ХИМИЯ И ТЕХНОЛОГИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ И БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ

CHEMISTRY AND TECHNOLOGY OF MEDICINAL COMPOUNDS AND BIOLOGICALLY ACTIVE SUBSTANCES

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RESEARCH ARTICLE

Screening of medicinal plant extracts in Vietnam and investigation of their combination for preventing and treating gout

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Abstract

Objectives. *The study aimed to examine the potential use of ethanol extracts of four medicinal plants to prevent and treat gout disease.*
Methods. *An investigation of some typical compound contents such as polyphenols, flavonoids, and tannins in terms of two bioactive abilities, including anti-xanthine oxidase and antioxidant was carried out in Eclipta prostrata L., Artemisia vulgaris L., Apium graveolens L., and Piper betle L samples. Subsequently, the weight ratios of Piper betle L. and Artemisia vulgaris L. were investigated to reduce the total tannin content and get the most suitable anti-xanthine oxidase activity.*
Results. *As well as having the highest target compound contents, Piper betle L. demonstrated the best anti-xanthine oxidase and antioxidant abilities even while its IC_{50} values were lower than positive control; however, its high total tannin content can cause some side effects. A mixture with a weight ratio of 1:1 of Piper betle L. and Artemisia vulgaris L. had a total tannin content half that of Piper betle L. as well as demonstrating potential anti-xanthine oxidase and antioxidant activities when IC_{50} was about 3.94 and 20.85 μg/mL, respectively.*

Conclusions. *Out of the four selected plants, Piper betle L. demonstrated the best potential material for preventing and treating gout disease. However, due to the high tannin content in it, a mix of Piper betle L. and Artemisia vulgaris L. at a weight ratio of 1:1 gave optimal results for application in treatment.*

Keywords: *gout disease, xanthine oxidase inhibitors, tannins, Piper betle L.*

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НАУЧНАЯ СТАТЬЯ

Скрининг экстрактов лекарственных растений во Вьетнаме и исследование их комбинации для профилактики и лечения подагры

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Аннотация

Цели. *Изучить потенциальное использование этанольных экстрактов четырех лекарственных растений для профилактики и лечения подагры.*
Методы. *Образцы эклипты простёртой (Eclipta prostrata L.), полыни обыкновенной (Artemisia vulgaris L.), сельдерея пахучего (Apium graveolens L.) и перца бетель (Piper betle L.) исследовались с точки зрения содержания в них полифенолов, флавоноидов и дубильных веществ, а также наличия биологически активных свойств, включая антиксантиноксидазную и антиоксидантную активность. Далее были найдены весовые соотношения Piper betle L. и Artemisia vulgaris L., позволяющие снизить общее содержание танина и получить наиболее подходящую антиксантиноксидазную активность.*
Результаты. *Помимо самого высокого содержания целевого соединения, Piper betle L. продемонстрировал наилучшие антиксантиноксидазные и антиоксидантные свойства, даже несмотря на то, что его значения IC_{50} были ниже положительного контроля. Однако высокое содержание общего танина в нем может вызывать некоторые побочные эффекты. Смесь Piper betle L. и Artemisia vulgaris L. с массовым соотношением 1:1 имела общее содержание танина вдвое меньше, чем Piper betle L., а также демонстрировала*

потенциальную антиксантиноксидазную и антиоксидантную активность, при этом IC_{50} составлял около 3.94 и 20.85 мкг/мл соответственно.

Выводы. *Из четырех отобранных растений Piper betle L. является наилучшим потенциальным материалом для профилактики и лечения подагры. Однако из-за высокого содержания в нем танина смесь Piper betle L. и Artemisia vulgaris L. в соотношении по массе 1:1 дала оптимальные результаты для применения в лечении.*

Ключевые слова: *болезнь подагра, ингибиторы ксантиноксидазы, дубильные вещества, Piper betle L.*

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INTRODUCTION

A significant global increase in the number of gout patients has recorded been in recent years. While the highest proportions of gout patients are experienced among the populations of North America and Europe, the increase has also been dramatic in in Asia [1]. Gout is a chronic syndrome caused by the deposition of urate crystals [2] and related to xanthine oxidase enzyme activities due to this enzyme playing a catalyst role in the reaction to uric acid from purine [3]. Thus, xanthine oxidase inhibition, representing one of the main therapies for avoiding increased concentrations of uric acid in human blood, can be used to reduce the risk of gout [4]. Although allopurinol is one of the most popular drugs for inhibiting xanthine oxidase enzyme activity, it is often associated with side effects [5, 6]. Therefore, the identification new potential substances for preventing and treating gout becomes an urgent task. In this connection, the investigation of plants containing chemical constituents having various biological activities has attracted a lot of interest from scientists [7]. Over 12000 valuable plant species in Vietnam have been identified, with over a third of them demonstrating biological and pharmacological activities [8]. Although anti-xanthine oxidase abilities have been reported [9, 10], many medicinal plants already used in alternative therapies have yet to be studied in terms of their phytochemical and biological activities. Therefore, in this study, four selected plants, including *Eclipta prostrata* L., *Artemisia vulgaris* L., *Apium graveolens* L., *Piper betle* L. were evaluated in terms of their anti-xanthine and antioxidant activities, as well as their polyphenol-, flavonoid-, and tannin content. The two plants identified as showing the best potential were additionally investigated in terms of their combined efficacy.

MATERIALS AND METHODS

Materials and chemicals

Leaves of *Eclipta prostrata* L., *Artemisia vulgaris* L., *Apium graveolens* L., *Piper betle* L. were collected in Hoocmon district, Hochiminh city, Vietnam, in February 2022 during the dry season, which is the most appropriate time for harvesting these plants. The plant samples, including leaves and trunk, are shown in Fig. 1. After washing with water and drying in shade until the moisture content was under 12%, the samples were stored in a sealed bag for further use. The plants were authenticated by the Department of Ecology and Evolutionary Biology,

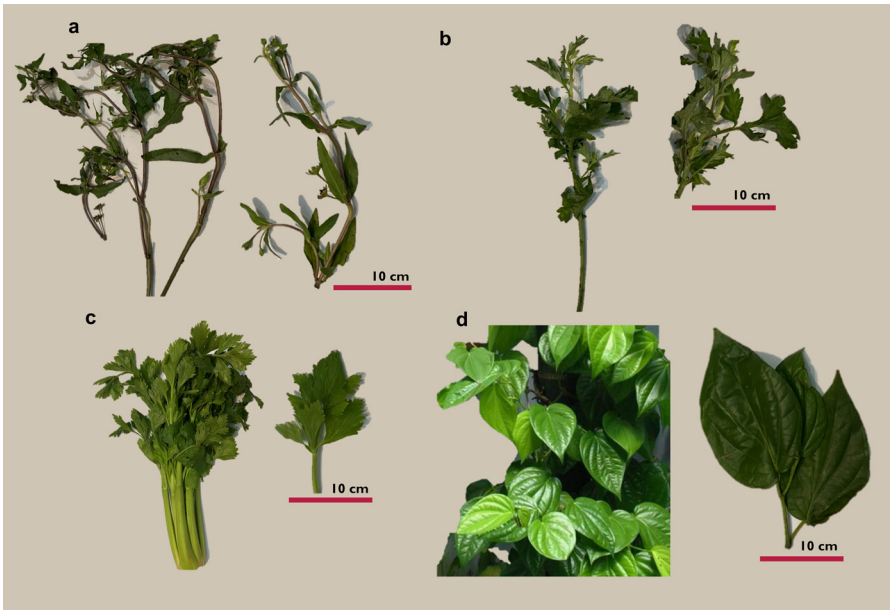

Fig. 1. Photographs of plants and leaves of (a) *Eclipta prostrata* L. (b) *Artemisia vulgaris* L. (c) *Apium graveolens* L. (d) *Piper betle* L. The photographs were captured and edited by authors.

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Absolute ethanol (C_2H_5OH), methanol (CH_3OH), sodium nitrite ($NaNO_2$), sodium carbonate (Na_2CO_3), sodium hydroxide (NaOH), aluminum chloride ($AlCl_3$), dimethyl sulfoxide (DMSO), iron(III) chloride ($FeCl_3$), diclofenac sodium and other reagents of analytical grade were obtained from *Merck* (Darmstadt, FR, Germany). Folin-Ciocalteu's reagent, quercetin, xanthine oxidase, xanthine, ascorbic acid, allopurinol, 1,1-diphenyl-2-picrylhydrazyl (DPPH), and gallic acid were provided by *Sigma-Aldrich* (Singapore).

Preparation of plant extract

The ethanolic extracts from each plant were extracted with absolute ethanol having a solid-to-liquid ratio of 1:10 g/mL at 45 °C for 45 min. Next, the extracts were filtered with vacuum filtration and evaporated until complete removal of excess solvent. The residue was then recovered for further extraction. The yield of extraction is determined by Eq.1:

$$\text{Extraction yield} = \frac{m_{\text{extract}}}{m_{\text{sample}}} \times 100\%, \quad (1)$$

where m_{extract} is the weight of dry extract (g) and m_{sample} is the weight of dry raw material (g).

Qualitative phytochemical screening

The presence of bioactive compounds: polyphenols, flavonoids, tannins, alkaloids, saponins, and carotenoids were determined with phytochemical screening [11–13].

Determination of total polyphenol content (TPC)

The TPC of the extracts was determined using the Folin–Ciocalteu reagent following the method of Sánchez-Rangel *et al*. [14]. Briefly, a mixture consisting of 200 µL of Folin–Ciocalteu reagent and 40 µL of the diluted extract was stored at 25 °C for 5 min prior to adding 600 µL of Na_2CO_3 20 w/v % and 3160 µL of distilled water. The absorbance of the mixture was determined using a UV–Vis spectrophotometer Genesys 10S (*Thermo Fisher Scientific*, USA) at 760 nm. TPC was expressed as milligram of gallic acid equivalent per gram of sample (mg GAE/g). The test sample without Folin–Ciocalteu reagent was considered as a control.

Determination of total flavonoid content (TFC)

The concentration of flavonoids in the extracts was determined using the aluminum chloride colorimetric assay method [15]. Initially, a mixture conprising 2 mL of distilled water, 0.15 mL of $NaNO_2$ 5%, and 0.5 mL of the extract dissolved

in methanol, was prepared and incubated for 5 min. Afterward, 0.15 mL of 10% $AlCl_3$, 1 mL of NaOH 1M, and 1.2 mL of distilled water were respectively added to the mixture. The absorbance of the mixture was measured at 425 nm using Genesys 10S UV–Vis spectrophotometer. The number of total flavonoids was shown as milligrams of quercetin equivalents per gram of sample (mg QUE/g). The test sample without $AlCl_3$ was considered blank.

Determination of total tannin content (TTC)

The concentration of tannins in the extracts was determined by the Folin–Ciocalteu method as described Maklar *et al*. [16]. A total of 2 mL of extract in methanol was mixed with 8 mL distilled water and 10 mL sodium acetate buffer (pH 5) to obtain solution 1. A mixture of 500 µL of solution 1 and 250 µL Folin–Ciocalteu reagent was sonicated in 5 min, and then 4250 µL Na_2CO_3 33% was added. The mixture was sonicated for 30 min before determining absorbance (A_1) at 720 nm. A total of 10 mL solution 1 reacts with 50 mg casein at 30 °C for 1 h. The mixture was filtered to recover solution 2. Then, a mixture of 500 µL of solution 2 and 250 µL Folin–Ciocalteu reagent was sonicated in 5 min. Then, 4250 µL Na_2CO_3 33% was added before sonicating in 30 min. The absorbance of solution 2 (A_2) was also measured at 720 nm. The test sample without Folin–Ciocalteu reagent was defined as a control. The tannin absorbance in the extract is calculated as Eq. 2:

$$A = (A_1 - B_1) - (A_2 - B_2), \quad (2)$$

where A, A_1, and A_2 are the absorbance of tannin for solution 1 and solution 2; B_1 and B_2 are the absorbance of the blank in solution 1 and solution 2, respectively.

The TTC is expressed as milligrams of tannic acid equivalents per gram of sample (mg TAE/g).

In vitro xanthine oxidase inhibitory activity assay

The Abd El-Rahman and Abd-ELHak method was applied to evaluate the xanthine oxidase inhibitory activity of studied extracts [17]. Firstly, the reaction mixture contains 250 µL extract in DMSO 5%, 175 µL of sodium phosphate buffer (pH 7.5), and 150 µL enzyme (0.2 units/mL of xanthine oxidase in phosphate buffer). The mixture was incubated for 15 min at 37 °C before adding 300 µL of xanthine (mM) and then further incubating for 30 min at 37 °C. The reaction was stopped with the addition of 125 µL HCl 1M. The absorbance was measured at 290 nm by Genesys 10S UV–Vis spectrophotometer. Allopurinol was used as a positive control. Xanthine oxidase inhibitory activity was expressed as the percentage inhibition of xanthine oxidase and calculated as Eq. 3:

$$\%\ \text{XO inhibition} = \frac{A_{\text{blank}} - A_{\text{sample}}}{A_{\text{blank}}} \times 100\%, \quad (3)$$

where XO is xanthine oxidase; A_{blank} is the absorbance at 290 nm of blank; A_{sample} is the absorbance at 290 nm of the sample.

In vitro antioxidant assay

The presence of free radicals is one of the consequences of diseases [18]. The DPPH radical is the most popular method to determine free radical scavenging activity, Sharma and Bhat method with slight modification was used in this study [19]. Briefly, 120 µL of extract in methanol at various concentrations were reacted with 180 µL of DPPH in methanol. The reaction mixture was stored in the dark at 25 °C for 30 min. The DPPH solution, ascorbic acid (vitamin C), and methanol were used as negative-, positive-, and blank controls, respectively. The absorbance was measured at 517 nm using a Genesys 10S UV–Vis spectrophotometer to calculate the percentage of inhibition (Eq. 4) as follows:

$$\%\ \text{DPPH radical scavenging activity} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100\%, \quad (4)$$

where A_{control} is the absorbance of the negative control and A_{sample} is the absorbance of the test solution.

Statistical analysis

All experiments were carried out in triplicate; the data were expressed as mean ± standard deviation.

RESULTS AND DISCUSSION

Extraction efficiency of medical plant extracts

In the present study, the first task was to investigate the number of extraction cycles. All four

materials were extracted four times; the results are shown in Fig. 2. There were significant differences among the researched materials and the cycles. The total extraction efficiency of *Apium graveolens* L. leaves was the highest at 21.18%. However, the total extraction efficiencies of the others were not much different, falling in the range of 11.87 to 13.26%. The main reasons for the variation were the significant amounts of petiole in the *Eclipta prostrata* L. and *Artemisia vulgaris* L. samples and high level of fiber in the *Piper betle* L. leaves. Meanwhile, the first-cycle extractions were the highest for all plants, with values falling in the range of 5.63 to 12.35%. In the first cycle, there were significant differences between compound concentrations in the internal and external plants. As a result, the diffusion was much easier than the others. The figure for *Apium graveolens* L., the first extraction yield, made up about 58% total one, whereas, in terms of *Piper betle* L., it accounted for roundly 72% total yield. The cycle extraction efficiency additionally decreased as the number of extracts increased, with fourth cycle extraction yields at less than 1%. Therefore, three-cycle extraction was applied in the following steps.

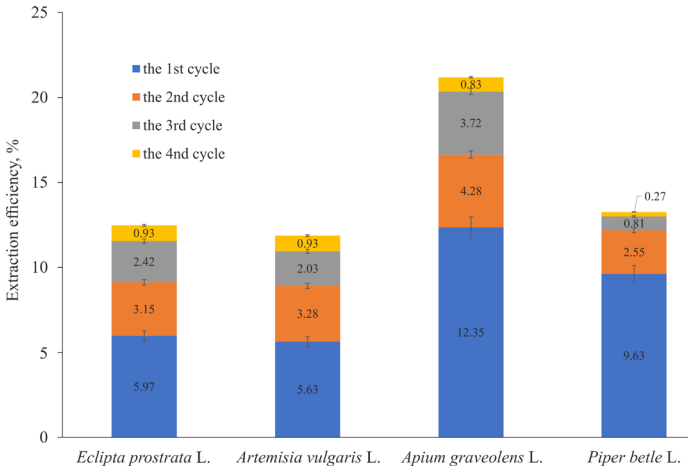


Fig. 2. Extraction efficiencies of four studied plants.

Phytochemical screening of medicinal plant extracts

Phytochemical screening was conducted to identify some bioactive compounds in the materials. The results can help to predict some bioactive abilities or side effects. In this study, typical natural compounds, including polyphenols, flavonoids, tannins, alkaloids, saponins, and carotenoids were determined; the results are shown in Table 1. Polyphenols demonstrate various bioactivity abilities, such as anti-xanthine oxidase, antioxidant, anti-carcinogenic, anti-oxygenase, and anti-telomerase [20, 21]. Flavonoids demonstrate significant bioactivity, especially anti-xanthine oxidase, antioxidant, anti-inflammatory, and antibacterial [21, 22]. Tannins are strongly antioxidant compounds due to the presence of many hydroxyls (–OH) in their structures, although they can be characterized by difficult absorption and associated digestion problems [23, 24]. Moreover, bioactive capabilities offered by alkaloids, such as anti-xanthine oxidase and anti-inflammatory effects, address gout symptoms [25, 26]. Saponins are known to play important roles in preventing or treating cancer, reducing inflammation, and increasing blood cholesterol [27, 28]. Finally, carotenoids are demonstrated as typical antioxidant compounds because of their reactions to superoxide radicals and peroxyl groups [29].

The experiment results (Table 1) demonstrated the presence of polyphenols, flavonoids, tannins, and saponins in all four extracts. As a result, it is predicted that these materials will exhibit anti-xanthine oxidase and antioxidant activities. In addition, the antioxidant effect of carotenoids found in in *Artemisia vulgaris* L. and *Piper betle* L. offers additional mechanisms to those of other antioxidant compounds such as polyphenols, flavonoids, tannins, and carotenoids. Antioxidant activity contributes to the balance of homeostasis when suffering from diseases [18].

TPC, TFC, and TTC of extract plants

As already mentioned, polyphenols, flavonoids, and tannins are considered in terms of their important xanthine oxidase inhibition and antioxidant roles. In this study, the TPC and TTC were measured using Folin–Ciocalteu reagent, while TFC was determined by the aluminum chloride method; these popular methods offer reliable results [15, 16]. The TPC, TFC, and TTC were determined as described in Fig. 3. The research materials demonstrated widely ranging differences in terms of these values. *Piper betle* L. had by far the highest values when the TPC, TFC, and TTC were 437.12 mgGA/g; 668.18 mgQEU/g, and 62.63 mgTAE/g, respectively. In contrast, the values of *Apium graveolens* L. were the lowest. It is forecasted that *Piper betle* L. shows the highest potential xanthine oxidase inhibition and antioxidant activity, whereas these bioactive abilities of *Apium graveolens* L. can be much worse. However, the high value of TTC of *Piper betle* L. can cause some side effects, especially in terms of difficult absorption and digestion of nutrients [24]. For this reason, it is necessary to use it cautiously.

Table 1. Phytochemical screening results from leaf extract of four plants

Bioactive compounds	Test/Reagent	Medicinal plants			
		Eclipta prostrata L.	*Artemisia vulgaris* L.	*Apium graveolens* L.	*Piper betle* L.
Polyphenols	Iron(III) chloride	+	+	+	++
Flavonoids	Lead acetate 10%	+	+	+	++
Tannins	Gelatin 1%	+	++	+	++
Alkaloids	Bouchardat	+	++	–	+
Saponins	Liebermann–Burchard	+	+	+	+
Carotenoids	Sulfuric acid	–	+	–	++

– Not detected, + Slightly positive reaction, and ++ Strong positive reaction.

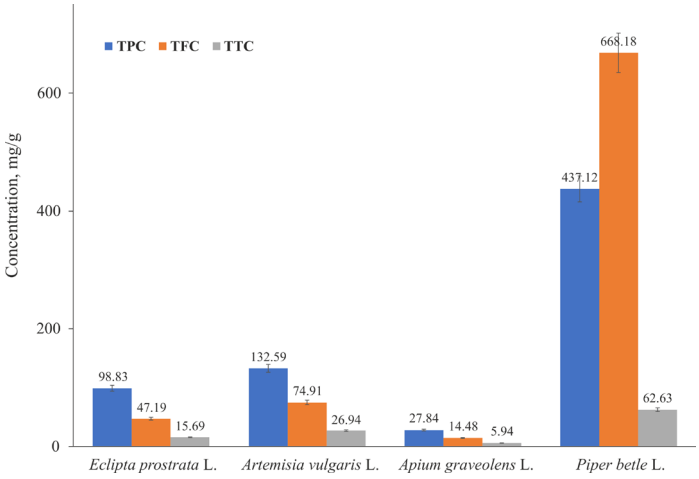


Fig. 3. Total content of polyphenols, flavonoids, and tannins of four extract plants.

Anti-xanthine oxidase and antioxidant activities

To confirm their bioactive abilities, *in vitro* assay of the the materials was carried out with anti-xanthine oxidase and antioxidant as illustrated in Table 2.

The bioactive properties as illustrated by IC_{50} values are shown in Table 2. As expected, *Piper betle* L. showed the most potential material, with IC_{50} values of anti-xanthine oxidase and antioxidant abilities being lower than the positive controls, such as allopurinol and ascorbic acid. The results agree with an earlier study carried out into the xanthine oxidase inhibitory effect of *Piper betle* L. [30]. Regarding anti-xanthine oxidase, the data of *Eclipta prostrata* L. and *Artemisia vulgaris* L. were almost the same, at 164 and 161.65 µg/mL, respectively. However, regarding antioxidant ability, *Artemisia vulgaris* L. was about 9 times better than *Eclipta prostrata* L. due to the difference in TTC values. In contrast, *Apium graveolens* L. had the worst anti-xanthine oxidase (IC_{50} 554.83 µg/mL) and antioxidant abilities (IC_{50} 309.52 µg/mL) due to the lowest TPC, TFC and TTC values.

Combination of *Piper betle* L. and *Artemisia vulgaris* L.

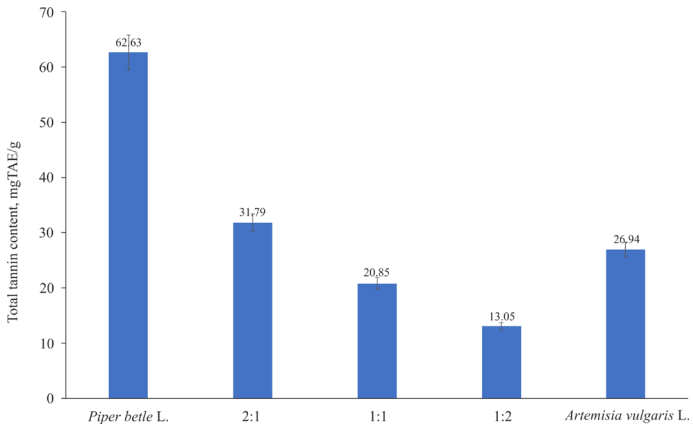
Out of four plants, *Piper betle* L. was demonstrated to be the most promising material for preventing and treating gout disease and its complications, primarily in terms of reducing free radicals. However, as already mentioned, its high TTC value can lead to some negative side effects. Moreover, the TTC value of *Artemisia vulgaris* L. was significantly lower than that of *Piper betle* L., which demonstrated potential bioactive properties. Therefore, in this

Table 2. Anti-xanthine oxidase and antioxidant of four studied extract plants

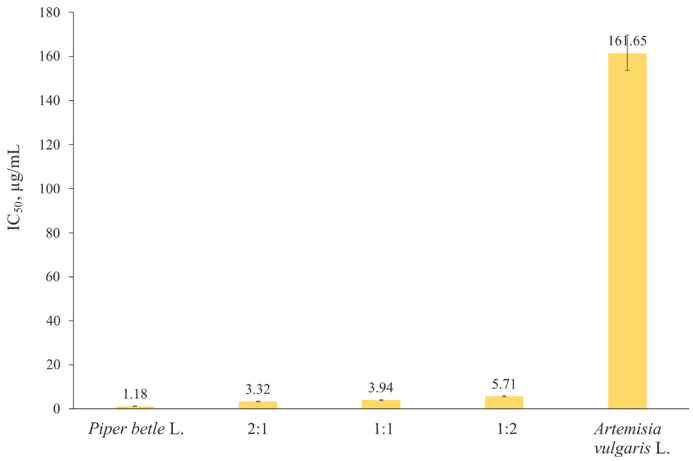
Materials	IC_{50}, µg/mL	
	Anti-xanthine oxidase	Antioxidant
Eclipta prostrata L.	164.00 + 2.51	56.80 + 2.75
Artemisia vulgaris L.	161.65 + 0.53	6.65 + 0.30
Apium graveolens L.	554.83 + 0.79	309.52 + 1.22
Piper betle L.	1.18 + 0.02	4.10 + 0.08
Positive control	1.57 + 0.01 *	5.87 + 0.12 **

* Allopurinol.
**Ascorbic acid.

study, the leaf powders of *Piper betle* L. and *Artemisia vulgaris* were mixed together in different ratios to lower the TTC and improve anti-xanthine oxidase ability. The effects of the mass ratio of *Piper betle* L. and *Artemisia vulgaris* on TTC and xanthin oxidase activity are shown on Fig. 4.



(a)



(b)

Fig. 4. TTC values (a) and xanthine oxidase inhibition (b) of different ratios of *Piper betle* L. and *Artemisia vulgaris* L. (w/w).

The findings showed a decline in the TTC data with an increase in the ratio of *Artemisia vulgaris* L. Here, the TTC value ratio 2:1 (w/w) was half that of *Piper betle* L. Meanwhile, the TTC data of the ratio 1:1 (w/w) was about three times lower than that of *Piper betle* L. In contrast, when increasing the content of *Piper betle* L., the combination shows better xanthine oxidase inhibition; all of these combinations showed dramatically better results than *Artemisia vulgaris* L. Both ratios 2:1 and 1:1 (w/w) had approximately similar IC_{50} values about 3.5 times higher than that of *Piper betle* L. Meanwhile, this value of 1:2 (w/w) was approximately 5 times higher than in the *Piper betle* L. data.

The decreasing TTC in the mixed extraction could be due to the low tannin content of *Artemisia vulgaris* L. Further, ethanol has more selectivity for polyphenol and flavonoid compounds; thus, with the high TFC and TPC in both plants, the tannin content in combination samples was lower than in the single samples. Accordingly, the ratio 1:1 (w/w) was the most promising when considering the aims of decreased TTC and the most effective xanthine oxidase inhibition.

CONCLUSIONS

The present work investigated four plants in terms of their concentrations of three main compound groups comprising polyphenols, flavonoids, and tannins, as well as in terms of their anti-xanthine oxidase and antioxidant activities. Although the leaves of *Piper betle* L. showed the most promising results, its TTC value was significant at 62.63 mgTAE/g. In order to reduce side effects, a combination of *Piper betle* L. and *Artemisia vulgaris* L. was prepared and investigated. As a result, the ratio 1:1 (w/w) showed the most potential when the TTC and IC_{50} were 20.85 mgTAE/g and 3.94 µg/mL.

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T.M. Ле – разработка концепции, формальный анализ, проведение исследований, написание текста статьи.

Authors' contributions

Anh C. Ha – writing the text of the review and editing, supervision, methodology, and conceptualization.

Tan M. Le – conceptualization, formal analysis, investigation, and writing the text of the article.

Авторы заявляют, что у них нет известных конкурирующих финансовых интересов или личных отношений, которые могли бы повлиять на работу, описанную в этом документе.

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this document.

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