International Journal of Secondary Metabolite
2023, Vol. 10, No. 4, 459–468
https://doi.org/10.21448/ijsm.1107376
Published at https://dergipark.org.tr/en/pub/ijsm
Research Article

Antioxidant and diuretic effects of flower extract of *Laurus nobilis*

Nor El Houda Tahiri[1,2,*], Asmae El Ghouizi[2], Abderrazak Aboulghazi[2], Najoua Soulo[2], Badiaa Lyoussi[2], Lalla Aicha Lrhorfi[1]

[1]Ibn Tofail University, Faculty of Sciences, Department of Biology, Natural Resources and Sustainable Development Laboratory, B.P. 133, Kenitra 14000, Morocco
[2]Sidi Mohamed Ben Abdellah University, Faculty of Sciences Dhar El Mehraz, Department of Biology, Laboratory of Natural Substances, Pharmacology, Environment, Modeling, Health and Quality of Life (SNAMOPEQ), Fez 30000, Morocco

Abstract: Diuretic medications are widely used and can come with negative effects. Because they are effective and have fewer adverse effects than other treatments for renal illness, medicinal plants have become increasingly important. This study aimed to investigate the antioxidant ability and the impact of *Laurus nobilis* extract (flower) on diuresis in rats. Two doses of 200 mg and 400 mg of *Laurus nobilis* extract were used to treat rats for thirty days. Then, we assessed all changes induced in urine and plasma parameters of rats, using furosemide as a standard drug. Further, we evaluated the total phenolic content (TPC), total flavonoid content (TFC), and antioxidant ability (DPPH and FRAP) of the tested extract. The results obtained show that the administration of a single dose of *Laurus nobilis* extract improved the urine flow significantly after 4 h of treatment. Similarly, both doses of the tested extract enhanced sodium, potassium, and chloride excretion without inducing hypokalemia. A similar tendency was recorded for both urine and creatinine, while the results of the furosemide group revealed a significant hypokalemia effect of the standard drug. *Laurus nobilis* demonstrated superior antioxidant and diuretic effects without inducing hypokalemia due to the higher content of phenolic and flavonoid content. However, more advanced studies are required to explore the constituents of *Laurus nobilis* extracts and essential oils, as well as to test their pertinent biological activities.

ARTICLE HISTORY
Received: May 05, 2022
Revised: May 17, 2023
Accepted: Aug. 21, 2023

KEYWORDS
Laurus nobilis flowers, Antioxidant activity, Diuretic effect.

1. INTRODUCTION

Natural and sustainable products have gained a reputation in different fields of drug discovery to treat the most devastating diseases, including diabetes, obesity, cancer, and kidney diseases (Soetan, 2008; Hosseinimehr, 2014; Chen *et al.*, 2018; Ojulari *et al.*, 2019). The interest in herbs arose as a result of the negative effects of conventional and chemical medication (Glynn & Bhikha 2019). Kidney diseases are noncommunicable pathologies that have risen in recent years and chronic kidney ailments affect approximately 10% of the adult population around the

*CONTACT: Nor El Houda Tahiri ✉ tahiri.nourelhouda12@gmail.com Ibn Tofail University, Faculty of Sciences, Department of Biology, Natural Resources and Sustainable Development Laboratory, B.P. 133, Kenitra 14000, Morocco

e-ISSN: 2148-6905 / **© IJSM 2023**

world (Vos *et al.*, 2017). Diuretic drugs adjust blood volume and mineral elements in body fluids. They have a significant effect on the treatment of numerous ailments, such as heart failure, hypertension, kidney failure, and edema (Hymes & Warshaw, 1987; Salvetti & Ghiadoni, 2006). Furosemide is a conventional drug widely used as a diuretic agent that mostly induces a wide range of side effects, including mineral element abnormalities, acid-base disturbance, and glomerular injuries (Eid *et al.*, 2021). Currently, scientists have found a wide variety of bioactive substances in natural and cultivated plant resources that have profound impacts, drawing a lot of interest to investigate their advantageous features.

Medicinal herbs are considered a good source of inexhaustible molecular entities, including bioactive molecules (Unuofin & Lebelo, 2020; Macharia *et al.*, 2022; Soussi *et al.*, 2022). *L. nobilis* is a small perennial tree and belongs to the Lauraceae family (Nava *et al.*, 2021). This plant is characterized by its aromatic and fragrant effects, and it is used traditionally against a wide range of diseases, including rheumatism, dermatitis, digestive system disorders, and eructation (Usmani *et al.*, 2021). For example, areal and ground parts of *L. nobilis* are traditionally used in the eastern Mediterranean basin, such as in Türkiye, as diuretic agents (Patrakar *et al.*, 2012). The abundance and diversity of phytochemical content in *L. nobilis* are suggested to be the principal factors of its various biological effects, including the antioxidant ability (Bourebaba *et al.*, 2021; Dobroslavić *et al.*, 2021), antihyperglycemic (Bourebaba *et al.*, 2021), antimicrobial effect (Fidan *et al.*, 2019), and anti-inflammatory effect (Brinza *et al.*, 2021).

Currently, the investigation of phytochemical constituents in *L.nobilis* using a UPLC–MS/MS approach has detected a large range of bioactive substances, including kaempferol and quercetin glycoside as the predominant bioactive compounds (Dobroslavić *et al.*, 2021). Similarly, phytochemical screening via gas chromatography-mass spectrometry analysis showed significant chemical constituents in the acetonic extracts of *Laurus nobilis* (Batiha *et al.*, 2020). The diversity and complexity of the chemical composition of this plant support its capability to normalize caspase activity through modulation of pro-apoptotic pathways and decreasing the gene expression of inflammatory markers such as c-Jun, NF-KB, and Tlr4 transcripts (Bourebaba *et al.*, 2021). Further, the antioxidant potential of *L. nobilis* was investigated on different occasions. Recently, the antioxidant potential of *L. nobilis* was proven by reducing reactive oxygen species (ROS) via the control of the mitochondrial OXPHOS pathway (Bourebaba *et al.*, 2021). By their ability to neutralize the free radical DPPH, the essential oils of *L. nobilis* also demonstrated significant overall antioxidant properties (Mssillou *et al.*, 2020). The chemical constituents of *Laurus nobilis*, such as kaempferol and quercetin, are effective against nephrotoxicity induced by cadmium and calcium oxalate crystal (Guan *et al.*, 2021; Yuan *et al.*, 2021). Further, the synergetic interaction between different pharmacological active components of *L. nobilis* can be attributed to kidney protection.

In this study, we looked into the antioxidant potential of flowers from the *Laurus nobilis* species that were gathered in Northwest Morocco. In parallel, we sought to assess the diuretic activity of two doses of *Laurus nobilis* flowers and contrasted them with a commonly prescribed standard medication. These findings may offer fresh information on the pharmacological characteristics of native *Laurus nobilis* in Morocco and Northwest Africa as well as open up new research directions for comparative investigations in the future.

2. MATERIAL and METHODS

2.1. Preparation Extract

In this study, we used flowers of wild *Laurus nobilis* to prepare the plant extracts. The plant samples were collected in the vicinity of Moulay Bouslham city, Northwest Morocco, in February 2019. Further, sampled flowers were air-dried and crushed to get a fine powder, which

was utilized to prepare the extract. The extraction procedure was performed using a hydroethanolic solution (70%) with maceration. A ratio of ¼ (solid/liquid) was used, and the obtained extract was filtered before future analysis.

2.2. Total Phenolic and Flavonoid Contents

The evaluation of *Laurus nobilis's* antioxidant capacity was built on the total phenolic content (TPC) and total flavonoid content (TFC) measurements. The phenolic content was ascertained using the colorimetric method that (Singleton *et al.,* 1999) had been previously discussed. In brief, 400 liters of sodium carbonate solution (7.5%) were added after 100 liters of extract had been mixed with 500 liters of Folin-Ciocalteu (0.2 N) and vortexed. After two hours of incubation, the absorbance at 760 nm was measured using a spectrophotometer (Perkin Elmer Lambda 40 UV/VIS) using gallic acid as a reference. The results were expressed as milligrams of gallic acid equivalent per gram of extract (mg GAE/g).

The steps provided by Kong *et al.,* (2012) were followed in order to evaluate the flavonoid content. In our case, 100 liters of extract were mixed with 150 liters of aluminum trichloride (AlCl3) (20%), 150 liters of sodium nitrite, and 200 liters of sodium solution. After one hour of incubation at room temperature, the mixture's absorbance was determined at 510 nm using a spectrophotometer (Perkin Elmer Lambda 40 UV/VIS). Mg QE/g, or milligrams of quercetin equivalent per gram of extract, was used to show the results.

2.3. Antioxidant Activity

The antioxidant activity of *Laurus nobilis* flower extract was examined using DPPH and FRAP assays. The scavenging effect of *L. nobilis* extract for the DPPH assay was evaluated using the technique defined by Miguel *et al.,* (2014). In our case, the decrease in absorbance was monitored at 517 nm. The following formula was used to determine the percentage of inhibition of the free radical DPPH:

$$\%\text{inhibition} = \left[\frac{A0 - A1}{A0}\right] * 100$$

where A0 refers to the absorbance of the control and A1 refers to the absorbance of the tested sample.

In addition, the inhibition percentage graph of the tested sample was used to determine the IC_{50} DPPH. On the other hand, the FRAP reagent was used to evaluate the capacity of the prepared extract to reduce ferric. In our case, we used the protocol described by Ferreira-Santos *et al.,* (2019), and the FRAP values were expressed as mg/mL.

2.4. Experimental Design

The investigation was conducted with 12 rats weighing between 180 and 200 g in conventional settings (25 °C, 55 % humidity, and 12/12 h (light/dark)). The methods used in the animal house at Sidi Mohamed Ben Abdellah University were the foundation for the manipulation of the animals. Our institutional committee on animal care approved the protocol, which followed the French Technical Specifications for the Production, Care, and Use of Laboratory Animals. Rats were handled and cared for in accordance with the generally acknowledged standards for the use of animals. The animals were then randomly divided into 4 groups of 3 rats each:

- Group 1: served as a control group and was treated with distal water (10 ml/kg b.w);
- Group 2: received furosemide at a dose of (10 mg/kg b.w);
- Group 3: received dose 1 of flower extract (200 mg/kg b.w);
- Group 4: received dose 2 of flower extract (400 mg/kg b.w).

To assess urine flow, urine volume excreted was measured 2, 4, 8, 12, and 24 hours after oral administration of the extract, furosemide, or distal water.

2.5. Biochemical Analysis

All plasma and urine samples from the tested rates were examined for levels of plasma and urinary creatinine, urea, and electrolytes (sodium, potassium, and chloride). On day 30, each rat's blood and urine were taken for various analyses.

2.6. Statistical Analysis

The findings are expressed as the mean ± SD. Graph Pad Prism 5 software was used to perform one-way analysis of variance (ANOVA) followed by Tukey's test. $p<0.05$ was considered significant.

3. RESULTS

3.1. Antioxidants Activity

The results of the phytochemical content and antioxidant capacity of *L.nobilis* flowers are illustrated in Table 1. The total phenol content of the extract was 14.515± 0.79 mg GAE/g, and the value of flavonoid content was 0.73± 0.19 mg QE/g. Concerning the antioxidant activity, the *L. nobilis* extract exhibited high antioxidant potential with IC_{50} DPPH equal to 0.33±0.04 µg/mL and EC50 FRAP equal to 0.67±0.03 mg/mL.

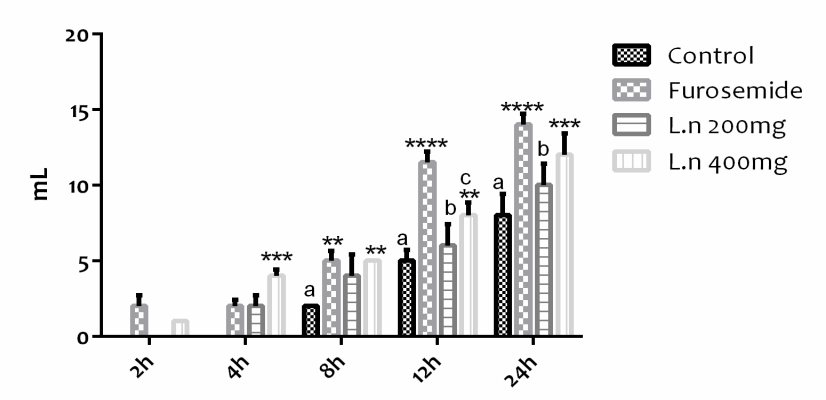
Table 1. Total phenolic and flavonoids contents and antioxidant ability of flower extracts of *L. nobilis.*

	TPC mg GAE/g	TFC mg QE/g	Antioxidant activity	
			IC_{50} DPPH µg/ml	EC_{50} FRAP mg/mL
L. nobilis extract	14.52± 0.79	0.73± 0.19	0.33±0.04	0.67±0.03

3.2. Effect of a Single Dose of *Laurus nobilis* or Furosemide on Urine Volume

The modification of urine flow 24 hours after the administration of both doses of flowers *L. nobilis* extract is presented in Figure 1. The treatment of rats with *L. nobilis* extracts significantly enhanced urine flow after 4 hours of administration. The urine excretion was also increased at each analysis, and the diuresis effect of both doses was significant after 4, 8, 12, and 24 hours ($p<0.05$) compared to the control group (untreated rates). On the other hand, furosemide induced a significant elevation in urine flow compared to the other groups ($p<0.05$).

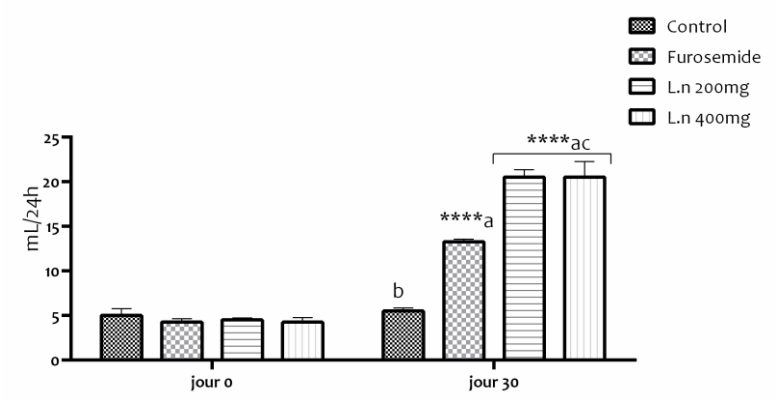
Figure 1. Urine flow of different tested groups during 2 to 24 h of treatment.
(a: Comparison between all groups and the control group;
b: comparison between all groups and the furosemide group; $^{****}<^{**}<^{*}$;
* denote that the value is significantly different from the control with $p<0.05$, $^{**}<0.01$, $^{***}<0.001$).



3.3. Results of Daily Administration of Urine Flow

The effect of *L. nobilis* extract and furosemide on the urine volume of tested rats is presented in Figure 2. The gavage of both doses of *L. nobilis* extracts significantly augmented the urine volume after 30 days of treatment compared to the control group of rats (p<0.05). Equally, the extract of *L. nobilis* significantly augmented the urine flow more than the standard drug (furosemide). The increased rate of urine flow was significantly superior (p<0.05) in the extracts compared to furosemide. In contrast, the obtained results revealed that there were no significant changes between all tested groups on the first day of treatment.

Figure 2. Urine volume in J0 (first day) and J30 (30 days) of treatment.
(a) Comparison between all groups and the control group; (b) comparison between all groups and the furosemide group; (c) comparison between treatments; * denote significant statistic difference and **** denote highly significant difference.



3.4. Impact of Daily Administration of *L. nobilis* Extract on Plasma Parameters

The results of the impact of daily administration of *L. nobilis* extract on plasma urea, creatinine, and electrolytes in tested rats are presented in Table 2. The administration of both doses of *L. nobilis* extract did not induce changes in plasmatic parameters (urea and creatinine) analyzed. Concerning plasmatic electrolytes, furosemide significantly decreased potassium levels after 30 days of treatment. Equally, furosemide induced hypokalemia and presented a significant difference compared to the control group (p<0.05). In contrast, both doses of *L. nobilis* did not induce perturbations of plasmatic electrolytes compared to the control group.

Table 2. Impact of daily administration of two doses of *L. nobilis* extract on plasma urea, creatinine, and electrolytes in normal rats on day 30 ($^{*}p$<0.05 vs control group; #p<0.05 vs the furosemide group).

	Kidney parameters (mg/ml)		Mineral elements (mmol/L)		
Groups	Urea	Creatinine	Sodium	Potassium	Chloride
Control	0.50±0.02	5.00±0.03	164.5±6.40	5.7±0.20#	102.5±5.10
Extract D1	0.43±0.09	5.16±0.22#	170.5±27.5#	5.06±0.44	97.33±1.77*
Extract D2	0.46±0.02	4.80±0.33*	163±15.33	5.1±0.53	107.5±1.50#
Furosemide	0.49±0.02	5.10±0.30	160.2±7.70*	3.9±0.30*	99.75±4.10

3.5. Impact of Daily Administration of *Laurus nobilis* Extract on Urine Parameters

The impact of daily administration of two doses of *Laurus nobilis* extract on urine parameters and electrolytes in rats during 30 days is presented in Table 3. The analysis of recorded results demonstrated that both administered doses of tested extracts significantly increased the elimination of urea and creatinine compared to both the control and furosemide groups (p<0.05). The increased elimination of urea and creatinine was with a dose-dependent effect. The same finding was stated for urine electrolytes. The administration of *L. nobilis* extract significantly boosted the excretion of sodium, potassium, and chloride compared to the standard

drug used (p<0.05). Equally, these results were with a dose-dependent effect. However, the increased excretion did not induce hypokalemia.

Table 3. Impact of daily administration of two doses of *Laurus nobilis* extract on urine urea, creatinine, and electrolytes in rats during 30 days ($^{*}p$<0.05 vs control group. #p<0.05 vs the furosemide group).

	Kidney parameters (mg/dl)		Mineral elements (mEq/dl)		
Groups	Urea	Creatinine	Sodium	Potassium	Chloride
Control	12.89±3.12	47±2.70	108±12.70	62.90±12.70	99±12.00
Extract D1	27.46±1.30*	172.15±28.12*#	122.33±3.77#	392.5±2.50*#	169.33±12.88*#
Extract D2	31±1.33*#	137.80±11.87*#	242±2.66*#	394±4.00*#	276.33±5.11*#
Furosemide	25.76±0.02*	53.1±0.30	147.80±11.90*	160.8±10.9*	198±10.00*

4. DISCUSSION and CONCLUSION

This study revealed new findings on the pharmacological properties and antioxidant potential of wild *L. nobilis* obtained in Northwest Morocco. Our findings assessed the antioxidant potential and determined the amounts of phenolic and flavonoid compounds present in L. nobilis flower extracts. Equally, we evaluated the capacity of *L. nobilis* extracts to improve plasma and urine parameters in rates, which is the first in Morocco and the entire North Africa.

The medicinal plant *L. nobilis* has a number of pharmacological effects (Anzano *et al.*, 2022). In this paper, we studied the antioxidant potential and diuretic effect of the hydroethanolic extract of the wildflowers of *L. nobilis*. The obtained experiments showed that the *L. nobilis* extract demonstrated important antioxidant potential. Moreover, the prepared extracts significantly improved diuretic kidney function with dose-dependent in tested rats. These results were obtained without inducing hypokalemia compared to the control and furosemide drugs (Tables 2 and 3). The standard medication for kidney diseases uses furosemide, which plays a principal role in inhibiting the $Na^{+}/K^{+}/2Cl^{-}$ co-transporter system that enhances urine flow and sodium excretion (Breyer & Jacobson, 1990). Both doses of *L. nobilis* extract enhanced the water, potassium, chloride, and sodium excretion in manipulated rats. In parallel, they prevent the perturbation of plasma electrolyte equilibrium, as shown with the furosemide group (Table 2). Generally, *L. nobilis* is a natural remedy used in traditional medicine and recommended by numerous traditional healers to treat kidney diseases and digestive system disorders (Usmani *et al.*, 2021). It has been demonstrated that extracts of *L. nobilis* show a nephroprotective effect in ant treatment at a level of 300 mg/kg for 9 days without altering kidney histological structure (Taroq *et al.*, 2021). Our results are in agreement with those reported by Taroq *et al.*, (2021). Similar results were also mentioned by Shnewer Mahdi Al-Turfi *et al.*, (2022) in the kidneys of female Wistar rats treated with alcoholic extracts of *L. nobilis*.

The importance of natural products extracted from plants resides in their limited side effects (Tungmunnithum *et al.*, 2018). In our case, treatment of rats with *L. nobilis* extracts did not induce hypokalemia compared to control and furosemide treatments. The beneficial properties of *L. nobilis* were highly associated with its rich chemical composition (Cherrat *et al.*, 2014; Muñiz-Márquez *et al.*, 2014) and predominant phenolic components represented by kaempferol-3-O- hexoside and quercetin-3-Oglucoside (Čulina *et al.*, 2021). In another study, seven compounds, including 1-tricosanol, reynosin, protocatechuic acid, vincetoxicoside B, and vitexin, with strong antioxidant action were detected in *L. nobilis* (Nagah *et al.*, 2021). Therefore, *L. nobilis* exhibits various biological activities, counting antifungal, antiproliferative, cytotoxic, and anti-inflammatory effects (Aourach *et al.*, 2021; Čulina *et al.*, 2021; Olazarán-Santibañez *et al.*, 2021).

Quercetin, as one of phenolic compound of *L. nobilis*, applies an effect on the vascular endothelium, inducing nitric oxide liberation and enhancing vasorelaxation by increasing

kidney filtration (Alarcón-Alonso *et al.*, 2012). Phenolic compounds of *L. nobilis* were implicated in inhibiting Na+/K+ ATPase as a potential way against numerous heart diseases, such as failure and cardiac arrhythmias (Lee *et al.*, 2012). This may be explained by the presence of 0.02±0.001 g EQ/g in the *L. nobilis* extract, and quercetin, as the main component, exerts an effect on the vascular endothelium, enhancing nitrogen monoxide, which is highly associated with diuresis and natriuretic effects (Perez-Rojas *et al.*, 2010). The administration of both doses of *L. nobilis* showed an interesting kind of diuretic ability, interestingly, maintaining the potassium levels in groups treated with the extract studied. In addition, the increase in urinary excretion of potassium and sodium may be due to the considerable content of herbs in mineral salts. The diversity of components of *L. nobilis* and their interaction in vivo could be responsible for the beneficial properties of the studied medicinal plant.

The analysis of the results obtained revealed that the *Laurus nobilis* extract exhibited remarkable antioxidant activity and had a potent diuretic effect after daily administration of two doses in normal rats. Both doses induced significant increases in urine flow and enhanced sodium, potassium, and chloride excretion without affecting serum potassium equilibrium compared to the furosemide group. The findings obtained confirm the utility of *L. nobilis* widely used in traditional medicine and recommended by trade-practitioners.

Acknowledgments

We are grateful to our colleagues who helped in collecting data.

Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

Nor El Houda Tahiri: Visualization, Formal analysis, Writing – original draft, Writing – review & editing. **Asmae El Ghouizi**: Visualization, Formal analysis, Writing – original draft, Writing – review & editing. **Abderrazak Aboulghazi**: Data curation, Writing – review & editing. **Najoua Soulo**: Data curation, Writing – review & editing. **Badiaa Lyoussi**: Data curation, Writing – review & editing. **Lalla Aicha Lrhorfi**: Data curation, Writing – review & editing.

Orcid

Nor El Houda Tahiri https://orcid.org/0000-0001-9483-0125
Asmae El Ghouizi https://orcid.org/0000-0002-7136-8422
Abderrazak Aboulghazi https://orcid.org/0000-0002-0354-7998
Najoua Soulo https://orcid.org/0000-0003-2091-489X
Badiaa Lyoussi https://orcid.org/0000-0001-6090-6558
Lalla Aicha Lrhorfi https://orcid.org/0000-0001-9045-6623

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