https://doi.org/10.48048/tis.2024.7339

# Effects of Solvent System and Storage Condition on Chemical Stability of 5α-Reductase Inhibitor Compounds in *Tectona grandis* L.f. Leaf Extracts

**Kamonlak Insumrong[1], Neti Waranuch[2,3], Kornkanok Ingkaninan[4], Nutchaninad Tanuphol[4], Wudtichai Wisuitiprot[5], Eakkaluk Wongwad[6], Ngamrayu Ngamdokmai[7] and Nungruthai Suphrom[1,8,*]**

*[1]Department of Chemistry, Faculty of Science, Naresuan University, Phitsanulok 65000, Thailand*
*[2]Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, and Center of Excellence for Innovation in Chemistry, Naresuan University, Phitsanulok 65000, Thailand*
*[3]Cosmetics and Natural Products Research Center, Faculty of Pharmaceutical Sciences, Naresuan University, Phitsanulok 65000, Thailand*
*[4]Centre of Excellence in Cannabis Research, Department of Pharmaceutical Chemistry and Pharmacognosy, Faculty of Pharmaceutical Sciences and Center of Excellence for Innovation in Chemistry, Naresuan University, Phitsanulok 65000, Thailand*
*[5]Department of Thai Traditional Medicine, Sirindhorn College of Public Health, Phitsanulok 65130, Thailand*
*[6]Department of Cosmetic Sciences, School of Pharmaceutical Sciences, University of Phayao, Phayao 56000, Thailand*
*[7]Center of Excellence in Marijuana, Hemp, and Kratom, Department of Applied Thai Traditional Medicine, School of Medicine, Walailak University, Nakhon Si Thammarat 80160, Thailand*
*[8]Center of Excellence in Biomaterials, Department of Chemistry, Faculty of Science and Center of Excellence for Innovation in Chemistry, Naresuan University, Phitsanulok 65000, Thailand*

**([*]Corresponding author's e-mail: suphrom.n1@gmail.com)**

*Received: 24 July 2023, Revised: 28 August 2023, Accepted: 6 September 2023, Published: 1 February 2024*

**Abstract**

*Tectona grandis* has been reported for its composition of two 5α-reductase inhibitors, specifically (+)−eperua-8,13-dien-15-oic acid (**1**) and (+)−eperua-7,13-dien-15-oic acid (**2**). These compounds exhibit potential as markers, enabling the standardization of leaf extracts during pre-formulation and formulation development. This study examined the effects of solvent system, pH, temperature and light on the stability of compounds **1** and **2** in the ethanolic extract and the ethanolic extract in PG with PEG-40 as a solubilizer. The remaining amount of the compounds at all test conditions was analyzed using HPLC. Compounds **1** and **2** exhibited greater stability in acidic solutions compared to neutral or basic environments. Their degradations were susceptible to light, particularly compound **1** of the ethanolic extract in PG. Both compounds in the solution form of the extract degraded rapidly at high temperature, whereas the present of PG minimized their degradation when the light was protected. According to the Q10 method, the calculated shelf-life of the extracts was 1.48 years. The extracts should be stored or prepared as a non-aqueous form or otherwise in a slightly acidic solution with appropriate light protection measures. The pre-formulation information obtained from this study holds significant value in informing the design and development of forthcoming anti-hair loss medications.

**Keywords:** *Tectona grandis*, 5α-Reductase inhibitor, Hair loss, Stability, Degradation, Shelf-life

## Introduction

*Tectona grandis* L.f. (also known as *Jatus grandis* (L.f.) Kuntze), which is native to South and South-East Asia, is a high-value timber plant of the Lamiaceae family, popularly known as teak. Various parts of *T. grandis* have been traditionally used for treating fever, cancer, bronchitis, inflammation, biliousness, skin diseases, stomatitis and urinary retention [1,2]. Seeds have been advised as a hair growth stimulator in traditional Indian medicine [1]. The pharmacological effects of *T. grandis*, including antioxidant, antimicrobial, antiplasmodial, anti-inflammatory, hypoglycemic, cytotoxic, antipyretic, antibacterial, hair growth and wound healing effects, have been extensively studied [3-11]. The hexane and ethyl acetate

extracts of *T. grandis* leaf were reported to exhibit a potent 5α-reductase inhibitory activity. Fachrunniza *et al*. [12] also described their anti-testosterone properties and anti-inflammatory via the suppression of interleukin 1 beta (IL-1β) secretion. These findings suggest that the *T. grandis* leaf extract might be a useful active ingredient in pharmaceutical products to treat hair loss.

Our group recently identified 2 diterpenes from the leaves of *T. grandis*: (+)–eperua-8,13-dien-15-oic acid (**1**) and (+)–eperua-7,13-dien-15-oic acid (**2**) (**Figure 1**). They potentially inhibited 5α-reductase, which converts testosterone to dihydrotestosterone, with $IC_{50}$ values about 14 μM, similar to the inhibitory activity of curcumin, a natural 5α-reductase inhibitor used as a positive control. The level of two 5α-reductase inhibitors (**1** and **2**) in *T. grandis* leaf extracts was quantified using high-performance liquid chromatography (HPLC). The *T. grandis* leaf extract, extracted with 95 % ethanol, yielded a higher amount of **1** and **2** than was found in the hexane extract, indicating that ethanol is a suitable solvent for extraction [13].

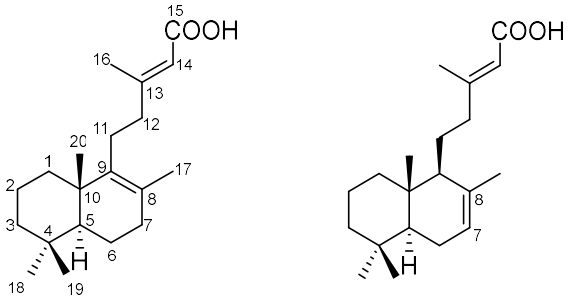


**Figure 1** Chemical structures of two 5α-reductase inhibitors (**1** and **2**) in *T. grandis* leaf extract.

In pre-formulation and formulation steps, crude extracts are usually prepared or dissolved with various carrier solvents. Propylene glycol (PG) and polyethylene glycol (PEG) are among the most pharmaceutical excipients widely used as solvents and solubilizers in formulations. These materials can absorb water and maintain moisture in many product formulae [14-16]. The crude *T. grandis* ethanolic extract prepared in PG solvent containing PEG-40 as a solubilizer is therefore one of the samples targeted for pre-formulation studies in the current investigation. *T. grandis* leaf extract has potential applications in pharmaceuticals and health products for the treatment of hair loss, so the effect of solvent and its chemical stability is essential. The effect of solvent on stability of these two 5α-reductase inhibitors, **1** and **2**, present in *T. grandis* extract has not yet been published in the literature. Therefore, the purpose of this work was to assess the effect of PG and PEG-40 on stability of **1** and **2** in *T. grandis* leaf ethanolic extract. We specifically examined their chemical stability under various pH, temperature and light conditions. The data from this pre-formulation study will be useful for future product design and development.

## Materials and methods

### Chemicals

HPLC grade of acetonitrile and methanol were purchased from RCI Labscan Ltd (Bangkok, Thailand). Formic acid was from KemAus (Cherrybrook, New South Wales, Australia). Ethanol (95 %) was from CHEMIPAN (Bangkok, Thailand). Polyethylene glycol-40 (PEG-40) hydrogenated castor oil was bought from Phitsanuchemicals (Phitsanulok, Thailand). PG was sourced from Ajax Finechem (New South Wales, Australia). All reagents were of analytical grade. Two 5α-reductase inhibitors (**1** and **2**) were used as the reference standards. They were isolated from *T. grandis* leaf extract and their structures were elucidated using NMR, MS and IR spectroscopic data as previously reported [13]. The purity of these 2 compounds was greater than about 99 % as measured by HPLC.

### Plant material and preparation of *T. grandis* extracts

Fresh mature *T. grandis* leaves were collected in September 2019 from Ban Na District, Nakhon Nayok Province, Thailand. The voucher specimen (collection number 05721) is kept at the Department of Biology, Faculty of Science, Naresuan University, Phitsanulok, Thailand. The leaves were cleaned and chopped which were then dried for 3 days at 55 °C. After drying, the material was pulverized and sieved

through a 60-mesh sieve. A crude ethanolic extract and a crude ethanolic extract in PG were prepared. Firstly, the leaf powder (292 g) was macerated 3 times with 95 % ethanol at room temperature in the ratio of 1:4 w/v for at least 5 days each time. The filtrates were combined and evaporated at low pressure to afford a viscous, deep-green crude ethanolic extract (32.90 g, 11.27 % yield). Secondly, a crude ethanolic extract was solubilized with PEG-40 hydrogenated castor oil at a 1:3 w/w ratio, followed by PG at a 1:4 w/w ratio to give a dark brown liquid of ethanolic extract in PG. The extracts were frozen at −20 °C until used.

**Stability studies**

***Effect of pH***

The optimal pH at which the stability of compounds **1** and **2** in the *T. grandis* extract is at a maximum was determined through acid-base degradation studies. Four different pH levels were tested: 2.0, 5.5, 7.4 and 9.0. The buffer solution systems were prepared using phosphate buffer solutions. One g of crude ethanolic extract was mixed with 2.5 mL PEG-40 before adding to the buffer solution to make a final volume of 100 mL. Then 1 mL solution was transferred into a glass vial. The vials were protected from light and stored at room temperature (25 °C). These samples were collected on days 0, 3, 5, 7, 15 and 30.

***Effect of temperature***

The degradation of compounds **1** and **2** in ethanolic extract and ethanolic extract in PG was assessed at various temperatures, encompassing 50, 60, 70 and 80 °C, over a period of 6 months. Glass vials containing 10 mg of the extracts were employed for the evaluation. Additionally, diluted solutions of both extracts were subjected to test. The diluted solutions were prepared by combining the extracts at a concentration of 10 mg/mL with a mixture of PEG-40 and buffer solution pH 5.5 (2.5:97.5 v/v). All samples were shielded from light during the storage period. At predetermined times (0, 30, 60, 90, 120, 150 and 180 days), the samples were examined and analyzed.

***Effect of light***

The effect of light on the degradation of compounds **1** and **2** in the extracts at various prepared forms was also investigated. The samples were stored according to ICH guidelines for photostability testing [17] by placing in a xenon test chamber (model Q-SUN XE-1-BC, USA) for 13.5 h with the following parameters: 420 nm wavelength at 1.10 W/m$^2$, UV irradiance at 49.7 W/m$^2$, the illuminance at 89.5 Klx, and the visible light dose at 1.21 million lux-h. All samples were conducted in triplicate and the remaining contents of **1** and **2** were analyzed.

**Prediction of shelf-life by the Q10 method**

A Q10 method is a technique for predicting product shelf life. The ratio of time to equal harm at 2 temperatures is assumed to increase at a constant rate for a 10 °C rise in temperature [18,19]. The shelf-life of **1** and **2** in ethanolic extract and crude ethanolic extract in PG at 30 °C (Zone IV mean kinetic temperature) was estimated using the following equation:

$$t_{90}(\mathrm{T2}) = \frac{t_{90}\,(\mathrm{T1})}{\mathrm{Q}^{(\Delta \mathrm{T}/10)}} \quad (1)$$

where $t_{90}$ (T2) is the predicted shelf-life at 30 °C and $t_{90}$ (T1) is the time at a tested temperature (50 °C) at which the active compounds **1** and **2** remained 90 % or higher. The Q value is set at 3 as the activation energy of many drugs is in the range of 18 - 20 kcal/mol. The △T is the temperature difference between T2 and T1 in degrees Celsius (°C).

**Quantitative analysis of the active compounds remaining in extracts**

The remaining of compounds **1** and **2** in *T. grandis* extracts were studied quantitively using HPLC-UV (Agilent Technology, model 1260 infinity with fraction collector, Santa Clara, CA, USA) connected with a C18(2) column (150×4.6 mm$^2$, 5 µm particle size, USA). The HPLC determination was carried out following the validated HPLC method previously described [13]. The isocratic elution system was used, with a flow rate of 0.8 mL/min of 85:15 (v/v) acetonitrile: 0.1 % (v/v) formic acid in purified water. The 20 µL injection volume and 220 nm UV detection wavelength were established. The linearity of **1** and **2** was determined at concentrations ranging from 1.56 - 200 µg/mL by correlation coefficient ($r^2$) values of 0.9997 for **1** and 0.9995 for **2**. The retention time for **1** was 14.52 min and 13.15 min for **2**.

**Identification of temperature-degradation products**

To identify the temperature-degradation products of **1** and **2**, the mixtures of **1** and **2** (6.3 mg) were kept at 80 °C for 14 days. The test samples were characterized at day 0 and day 14 (after the test) using thin-layer chromatography (TLC) and liquid chromatography-mass spectrometry (LC-MS). For TLC analysis, 2.0 µL of a 20 mg/mL sample (in methanol) was applied to a TLC silica gel 60 F254 plate. The plate was developed in a mixture of hexane and ethyl acetate (7:3 v/v), and the results were then monitored under UV light at 254 nm. For LC-MS analysis, an ESI-Q-TOF-MS (Agilent 1260 Infinity Series) was used, and analytical settings were set to negative mode with a mass range of 50 - 500 amu. The chromatographic separation was conducted with an isocratic mobile phase system containing acetonitrile and purified water (85:15 v/v), both of which contained 0.1 % (v/v) formic acid for ionization enhancement. The stationary phase, flow rate and injection volume were carried out under the same conditions as indicated in the section on quantitative analysis of the active compounds remaining in extracts. TLC fingerprints and LC-MS profiles revealed polar degradation compounds of mixtures **1** and **2** after 14 days of storage at 80 °C. The sample (6.3 mg) was fractionated over a silica gel column with a gradient of hexane and ethyl acetate as the eluent to give 4 sub-fractions (A-D). The major polar spot was observed at $R_f$ = 0.43 for fraction C, which was then preliminarily identified using the LC-MS technique under the described analysis conditions.

**Statistical analysis**

The results of at least 3 experiments were presented as the mean ± standard deviation (SD). Statistical comparisons were evaluated using one-way analysis of variance (ANOVA) followed by Duncan's test. In all cases, $p < 0.05$ was considered statistically significant.

## Results and discussion

**Effect of pH**

The ethanolic extract was dissolved in various pH buffer solutions (pH 2.0, 5.5, 7.4 and 9.0) and kept at 25 ± 2 °C. After predetermined incubation periods, the remaining **1** and **2** contents were measured by HPLC (**Figure 2**). Similar trends of degradation were observed for both **1** and **2**. Compounds **1** and **2** were stable in acidic solutions (pH 2.0 - 5.5) for up to 30 days, while in neutral to basic environments (pH 7.4 - 9.0), they showed a slight but statistically significant degradation after 7 days. This finding suggests that the degradation of **1** and **2** in basic solutions was possibly deprotonated at the carboxylic acid position to produce the carboxylate anion [20]. However, the residual contents of **1** and **2** remained above 90 % at pH 2.0 - 9.0 for at least 30 days. As topical drug products are often designed with a pH range of 4 to 6, [21] a pH value of 5.5 was employed in subsequent testing.

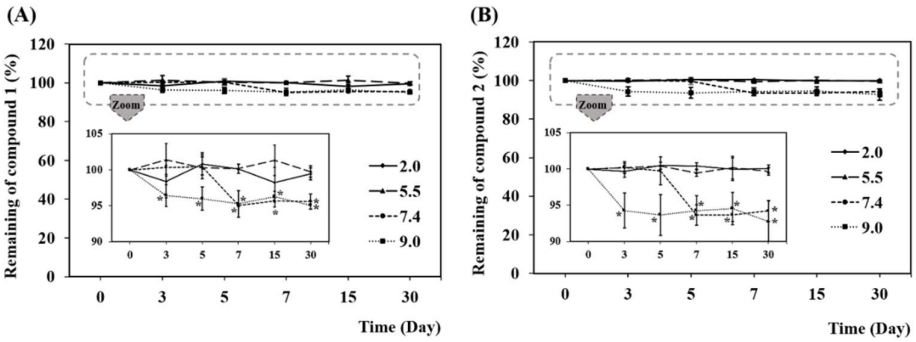


**Figure 2** The effect of various pH conditions (pH 2.0, 5.5, 7.4 and 9.0) on the stability of (A) compound **1** and (B) compound **2** in buffered solution of *T. grandis* ethanolic extract analyzed by HPLC (*$p < 0.05$ against data of day 0).

**Effect of temperature**

The ethanolic extract and ethanolic extract in PG were stored for up to 180 days variously at 50, 60, 70 and 80 °C. The extracts in diluted solution forms (at pH 5.5) were also tested. The degradations of **1** and **2** are depicted in **Figure 3** (for **1**) and **Figure 4** (for **2**). After being stored for 30 days at 50 and 60 °C, the remaining contents of **1** and **2** in ethanolic extract and ethanolic extract in PG were slightly decreased. However, after 180 days of storage, the remaining contents of **1** and **2** in extracts were still present at greater

than 80 %. At the higher temperatures (70 and 80 °C), the difference in degradation profiles of the 2 markers in the extract of different solvents was obvious. At 80 °C, it was clear that **1** in the buffered solution (pH 5.5) of the ethanolic extract degraded most rapidly, with significant degradation as early as 90 days, and was completely degraded after 120 days (**Figure 3**(**C**)). Similarly, after 90 days, there were statistically significant differences in the same sample kept at 70 °C, and after 180 days there was a complete loss (**Figure 3**(**C**)). On the other hand, the degradation was delayed when PG was present in the extract and kept at 70 and 80 °C (**Figure 3**(**D**)). Additionally, **1** in the ethanolic extract as the prepared extract form was sensitive to temperature, especially at 80 °C, which also showed significant degradation after 60 days of storage (**Figure 3**(**A**)), whereas it was more stable in PG, with a remaining of 86.33 ± 0.76 % at day 60 (**Figure 3**(**B**)).

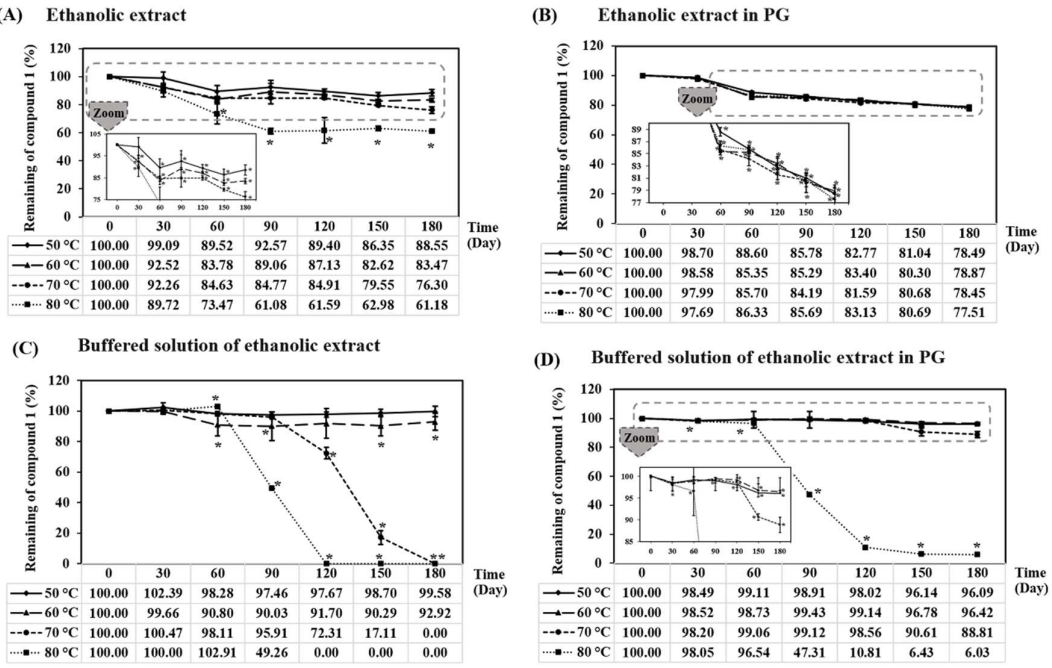


**Figure 3** The effect of temperature on the stability of **1** in (A) ethanolic extract (B) ethanolic extract in PG (C) buffered solution (pH 5.5) of ethanolic extract and (D) buffered solution (pH 5.5) of ethanolic extract in PG. ($^{*}p < 0.05$ against data of day 0).

The content of **2** in the ethanolic extract significantly decreased after 30 days when stored at 80 °C (**Figure 4**(**A**)). Unlike the remaining content of **2** in the ethanolic extract in PG stored under the same conditions, it was stable for at least 180 days (**Figure 4**(**B**)). Likewise, the degradation of **2** in the buffered solution of ethanolic extract was highly at 80 °C after only 30 days and it was completely degraded after 90 days (**Figure 4**(**C**)). Furthermore, compound **2** was found to be unstable in the buffered solution of ethanolic extract stored at 70 °C. After 90 days in this condition, **2** began to degrade significantly. After 180 days, it was completely degraded (**Figure 4**(**C**)), similar to what we observed in **1** (**Figure 3**(**C**)). Over 120 days at 70 °C, the content of **2** in the buffered solution of ethanolic extract in PG was stable, with more than 80 % remaining (**Figure 4**(**D**)). Specifically, **1** was more stable at high temperatures than **2**. This may be associated with the number of substituents connected to the double bonds at $C_8$ - $C_9$ (for **1**) and $C_7$ - $C_8$ (for **2**). In general, a higher level of substituted alkene is more stable than a lower level of substituted alkene due to hyperconjugation and bond strength effects [22]. This may explain the difference in the stability of the **2** compounds. As a result, a tetrasubstituted alkene of **1** has more stability than a trisubstituted alkene of **2**.

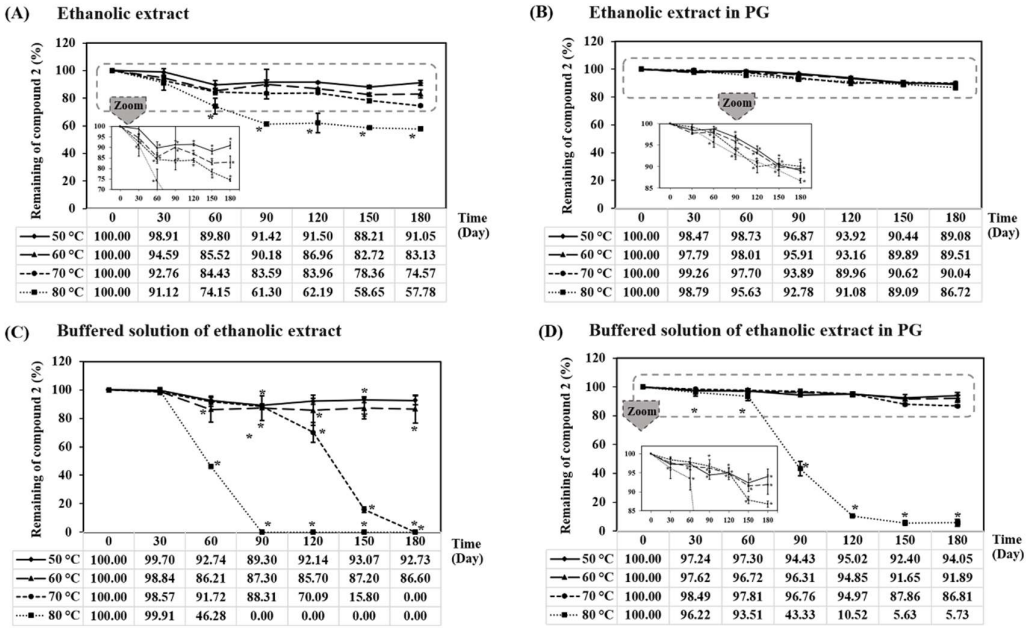


**Figure 4** The effect of temperature on the stability of **2** in (A) ethanolic extract (B) ethanolic extract in PG (C) buffered solution (pH 5.5) of ethanolic extract and (D) buffered solution (pH 5.5) of ethanolic extract in PG. ($^{*}p < 0.05$ against data of day 0).

In our investigation, the stability profiles of **1** and **2** in the buffered solution of the ethanolic extract in PG were notably superior to those observed in the buffered solution of ethanolic extract. Remarkably, our findings align with the stability study of Kao *et al*. [14], where they reported that the 4 major components of *Scutellaria baicalensis* (baicalin, baicalein, wogonin and wogonoside) exhibited greater stability in a 20 % PG solvent compared to a water-based storage solvent. It has been proposed that 2 hydroxyl (–OH) groups in PG are easily hydrated by the surrounding water molecules via the donation and acceptance of hydrogen bonds [16]. Adding PG may thus reduce water activity to prevent chemical degradation. As well, the polarity of the aqueous medium and the dielectric constant was also reduced in PG/water mixtures. Such a reason might be a decrease in the rate constant of degradation, thereby increasing its stability [23]. As well, the addition of PEG-40 to the ethanolic extract in PG may prevent the degradation of its bioactive compounds. This may be because the formation of a covalent bond with PEG facilitates the stabilization and solubilization of active ingredients, thereby reducing their oxidation processes by forming micelles [24,25]. As expected, our data showed that both prepared extracts were more thermally stable than those in the buffered solution form. The observed finding suggests that compounds **1** and **2** were susceptible to degradation under high temperature conditions when they were present in an aqueous environment. This susceptibility to degradation may be attributed to the accelerated occurrence of oxidative reactions [26,27].

**Identification of temperature-degradation products**

As depicted in **Figure 5**(**A**), the spot of unidentified polar compounds was observed on the TLC fingerprint at the $R_f$ value of 0.43 when a mixture of compounds **1** and **2** was maintained at 80 °C for 14 days. These polar degradation products were also detected in the baseline peak chromatogram (BPC) from LC-MS (**Figure 5**(**B**)). Comparing the degradation profiles of these 2 samples at days 0 and 14 revealed that the peak intensities of polar compounds increased after keeping at 80 °C for 14 days, while the peaks of compounds **1** and **2**, particularly **2**, decreased (**Figure 5**(**B**)).

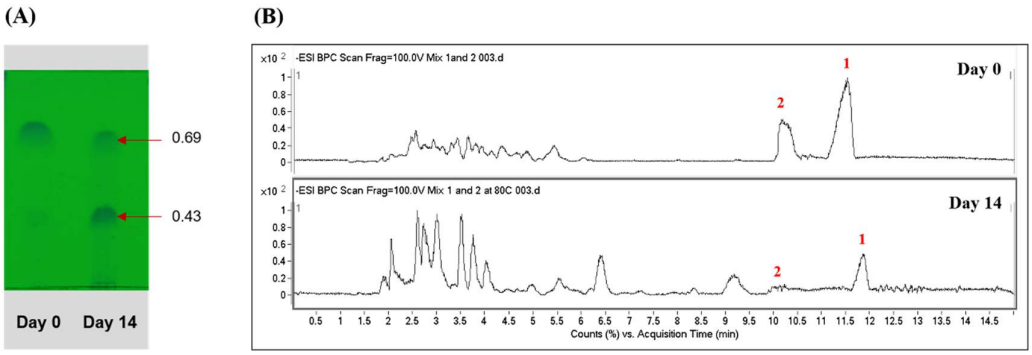


**Figure 5** The degradation profiles of compounds **1** and **2** mixture before (day 0) and after being kept at 80 °C for 14 days using (A) TLC and (b) LC-MS techniques.

These degradation products were re-chromatographed using silica gel column chromatography to yield 4 sub-fractions (A - D). Sub-fraction C (1 mg) contained the major polar spots at $R_f$ = 0.43, which were then identified using the LC-MS method. Two degradation products were detected at the retention time of 2.78 min for peak A and 3.55 min for peak B (**Figure 6(A)**). The ESI-MS spectra revealed *m/z* 331.1934, 367.1707 for peak A and 317.2002, 335.2096 for peak B (**Figure 6(B)**), which differed from the molecular masses of **1** and **2** as previously reported [13]. Their structures could not be exactly confirmed due to a low yield of isolated degradation products. Additional research is required to clarify the structure of degradation products, which should be done in the future.

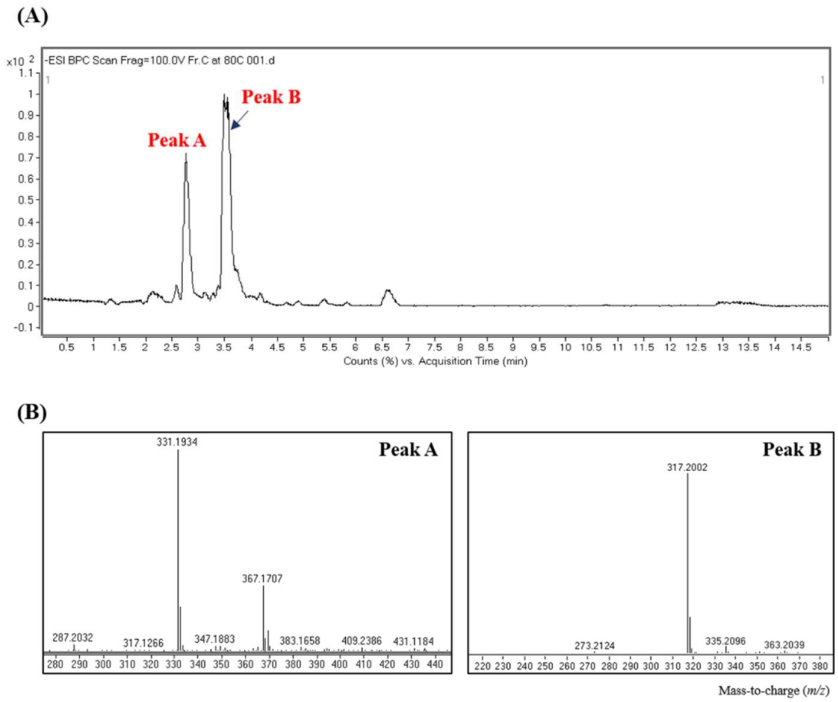


**Figure 6** The (A) baseline peak chromatogram (BPC) of sub-fraction C (10 mg/mL) from LC-MS and (B) mass fragmentation (in negative mode) of peaks A and B.

**Effect of light**

The prepared extracts (ethanolic extract and ethanolic extract in PG), as well as the diluted solution of the extracts in buffer solution pH 5.5, were kept in well-closed containers and exposed to 1.21 million lux-h of light for 13.5 h during which time the presence of **1** and **2** of the ethanolic extract in PG rapidly degraded by ~ 90 % for **1** and ~ 40 % for **2**, whereas **1** and **2** in the ethanolic extract showed superior stability

profile (**Figure 7**(**A**)). The buffered solution prepared from an ethanolic extract in PG lost **1** faster than that from the ethanolic extract without PG during the 13.5 h period of light exposure. The remaining content of **2** was statistically significantly more stable than that of **1** (**Figure 7**(**B**)). In both preparations, the ethanolic extract in PG was degraded faster than the ethanolic extract.

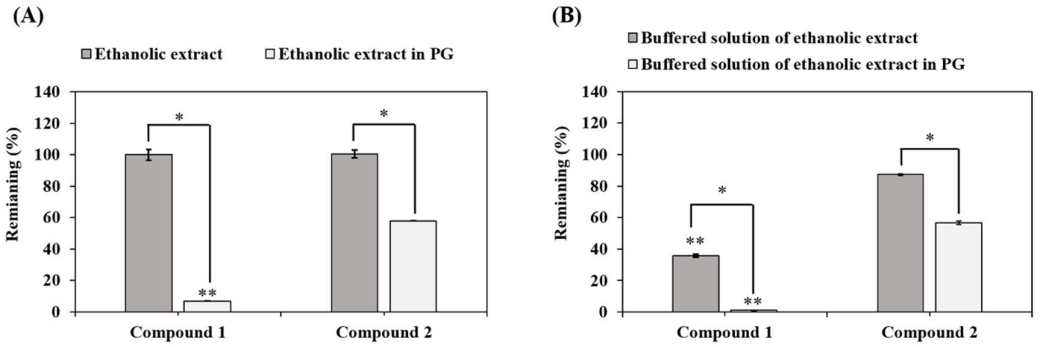


**Figure 7** Degradation of compounds **1** and **2** in (A) ethanolic extract and ethanolic extract in PG, (B) buffered solution (pH 5.5) of ethanolic extract and buffered solution (pH 5.5) of ethanolic extract in PG after exposed to light for 13.5 h. ($^{*}p < 0.05$, $^{**}p < 0.05$ vs compound **2**).

The data clearly indicate that the impact of light-induced degradation on **1** and **2** degradations in solvents containing PG surpasses that observed in solvents without PG. This may occur due to the ability of light components such as UV to activate the PG which in turn acts as a radical initiator to promote the oxidation reaction of **1** and **2** in solution [28]. These results suggest that the use of light-protective packaging and UV absorbents could improve the photostability of **1** and **2** in *T. grandis* extract.

**Calculation of the shelf-life of 1 and 2 by the Q10 method**

The shelf-life estimation of **1** and **2** in ethanolic extract and ethanolic extract in PG was calculated using the Q10 equation, which predicts the potential shelf-life of compounds with heat-sensitive degradation. At 60 days, the remaining content of **1** and **2** in the ethanolic extract and ethanolic extract in PG stored at 50 °C was approximately 90 % or higher. The value of Q was set to 3 due to the activation energy of most compounds is in the range of 18 - 20 kcal/mol and the estimated shelf-life of **1** and **2** was calculated as follows:

$$t_{90}(30\ ^{\circ}\mathrm{C}) = \frac{60}{3^{(30-50)/10}} = 540 \text{ days or } 1.48 \text{ years} \quad (2)$$

Therefore, with respect to the remaining amount of both **1** and **2**, the shelf-life of the prepared extracts (ethanolic extract and ethanolic extract in PG) and their buffered solutions pH 5.5 at 30 °C is estimated to be 1.48 years.

## Conclusions

Two 5α-reductase inhibitors ((+)–eperua-8,13-dien-15-oic acid (**1**) and (+)–eperua-7,13-dien-15-oic acid (**2**)) in an ethanolic extract demonstrated greater stability in an acidic solution than in neutral or basic solutions. The presence of PG in the extract exerted a protective effect against the degradation of both compounds. However, caution should be exercised when employing PG in situations where protection against light exposure is not feasible. Furthermore, it was noted that the degradation of **1** and **2** was more pronounced in a solution form rather than in the extract. Utilizing Q10 method, the estimated shelf-life of prepared extract forms (ethanolic extract and ethanolic extract in PG) and their solution forms at pH 5.5 was determined to be 1.48 years. It is worth considering further research on the degraded products of the compounds. Based on our finding, it is recommended that PG be included in the extract of *T. grandis* leaf, as well as in their solution forms, to enhance stability. Additionally, the use of light-protective containers is strongly recommended as a standard practice to mitigate the effect of light on the chemical degradation of the compounds.

**Acknowledgements**

This work was financially supported by the grant under the Science Achievement Scholarship of Thailand (SAST), National Research Council of Thailand (NRCT), the NSRF via the Program Management Unit for Human Resources & Institutional Development, Research and Innovation (grant number C00SC65030008), and Department of Chemistry, Faculty of Science, Naresuan University of Thailand. This work was also supported by Global and Frontier Research University Fund, Naresuan University of Thailand (Grant number R2566C053). We gratefully acknowledge Mr. Roy I. Morien of the Naresuan University of Thailand Graduate School for his editing of the grammar, syntax, and general English expressions in this document.

**References**

[1] CP Khare. *Indian medicinal plants: An illustrated dictionary*. Springer Berlin Heidelberg, New York, 2008.

[2] P Vyas, DK Yadav and P Khandelwal. *Tectona grandis* (teak) - A review on its phytochemical and therapeutic potential. *Nat. Prod. Res.* 2019; **33**, 2338-54.

[3] N Nayeem and MD Karvekar. Anti microbial and anti-oxidant properties of the isolated compounds from the methanolic extract from the leaves of *Tectona grandis. J. Basic Clin. Pharm.* 2011; **2**, 163-5.

[4] TK Kopa, AT Tchinda, MF Tala, D Zofou, R Jumbam, HK Wabo, VPK Titanji, M Frédérich, NH Tan and P Tane. Antiplasmodial anthraquinones and hemisynthetic derivatives from the leaves of *Tectona grandis* (Verbenaceae). *Phytochemistry Lett.* 2014; **8**, 41-5.

[5] S Ramachandran, BR Kanth, A Rajasekaran and KTM Kumar. Evaluation of anti-inflammatory and analgesic potential of methanol extract of *Tectona grandis* flowers. *Asian Pac. J. Trop. Biomed.* 2011; **1**, S155-S158.

[6] PV Sharma and KC Samanta. Hypoglycemic activity of methanolic extract of *Tectona grandis* Linn. root in alloxan induced diabetic rats. *J. Appl. Pharmaceut. Sci.* 2011; **1**, 106-9.

[7] RM Khan and SM Mlungwana. 5-Hydroxylapachol: A cytotoxic agent from *Tectona grandis. Phytochemistry* 1999; **50**, 439-42.

[8] GJ Rani and NL Bhavani. Phytochemical investigation and antipyretic activity of *Tectona grandis* Linn. *Res. J. Pharm. Tech.* 2021; **14**, 4221-5.

[9] MS Krishna and AJ Nair. Antibacterial, cytotoxic and antioxidant potential of different extracts from leaf, bark and wood of *Tectona grandis. Int. J. Pharmaceut. Sci. Drug Res.* 2010; **2**, 155-8.

[10] D Jaybhaye, S Varma, N Gagne, V Bonde, A Gite and D Bhosle. Effect of *Tectona grandis* Linn. seeds on hair growth activity of albino mice. *Int. J. Ayurveda Res.* 2010; **1**, 211-5.

[11] SB Varma and SP Giri. Study of wound healing activity of *Tectona grandis* Linn. leaf extract on rats. *Ancient Sci. Life* 2013; **32**, 241-4.

[12] Y Fachrunniza, J Srivilai, V Wisuitiprot, W Wisuitiprot, N Suphrom, P Temkitthawon, N Waranuch and K Ingkaninan. *Tectona grandis*, a potential active ingredient for hair growth promotion. *Songklanakarin J. Sci. Tech.* 2020; **42**, 1352-9.

[13] K Insumrong, K Ingkaninan, N Waranuch, N Tanuphol, W Wisuitiprot, T Promgool and N Suphrom. Isolation and HPLC quantitative determination of 5α-reductase inhibitors from *Tectona grandis* L.f. leaf extract. *Molecules* 2022; **27**, 2893.

[14] TT Kao, MC Wang, YH Chen, YT Chung and PA Hwang. Propylene glycol improves stability of the anti-inflammatory compounds in *Scutellaria baicalensis* extract. *Processes* 2021; **9**, 894.

[15] M Canton, S Poigny, R Roe, JM Nuzillard and JH Renault. Dereplication of natural extracts diluted in propylene glycol, 1,3-propanediol and glycerin. Comparison of *Leontopodium alpinum* Cass. (Edelweiss) extracts as a case study. *Cosmetics* 2021; **8**, 10.

[16] NH Rhys, RJ Gillams, LE Collins, SK Callear, MJ Lawrence and SE McLain. On the structure of an aqueous propylene glycol solution. *J. Chem. Phys.* 2016; **145**, 224504.

[17] ICH Q1B. Stability testing: Photostability testing of new drug substances and products, Available at: https://database.ich.org/sites/default/files/Q1B%20Guideline.pdf, accessed March 2023.

[18] N Ngamdokmai, K Ingkaninan, N Chaichamnong, K Chootip, N Neungchamnong and N Waranuch. Development, characterization, and stability evaluation of the anti-cellulite emgel containing herbal extracts and essential oils. *Pharmaceuticals* 2021; **14**, 842.

[19] KK Onyechi and CA Igwegbe. Shelf life assessment of *Picralima nitida* and glibenclamide using bio-based dose-response relationship method. *Asian J. Res. Med. Pharmaceut. Sci.* 2019; **6**, 1-10.

[20] A Ornelas, N Zacharias-Millward, DG Menter, JS Davis, L Lichtenberger, D Hawke, E Hawk, E Vilar, P Bhattacharya and S Millward. Beyond COX-1: The effects of aspirin on platelet biology and potential mechanisms of chemoprevention. *Canc. Metastasis Rev.* 2017; **36**, 289-303.
[21] M Lukić, I Pantelić and SD Savić. Towards optimal pH of the skin and topical formulations: From the current state of the art to tailored products. *Cosmetics* 2021; **8**, 69.
[22] JE McMurry. *Organic chemistry with biological applications*. Cengage Learning, Massachusetts, 2007, p. 223-6.
[23] PJ Sinko. *Martin's physical pharmacy and pharmaceutical sciences*. Lippincott Williams and Wilkins, Pennsylvania, 2006.
[24] R Cassano, T Ferrarelli, MV Mauro, P Cavalcanti, N Picci and S Trombino. Preparation, characterization and *in vitro* activities evaluation of solid lipid nanoparticles based on PEG-40 stearate for antifungal drugs vaginal delivery. *Drug Deliv.* 2016; **23**, 1037-46.
[25] A Wichit, A Tangsumranjit, T Pitaksuteepong and N Waranuch. Polymeric micelles of PEG-PE as carriers of all-trans retinoic acid for stability improvement. *AAPS PharmSciTech* 2012; **13**, 336-43.
[26] SA Khayyat and LS Roselin. Recent progress in photochemical reaction on main components of some essential oils. *J. Saudi Chem. Soc.* 2018; **22**, 855-75.
[27] GW McGraw, RW Hemingway, LL Ingram, CS Canady and WB McGraw. Thermal degradation of terpenes: Camphene, $\Delta^3$-carene, limonene, and $\alpha$-terpinene. *Environ. Sci. Tech.* 1999; **33**, 4029-33.
[28] Bharat Petroleum. Preliminary feasibility report for polyol/propylene glycol/mono ethylene glycol petrochemical project, Available at: https://environmentclearance.nic.in/writereaddata/Online/TOR/24_Nov_2017_175437307BRBUXERUPreliminaryFeasibilityReport.pdf, accessed July 2023.