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Unlocking Antioxidant Potential in *Symplocos racemosa* Roxb. (*Lodhra*): A Phytochemical Exploration via High-Resolution Mass Spectrometry

Research Article

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Abstract

Symplocos racemosa Roxb., typically referred to as *Lodhra*, is a highly esteemed medicinal plant in traditional Indian medicine. Belonging to the Symplocaceae family, it is recognized for its wide-ranging therapeutic benefits, particularly in supporting dermatological health and fostering skin rejuvenation. This study delves into the phytochemical composition of S. racemosa by employing high-resolution mass spectrometry (HRMS) as a key analytical tool to assess its antioxidant potential. Antioxidants are bioactive compounds that mitigate oxidative stress by neutralizing free radicals that can cause cellular damage and contribute to ageing and disease progression. Oxidative stress is a major contributor to various chronic diseases, and antioxidants play a vital role in mitigating the damaging effects of reactive oxygen species (ROS). Identifying and characterizing potent antioxidant molecules within natural sources like *Lodhra* could open pathways to various therapeutic approaches. Renowned in traditional medicine for its multifaceted therapeutic properties, *Lodhra* was therefore systematically analyzed to elucidate its diverse array of bioactive compounds. HRMS facilitated the identification and characterisation of these metabolites, revealing a complex and rich biochemical profile. Through HRMS, seven metabolites namely Diselane, Catechin, Fraxetin, Eriodictyol, Coumarin, Panaxynol, and Ursolic acid have been identified to exhibit significant antioxidant activity. In vitro tests showed strong free radical scavenging activity, clearly linking certain phytochemicals to their antioxidant effectiveness. Previous in vitro tests demonstrated strong free radical scavenging activity of the isolated components, clearly justifying their antioxidant effects. The findings of this study highlight the significance of *Symplocos racemosa* as a potent source of natural antioxidants. The characterization of its bioactive compounds paves the way for further pharmacological research and possible development of antioxidant-based therapeutics from Ayurvedic resources.

Keywords: *Symplocos racemosa* Roxb., *Lodhra*, High-Resolution Mass Spectrometry, Oxidative stress, Antioxidant activity.

Introduction

Symplocos racemosa, commonly known as *Lodhra*, is a distinguished medicinal plant in traditional Indian medicine, particularly within the Ayurvedic system. It belongs to the Symplocaceae family, which comprises only the single genus Symplocos. This genus is prevalent in the tropical and subtropical regions of Asia, America, Australia, and Malaysia (1). *Lodhra* has been utilized for centuries for its numerous therapeutic properties, especially for its beneficial effects on skin health and overall vitality. The plant is characterized by its distinctive bark, which is often the primary source of its medicinal extracts. In Ayurveda, the astringent bark of S. racemosa is valued as a potent medicinal remedy for treating diverse ailments, including diarrhea, dysentery, ocular disorders, gum bleeding, menorrhagia, and other uterine issues (1). Rich in bioactive compounds, *S. racemosa* contains a variety of phytochemicals, which contribute to its notable antioxidant properties. These compounds play a crucial role in neutralizing free radicals and mitigating oxidative stress, a key factor in the development of various chronic diseases and skin ageing.

Oxidative stress is defined as a condition characterized by the overproduction of reactive oxygen species (ROS), resulting in damage to proteins, lipids, cell membranes, and, importantly, genetic material. Studies have established that oxidative stress is a critical contributor to numerous pathological conditions, especially in the context of neurological disorders, cancer and complication associated with diabetes (2). Furthermore, the ageing process can be linked to the harmful effects of free radicals, which contribute to DNA damage, lipid peroxidation, and protein oxidation (3). The cells generally respond to oxidative stress by activating compensatory mechanisms known as the antioxidant defense system. Among these, the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway plays a vital role in maintaining cellular homeostasis by promoting redox balance (4). Antioxidants can be either

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exogenous (natural or synthetic) or endogenous compounds that function to reduce or alleviate oxidative stress. (5). They prevent oxidation by functioning as reductants, chelating agents, and free radical scavengers, with a significant capacity to donate hydrogen. (6). A study revealed that the ethanolic extract of S. racemosa bark exhibit robust 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging activity, along with moderate scavenging effects against 1,1-diphenyl-2-picrylhydrazyl (DPPH), nitric oxide, and hydroxyl radicals, in comparison to the standard antioxidant ascorbic acid (7). Consequently, an effort has been undertaken to isolate the bioactive metabolites responsible for the antioxidant activity in *Symplocos racemosa* Roxb. (*Lodhra*) utilizing high-resolution mass spectrometry (HRMS).

Materials and Methods

Collection of *Lodhra*

The raw material of *Lodhra* for the analysis via High-Resolution Mass Spectrometry (HRMS) was procured from the local herbal drug market in Varanasi. Subsequently, it was authenticated in the Department of Botany, assigned Voucher Specimen No. Symploca. 2024/02.

Symplocos racemosa Roxb. (stem bark), methanol, distilled water, and Eppendorf tubes were utilized. The analysis was carried out with a High-Resolution Accurate Mass Spectrometry system, specifically the Orbitrap Eclipse Tribrid Mass Spectrometer developed by Thermo Fisher Scientific. For the characterization of small molecules, the Dionex UltiMate 3000 RSU HPLC system was employed for phytochemical evaluation (8).

Method employed for HRMS analysis

The sample preparation for HR-MS analysis began with the addition of 100 mg of the individual optimized sample of *Symplocos racemosa* Roxb. to 1.5 ml of solvent (Methanol:Water; 80:20), which was then homogenized using an Eppendorf Thermo-mixer at 750 rpm for 30 minutes at 25°C. Following this, the sample was centrifuged at 3500 rpm for 10 minutes at 25 °C. The supernatant was filtered through a 0.22 µ PTFE syringe filter, and 4 µl of the filtrate was used as the injection volume on a C18 RP-HPLC column (Hypersil GOLD™: Particle size 1.9 µ, dimensions 2.1 mm × 100 mm).

Reversed-phase chromatographic separation commenced with a highly aqueous phase (+0.1% formic acid) and transitioned to a predominantly organic phase (MeOH +0.1% formic acid), typically ranging from 100% aqueous to 100% organic. The gradient parameters for the liquid chromatography were as follows: 0-6 minutes at 5% methanol, 6-10 minutes at 30% methanol, 10-20 minutes at 50% methanol, 20-25 minutes at 90% methanol, and returning to 5% from 27 to 30 minutes. The flow rate was maintained at 300 l/min, and the column oven temperature was set at 40°C.

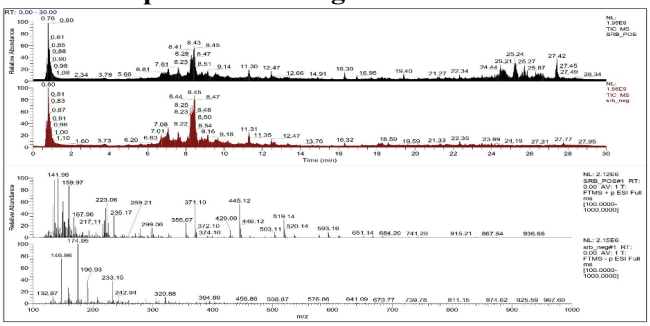
The optimized *Lodhra* sample underwent metabolomics analysis using a Thermo Fisher Scientific High-Resolution Accurate Mass Spectrometry System, specifically the Orbitrap Eclipse Tribrid Mass Spectrometer, in conjunction with Nano Liquid Chromatography and Ultra High-Pressure Liquid Chromatography (Dionex Ultimate 3000 RSLC). A Heated Electro Spray Ionization (HESI) source was employed to introduce the sample into the mass spectrometer following chromatographic separation. The Orbitrap analyzer operated at a resolution of 60,000 for both positive and negative polarities, covering a mass range (m/z) of 100-1000, with a 35% RF lens, a 25% Normalized Automatic Gain Control (AGC) target, and an intensity threshold set at 2.0e5 for the MS-OT (Master scan). For the ddMS2 OT HCD analysis, parameters included quadrupole isolation mode with a 1.5 m/z isolation window, HCD activation types with collision energies of 30%, 45%, and 60%, an Orbitrap resolution of 15,000, and a 20% Normalized AGC target (9).

The raw data from the mass analyser was processed using the default settings of "Compound Discoverer 3.3.2.31," in conjunction with online databases. The selected workflow, termed Natural Product Unknown ID, involved searches in both online and local databases. This untargeted food research workflow, which does not include statistical analysis, is designed to detect and identify unknown compounds. It aligns retention times, identifies these compounds, and groups them across all samples. The workflow also predicts elemental compositions for all compounds and reduces chemical background interference by utilizing blank samples. Compound identification is performed using mzCloud (with ddMS2 and/or DIA), ChemSpider (based on exact mass or formula), and local database searches against mass lists (exact mass, with or without retention time). Additionally, it conducts spectral similarity searches against mzCloud for compounds with ddMS2 and applies spectral distance scoring to matches identified in ChemSpider and the mass lists (10).

Results

A total ion chromatogram (TIC) is a graphical representation of the total ion count detected over time during a mass spectrometry analysis, showing all the ions generated from a sample. The total ion chromatogram of the compounds found in *Symplocos racemosa* Roxb. is shown in Figure 1.

Figure 1: Illustrates the total ion chromatogram of the compounds found in *Symplocos racemosa* Roxb. in positive and negative ion modes



A standard ion chromatogram (SIC) tracks the intensity of a specific ion or set of ions over time during a mass spectrometry analysis, providing detailed information about a particular compound in the sample.

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The metabolites identified in *S. racemosa* were quantified and characterized based on their retention times and peak intensities, as illustrated in Figure 2-8.

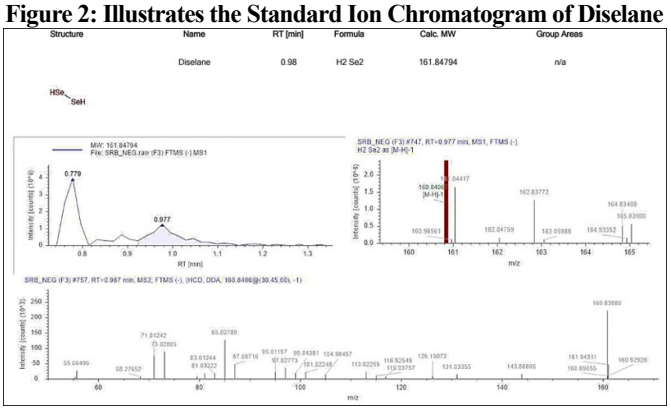
Antioxidant Activity of Bioactive Metabolites isolated from Symplocos racemosa

High-Resolution Mass Spectrometry (HRMS) identified 1,553 phytochemical constituents in *Symplocos racemosa*. Among these, the following compounds have been noted for their antioxidant properties: 1) Diselane, 2) Catechin, 3) Fraxetin, 4) Eriodictyol, 5) Coumarin, 6) Panaxynol, and 7) Ursolic acid, as supported by the references below.

1) Diselane

Studies revealed that the novel diselenides exhibited mimetic activity akin to glutathione peroxidase (GPx) and enhanced thioredoxin reductase (TrxR) activity in vitro. The GPx enzyme is essential for neutralizing the harmful or signaling effects of hydrogen and lipid peroxides. The observed GPx mimetic effect, coupled with the increased TrxR activity, is likely attributable to the generation of selenol groups, such as p-methyl-selenol and o-methoxy-selenol. The presence of diselanes /diselenides is expected to confer a more pronounced antioxidant effect, due to formation of these selenol groups, along with their GPx mimetic and elevated TrxR activities (11). Thioredoxin reductase (TrxR) is an enzyme that contains selenocysteine and plays a critical role in protecting cells from oxidative stress (12). Another study demonstrated that in mammals, GPx collaborates with superoxide dismutase and catalase to establish an enzymatic antioxidant system that diminishes reactive oxygen species (ROS) and curtails their toxicity. GPx predominantly utilizes glutathione (GSH) as a reducing agent to catalyze the conversion of hydrogen peroxide and organic peroxides into water or corresponding alcohols, respectively, thereby safeguarding cells from oxidative damage (13). The standard ion chromatogram is depicted in Figure 2.

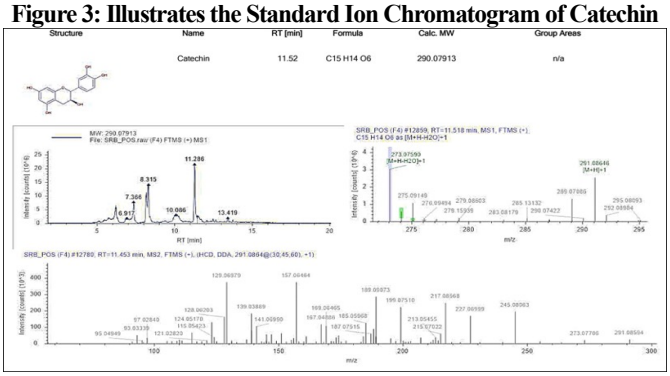
Figure 2: Illustrates the Standard Ion Chromatogram of Diselane



2) Catechins

Catechins are phytochemical compounds classified as secondary metabolites within the flavonoid family. Catechins protect keratinocytes primarily by mitigating damage caused by UVB radiation and reactive oxygen species (ROS) (14). As per Research articles, Catechin generates and eliminates free radicals via several pivotal direct and indirect antioxidant mechanisms. The direct mechanism entails the scavenging of reactive oxygen species (ROS), while the indirect mechanism enhances the activity of antioxidant enzymes and inhibits the pro-enzyme involved in oxidative stress. The phenolic hydroxyl groups in catechin play a critical role in ROS scavenging, indicating that an increased number of hydroxyl groups would enhance its antioxidant efficacy (15). The standard ion chromatogram is depicted in Figure 3.

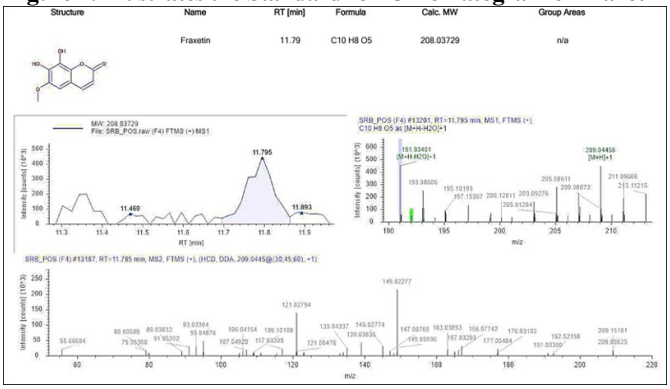
Figure 3: Illustrates the Standard Ion Chromatogram of Catechin



3) Fraxetin

Previous research suggests that the overall antioxidant activity mechanisms of fraxetin in aqueous media at physiological pH and lipid environments involve three primary reaction pathways: single electron transfer (SET), hydrogen transfer (HT), and radical adduct formation (RAF). In aqueous conditions, fraxetin interacts with peroxyl radicals through mechanisms based on its acid-base form. Specifically, neutral fraxetin predominantly engages via the HT mechanism, while its anionic form reacts primarily through the SET mechanism. Furthermore, our findings indicate that fraxetin exhibits remarkable scavenging activity against various free radicals under similar conditions, with the anion (HFR−) being the predominant contributor to its overall reactivity toward the examined peroxyl radicals. Consequently, the phenoxide anion emerges as the crucial species in the peroxyl radical scavenging capacity of fraxetin. Therefore, we can confidently assert that fraxetin is an exceptional and versatile antioxidant in aqueous media at physiological pH (16). The standard ion chromatogram is depicted in Figure 4.

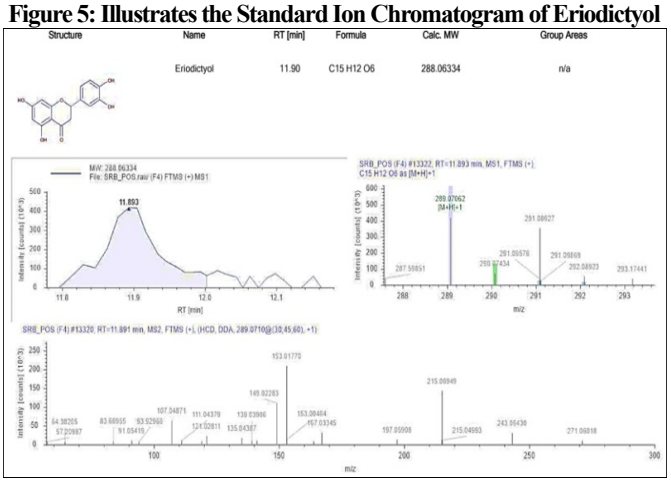
Figure 4: Illustrates the Standard Ion Chromatogram of Fraxetin



4) Eriodictyol

Studies demonstrated that Eriodictyol exerts its antioxidant effects on dermal fibroblasts in response to H_2O_2 through several mechanisms: (i) direct neutralization of reactive oxygen species; (ii) enhancement of H_2O_2-detoxifying enzyme activities, notably catalase (CAT) and glutathione peroxidase (GPx). CAT primarily detoxifies high concentrations of H_2O_2, while GPx is pivotal for eliminating low levels of H_2O_2; and (iii) induction of catalase and glutathione peroxidase 1 expression via activation of the Nrf2 signaling pathway. The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway serves as a master regulator of redox homeostasis and the antioxidative response. Activation of this pathway promotes the upregulation of various cellular antioxidant defenses, including CAT and GPx1, thereby enhancing cellular resistance against oxidative stress. These findings underscore the potential utility of eriodictyol as an ingredient in skincare formulations for cosmeceutical and pharmaceutical applications (17). The standard ion chromatogram is depicted in Figure 5.

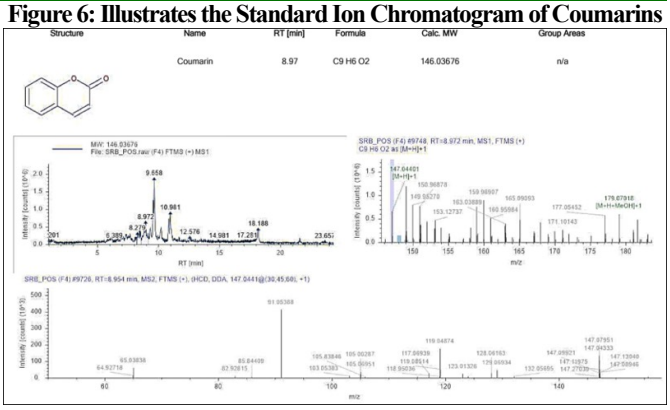
Figure 5: Illustrates the Standard Ion Chromatogram of Eriodictyol



5) Coumarins

Coumarins are recognized for their capacity to mitigate the generation of reactive oxygen species (ROS) and enhance their scavenging, thereby exhibiting significant antioxidant properties that protect against tissue damage. The underlying mechanisms of this antioxidant activity are multifaceted and likely attributable to their structural resemblance to flavonoids. Notably, the position and nature of substituents on the aromatic ring of coumarin molecules play a critical role in modulating their antioxidant efficacy. Specifically, the number of hydroxyl groups on the ring structure of coumarins is associated with their ability to suppress ROS. This relationship highlights the pivotal role of free radicals and ROS in the pathogenesis of complex diseases, indicating that coumarins may serve as valuable agents in alleviating oxidative stress (18). The standard ion chromatogram is depicted in Figure 6.

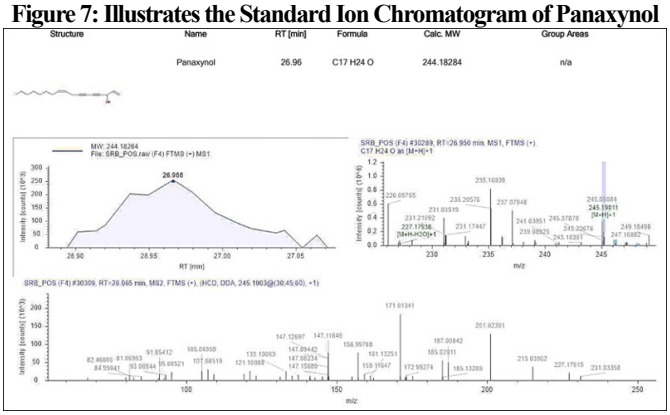
Figure 6: Illustrates the Standard Ion Chromatogram of Coumarins



6) Panaxynol

Research suggested that Panaxynol derived from plants exhibited considerable antioxidant activity by counteracting oxidative stress through the activation of the Kelch-like ECH-associated protein 1 (Keap1) and nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, reducing lipid peroxidation (LPO) and its associated biomarkers, as well as the promotion of nitric oxide synthase 1 (NO1) and heme oxygenase (HO) activation (19). Panaxynol is reported to inhibit elevated levels of reactive oxygen species (ROS), thereby alleviating oxidative stress due to its inherent antioxidant properties (20). The standard ion chromatogram is depicted in Figure 7.

Figure 7: Illustrates the Standard Ion Chromatogram of Panaxynol



7) Ursolic acid

Ursolic acid has been found to significantly enhance levels of superoxide dismutase (SOD) and glutathione (GSH), while substantially decreasing malondialdehyde (MDA) levels in animal tissues. In vitro studies further indicate that ursolic acid notably increases GSH and reduces MDA levels. Therefore, it is reasonable to consider ursolic acid as a non-enzymatic antioxidant that reinforces both cellular and organismal antioxidant defenses, effectively mitigating oxidative stress. Regarding its antioxidant mechanisms, ursolic acid may function by scavenging free radicals. Additionally, ursolic acid has been shown to combat oxidative stress through the liver kinase B1 (LKB1)-activated protein kinase (AMPK) signaling pathway (21). The standard ion chromatogram is depicted in Figure 8.

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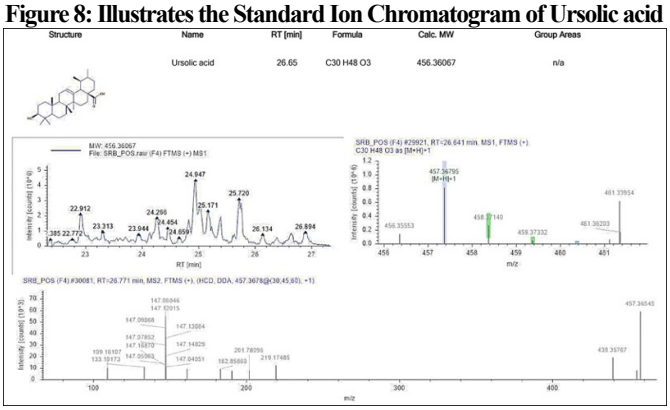
Figure 8: Illustrates the Standard Ion Chromatogram of Ursolic acid



Discussion

Antioxidant activity refers to the capacity of molecules to shield biomolecules from oxidative damage by neutralizing free radicals. It plays a crucial role in maintaining the body's redox balance and minimizing damage linked to various diseases. In Ayurveda, antioxidant properties align with balancing doshas and preventing *ama* (toxins). Several herbs act as *rasayanas*, rejuvenating and protecting tissues from oxidative damage, thereby enhancing vitality and longevity. *Symplocos racemosa* (*Lodhra*) demonstrates strong antioxidant properties, effectively neutralizing free radicals and safeguarding tissues from oxidative stress. It helps to reduce inflammation, supports skin health, and promotes cellular wellness. Traditionally used in Ayurveda, *Lodhra* aids in restoring balance and enhancing overall healing. Therefore, *Symplocos racemosa* was analyzed using High-Resolution Mass Spectrometry (HRMS) to identify the metabolites responsible for its antioxidant properties and understand their mechanisms. The analysis employed the Orbitrap Eclipse Tribrid Mass Spectrometer from Thermo Fisher Scientific for accurate and detailed results. Notably seven metabolites namely Diselane, Catechin, Fraxetin, Eriodictyol, Coumarin, Panaxynol, and Ursolic acid were identified to exhibit significant antioxidant activity.

Diselenides exhibit glutathione peroxidase (GPx)-like activity and enhance thioredoxin reductase (TrxR) activity, likely due to the generation of selenol groups. These properties are expected to provide a stronger antioxidant effect through GPx mimetic action and elevated TrxR activity (11). Catechin combats oxidative stress through both direct and indirect antioxidant mechanisms. Directly, it scavenges reactive oxygen species (ROS), while indirectly, it boosts antioxidant enzyme activity and inhibits pro-enzymes that contribute to oxidative stress (15). The antioxidant activity of Fraxetin in aqueous media at physiological pH and lipid environments follows three main pathways: single electron transfer (SET), hydrogen transfer (HT), and radical adduct formation (RAF). Its potent free radical scavenging ability is primarily attributed to the phenoxide anion, which plays a key role in neutralizing peroxyl radicals (16). Eriodictyol protects dermal fibroblasts from H_2O_2-induced oxidative stress by directly neutralizing reactive oxygen species (ROS) and boosting the activity of detoxifying enzymes, particularly catalase (CAT) and glutathione peroxidase (GPx) (17). Coumarins exhibit strong antioxidant properties by reducing the generation of reactive oxygen species (ROS) and enhancing their scavenging, thereby protecting tissues from damage. Their structural similarity to flavonoids and the presence of hydroxyl groups on the ring are key factors in their ROS-suppressing ability (18). Panaxynol demonstrates significant antioxidant activity by activating the Keap1-Nrf2 signaling pathway, reducing lipid peroxidation (LPO) and related biomarkers, while promoting nitric oxide synthase 1 (NO1) and heme oxygenase (HO) activation. This helps counter oxidative stress effectively (19). Ursolic acid exerts antioxidant effects by scavenging free radicals and combating oxidative stress through the activation of the liver kinase B1 (LKB1)-AMPK signaling pathway. These mechanisms contribute to its overall protective role against oxidative damage (21). A summarized overview about the details of the isolated components is shown in Table 1.

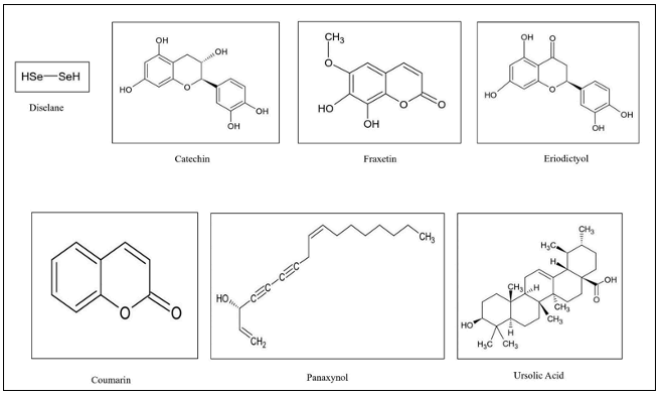
Table 1: Depicts the details of the Metabolites isolated by HRMS. It shows the Chemical formula, Calculated Molecular Weight (MW), Retention Time (RT) values, Delta Mass and the Peak area under Negative (NEG) / Positive (POS) ion mode of the bioactive metabolites

Bioactive Metabolite	Formula	Calc. MW	Retention Time (min)	Delta Mass (ppm)	Area NEG	Area POS
Diselane	H_2Se_2	161.84794	0.977	-4.63	5743307.77	-
Catechin	$C_{15}H_{14}O_6$	290.07913	11.524	0.33	-	39541920.22
Fraxetin	$C_{10}H_8O_5$	208.03729	11.789	0.56	-	2049729.26
Eriodictyol	$C_{15}H_{12}O_6$	288.06334	11.896	-0.16	-	2217013.03
Coumarin	$C_9H_6O_2$	146.03676	8.967	-0.16	-	10226194.93
Panaxynol	$C_{17}H_{24}O$	244.18284	26.958	0.51	-	1228056.59
Ursolic acid	$C_{30}H_{48}O_3$	456.36067	26.646	0.72	-	6512604.28

The molecular structure of antioxidants plays a key role in their effectiveness. Functional groups like hydroxyl and amine groups help scavenge free radicals, while conjugated systems and electron delocalization enhance stability. Steric hindrance affects reactivity, and the redox potential influences the molecule's ability to donate electrons or hydrogen atoms. Additionally, some antioxidants can chelate metal ions, preventing oxidative reactions. Together, these structural features determine how well an antioxidant neutralizes free

radicals and mitigates oxidative stress. Hence, the molecular structure of the isolated components are depicted in Figure 9.

Figure 9: Illustrates the molecular structures of phytochemical constituents isolated from Symplocos racemosa possessing antioxidant properties as identified through High-Resolution Mass Spectrometry analysis



While this study provides valuable insights into the antioxidant potential of *Symplocos racemosa*, several limitations must be acknowledged. First, the research was confined to in vitro experiments, which, while effective for identifying free radical scavenging activity, may not fully translate to in vivo conditions. The biological interactions and effects in complex living systems remain unexplored. Additionally, this study did not evaluate the potential synergistic interactions between the identified compounds, which could enhance or alter their antioxidant activity. Another limitation is the lack of investigation into the bioavailability and metabolism of these compounds, which are critical factors in determining their efficacy as therapeutic agents.

Conclusion

This study successfully identified and characterized key bioactive compounds in *Symplocos racemosa* that exhibit significant antioxidant activity, reinforcing the plant's traditional use in skin health and disease prevention. High-resolution mass spectrometry revealed a diverse array of phytochemicals, such as catechin and ursolic acid, which demonstrated strong free radical scavenging activity in vitro. These findings highlight *S. racemosa* as a promising source of natural antioxidants with potential therapeutic applications. However, further in vivo studies, along with investigations into bioavailability and synergistic effects, are essential to fully harness the medicinal potential of these compounds.

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