Investigation of Antioxidant, Antifungal, and Antibiofilm Properties of *Lindera subumbelliflora* (Blume) Kosterm and *Lindera caesia* Reinw. ex Fern.-Vill. from Malaysia

Nur Nabilah Mohd ZAINI[1]
Wan Mohd Nuzul Hakimi Wan SALLEH[1] (✉)
Abubakar Siddiq SALIHU[1,2]
Mohd Hafiz ARZMI[3]

Summary

The genus *Lindera* in the family Lauraceae, is widely distributed in tropical and subtropical areas throughout the world. Its roots and leaves have been used for thousands of years as a traditional Chinese medicine and functional food. This study was carried out to investigate the antioxidant, antifungal, and antibiofilm properties from *Lindera subumbelliflora* (Blume) Kosterm (leaves and roots) and *L. caesia* Reinw. ex Fern.-Vill. (leaves) growing in Malaysia. Antioxidant activity was determined using DPPH assay, antifungal activity by microdilution method for determination of MIC and MFC, whereas antibiofilm was determined using a semi-quantitative static biofilm. The *L. caesia* leaf extract revealed strong activity in DPPH assay with IC_{50} value of 65.6 μg mL^{-1}, while the *L. subumbelliflora* roots extract exhibited the best antifungal activity against *Candidca albicans* ECE1 with MIC and MFC value of 250 μg mL^{-1}. In addition, all *Lindera* extracts showed promising antibiofilm inhibitory activity against different *Candida* strains with biofilm inhibition values ranging from 50.2 to 78.0%. This study suggests that *Lindera* species might be an excellent source of antifungal, antibiofilm, and antioxidant drugs and would be helpful in minimizing the spreading of pathogenic microorganisms or preventing stress-related diseases.

Key words

Lauraceae, *Lindera*, antioxidant, antifungal, biofilm, DPPH, *Candida albicans*

[1] Department of Chemistry, Faculty of Science and Mathematics, Universiti Pendidikan Sultan Idris, 35900 Tanjong Malim, Perak, Malaysia

[2] Department of Pure and Industrial Chemistry, Faculty of Natural and Applied Sciences, Umaru Musa Yar'adua University, Katsina, Nigeria

[3] Department of Fundamental Dental and Medical Sciences, Kuliyyah of Dentistry, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia

✉ Corresponding author: wmnhakimi@fsmt.upsi.edu.my

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Introduction

Lauraceae family comprises approximately 55 genera over 3000 species and is particularly diverse in Southeast Asia, Madagascar, northern South America, and the eastern coast of Brazil. This family holds a prominent position within the Magnoliids and significantly contributes to the diversity of flora in the Neotropics (Salleh et al., 2016a). Plants belonging to the Lauraceae family have high economic importance for traditional uses. *Laurus nobilis* L. has traditionally been employed to address digestive issues (Alejo-Armijo et al., 2017). The bark of *Cinnamomum verum* J.Presl has been utilized in traditional medicine to treat respiratory infections and digestive ailments (Ranasinghe et al., 2013). Additionally, the fruit of *Persea americana* Mill. has found topical applications in treating various skin conditions (Nayak et al., 2008).

The family of Lauraceae consists of approximately 100 species of *Lindera*, which are found in intermittent distribution across tropical, subtropical, and temperate regions of Asia, as well as the Midwest region of the United States (Salleh, 2020). This extensive geographical distribution allows *Lindera* plants to produce diverse secondary metabolites having novel structures. Phytochemical investigations have shown that *Lindera* plants produce sesquiterpenoids, alkaloids, butanolides, lucidones, flavonoids, and phenylpropanoids (Tao et al., 2020). Moreover, *Lindera* plants show various pharmacological and biological properties, their anticancer, antihypertensive, anti-inflammatory, and analgesic properties. Meanwhile, butanolides and lucidones have shown great potential in developing anticancer agents, while aporphine alkaloids have shown great potential in developing antiarthritic and antinociceptive agents (Cao et al., 2016).

Lindera plants are appropriate for manufacturing soaps and lubricants and are used for extracting lauric acid. Many *Lindera* plants are rich in essential oils and are used for producing spices, fragrances, and building timber (Zaini et al., 2023). In China, the leaves of *L. aggregata* (Sims) Kosterm. have been used in traditional Chinese medicine to treat a number of conditions, such as pain, inflammation, and gastrointestinal problems (Lai et al., 2021). The aerial parts of *L. akoensis* have been used in Taiwanese folk therapy for inflammation (Yang et al., 2019). Besides, the bark of *L. erythrocarpa* Makino was used to treat diabetic properties and breast cancer (Haque et al., 2020). The barks of *L. obtusiloba* Blume are used for treating bruises and throat congestion, and the roots of *L. glauca* are used for treating fatigue caused by physical collapse and rheumatoid arthritis. The roots, bark, and twigs of *L. umbellata* have beneficial effects on gastric ulcer, abdominal pain, cholera, and beriberi, and its volatile oil has antispasmodic effects (Tanaka et al. 1985).

Based on these findings, there is a need to investigate other *Lindera* species from other origins to further develop the standardized extract for specific medicinal purposes in the future. Thus, we present the first report on the antioxidant, antifungal, and antibiofilm of two *Lindera* species (*Lindera subumbelliflora* (Blume) Kosterm and *Lindera caesia* Reinw. ex Fern.-Vill.) originated from Malaysia. This study focuses on the analysis of antioxidant, antifungal, and antibiofilm of the leaf and root extracts of *L. subumbelliflera* and the leaf extract of *L. caesia*.

Material and Methods

Plant Materials

The leaves and roots of *L. subumbelliflora* (SB61-22) and the leaves of *L. caesia* (SA13-09) were collected from Fraser Hill, Pahang in January 2023. Both samples were identified by Dr. Shamsul Khamis from Universiti Kebangsaan Malaysia (UKM). The voucher specimens were deposited at the Herbarium of UKM, Faculty of Science and Technology, UKM.

Plant Extraction

The dried powdered leaves (100 g) and roots (100 g) of *L. subumbelliflora* and the leaves (100 g) of *L. caesia* underwent a cold extraction process using methanol as solvent. The selection of plant parts for this study was based on specific criteria. Specifically, the leaves of both species were chosen due to their accessibility and well-documented traditional medicinal uses of leaves from this genus. Additionally, the roots of *L. subumbelliflora* were included in the investigation based on its availability and accessibility. Following extraction, the obtained extracts were filtered, and the solvent was removed under vacuum conditions using a rotary evaporator. These extracts were then preserved by freezing them until they were ready to be used in the experiments. The yield percentage (w/w) of the leaves and roots of *L. subumbelliflora* was 2.52 g and 2.89 g, respectively, while the leaves of *L. caesia* yielded 2.65 g.

Solvents and Chemicals

Analytical grade methanol used for extraction were purchased from Merck (Germany). Antioxidants:1,1-diphenyl-2-picrylhydrazyl (DPPH), ascorbic acid, butylated hydroxytoluene (BHT) were obtained from Sigma-Aldrich (Germany). Antifungal/Antibiofilm: nutrient agar (NA), nutrient broth (NB), sabouraud dextrose agar (SDA), sabouraud dextrose broth (SDB), and chlorhexidine were purchased from Oxoid (Italy). The fungal used in this study was *Candida* spp. from American Type Culture collection (ATCC) strain. The clinical strain was isolated from an oral cancer patient. The strains were kept in glycerol (25%) at -80 °C freezer.

Antioxidant Activity

The free radical scavenging activity was measured by the DPPH method with minor modifications (Salleh et al., 2016b). Briefly, 1 mg DPPH radical was dissolved in 50 mL MeOH and immediately measured at 0 min to obtain A_{blank}. Each methanolic sample of the stock solution was diluted to 1 mg mL^{-1} in MeOH in various concentrations (200, 150, 100, 50, 25 µg mL^{-1}). Ascorbic acid and butylated hydroxytoluene (BHT) were prepared with the same range of concentration and used as reference standards. Then, 75 µL (0.1 µM) DPPH methanolic solution was added to 225 µL of each sample solution and allowed to incubate in the dark for 30 min at room temperature. Then the absorbance at 515 nm was measured with a UV–vis spectrophotometer using ELX-500 UV plate reader (Bio-Tek). The recorded optical densities were used to calculate the percentage of DPPH radical scavenging, which is proportional to the antioxidant power of the sample. The percentage inhibition (I%) of DPPH radicals were calculated as follows:

$$I\% = [\ A_{blank} - A_{sample} / A_{blank}\ ] \times 100$$

where A_{blank} is the absorbance value of the control reaction (containing all reagents except the test extracts) and A_{sample} is the absorbance value of the test extracts/standard. The sample concentration providing 50% inhibition (IC_{50}) was calculated by plotting the inhibition percentages against concentration of the sample.

Antifungal Activity

To grow *Candida* spp, the yeast's stock culture was revived in Yeast Peptone Dextrose (YPD) broth (Difco, USA) and incubated overnight at 37 °C. The yeast was then transferred to YPD agar and incubated aerobically at 37 °C for 24 h. Each of the *Candida* spp were standardized to 10^6 cells/mL equivalent to an absorbance of 0.5 at 620 nm wavelength (OD_{620nm}). The prepared *Candida* spp was used to study the antifungal efficacy of the methanol extract by evaluating the visible growth of the fungus in the YPD broth. Using serial two-fold dilutions of the extract (concentrations from 500 to 7.81 µg mL^{-1}) with adjusted concentration of *Candida* spp (3×10^6 cells mL^{-1}), we determined the Minimum Inhibitory Concentration (MIC) in YPD broth. The negative control contained only inoculated broth and incubated for 24 h at 37 °C while the positive control contained 0.12% chlorhexidine. The MIC endpoint was identified as the lowest extract concentration showing no visible growth. We assessed turbidity visually before and after incubation to confirm MIC values. This experiment included three biological and three technical replicates for accuracy. After determining the MIC of the extract, 100 µL samples from tubes with no visible bacterial growth were plated on agar and incubated for 24 h at 37 °C. When 99.9 % of the microbial population was killed at the lowest concentration of an antimicrobial agent, it was termed as Minimum Bactericidal Concentration (MBC) endpoint. This was done by observing the pre- and post-incubated agar plates for the presence or absence of microorganisms.

Antibiofilm Activity

The antibiofilm was investigated against four *Candida* spp. (*C. albicans* 4901, *C. albicans* ECE1 mutant, *C. lusitanae*, and *C. auris*) on biofilms and activities were determined using a semiquantitative static biofilm assay (Mokhtar et al., 2021). The standardized *Candida* spp (OD_{620nm}) that were prepared were used in this biofilm procedure. To determine the effect of the methanolic extract on the biofilms, 200 µL of RPMI-1640 (conc. 500 µg mL^{-1} of the extract) of *Candida* spp (3×10^4 cells) were inoculated in the same well of a 96-well plate. Wells containing *Candida* spp only served as the negative control. Meanwhile, wells containing *Candida* spp with 0.12% CHX served as the positive control. The suspensions were mixed thoroughly using a vortex mixer for 30 sec. Subsequently, 200 µL of each suspension containing 2×10^5 cells (*Candida* spp.) of the initial inoculum were pipetted into each well of a sterile 96-well plate. Finally, the 96-well plate was incubated for 72 h at 37 °C aerobically, and the medium was replenished aseptically every 24 h. The experiment was performed in three biological replicates and three technical replicates to ensure reproducibility. After incubation, the crystal violet (CV) assay was performed according to the protocol by (Arzmi et al., 2016) to quantify the biofilm biomass. Initially, the wells containing biofilms were washed twice with sterile PBS to remove the non-adherent cells. Later, the biofilms in the wells were fixed by adding 200 µL of methanol and incubating for 15 min at 25 °C. The supernatant was discarded, and the plate was air-dried for 45 min. Later, 200 µL of 0.1 % (w/v) CV solution was added to each well and incubated for 20 min at 25 °C. The plate was washed gently twice using sterile distilled water to remove the unbound stain. Subsequently, the biofilms were detained with 200 µL of 33% (v/v) acetic acid for 5 min at room temperature. Finally, 100 µL of the acetic acid solution was transferred to a new sterile 96-well plate, and the absorbance was measured at the optical density (OD) 620 nm wavelength (OD_{620nm}) using a microtiter plate reader (Tecan NanoQuant Infinite M200). The mean absorbance values were used to measure the inhibition of biofilm formation as follows:

[mean OD_{620nm} of positive control – mean OD_{620nm} of experimental /mean OD_{620nm} of positive control) × 100]

Statistical Analysis

All data were statistically analysed using SPSS version 27.0. Independent t-test was conducted to compare between extracts-treated and untreated biofilms. The analyses were performed in triplicate; the results were expressed as a mean ± standard deviation. Data were considered significant when $P < 0.05$.

Results and Discussion

The DPPH radical scavenging was chosen to gain understanding of the true antioxidant potential of the *Lindera* extracts. The antioxidant activity of the two *Lindera* species is summarised in Table 1. Fig. 1 illustrates a significant ($P < 0.05$) decrease in the concentration of DPPH radicals. The antioxidant activity, measured by the DPPH assay, showed inhibition percentages ranging from 24.8% to 88.3%, with IC_{50} values between 57.9 µg mL^{-1} and 80.3 µg mL^{-1} for the different extracts. The highest activity was found in the leaf extract of *L. caesia* with IC_{50} value of 57.9 µg mL^{-1}.

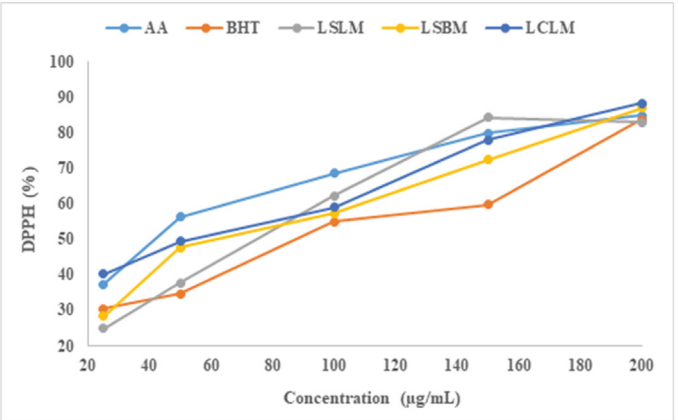

Figure 1. Percentage inhibition of DPPH radical scavenging of *Lindera* extract

Note: AA - Ascorbic acid; BHT - butylated hydroxytoluene extract; LSLM. *subumbelliflora* leaves extract; LSRM - *L. subumbelliflora* roots extract; LCLM. caesia leaves extract

Table 1. Antioxidant activity of *Lindera* extracts

Concentration (μg mL^{-1})	DPPH Inhibition (%)*				
	LSLM	LSRM	LCLM	AA	BHT
200	83.0 ± 0.01	86.9 ± 0.01	88.3 ± 0.01	83.7 ± 0.03	84.9 ± 0.54
150	84.7 ± 0.02	72.4 ± 0.01	78.0 ± 0.02	59.6 ± 0.01	79.9 ± 0.09
100	62.5 ± 0.02	57.1 ± 0.02	59.0 ± 0.02	54.9 ± 0.01	68.5 ± 0.24
50	37.8 ± 0.01	47.6 ± 0.03	49.4 ± 0.01	34.7 ± 0.13	56.3 ± 0.66
25	24.8 ± 0.01	28.3 ± 0.02	40.2 ± 0.02	30.4 ± 0.25	37.3 ± 0.22
IC_{50} value (μg/mL)	80.3	77.4	57.9	44.5	35.8

Note: *Data represent mean ± SD of three independent experiments; AA - Ascorbic acid; BHT - butylated hydroxytoluene extract; LSLM - *L. subumbelliflora* leaves extract; LSRM - *L. subumbelliflora* roots extract; LCLM - *L. caesia* leaves extract

However, these values were lower than the positive control. This indicates that while the extract is effective, it is not as potent as standard antioxidants, ascorbic acid. In DPPH assays, the test intends to measure the hydrogen atom or electron donor capacity of the extract to scavenge free radicals in the solution. The degree of discoloration indicates the scavenging potential of the antioxidant compounds present in the sample, where the higher the percentage of inhibition, the stronger the antioxidant activity (Salleh et al., 2015). Phenolic compounds are known as plant antioxidant agents due to their ability as reducing agents, hydrogen donors, and singlet oxygen scavengers. Phenolic compounds such as flavonoids are particularly effective due to their chemical structure, which allows them to act as reducing agents and singlet oxygen scavengers. The plant extracts of these species contained flavonoids as reported previously from *L. aggregata* (Zhang et al., 2023), *L. umbellata* (Kusumoto et al., 2022), *L. glauca* (Siebold & Zucc.) Blume (Huh et al., 2014), *L. oxyphylla* (Nees) Hook.f. (Hosseinzadeh et al., 2013), and *L. erythrocarpa* (Liu et al., 1976). The likely presence of similar compounds in *L. caesia* and *L. subumbelliflora* contributes to their antioxidant activity, as indicated by the DPPH assay.

Moreover, the evaluations of antifungal potential were determined and the results are shown in Table 2. The MIC is the lowest concentration of an antifungal agent needed to prevent the growth of a fungus, while the MFC is the lowest concentration required to kill the fungus (Balouiri et al., 2016). In antifungal assays, the minimum inhibitory concentrations (MIC) ranged from 250 μg mL^{-1} to >1000 μg mL^{-1}, and the minimum fungicidal concentrations (MFC) were uniformly >1000 μg mL^{-1} except for the root extract of *L. subumbelliflora*. The root extract of *L. subumbelliflora* showed the most active compared to other extracts, which gave MIC value 250 μg mL^{-1} against *C. albicans* ECE1 strain. The variation in susceptibility among strains could be due to genetic differences, fungal cell wall structure, or the presence of efflux mechanisms that affect the penetration and action of the extracts' active compounds (Vaou et al., 2021). Several reported compounds such as Lindenane sesquiterpenoid monomers and oligomers, known for their antifungal properties, have been reported in various *Lindera* species (Chen et al., 2023). The presence of these compounds in *L. subumbelliflora* could explain the observed antifungal activity. Future studies focusing on the phytochemical characterization of the extracts are necessary to identify and confirm the specific compounds responsible for these effects.

Furthermore, the effect of *Lindera* extracts to prevent or disrupt biofilm formation was also investigated, with the results presented in Table 3. The antibiofilm is the ability to prevent or disrupt the formation of biofilms or to eradicate established biofilms. In this study, the antibiofilm activity demonstrated inhibition percentages ranging from 44.8% to 78.0% at a concentration of 500 μg mL^{-1}.

Table 2. Antifungal activity of *Lindera* extracts

Extracts/ Microbes	C.A 4901		C.A ECE1		C.L		C.A	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
LSLM	1000	>1000	1000	>1000	1000	>1000	1000	>1000
LSRM	1000	>1000	250	250	1000	>1000	1000	>1000
LCLM	1000	>1000	1000	>1000	500	500	1000	>1000

Note: C.A 4901 - *Candida albicans* 4901; C.A ECE1 - *Candida albicans* ECE1; C.L - *Candida lusitanae*; C.A - *Candida auris*; LSLM - *L. subumbelliflora* leaves extract; LSRM - *L. subumbelliflora* roots extract; LCLM - *L. caesia* leaves extract

Table 3. Biofilm activity of *Lindera* extracts at concentration of 500 µg mL^{-1}

Extracts/ Microbes	Percentage inhibition (%)			
	C.A 4901	C.A ECE1	C.L	C.A
LSLM	44.8 ± 1.81	48.5 ± 1.52	66.6 ± 2.05	62.2 ± 2.15
LSRM	47.6 ± 2.07	51.4 ± 1.29	69.5 ± 1.03	68.1 ± 2.08
LCLM	50.2 ± 1.36	58.7 ± 0.61	78.0 ± 2.75	66.3 ± 1.82
Chlorhexidine	122.7 ± 0.31	132.8 ± 1.11	167.0 ± 0.97	158.1 ± 1.91

Note: C.A 4901 - *Candida albicans* 4901; C.A ECE1 - *Candida albicans* ECE1; C.L - *Candida lusitanae*; C.A - *Candida auris*; LSLM - *L. subumbelliflora* leaves extract; LSRM - *L. subumbelliflora* roots extract; LCLM - *L. caesia* leaves extract

The leaf extract of *L. caesia* revealed the highest antibiofilm activity against all tested strains. The extract gave an inhibition of 78.0% and 66.3% against *C. lusitanae* and *C. albicans*, respectively.

Candida spp. biofilms are complex microbial communities that have been associated with increased resistance to clinically available antifungal drugs. The ability of *Candida* species is to infect diverse hosts as a result of a wide range of virulent factors such as their morphological transition between yeast and hyphal forms, expression of adhesins and invasins on cell surfaces, thigmotropism, phenotypic switching, secretion of hydrolytic enzymes and formation of biofilms. The biofilms formed are intrinsically resistant to antifungal drugs at therapeutic concentrations effective against non-adhering cells, thus needing higher concentrations resulting in a plethora of adverse effects such as hepatotoxicity and nephrotoxicity (Harley et al., 2022).

Conclusion

In summary, the present paper reports for the first time a preliminary study on *L. subumbelliflora* and *L. caesia* extracts of Malaysian origin for antioxidant, antifungal and antibiofilm properties. These results highlight the potential of *L. caesia* extract to have the highest antioxidant (IC_{50} value 57.9 µg mL^{-1}) and antibiofilm inhibitory activities against *C. lusitaniae* (78.0%). Meanwhile, the root extract of *L. subumbelliflora* revealed the strongest antifungal activity against *C. albicans* ECE1 (MIC value 250 µg mL^{-1}). These results suggest that both *Lindera* species possess bioactive compounds with potential applications in medicine. Further studies, including phytochemical characterization and *in vivo* testing, are necessary to confirm these activities and explore their practical applications in medicine and other fields.

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CRediT Authorship Contribution Statement

Nur Nabilah Mohd Zaini: Conceptualization, investigation, performed the experiments and original draft preparation. **Wan Mohd Nuzul Hakimi Wan Salleh:** Funding, supervision and manuscript editing. **Abubakar Siddiq Salihu:** Field collection and data analysis of antioxidant. **Mohd Hafiz Arzmi:** Data analysis of antifungal and antibiofilm.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Alejo-Armijo A., Altarejos J., Salido S. (2017). Phytochemical and Biological Activities of Laurel Tree (*Laurus nobilis*). Nat Prod Commun. 12 (5): 1-5. doi: 10.1177/1934578X1701200519

Arzmi M. H., Alnuaimi A. D., Dashper S., Cirillo N., Reynolds E. C., McCullough M. (2016). Polymicrobial Biofilm Formation by *Candida albicans*, *Actinomyces naeslundii*, and *Streptococcus mutans* is *Candida albicans* Strain and Medium Dependent. Med Mycol. 54 (1): 856-864. doi: 10.1093/mmy/myw042

Balouiri M., Sadiki M., Ibnsouda S. K. (2016). Methods for *in vitro* Evaluating Antimicrobial Activity: A Review. J Pharm Anal. 6 (2): 71-79. doi: 10.1016/j.jpha.2015.11.005

Cao Y., Xuan B., Peng B., Li C., Chai X., Tu P. (2016). The Genus *Lindera*: A Source of Structurally Diverse Molecules Having Pharmacological Significance. Phytochem Rev. 15: 869-906. doi: 10.1007/s11101-015-9432-2

Chen F., He M., Xu L., Liu Y., Yang B., Luo Y. (2023). Lindenane Sesquiterpenoid Monomers and Oligomers: Chemistry and Pharmacological Activities. Phytochemistry 215: 113866. doi: 10.1016/j.phytochem.2023.113866

Haque M. E., Azam S., Balakrishnan R., Akther M., Kim I. S. (2020). Therapeutic Potential of *Lindera obtusiloba*: Focus on Antioxidative and Pharmacological Properties. Plants 9 (12): 1765. doi: 10.3390/plants9121765

Harley B. K., Quagraine A. M., Neglo D., Aggrey M. O., Orman E., Mireku-Gyimah N. A., Amengor C. D., Jato J., Saaka Y., Fleischer T. C. (2022). Metabolite Profiling, Antifungal, Biofilm Formation Prevention and Disruption of Mature Biofilm Activities of *Erythrina senegalensis* Stem Bark Extract against *Candida albicans* and *Candida glabrata*. PLoS One 17 (11): e0278096. doi: 10.1371/journal.pone.0278096

Hosseinzadeh M., Hadi A. H., Mohamad J., Khalilzadeh M. A., Cheahd S. C., Fadaeinasab M. (2013). Flavonoids and Linderone from *Lindera oxyphylla* and Their Bioactivities. Comb Chem High Throughput Screen. 16 (2): 160-166. doi: 10.2174/1386207311316020010

Huh G. W., Park J. H., Kang J. H., Jeong T. S., Kang H. C., Baek N. I. (2014). Flavonoids from *Lindera glauca* Blume as Low-Density Lipoprotein Oxidation Inhibitors. Nat Prod Res. 28 (11): 831-834. doi: 10.1080/14786419.2013.879583

Kusumoto N., Morikawa T., Hashida K., Matsui N., Ohira T. (2022). The Variability of Terpenoids and Flavonoids in Native *Lindera umbellata* from the Same Region. J Wood Sci. 68 (1): 58. doi: 10.1186/s10086-022-02066-x

Lai H., Yang Z., Li F., Pan W., Xu C., Zhang L., Zhang S., Zhang L., Huang M. (2021). Roots Extract of *Lindera aggregata* (Sims) Kostem Modulates the Th17/Treg Balance to Attenuate DSS-Induced Colitis in Mice by IL-6/STAT3 Signaling Pathway. Front Pharmacol. 12: 615506. doi: 10.3389/fphar.2021.615506

Liu S., Takai M., Ogihara Y. (1976). Studies on the Constituents of *Lindera erythrocarpa* Makino. II. Mass Spectrometry of the Flavonoids from the Fruits. Yakugaku Zasshi 96 (4): 511-518. doi: 10.1248/yakushi1947.96.4_511

Mokhtar M., Rismayuddin N. A. R., Yassim A. M. S., Ahmad H., Wahab R. A., Dashper S. G., Arzmi M. H. (2021). *Streptococcus salivarius* K12 Inhibits *Candida albicans* Aggregation, Biofilm Formation and Dimorphism. Biofouling 37 (7): 767-776. doi: 10.1080/08927014.2021.1967334

Nayak B. S., Raju S. S., Chalapathi R. A. V. (2008). Wound Healing Activity of *Persea americana* (Avocado) Fruit: A Preclinical Study on Rats. J Wound Care 17 (3): 123-126. doi: 10.12968/jowc.2008.17.3.28670

Ranasinghe P., Pigera S., Premakumara G. A., Galappaththy P., Constantine G. R., Katulanda P. (2013). Medicinal Properties of 'True' Cinnamon (*Cinnamomum zeylanicum*): A Systematic Review. BMC Complement Altern Med. 13: 275. doi: 10.1186/1472-6882-13-275

Salleh W. M. N. H. W., Ahmad F., Khong H. Y., Zulkifli R. M., Chen J. J., Nahar L., Wansi J. D., Sarker S. D. (2016b). Beilschglabrines A and B: Two New Bioactive Phenanthrene Alkaloids from the Stem Bark of *Beilschmiedia glabra*. Phytochem Lett. 16: 192-196. doi: 10.1016/j.phytol.2016.04.013

Salleh W. M. N. H. W., Ahmad F., Khong H. Y., Zulkifli R. M. (2016a). Essential Oil Composition of Malaysian *Lauraceae*: A Mini Review. Pharm Sci. 22 (1): 60-67. doi: 10.15171/PS.2016.11

Salleh W. M. N. H. W., Ahmad F., Khong H. Y. (2015). Evaluation of Antioxidant, Anticholinesterase and Antityrosinase Activities of Five *Cinnamomum* Species. Dhaka Univ J Pharm Sci. 14 (2): 125-132. doi: 10.3329/dujps.v14i2.28500

Salleh W. M. N. H. W. (2020). *Lindera aggregata* (Sims) Kosterm: Review on Phytochemistry and Biological Activities. Latin Amer Carib Bull Med Arom Pl. 19 (6): 527-541. doi: 10.37360/blacpma.20.19.6.37

Tanaka H., Ichino K., Ito K. (1985). A Novel Flavanone, Linderatone, from *Lindera umbellata*. Chem Pharm Bull. 33 (6): 2602-2604. doi: 10.1248/cpb.33.2602

Tao Y., Deng Y., Wang P. (2024). Traditional Uses, Phytochemistry, Pharmacology, Processing Methods and Quality Control of *Lindera aggregata* (Sims) Kosterm: A Critical Review. J Ethnopharmacol. 318: 116954. doi: 10.1016/j.jep.2023.116954

Vaou N., Stavropoulou E., Voidarou C., Tsigalou C., Bezirtzoglou E. (2021). Towards Advances in Medicinal Plant Antimicrobial Activity: A Review Study on Challenges and Future perspectives. Microorganisms 9 (10): 2041. doi: 10.3390/microorganisms9102041

Yang C. P., Shie P. H., Huang G. J., Chien S. C., Kuo Y. H. (2019). New Anti-Inflammatory Flavonol Glycosides from *Lindera akoensis* Hayata. Molecules 24 (3): 563. doi: 10.3390/molecules24030563

Zaini N. N. M., Salleh W. M. N. H. W., Arzmi M. H., Salihu A. S., Ghani N. A. (2023). Chemical Composition of Essential Oil from *Lindera subumbelliflora* Kosterm and Its Effect on the Susceptibility and Biofilm Activities of *Candida albicans* and *Streptococcus mutans*. Nat Prod Res. 1-6. doi: 10.1080/14786419.2023.2278164

Zhang Y. J., Yang Y. X., Liu J. H., Sun C. L. (2023). Simultaneous Determination of Six Flavonoids in *Lindera aggregata* Leaf by UPLC-MS/MS. Tianran Chanwu Yanjiu Yu Kaifa 35 (5): 798-806. doi: 10.1016/j.jchromb.2014.11.021

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