

BIBLIOGRAPHIC INFORMATION SYSTEM

Journal Full Title: [Journal of Biomedical Research & Environmental Sciences](#)

Journal NLM Abbreviation: J Biomed Res Environ Sci

Journal Website Link: <https://www.jelsciences.com>

Journal ISSN: 2766-2276

Category: Multidisciplinary

Subject Areas: [Medicine Group](#), [Biology Group](#), [General](#), [Environmental Sciences](#)

Topics Summation: 133

Issue Regularity: [Monthly](#)

Review Process: [Double Blind](#)

Time to Publication: 21 Days

Indexing catalog: [IndexCopernicus ICV 2022: 88.03](#) | [GoogleScholar](#) | [View more](#)

Publication fee catalog: [Visit here](#)

DOI: 10.37871 ([CrossRef](#))

Plagiarism detection software: [iThenticate](#)

Managing entity: USA

Language: English

Research work collecting capability: Worldwide

Organized by: [SciRes Literature LLC](#)

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**IndexCopernicus
ICV 2022:
83.03**

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ORIGINAL ARTICLE

Evaluation of the Effect of *Ligaria cuneifolia* Infusion on Plasma Cholesterol and Liver and Kidney Function in Patients with Cardiovascular Risk

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Abstract

Ligaria cuneifolia (R. et P.) Tiegh. –Loranthaceae– (*Lc*), commonly used in traditional medicine, is believed to reduce total plasma cholesterol (TC) and improve blood flow.

Objective: To evaluate the effect of ingesting *Lc* infusions on plasma cholesterol, Whole Blood Viscosity (WBV), Hepatic Function (HF), and Renal Function (RF) in patients with cholesterol levels >200 mg/dL.

Methods: Twelve patients were studied. Baseline venous Blood samples (B) were collected for initial measurements. Each participant received freeze-dried *Lc* extract to be ingested as an infusion three times per week. After 31 days, post-treatment blood samples (*TLc*) were obtained. Plasma determinations included: TC, High-Density Lipoprotein Cholesterol (HDL-C), Low-Density Lipoprotein Cholesterol (LDL-C), urea, and creatinine using enzymatic methods (mg/dL); Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), and Aspartate Aminotransferase (AST) using kinetic methods (U/L); and WBV using a rotational viscometer. Relative Blood Viscosity (RBV) was calculated.

Statistical analysis

Wilcoxon test for paired data. Results (median and 95% CI): TC: B: 230 (205-278); *TLc*: 229.6 (200-251) ns; HDL-C: B: 59 (42-84); *TLc*: 63.5 (35-76) ns; LDL-C: B: 185.5 (140-239); *TLc*: 169.5 (135-215) *; RBV: B: 2.99 (2.5-3.38); *TLc*: 3.05 (2.20-3.79) ns; AST: B: 21.5 (15-30); *TLc*: 20.5 (15-32) ns; ALT: B: 21 (6-31); *TLc*: 17.5 (7-27) *; ALP: B: 77 (55-100); *TLc*: 77 (70-100) ns; urea: B: 31.5 (22-52); *TLc*: 33 (22-49) ns; creatinine: B: 0.89 (0.711-1.22); *TLc*: 0.83 (0.580-1.13) ns. (**p* < 0.05 vs B; ns = n significant vs B). Conclusion: The treatment significantly reduced LDL-C levels without altering TC, HDL-C, RBV, RF, AST, or ALP. ALT, a biochemical marker of hepatic steatosis, was also significantly reduced. Given the association between LDL-C and atherosclerosis, these findings suggest *Lc* could be a viable option for cardiovascular disease prevention.

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DOI: 10.37871/jbres2139

Submitted: 27 June 2025

Accepted: 04 July 2025

Published: 09 July 2025

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OPEN ACCESS

VOLUME: 6 ISSUE: 7 - JULY, 2025



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How to cite this article: Pons F, Perez M, Ferrero M, Urli L, Gonzalez J, Alonso J, De Vuono D, Dobrecky C, Leiva R, Wagner M, Carnovale C, Luquita A. Evaluation of the Effect of *Ligaria cuneifolia* Infusion on Plasma Cholesterol and Liver and Kidney Function in Patients with Cardiovascular Risk. J Biomed Res Environ Sci. 2025 Jul 09; 6(7): 862-867. doi: 10.37871/jbres2139, Article ID: JGRES2139, Available at: <https://www.jelsciences.com/articles/jbres2139.pdf>

Introduction

Argentina is home to a rich biological diversity, much of which is concentrated in its forest regions. Indigenous and rural communities have long-standing relationships with nature and make use of its resources. Among the species found in these regions is *Ligaria cuneifolia*, commonly known as “muérdago criollo” or “liga,” traditionally used to alleviate hypertension and promote blood circulation (Figure 1).

The validation of traditional knowledge about this plant is essential—not only for the identification of bioactive compounds but also for its potential as a phytotherapeutic agent in primary healthcare. A survey in Buenos Aires-area clinics revealed that 50% of patients reported using medicinal plants alongside or instead of prescribed medications, with higher percentages in other provinces [1].

This growing interest in natural therapies is driven by multiple factors: a cultural shift toward inclusive public health practices, perceived lower side-effect profiles of natural remedies, a generalized belief that “natural” means harmless, the adverse effects of polypharmacy, and increased popularity of “bio” consumption in urban cultures. Simultaneously, the global market for herbs, essential oils, and over-the-counter phytotherapeutic products continues to expand [2], supported in Argentina by ANMAT regulations since 1998.

In 2012, the National Strategic Socio-Productive Core in Phytomedicine was launched under the Argentina Innovadora 2020 plan, promoting the application of scientific research in the development of phytopharmaceuticals. Twelve native species were



Figure 1 *Ligaria cuneifolia* (Ruiz & Pav.) Tiegh, Lorantheaceae.

prioritized for bioprospective research, among them *Ligaria cuneifolia*.

Despite growing interest, most studies on medicinal plants still focus primarily on toxicology rather than efficacy or safety, and often isolate single compounds, ignoring their traditional and cultural context.

Ligaria cuneifolia (*Lc*), commonly known as “liga,” “liguilla,” or “muérdago criollo,” is a hemiparasitic plant widely distributed throughout central and northern Argentina. It belongs to the Loranthaceae family and, like other species in this group, infusions made from its leaves and stems have been traditionally used in folk medicine due to their therapeutic properties [3].

Traditionally, *Lc* infusions have been used to lower blood pressure and plasma cholesterol levels, enhancing blood “fluidity,” in a way like European mistletoe, to which such effects were originally attributed [4]. Although *Lc* has been used as a natural substitute for European mistletoe due to their similar appearance, anatomical analyses revealed that they belong to different botanical families and that their macro- and micromolecular components differ significantly. This distinct chemical composition has led to the detection of mixed or adulterated preparations, where European mistletoe is replaced by the Argentine species [5,6].

In dogs, intravenous administration of a 30% maceration or 5% infusion of *Lc* induced a decrease in blood pressure [7]. Pharmacological and phytochemical studies conducted by the Pharmacobotany Department at UBA revealed the presence of tyramine [8,9], a compound with sympathomimetic activity. This implies that intravenous administration of *Lc* extract could potentially induce hypertension. Previous studies in rats have identified a vasoactive agent in *Lc* infusions with a pressor effect mediated by direct action on alpha-adrenoreceptors, and a hypotensive agent mediated by beta-adrenoreceptors. These effects were observed particularly when the plant parasitized hosts like *Acacia caven* (Mol.) Molina (Mimosaceae) and *S. polygamus*. Thus, the physiological impact varies depending on the plant’s origin and host species [10].

Since 1998, our research team has been conducting a project using *Ligaria cuneifolia* extracts, involving collaboration between the Department



of Pharmacobotany at the Faculty of Pharmacy and Biochemistry (UBA), the Department of Biophysics at the Faculty of Medical Sciences (UNR), and the Institute of Experimental Physiology (IFISE-UNR).

Through both in vitro and in vivo experiments (using Wistar rats), we have generated data that support a scientific reinterpretation of *Lc*'s traditional use and open new experimental horizons.

Laboratory studies have shown that administering crude *Lc* extract intraperitoneally in Wistar rats (doses of 1.5, 2.5, 3.5, 5.5, and 8.3 mg/100g body weight) led to a 40% reduction in plasma cholesterol levels. This reduction was associated with increased biliary excretion of cholesterol and bile salts-end products of hepatic cholesterol metabolism-resulting in elevated overall bile flow [11]. However, a concurrent increase in blood viscosity and erythrocyte rigidity was also observed. Clinically, this finding contradicts traditional beliefs, which claim that *Lc* consumption improves blood fluidity (i.e., reduces viscosity). This research project was approved by the Bioethics Committee of the Faculty of Medical Sciences under Resolution No. 873/1999.

Intravenous administration of crude *Lc* extract (at doses of 2.5 and 5.5 mg/100g body weight) did not significantly alter biliary parameters or plasma cholesterol levels. However, as with the intraperitoneal route, an increase in erythrocyte rigidity and blood viscosity was observed, suggesting a direct effect of *Lc* on red blood cell internal viscosity [12].

Subsequently, with the intraperitoneal administration of the Methanolic Fraction of *Ligaria cuneifolia* (FMLc), a behavior like that of the total extract was observed both in the hemorheological profile and in liver function [13].

Given these findings and recognizing that *Lc* is frequently consumed as an herbal infusion readily available in commercial preparations, we were prompted to investigate its hemorheological, hepatic, and renal effects in patients with cardiovascular risk factors under clinical observation.

Objectives

To analyze the effect of ingesting aqueous infusions made from the leaves and stems of *Ligaria cuneifolia* on plasma cholesterol levels in patients with cardiovascular risk, and to evaluate the potential

occurrence of undesirable effects on Hepatic Function (HF) and Renal Function (RF) that may be attributable to the infusion.

Materials and Methods Plant Material

The plant material was collected in the province of Córdoba, selecting specimens that parasitized Chañar trees. The harvested plants were then dried at room temperature. Sufficient quantities of ground leaves and herbaceous stems of *Ligaria cuneifolia* were weighed to prepare a 5% infusion, following the standards of the Argentine Pharmacopeia, 8th edition. The infusion was freeze-dried and packaged into individual sachets (2.5 g each), which were subsequently sent to the Department of Biophysics at the Faculty of Medical Sciences, National University of Rosario (UNR).

Both the collection of specimens and their processing, packaging, and transportation were conducted by the team from the Department of Pharmacobotany, Faculty of Pharmacy and Biochemistry, University of Buenos Aires (UBA).

Patients

Twelve volunteer patients were studied (age: 50 ± 15 years; 8 women and 4 men), all attending the outpatient clinic of the Cardiology Service at the Provincial Hospital "Centenario" for routine follow-up. An interview was conducted to collect medical history regarding previous hypercholesterolemia, presence of established atherosclerotic disease, diabetes, or cardiovascular risk factors other than dyslipidemia, in order to stratify individual cardiovascular risk according to ATP III guidelines and Framingham tables. For this purpose, a questionnaire was designed based on the WHO STEPwise approach for monitoring chronic diseases.

Inclusion criteria included elevated cholesterol levels according to ATP III guidelines and Framingham tables (considering sex, age, hypertension, smoking status), without current indication for statin therapy. Exclusion criteria included patients with established cardiovascular disease, diabetes, strict indication for statins, chronic renal or hepatic disease, cancer, infectious diseases, or any medication with hemorheological effects.

All patients received clear and updated information about *Lc* and the objectives of the study. Upon providing written informed consent, participants

completed the questionnaire to gather demographic and clinical risk factor data.

Each participant was scheduled for an appointment at the Central Laboratory of the Provincial Hospital “Centenario.” Venous blood samples were collected after 9 to 12 hours of fasting to obtain baseline cholesterol levels and hemorheological parameters. Additional laboratory tests included hematimetric indices, glycemia, renal, hepatic, and thyroid function to identify potential confounding factors.

Following this initial evaluation, each patient was offered a regimen of *Lc* extract to be ingested three times per week for one month. The herbal preparation was delivered in pre-dosed sachets with instructions for infusion preparation using potable hot water.

Administration of the Extract

The freeze-dried *Lc* extract was provided in 2.5 g sachets to be dissolved in 100 ml of potable hot water (equivalent to a cup of tea). The prescribed intake was three times per week, between meals, over a period of 30 days.

Laboratory Determinations

Biochemical analyses were performed at the Central Laboratory of the Hospital Centenario, while hemorheological assessments were carried out in the Blood Biology Laboratory of the Department of Biophysics, Faculty of Medical Sciences, UNR.

The following biochemical and hemorheological tests were performed:

Cholesterol determinations: Total Cholesterol (TC), High-Density Lipoprotein Cholesterol (HDL-C), and Low-Density Lipoprotein Cholesterol (LDL-C) were measured using enzymatic esterase-oxidase methods (mg/dL) with commercial detection kits.

- **Hematologic tests:** Red Blood Cell (RBC) count, White Blood Cell (WBC) count, platelet count, leukocyte differential, Hematocrit (Hct), and Hemoglobin (Hb) levels.
- **Blood and Plasma Viscosity (WBV and PV):** Measured using a Wells-Brookfield LVT-CP rotational viscometer at a shear rate of 230 s⁻¹. Relative blood viscosity standardized to a hematocrit of 45% (RBV) was calculated using the formula: $(WBV/PV)^{45/Hct}$.

- **Hepatic function:** Enzyme activity in serum was measured for Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT) using kinetic methods (U/L) with Wiener Lab instruments.
- **Renal function:** Serum concentrations of urea and creatinine were measured using enzymatic methods (mg/dL), also with Wiener Lab instruments.

All tests were conducted both prior to and following the 30-day treatment period with *Lc*, in order to assess any statistically significant changes.

Statistical Analysis

In all cases, the Wilcoxon test for paired data was applied.

Results and Discussion

As shown in table 1, treatment with aqueous infusions of *Ligaria cuneifolia* over a 31-day period in hypercholesterolemic patients resulted in a significant reduction in LDL-C levels, without causing changes in Total Cholesterol (TC) or HDL-C levels.

Regarding Hepatic Function (HF), a significant decrease in ALT levels was found after treatment with *Lc* compared to baseline values. The observed decrease in ALT levels after treatment with *Ligaria cuneifolia* may reflect an improvement in subclinical hepatic stress or lipid-related hepatocellular dysfunction commonly present in hypercholesterolemic states. Alanine Aminotransferase (ALT) is a sensitive marker of hepatocellular injury and is often modestly elevated in patients with dyslipidemia or early Non-Alcoholic Fatty Liver Disease (NAFLD), even in the absence of overt clinical symptoms [14]. The reduction in ALT, in the absence of changes in other hepatic enzymes (ALP), supports the hypothesis of a mild hepatoprotective effect exerted by the extract. This is consistent with previous preclinical studies in hypercholesterolemic Wistar rats, where *Lc* extracts rich in proanthocyanidins were associated with attenuation of hepatic steatosis in histological analyses [15]. Taken together, these findings suggest that *Ligaria cuneifolia* may exert beneficial effects not only on lipid metabolism but also on liver function, potentially reducing the risk of hepatic complications commonly associated with atherogenic dyslipidemia (Table 2).

Table 1: Plasma values of TC, HDL-C, and LDL-C in hypercholesterolemic patients: Baseline vs. post-treatment with Lc (30 days).

	TC (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)
B	230 (205-278)	59 (42-84)	185.5 (140-239)
Tlc	229.6 (200-251) ns	63.5 (35-76) ns	169.5 (135-215)*

Data are presented as median (95% CI). $p < 0.05$ vs baseline; ns: not significant vs baseline.

TC: Total Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; Tlc: post-treatment with *Ligaria cuneifolia*.

Treatment with *Ligaria cuneifolia* significantly reduced LDL-C levels after 30 days, with no significant change in total or HDL cholesterol.

Table 2: Hepatic function parameters in hypercholesterolemic patients: Baseline vs. treated with Lc (30 days).

	AST (U/I)	ALT (U/I)	ALP (U/I)
B	21.5 (15-30)	21 (6-31)	77 (55-100)
Tlc	20.5 (15-32) ns	17.5 (7-27)*	77 (70-100) ns

Data are expressed as median (95% CI). $p < 0.05$ vs baseline; ns: not significant vs baseline. AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; Tlc: post-treatment with *Ligaria cuneifolia*.

ALT levels were significantly reduced after treatment, suggesting a potential improvement in hepatic steatosis, while AST and ALP remained unchanged.

As shown in table 3, no significant differences were observed in Renal Function (RF) parameters between Baseline (B) and post-treatment (Tlc) values in the patients studied.

Regarding blood rheological properties, no significant differences were observed in the relative blood viscosity standardized to a hematocrit of 45% (RBV) between baseline and post-treatment samples:

B: 3.50 (3.47–3.50) vs Tlc: 3.06 (3.02–3.10) ns.

Conclusions

In the patients studied, the treatment with aqueous extract of *Ligaria cuneifolia* leaves and stems produced a significant reduction in LDL-C levels without inducing changes in Total Cholesterol (TC), HDL-C, or in blood fluidity, as assessed by standardized Relative Blood Viscosity (RBV).

In addition to its LDL cholesterol-lowering

effect, treatment with the aqueous extract of *Ligaria cuneifolia* produced a significant reduction in serum ALT levels, without affecting ALP levels.

Given that ALT is an established biochemical marker of hepatic stress and steatosis, this finding may indicate a hepatoprotective action, consistent with previous experimental evidence in animal models. The absence of changes in renal function and the favourable safety profile observed reinforce the potential of *Ligaria cuneifolia* as a safe adjunct therapy in patients with dyslipidemia and elevated cardiovascular risk, potentially contributing to the maintenance of hepatic metabolic homeostasis.

As for renal function, no significant differences were observed in serum levels of urea or creatinine following treatment.

These results suggest that *Ligaria cuneifolia* may be a potentially useful therapeutic tool for the prevention

Table 3: Renal function parameters in hypercholesterolemic patients: Baseline vs. treated with Lc (30 days).

	Urea (mg/dl)	Creatinine (mg/dl)
B	31.5 (22-52)	0.86 (0.71-1.22)
Tlc	33 (22-49) ns	0.80 (0.58-0.13) ns

Data are presented as median (95% CI). $p < 0.05$ vs baseline; ns: not significant vs baseline. Tlc: post-Treatment with *Ligaria cuneifolia*.

No significant changes were observed in renal function markers after 30 days of treatment, suggesting that *Ligaria cuneifolia* did not adversely affect kidney function.

of cardiovascular disease, by reducing plasma levels of LDL-C, a lipoprotein fraction strongly associated with the development of atherosclerosis.

Acknowledgment

We thank the Research Council of the National University of Rosario (UNR), IFISE-CONICET, and the University of Buenos Aires (UBA) for their financial support.

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