers, inflammatory conditions, gastrointestinal disturbances, and infectious diseases [7-9].

Different extraction methods significantly influence the phytochemical composition of *Ocimum* preparations, as different solvents and processing conditions can alter the solubility, stability, or transformation of secondary metabolites, ultimately impacting therapeutic efficacy [10]. *Ocimum tenuiflorum* has been widely investigated using GC–MS and LC–MS techniques, which have

revealed the presence of diverse phytochemicals, including phenolics, flavonoids, terpenoids, and essential oil constituents such as eugenol, ursolic acid, rosmarinic acid, and various hydroxycinnamic acid derivatives [11-13]. These studies collectively underscore the phytochemical richness of the species and support ongoing research into its bioactive potential. Human immunodeficiency virus (HIV) remains a major life-threatening pathogen with widespread global prevalence. Current therapeutic strategies primarily rely on antiretroviral drugs targeting key stages of the viral replication cycle. Raltegravir the first approved HIV-1 integrase inhibitor, has side effects such as nausea, headache, and elevated liver enzymes [14, 15]. Dolutegravir, a second-generation integrase inhibitor, also causes adverse effects such as increases in creatine phosphokinase and gastrointestinal symptoms [16, 17]. An alternative and increasingly promising approach targets the viral capsid protein. Lenacapavir, a pioneering long-acting capsid inhibitor, disrupts late-stage virion maturation, resulting in malformed, non-infectious viral particles [18].

In the present study, a unique extraction method was employed to obtain antiviral constituents, particularly those with potential anti-HIV activity. It is well documented that phytochemical extracts can undergo chemical transformations during storage or because of intermolecular interactions, leading to the formation or modification of bioactive compounds. Such transformations often enhance the therapeutic potency of the resultant molecules, as exemplified in *Catharanthus roseus*, where vinblastine is biosynthetically derived from vincristine during the storage of the extract [19-22]. Following this rationale, the aqueous extract of *Ocimum tenuiflorum* was processed using a modified extraction procedure designed to maximize the yield of potentially active antiviral metabolites. The final extract was subsequently subjected to liquid chromatography–mass spectrometry (LC–MS) analysis to characterize and identify the constituent phytochemicals for further ADMET and PASS server-based prediction for their anti-HIV potential.

MATERIALS AND METHODS:

Plant Material: Twigs of *Ocimum tenuiflorum* with a reddish hue, growing wild in parts of Hubli, Karnataka, were collected and identified. The fresh leaves were separated and thoroughly washed to remove the dirt and soil. The washed leaves were gently dried in the shade and the completely dried leaves were stored for further use.

Extract Preparation: One kilogram of dried leaves of holy basil (Tulasi) was boiled in distilled water for 1 hour and the decoction was drained off through a coarse cloth into a large jar. Two drops of strong sulfuric acid (H_2SO_4) were added to the decoction and left undisturbed. Then the extract was filtered using Whatman No. 1 filter paper. 5g of Ammonium carbonate was added to the filtrate and allowed to stand for 24 hrs. The supernatant was drained and the dried powder obtained was redissolved in ethanol for further analysis.

Instrumentation LC-MS/MSQTOP: To obtain sensitive and stable responses, the negative ionization mode was selected for the higher and more stable signal strengths. Subsequently, the MS/MS ion transitions were screened in MRM scanning mode to enhance the selectivity of detection. The Agilent ChemVista library was used in the selected and listed compounds.

Sample Preparation: 50 mg of the residue of *Ocimum tenuiflorum* extract was dissolved in 50 ml of distilled water. The upper aqueous layer was collected and filtered through a 0.45 µm Millipore membrane filter to remove particulate matter. A 3 µL aliquot of the resulting filtrate was used for LC–MS analysis.

Liquid Chromatography (LC) Conditions: Chromatographic separation was performed using a UPLC system equipped with a binary solvent pump. A reverse-phase Hypersil Phenyl BDS column (50 × 4.6 mm, 2.4 µm) was used, maintained at a column oven temperature of 40°C.

An isocratic mobile phase comprising 20:80 (v/v) 5 mM ammonium acetate solution and acetonitrile containing 0.1% formic acid was employed. The flow rate was set at 0.4 mL/min, and the total run time was 30 minutes.

Mass Spectrometry (MS) Conditions: Mass spectrometric analysis was conducted using an Agilent G6550A QTOF mass spectrometer coupled with an electrospray ionization (ESI) source

operated in negative ionization mode. The ESI parameters were as follows: Capillary temperature was maintained at 150°C, the Gas atomizer flow was 13 L/min, Source voltage was –2.7 kV, Full-scan mass range was m/z 150–1000 and the Source temperature was kept 250°C. Data acquisition was performed in full-scan mode to facilitate comprehensive profiling of phytoconstituents present in the extract.

Pharmacokinetic Studies:

ADMET Analysis: The identified phytoconstituents were subjected to comprehensive *in-silico* ADMET evaluation to assess their pharmacokinetic and toxicity profiles. ADMET properties (Absorption, Distribution, Metabolism, Excretion, and Toxicity) were predicted using the established online tool SwissADME platform to determine drug-likeness, bioavailability, and safety. These parameters facilitated the initial screening and prioritization of compounds with suitable pharmacokinetic characteristics for further evaluation.

PASS Server Prediction: The Prediction of Activity Spectra for Substances (PASS) online tool (https://www.way2drug.com/) was employed to predict the probable pharmacological activities of the selected compounds based on their structural descriptors. The search targeted potential bioactives with antiviral properties, with a specific focus on anti-HIV and integrase inhibitory activities.

RESULTS AND DISCUSSION: The search for novel phytoconstituents from plant sources remains a constant area of interest worldwide. In recent years, the emergence of new pathogens, diseases, and illnesses has posed significant challenges to drug discovery. In this context, the present study explored potential phytoconstituents from *Ocimum tenuiflorum* with targeted anti-HIV activity.

Ocimum tenuiflorum, extracted using a unique process, resulted in a cherry-red coloured aqueous solution. Acidification of the extract using H_2SO_4 resulted in the precipitation of proteins, and alkalization led to the formation of salts of the bioactives. The solution filtered over Whatman filter paper yielded a dark deposit, which is the salts of the extracted bioactives. The filtrate was separated and stored for further study.

LC–MS QTOF Profile: The LC–MS QTOF analysis of the uniquely processed *Ocimum tenuiflorum* aqueous extract-derived substances revealed a diverse range of bioactive metabolites. The identified phytochemicals belong to phenolic acids, flavonoids, triterpenoids, fatty acids, and glycosides. The chromatographic separation revealed 17 major compounds, each confirmed by accurate mass determination and molecular ion peaks in negative ionization mode ($[M–H]^-$), indicating the predominance of acidic and phenolic constituents **Table 1**, **Fig. 1**. Several of these compounds are known to possess antiviral and immunomodulatory activities.

Notably, the presence of multiple phenolic acids such as chicoric acid, caffeoylquinic acids, and caffeic acid derivatives suggests a strong potential for antioxidant-mediated antiviral effects. Several phenolic acids have been reported to interfere with viral replication pathways and can synergize with flavonoids to enhance antiviral potency. L-chicoric acid, for example, inhibits HIV-1 integrase *in-vitro* and reduces viral integration in cell-based systems [22-25].

The detection of flavonoid aglycones and glycosides, such as apigenin 7-O-glucuronide, kaempferol glycoside, myricetin 3-O-rhamnoside, and quercetin-O-glucoside, is particularly noteworthy. Flavonoids are widely recognized for their capacity to bind to HIV integrase and reverse transcriptase via hydrogen bonding and π–π interactions, thereby inhibiting viral integration and replication [26, 27]. Their presence aligns strongly with *in-silico* predictions (such as PASS), indicating high integrase inhibitory potential among the identified compounds.

Among the triterpenoids, ursolic acid stands out as a well-established antiviral agent with documented anti-HIV activity. Ursolic acid has been shown to inhibit HIV-1 protease [28-31]. Its detection in significant abundance reinforces the therapeutic relevance of *O. tenuiflorum* as a source of anti-HIV natural compounds.

The identification of α-linolenic acid and other long-chain polyunsaturated fatty acids (PUFAs) in the extract may enhance its therapeutic profile since PUFAs are well-described modulators of

innate and adaptive immune responses. They can influence inflammation resolution, membrane fluidity, and cell signalling pathways important for antiviral defence. Several *in-vitro* studies have demonstrated broad-spectrum antiviral activity of α-linolenic acid (ALA) and other PUFAs against enveloped viruses by interfering with viral entry and disrupting virion membranes, although direct reports specifically demonstrating ALA-mediated inhibition of HIV replication are relatively scarce compared with other viruses. Conversely, several in vitro and biochemical studies have reported that certain long-chain fatty acids, such as linoleic and oleic acids, inhibit HIV-1 enzymes or interfere with viral entry, suggesting the anti-viral potential of fatty acids against HIV. Clinical and lipidomic studies in people living with HIV show altered PUFA levels and associations between PUFA abundance and markers of immune activation, supporting the biological relevance of PUFA–immune interactions in HIV infection. These lines of evidence may support the hypothesis that linolenic acid in the extract could contribute indirectly to anti-HIV activity through immunomodulation [32-37].

Other notable compounds include nicotiflorin, basmantin, and cucurbit-O-glucoside, are reported to possess antimicrobial or anti-inflammatory actions in previous studies. Additionally, the detection of diteryl 2,3-chloro-6,7-dinitro-[1,3]benzoxazol-4-amine suggests the presence of unique or modified phytochemical structures that may contribute unexplored bioactivities.

A thorough review of the literature revealed that the hydroalcoholic fraction of *O. sanctum* possesses active metabolites such as luteolin, orientin, cosmosiin, eugenol, apigenin, luteolin 5-0-beta-d-glucopyranoside, eupalitin, ocimarin, molludistin, nepetoidin, xanthomicrol, hymenoxin, carnosic acid, demethylnobiletin, salvigenin, gardenin B, palmitic acid, methyl acetate, ursolic acid and basilimoside, which were detected at positive ion mode. Further, rosmarinic acid and genkwanin were detected at the negative ion mode [38]. There are no reports on the presence of modified benzylpyrone components when extracted using the general procedures. Interestingly, the presence of rare or modified benzopyrone derivatives in the present study may indicate that the unique extraction method facilitated the formation or concentration of structurally transformed molecules. Such derivatives often possess strong antiviral, antimicrobial, and enzyme-inhibitory activities, making them attractive candidates for further computational and experimental validation.

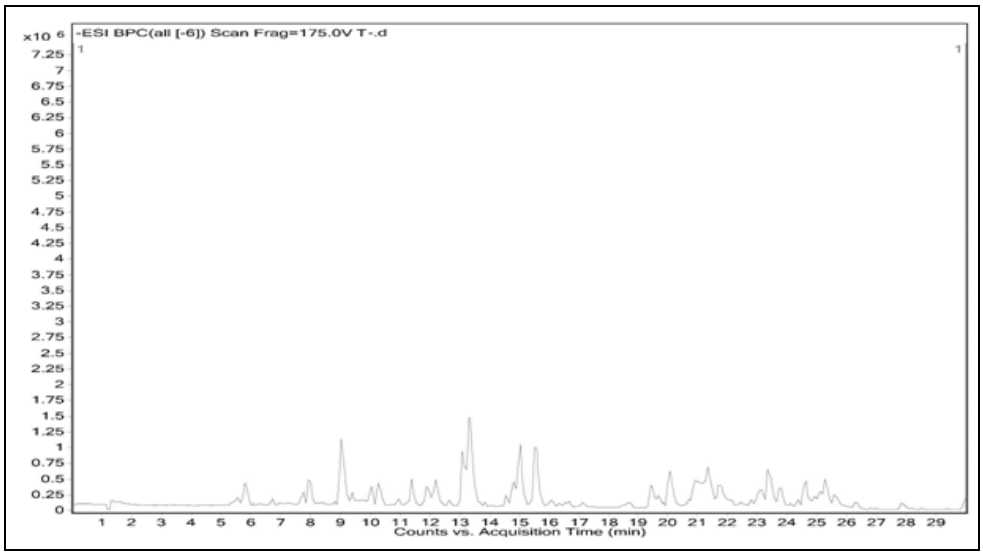

FIG. 1: CHROMATOGRAM OF MRM NEGATIVE ION MODE

TABLE 1: PHYTOCHEMICAL COMPOUNDS DETERMINED BY LC-MS/MS

S. no.	Proposed Phyto Compounds	Retention Time (min)	Molecular Formula	Ionization ESI (+/--)	Molecular Weight	Observed (Parent) (m/z)
1	Chicoric acid	6.687	$C_{22}H_{18}O_{12}$	$[M-H]^-$	474.3714	473.0828
2	Gallocatechin	7.713	$C_{15}H_{14}O_7$	$[M-H]^-$	306.0740	305.2089

3	Ursolic acid	9.425	$C_{30}H_{48}O_3$	$[M-H]^-$	456.6741	455.2209
4	Apigenin 7-O-glucuronide	10.085	$C_{21}H_{18}O_{11}$	$[M-H]^-$	446.0219	445.3470
5	Cryptochlorogenic acid	10.953	$C_{16}H_{18}O_9$	$[M-H]^-$	354.0947	353.0875
6	4-caffeoyl-1,5-quinolactone (Coumaric acid or derivatives)	11.385	$C_{16}H_{16}0_8$	$[M-H]^-$	336.0836	335.0892
7	5-O-Feruloylquinic acid (Ferulic acid)	12.685	$C_{17}H_{20}O_9$	$[M-H]^-$	368.1102	367.1030
8	Flavonol 3-O-D-xylosylgalactoside (Kaempferol)	13.784	$C_{26}H_{28}O_{12}$ $[M-H]^-$		532.1565	531.1494
9	Linolenic acid	16.095	$C_{18}H_{30}O_2$	$[M-H]^-$	279.3314	278.0567
10	Myricetin 3-O-rhamnoside	17.156	$C_{21}H_{20}O_{12}$	$[M-H]^-$	464.0853	463.2669
11	3-Hydroxy-3-(3-hydroxyphenyl) propionic acid(Caffeic acid)	19.405	$C_9H_{10}O_4$	$[M-H]^-$	182.0148	181.1230
12	Rosmarinic acid	20.115	$C_{18}H_{16}O_8$	$[M-H]^-$	360.3145	359.2657
13	Nicotiflorin	21.372	$C_{27}H_{30}O_{15}$	$[M-H]^-$	594.5105	593.2286
14	1,1-diphenyl-4-phenylthiobut-3-en-1-ol	22.801	$C_{22}H_{20}OS$	$[M-H]^-$	332.4581	321.0520
15	Quercetin-O-glucoside	`24.425	$C_{21}H_{18}O_{13}$	$[M-H]^-$	464.3678	463.2209
16	Diethyl 2-(3-chloro-6,7-difluoro-[1,3]thiazolo[3,4-a]quinoxalin-1-ylidene)propanedioate	25.612	$C_{17}H_{13}ClF_2N_2O_4S$	$[M-H]^-$	414.7985	413.0443
17	Umbelliferone	27.023	$C_9H_6O_3$	$[M-H]^-$	162.0317	161.1255

ADMET and PASS Server Predictions: Computational screening has emerged as a critical component in modern drug discovery, enabling efficient identification of therapeutically relevant compounds while reducing experimental complexity. In this study, drug-likeness prediction using the SwissADME platform revealed that the majority of the identified phytoconstituents complied with Lipinski's Rule of Five, indicating favorable physicochemical properties for oral bioavailability **Table 2**.

The SMILES-based ADME evaluation further demonstrated acceptable absorption, distribution, metabolism, and excretion profiles for these molecules, supporting their suitability as potential lead candidates [39]. Toxicity prediction through the ProTox 3.0 platform indicated that most of the compounds fell within low-to-non-toxic categories, suggesting a favourable safety margin for further investigation [40]. PASS server analysis provided additional insight into the pharmacological potential of the shortlisted molecules. The predicted activity spectra showed high Pa values for antiviral properties, particularly for HIV integrase inhibition, with Pa values consistently exceeding corresponding Pi values.

These predictions aligned with molecular docking results (unpublished data), indicating that the compounds not only possess drug-like characteristics but also exhibit a strong likelihood of exerting anti-HIV activity at the molecular level (Way2Drug platform). Collectively, the computational findings support the therapeutic relevance of the identified *Ocimum tenuiflorum* compounds and highlight their potential as promising candidates for further validation.

TABLE 2: PASS SERVER PREDICTION OF BIOACTIVITY OF METABOLITES IDENTIFIED IN LC-MS/QTOF ANALYSIS

S. no.	Chemical Com.	PUB CHEM ID	Nature of Compounds	MW	Molecular Formula	No. of. Hydrogen Donors	No.of Hydrogen acceptors	Water Solubility	CYP1A2 inhibitor	Lipinski's Rule	Bioavailability Score	Predicted Toxicity Class	PASS server
1	Chicoric acid	5281764	Caffeic acid derivative (polyphenol)	474.4 g/mol	C22H18O12	6	12	Soluble	No	No; 2 violations: NorO>10, NHorOH>5	0.11	5	0.619-HIV-1 integrase inhibitor;0.598-HIV-1 integrase (3'-Processing) inhibitor;0.529-HIV-1 integrase (Strand Transfer) inhibitor
2	Gallocatechin	65084	Flavan-3-ol (flavonoid subclass)	306.27 g/mol	C15H14O7	7	6	Soluble	No	Yes; 1 violation: NHorOH>5	0.55	6	0.459-Antiviral;0.352-Antiviral HIV;0.183-HIV-2 reverse transcriptase inhibitor
3	Ursolic acid	64945	Pentacyclic triterpenoid	456.7 g/mol	C30H48O3	2	3	Poorly Souble	No	Yes; 1 violation: MLOGP>4.15	0.85	4	0.166-Antiviral;0.381-Immunostimulant(inducer-causes treatment failure)

4	Apigenin-7-O-glucuronide	12912214	Flavone glycoside	446.4 g/mol	C21H18O11	6	11	Soluble	No	No; 2 violations: NorO>10, NHorOH>5	0.11	5	0.231-Antiviral;0.117-HIV-1 integrase inhibitor;0.121-HIV-1 integrase (Strand Transfer) inhibitor;0.119-HIV-1 integrase (3'-Processing) inhibitor
5	Cryptochlorogenic acid	9798666	Phenolic acid (chlorogenic acid isomer)	354.31 g/mol	C16H18O9	6	9	Very Soluble	No	Yes; 1 violation: NHorOH>5	0.11	5	0.525-HIV-1 integrase (3'-Processing) inhibitor;0.465-HIV-1 integrase (Strand Transfer) inhibitor;0.452-HIV-1 integrase inhibitor;0.258-Antiviral HIV
6	4-Caffeoyl-1,5-quinolactone (Coumaric acid derivative)	1.02E+08	Hydroxycinnamic acid derivative	336.29 g/mol	C16H16O8	4	8	Soluble	No	Yes; 0 violation	0.55	5	0.239-HIV-1 integrase (3'-Processing) inhibitor;0.29-HIV-1 integrase (Strand Transfer) inhibitor;0.199-HIV-1 integrase inhibitor;0.121-Antiviral HIV
7	5-O-Feruloylquinic acid (Ferulic acid derivative)	10133609	Hydroxycinnamic acid derivative	368.3 g/mol	C17H20O9	5	9	Very Soluble	No	Yes; 0 violation	0.11	5	0.429-HIV-1 integrase (3'-Processing) inhibitor;0.413-HIV-1 integrase (Strand Transfer) inhibitor;0.386-HIV-1 integrase inhibitor
8	(Flavonol)Kaempferol-3-O-D-xylosylgalactoside	1.32E+08	Flavonol glycoside	580.5 g/mol	C26H28O15	9	15	Soluble	No	No; 3 violations: MW>500, NorO>10, NHorOH>5	0.17	5	0.115-HIV-1 integrase inhibitor;0.104-HIV-1 integrase (Strand Transfer) inhibitor;0.146-Antiviral HIV
9	Linolenic acid	5280934	Polyunsaturated fatty acid (ω-3 type)	278.4 g/mol	C18H30O2	1	2	Soluble	0	Yes; 0 violation	0.7	6	0.388-HIV-2 reverse transcriptase inhibitor;0.118-HIV-1 integrase (Overall Integration) inhibitor
10	Myricetin-3-O-rhamnoside	56843093	Flavonol glycoside	464.4 g/mol	C21H20O12	8	12	Soluble	No	No; 2 violations: NorO>10, NHorOH>5	0.17	5	0.265- HIV-1 integrase (3'-Processing) inhibitor;0.256-HIV-1 integrase (Strand Transfer) inhibitor;0.213-HIV-1 integrase inhibitor
11	Caffeic acid (3-hydroxy-3-phenylpropanoic acid)	689043	Hydroxycinnamic acid (phenolic acid)	180.16 g/mol	C9H8O4	3	4	Very Soluble	No	Yes; 0 violation	0.56	5	0.498-HIV-1 integrase (3'-Processing) inhibitor;0.446-HIV-1 integrase inhibitor;0.429- HIV-1 integrase (Strand Transfer) inhibitor
12	Rosmarinic acid	5281792	Caffeic acid ester (polyphenolic compound)	360.3 g/mol	C18H16O8	5	8	Soluble	No	Yes; 0 violation	0.56	5	0.453-HIV-1 integrase (3'-Processing) inhibitor;0.418-HIV-1 integrase (Strand Transfer) inhibitor;0.393- HIV-1 integrase inhibitor
13	Nicotiflorin (Kaempferol-3-O-rutinoside)	5318767	Flavonol glycoside	594.5 g/mol	C27H30O15	9	15	Soluble	No	No; 3 violations: MW>500, NorO>10, NHorOH>5	0.17	5	0.111-HIV-1 integrase inhibitor;0.099-HIV-1 integrase (Strand Transfer) inhibitor
14	1,1-Diphenyl-4-phenylthiobut-3-en-1-ol	5363672	Phenylthio derivative / phenolic compound	332.5 g/mol	C22H20OS	1	1	Moderately soluble	Yes	Yes; 1 violation: MLOGP>4.15	0.55	4	0.185-HIV-2 reverse transcriptase inhibitor;
15	Quercetin-O-glucoside	44259229	Flavonol glycoside	464.4 g/mol	C21H20O12	8	12	Soluble	No	No; 2 violations: NorO>10, NHorOH>5	0.17	5	0.193-HIV-1 integrase (3'-Processing) inhibitor;0.187-HIV-1 integrase (Strand Transfer) inhibitor

16	Diethyl 2-(3-chloro-6,7-difluoro-[1,3]thiazolo[3,4-a]quinoxalin-1-ylidene) propanedioate	10341762	Heterocyclic thiazoloquinoxaline derivative (N-containing compound)	414.8 g/mol	C17H13ClF2N2O4S	0	7	Moderately soluble	yes	Yes; 0 violation	0.55	5	No pass prediction related to HIV
17	Umbelliferone	5281426	Coumarin derivative (benzopyrone)	162.14 g/mol	C9H6O3	1	3	Soluble	Yes	Yes; 0 violation	0.55	5	0.477-HIV-2 reverse transcriptase inhibitor;0.206-Antiviral (HIV);0.173-HIV-1 integrase inhibitor

CONCLUSION: The present study successfully demonstrated unique extraction methodology for obtaining compounds with anti-HIV potential from *O. tenuiflorum*. The presence of rare or modified benzopyrone derivatives detected in LCMS/Q-TOF analysis has shown that the unique extraction method facilitated the formation or concentration of structurally transformed molecules. Also, LC-MS/ QTOF results revealed that the *Ocimum* extract contains a pharmacologically rich mixture of phenolics, flavonoids, and terpenoids, many of which have documented or predicted antiviral effects. These findings support the subsequent computational analysis, including ADMET evaluation and PASS activity prediction, to prioritize compounds with the highest therapeutic potential against HIV target proteins. The combined presence of antioxidant, anti-inflammatory, and antiviral bioactives provides a strong biochemical basis for the observed and predicted anti-HIV properties of the compounds identified in *O. tenuiflorum*. Further studies are required to understand the drug potential of the compounds identified.

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