DIHYDROBENZOFURAN NEO-LIGNAN DERIVATIVES ISOLATED FROM THE WHOLE PLANTS OF LYCOPODIELLA CERNUA AND THEIR ANTIOXIDANT ACTIVITY

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Received: 19/3/2024 Reviewed: 8/4/2024
Revised: 8/5/2024 Accepted: 12/6/2024

DOI: *https://doi.org/10.58902/tcnckhpt.v3i2.130*

Abstract:

The entire plants of *Lycopodiella cernua L.* are utilized in Vietnam and China as traditional herbal medicine due to their anti-inflammatory activity and neuroprotective effect. In this current research, four dihydrobenzofuran neolignan derivatives (1–4) have been purified from the ethanol extract of *L. cernua*. Through the analysis of their observed and reported spectroscopic data, their structures were determined to be lycocernuaside A (1), dihydrodehydrodiconiferyl alcohol 4'-*β*-D-glucoside (2), lycocernuaside C (3), and cedrusin (4). Additionally, the DPPH radical-scavenging abilities of substances were assessed. Notably, compounds 3 and 4 showed potent DPPH scavenging capacity, with ED_{50} data of 8.6 ± 0.2 and 13.7 ± 0.4 μM, respectively. The effects were similar to ascorbic acid (ED_{50} = 23.6 ± 0.8 μM), the positive control. The findings suggest the potential *in vitro* antioxidant activity of dihydrobenzofuran neolignane derivatives from *L. cernua*. Nevertheless, further investigations, both *in vivo* and *in silico*, are necessary to confirm their therapeutic antioxidant effects.

Keywords: *Traditional medicine; Dihydrobenzofuran neolignan; Antioxidant activity; Lycopodiella cernua L.*.

1. Introduction

In recent years, there has been a growing interest in exploring natural products as potential sources of antioxidants to combat free radicals. These highly reactive molecules can cause oxidative damage to cells and tissues, leading to various diseases such as cancer, cardiovascular disorders, and neurodegenerative conditions (Singh et al. 2019). While synthetic antioxidants are available, concerns about their safety and long-term effects have prompted researchers to seek alternative solutions from natural sources. Natural products, derived from plants, fungi, marine organisms, and microorganisms, provide a rich reservoir of bioactive compounds with diverse chemical structures and pharmacological activities (Liu et al. 2023, Nguyen et al. 2020, Vinh et al. 2023, Vinh et al. 2019a). These compounds have evolved in plants and other organisms as defence mechanisms against

environmental stresses, including UV radiation, pathogens, and oxidative stress. Consequently, they often possess potent antioxidant properties, making them promising candidates for therapeutic interventions against oxidative stress-related diseases. Moreover, natural products are generally perceived as safer alternatives to synthetic antioxidants due to their long history of use in traditional medicine and their perceived lower risk of adverse effects (Han et al. 2023). Additionally, natural products are often more cost-effective to isolate and produce, which is particularly advantageous for resource-limited settings and the development of affordable healthcare solutions. Given the vast biodiversity of medicinal plants and other natural sources, there is a compelling need to continue exploring and harnessing their potential for antioxidant activity. This includes the isolation and characterization of bioactive compounds from medicinal plants through rigorous screening processes. Such efforts not only contribute to expanding our knowledge of natural product chemistry but also hold promise for the development of novel antioxidant therapies with enhanced safety, efficacy, and affordability (Kim et al. 2020).

Lycopodiella cernua L., a member of the Lycopodiaceae (formerly Huperziaceae) family, holds a significant place in Vietnamese traditional medicine, commonly used to treat ailments such as liver inflammation, musculoskeletal disorders, and neurological disorders (Chuong et al. 2014). Previous studies have documented various secondary metabolites found in *L. cernua*, including alkaloids, triterpenoids and phenolics (Giang et al. 2021). Extracts from *L. cernua* have been the focus of numerous investigations, revealing diverse pharmacological properties such as antioxidative, anti-proliferative, anti-inflammatory, cytotoxic effects, as well as inhibitory characteristics (Chuong et al. 2014). Notably, recent study has highlighted the ability of triterpenoids extracted from the entire plants of *L. cernua* to inhibit acetylcholinesterase, butyrylcholinesterase, and β-secretase enzymes. As part of our ongoing exploration into bioactive substances from Vietnamese herbal medicines, we conducted a phytochemical investigation on *L. cernua* whole plants, leading to the isolation of four neolignans (1−4). Structural elucidation was achieved through comprehensive 1D and 2D NMR spectroscopic analyses. Furthermore, the potential in vitro antioxidant effect of the isolated substances was assessed.

2. Research overview

The possible therapeutic ramifications of *L. cernua*'s chemical makeup have attracted a lot of research recently. Traditional medicine makes extensive use of *L. cernua* to treat a wide range of illnesses. Extensive studies have focused on elucidating the chemical constituents present in *L. cernua*, revealing a diverse array of bioactive compounds. These include triterpenoids, phenolics, alkaloids and phenolics (Giang et al. 2021). Among these compounds, neo-lignans have emerged as particularly noteworthy due to their intriguing biological activities. Neo-lignans, a class of phytochemicals found in *L. cernua*, have attracted considerable interest for their potential therapeutic applications. Studies have shown that neo-lignans showed a wide range of biological properties, including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties (Hung et al. 2015). Notably, neo-lignans have demonstrated potent antioxidant activity, effectively scavenging free radicals and protecting cells from oxidative damage (Chuong et al. 2014). Furthermore, their anti-inflammatory effects contribute to mitigating inflammatory responses, thereby potentially alleviating various inflammatory conditions. Moreover, neo-lignans have shown promising anticancer activity, inhibited the proliferation of cancer cells and induced apoptosis. These findings underscore the potential of neo-lignans as valuable therapeutic agents for the treatment and management of various diseases. Further research is warranted to elucidate the underlying mechanisms of action and to explore their clinical applications.

3. Material and methods

3.1 General experimental procedures

The experimental procedures closely followed those of our prior studies. In summary, we

conducted measurements of 1D and 2D spectra using Bruker AM500 spectrometers (MA, USA), employing tetramethyl silane as the calibration reference. Surface chromatography was conducted using silica gel and C18 standards, and substances were identified by treating with 10% H_2SO_4 and heating for 3-5 minutes. The CD data was recorded with a Chirascan spectropolarimeter (Applied Photophysics, UK). An Agilent 6530 LC-QTOF-MS instrument (USA) was used to record the HR-ESI-MS.

3.2. Sample selection for study

The entire plants of *Lycopodiella cernua* were harvested at Sapa, Laocai province, Vietnam in August 2020, and were taxonomically verified by Mrs. Nguyen Thi Thu (Institute of National Medicinal Materials, Hanoi, Vietnam). A representative specimen (Code: TD 06) has been stored at the botanical collection of INMM.

3.3. Purification process

The entire plants of *Lycopodiella cernua* (8 kg) were sliced and subjected to treatment with ethanol (30 L × 4 times) at room temperature. A rotary evaporator was used to concentrate the resultant ethanol solution, producing a 1200 g MeOH extract residue. After that, this residue was interrupted in water and divided into *n*-hexane (H), ethyl acetate (EtOAc), and aqueous (W) extracts, in that order. Using a gradient solvent mixture of MeOH-H_2O (95:1, 75:25, 25:75, v/v), the water layer (W) was isolated based on Styrene-divinylbenzene resin HP-20 column chromatography (CC) to yield four subfractions (W-1 to W-4), respectively. Fraction W3 (320 g) underwent fractionation using RP-C18, with the ratio acetone-H_2O gradient (1:3 to 3:1, v/v), resulting in five subfractions (W2A-W2E), respectively. Subfraction W3C was subjected to silica gel CC, eluting with $CHCl_3$-MeOH-H_2O (5:1.2:0.02, v/v/v) to yield subfractions W3C1-W3C3. Subfraction W3C3 (154.0 g) was isolated via silica gel column chromatography eluted with EtOAc-MeOH-H_2O (8:1:0.01, v/v/v) and purified using RP-C18 (acetone-H_2O, 1:4, 1:4, v/v) to yield compounds 1 (54.0 mg) and 2 (97.0 mg). Fraction (W3D, 80 g) was isolated by silica gel CC eluting with $CHCl_3$-MeOH- H_2O (5:1:0.01, v/v/v) and Sephadex™ LH-20 CC based on mixtures of MeOH-H_2O (10:1, v/v) to obtain substances 3 (63.5 mg) and 4 (96.2 mg).

3.4. Antioxidant activity

We conducted measurements of DPPH radical-inhibitory effect following standard procedures (Vinh et al. 2019b). In short, 100µL of the sample was thinned with purified water to attain ultimate concentrations. Additionally, the sample was mixed with 100 µL of DPPH that had been diluted to 100 µM in an ethanol solution. Water was used in place of samples in control wells, which contained the same reaction components. The contents of the wells were thoroughly mixed and then incubated at room temperature for 30 minutes. The reaction progress was monitored by observing the color change ranging from deep purple to pale yellow, with absorbance readings taken at 517 nm using a microplate reader. The antioxidant activity was quantified as percentage inhibition (EC%) and computed using the subsequent formula:

Percentage effect (EC%) = $\frac{A\ control - A\ sample}{A\ control} \times 100$

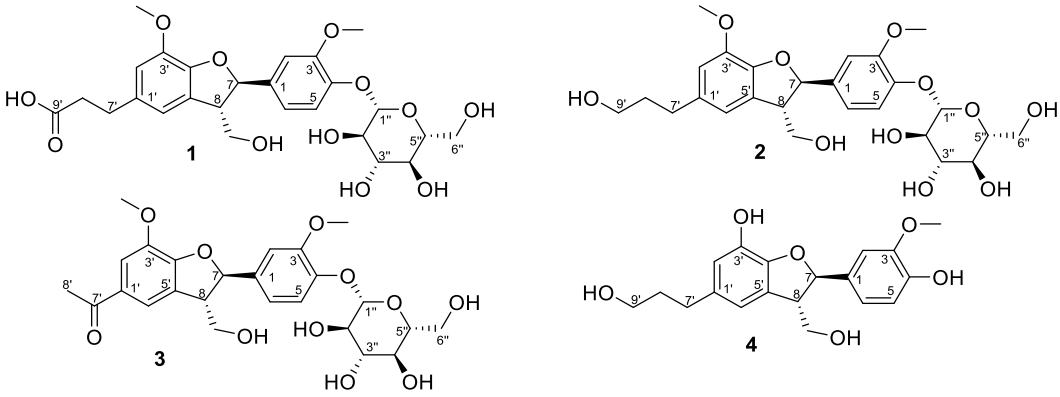
A sample = sample absorbance, A control = positive control absorbance

Various sample concentrations were employed to generate anti-radical curves to compute the EC_{50} values.

4. Results

N-hexane, EtOAc, and H_2O are organic solvents with increasing polarity that were used to fractionate the *L. cernua* EtOH extract. Four substances (1–4) (Figure 1) were purified by the combined CC separations on Sephadex LH-20, RP-18, and silica gel. Drawing from an exhaustive examination of spectroscopic values and juxtaposition with prior findings, the isolated compounds were discerned to be lycocernuaside A (1), dihydrodehydrodiconiferyl alcohol 4'-*β*-D-glucoside (2), lycocernuaside C (3), and cedrusin (4), respectively. The intricate NMR data of isolated compounds are provided within this document.

Fig.1. Dihydrobenzofuran neolignan compounds 1–4 isolated from whole plants of *L. cernua*



4.1 Lycocernuaside A (1)

White amorphous powder, ^{1}H NMR (500 MHz, MeOD): δ_H (ppm) 6.78 (1H, s, H-2), 6.75 (1H, s, H-6), 2.88 (2H, t, *J* = 7.5 Hz, H-7), 2.59 (2H, t, *J* = 7.5 Hz, H-8), 7.04 (1H, br s, H-2'), 7.16 (1H, d, *J* = 8.0 Hz, H-5'), 6.95 (1H, d, *J* = 8.0 Hz, H-6'), 5.57 (1H, d, *J* = 8.0 Hz, H-7'), 3.46 (1H, m, H-8') , 4.90 (1H, d, *J* = 7.0 Hz, H-1"), 3.88 (3H, s, 3-OCH_3), 3.85 (3H, s, 3'-OCH_3). ^{13}C NMR (125MHz, MeOD): δ_C (ppm) 135.9 (C-1), 114.1 (C-2), 145.3 (C-3), 147.6 (C-4), 129.7 (C-5), 117.8 (C-6), 32.0 (C-7), 37.5 (C-8), 177.5 (C-9), 138.3 (C-1'), 111.2 (C-2'), 150.9 (C-3'), 147.8 (C-4'), 118.1 (C-5'), 119.3 (C-6'), 88.5 (C-7'), 55.6 (C-8'), 65.0 (C-9'), 102.8 (C-1"), 74.9 (C-2"), 78.1 (C-3"), 71.3 (C-4"), 77.8 (C-5"), 62.5 (C-6"), 56.8 (3-OCH_3), 56.7 (3'-OCH_3).

4.2 Dihydrodehydrodiconiferyl alcohol 4'-β-D-glucoside (2)

White amorphous powder, ^{1}H NMR (500 MHz, MeOD): δ_H (ppm): 6.75 (1H, s, H-2), 6.73 (1H, s, H-6), 2.64 (2H, t, *J* = 8.0 Hz, H-7), 1.88 (2H, m, H-8), 3.58 (2H, t, *J* = 7.0 Hz, H-9), 7.05 (1H, br s, H-2'), 7.15 (1H, d, *J* = 8.5 Hz, H-5'), 6.95 (1H, d, *J* = 8.5 Hz, H-6'), 5.57 (1H, d, *J* = 6.0 Hz, H-7'), 3.46 (1H, m, H-8'), 3.77 (1H, dd, J = 7.5, 11.0 Hz, H_a-9'), 3.87 (1H, m, H_b-9'), 4.90 (1H, d, *J* = 7.0 Hz, H-1"), 3.89 (3H, s, 3-OCH_3), 3.85 (3H, s, 3'-OCH_3). ^{13}C NMR (125MHz, MeOD): δ_C (ppm) 137.0 (C-1), 114.1 (C-2), 145.2 (C-3), 147.4 (C-4), 129.5 (C-5), 117.9 (C-6), 32.8 (C-7), 35.7 (C-8), 62.2 (C-9), 138.3 (C-1'), 111.2 (C-2'), 150.9 (C-3'), 147.5 (C-4'), 118.0 (C-5'), 119.3 (C-6'), 88.4 (C-7'), 55.6 (C-8'), 65.0 (C-9'), 102.7 (C-1"), 74.8 (C-2"), 78.1 (C-3"), 71.3 (C-4"), 77.8 (C-5"), 62.4 (C-6"), 56.7 (3-OCH_3), 56.7 (3'-OCH_3).

4.3 Lycocernuaside C (3)

White amorphous powder, ^{1}H NMR (500 MHz, MeOD): δ_H (ppm): 6.78 (1H, s, H-2), 6.75 (1H, s, H-6), 2.88 (2H, t, *J* = 7.5 Hz, H-7), 2.59 (2H, t, *J* = 7.5 Hz, H-8), 7.04 (1H, br s, H-2'), 7.16 (1H, d, *J* = 8.0 Hz, H-5'), 6.95 (1H, d, *J* = 8.0 Hz, H-6'), 5.57 (1H, d, *J* = 8.0 Hz, H-7'), 3.46 (1H, m, H-8') , 4.90 (1H, d, *J* = 7.0 Hz, H-1"), 3.88 (3H, s, 3-OCH_3), 3.85 (3H, s, 3'-OCH_3). ^{13}C NMR (125MHz, MeOD): δ_C (ppm) 135.9 (C-1), 114.1 (C-2), 145.3 (C-3), 147.6 (C-4), 129.7 (C-5), 117.8 (C-6), 32.0 (C-7), 37.5 (C-8), 177.5 (C-9), 138.3 (C-1'), 111.2 (C-2'), 150.9 (C-3'), 147.8 (C-4'), 118.1 (C-5'), 119.3 (C-6'), 88.5 (C-7'), 55.6 (C-8'), 65.0 (C-9'), 102.8 (C-1"), 74.9 (C-2"), 78.1 (C-3"), 71.3 (C-4"), 77.8 (C-5"), 62.5 (C-6"), 56.7 (3-OCH_3), 56.7 (3'-OCH_3).

4.4 Cedrusin (4)

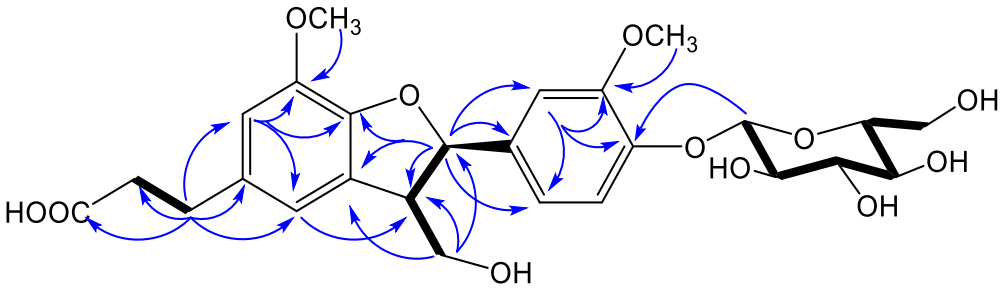
White amorphous powder, ^{1}H NMR (500 MHz, MeOD): δ_H (ppm): 6.58 (1H, d, *J* = 1.5 Hz, H-2), 6.63 (1H, s, H-6), 2.58 (2H, t, *J* = 8.0 Hz, H-7), 1.81 (2H, m, H-8), 3.58 (2H, t, *J* = 7.0 Hz, H-9), 7.00 (1H, d, *J* = 1.5 Hz, H-2'), 6.78 (1H, d, *J* = 8.0 Hz, H-5'), 6.86 (1H, dd, *J* = 1.5, 8.5 Hz, H-6'), 5.51 (1H, d, *J* = 6.0 Hz, H-7'), 3.47 (1H, dd, J = 6.0, 12.5 Hz, H-8'), 3.77 (1H, dd, *J* = 7.5, 11.5 Hz, H_a-9'), 3.84 (1H, dd, J = 5.5, 11.5 Hz, H_b-9'), 3.84 (3H, s, 3'-OCH_3). ^{13}C NMR (125MHz, MeOD): δ_C (ppm) 136.7 (C-1), 117.0 (C-2), 141.8 (C-3), 146.5 (C-4), 129.8 (C-5), 116.6 (C-6), 32.7 (C-7), 35.7 (C-8), 62.3 (C-9), 135.1 (C-1'), 110.5 (C-2'), 149.0 (C-3'), 147.3 (C-4'), 116.1 (C-5'),

119.6 (C-6'), 88.7 (C-7'), 55.7 (C-8'), 65.1 (C-9'), 56.3 (3'-OCH_3).

5. Discussions

Compound 1 was yielded as a white amorphous powder. The molecular formula was identified as $C_{26}H_{32}O_{12}$ based on the sodium adduct molecular ion peak at *m/z* 559.1767 $[M + Na]^+$ (cacld $C_{26}H_{32}O_{12}Na^+$ 559.1768). The ^{1}H-NMR spectrum of 1 showed the hydrogen resonances at 6.78 (br s, H-2), 7.16 (d, J = 8.0 Hz, H-5'), and 6.95 (d, J = 8.0 Hz, H-6'), together with individual aromatic nucleus at 7.04 (br s, H-2′) and 6.75 (s, H-6). Functional groups observed include propanoic acid protons at 2.88 (J = 7.5 Hz, H-7), 2.59 (J = 7.5 Hz, H-8) both 2H triplet, an oxygenated methine proton at 5.57 (1H, d, J = 6.0 Hz, H-7'), a methine proton at 3.51 ppm (1H, m, H-8), a pair of oxygenated methylene protons at 3.88 (1H, m, H-9a) and 3.78 ppm (1H, m, H-9b), two methoxyl signals at 3.85 and 3.88 (3H, s), in addition to a glucosyl anomeric proton at 4.90 ppm (1H, d, J = 7.0 Hz, H-1″). 26 carbon peaks were identified by combining the ^{13}C NMR and HSQC spectra of 1; these included 12 aromatic carbons and 6 carbons associated with a glucosyl moiety. The NMR data of 1 led to the deduction that it is a dihydrobenzofuran neolignan glycoside. By analysis of key correlations of COSY, HSQC, and HMBC confirmed the planar structure of 1 (Fig. 2). Indeed, the HMBC spectrum showed the correlations from H-2/H-6 to C-7, and from the H-7′/H-8′ to C-1′ and C-9′ (Fig. 2). The two methoxyl groups located at C-3 and C-3′ were confirmed by the HMBC correlations between 3.85 and 3.88 ppm, and 150.9 and 145.3 ppm, respectively. Additionally, the HMBC cross peak from H-1″ (δ_H 4.90) to C-4 (δ_C 147.8) confirmed that the glucopyranosyl unit was connect to the oxygen at C-4, and the coupling constant value (*J*) of the anomeric position (J = 7.0 Hz) deduced its linkage to *β*-glucoside. Additionally, the NOE cross-peak from H-7 to H-9 as well as the J value (6.0 Hz) were used to corroborate the *trans* configuration between H-7 and H-8. Additionally, the chiral signal profile exhibited negative circular dichroism signals at 230 and 280 nm, accompanied by an enhanced Cotton effect at 215 nm, suggesting the stereochemistry to be 7R and 8S. Hence, the substances of 1 was determined to be lycocernuaside A.

Fig.2. Key COSY (bold black strokes) and HMBC (blue arrow) correlations of 1



Using the same evaluation criteria based on 1D and 2D NMR spectroscopic data, compounds 2-4 were identified asdihydrodehydrodiconiferyl alcohol 4'-*β*-D-glucoside, lycocernuaside C, and cedrusin, respectively.

Additionally, the DPPH radical-scavenging abilities of substances were assessed. Notably, compounds 3 and 4 showed potent DPPH scavenging capacity, with ED_{50} data of 8.6 ± 0.2 and 13.7 ± 0.4 µM, respectively. The effects were similar to ascorbic acid (ED_{50} = 23.6 ± 0.8 µM), the positive control. The results deduced that neolignan glycosides from *L. cernua* are responsible for antioxidant activity.

6. Conclusion

In summary, the phytochemical exploration of the ethanol extract from whole plants of *L. cernua* resulted in the isolation of dihydrobenzofuran neolignan derivatives (1–4). Through the analysis of their observed and reported spectroscopic data, their structures were determined to be lycocernuaside A (1), dihydrodehydrodiconiferyl alcohol 4'-*β*-D-glucoside (2), lycocernuaside C (3), and cedrusin (4). Additionally, the DPPH

radical-scavenging abilities of substances were assessed. Notably, compounds 3 and 4 exhibited potent DPPH radical-scavenging effects, with ED_{50} values of 8.6 ± 0.2 and 13.7 ± 0.4 μM, respectively. These effects were comparable to those of the positive control, ascorbic acid (ED_{50} = 23.6 ± 0.8 μM). The findings suggest the potential *in vitro* antioxidant activity of dihydrobenzofuran neolignane derivatives from *L. cernua*. Nevertheless, further investigations, both *in vivo* and *in silico*, are necessary to confirm their therapeutic antioxidant effects.

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CÁC HỢP CHẤT DIHYDROBENZOFURAN NEO-LIGNAN TỪ LOÀI THÔNG ĐẤT VÀ HOẠT TÍNH CHỐNG OXY HÓA CỦA CHÚNG

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Ngày nhận bài: 19/3/2024 Ngày phản biện: 8/4/2024
Ngày tác giả sửa: 8/5/2024 Ngày duyệt đăng: 12/6/2024

DOI: *https://doi.org/10.58902/tcnckhpt.v3i2.130*

Tóm tắt:

Toàn bộ cây của Lycopodiella cernua L. được sử dụng ở Việt Nam và Trung Quốc như một loại dược liệu truyền thống do khả năng kháng viêm và bảo vệ thần kinh của chúng. Trong nghiên cứu hiện tại này, 4 dẫn xuất dihydrobenzofuran neolignan (1–4) đã được phân lập từ chiết xuất ethanol của L. cernua. Qua phân tích dữ liệu phổ hiện và các báo cáo trước đây, cấu trúc của chúng được xác định là lycocernuaside A (1), dihydrodehydrodiconiferyl alcohol 4'-β-D-glucoside (2), lycocernuaside C (3), và cedrusin (4). Ngoài ra, khả năng chống oxy hóa của các chất đã được đánh giá. Đáng chú ý, các hợp chất 3 và 4 đã thể hiện hiệu quả chống oxy hóa mạnh mẽ đối với radical DPPH, với giá trị ED_{50} lần lượt là 8.6 ± 0.2 và 13.7 ± 0.4 μM. Các hoạt tính này tương đương với chất đối chứng dương, axit ascorbic (ED_{50} = 23.6± 0.8 μM). Các kết quả này ngụ ý khả năng hoạt động chống oxy hóa in vitro của các dẫn xuất dihydrobenzofuran neolignan từ L. cernua. Tuy nhiên, cần tiến hành các nghiên cứu tiếp theo, cả in vivo và in silico, để xác nhận hiệu ứng chống oxy hóa điều trị của chúng.

Từ khóa: *Cây thuốc; Dihydrobenzofuran neolignan; Hoạt tính chống oxy hóa; Thông đất Lycopodiella cernua L..*