Ensaios e Ciência
ISSN 1415-6938 e ISSN 2178-695X

DOI: 10.17921/1415-6938.2025v29n3p670-680

Antimicrobial Activity and Synergism Between *Coix lacryma-jobi* Extract and Three Antibiotics Against *Pseudomonas aeruginosa*

Atividade Antimicrobiana e Sinergismo Entre o Extrato de *Coix lacryma jobi* e Três Antibióticos Contra *Pseudomonas aeruginosa*

Received on: February 04, 2025
Accepted on: June 23, 2025

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Abstract

There is a wide variety of plants with active ingredients with antimicrobial activity. *Coix lacryma-jobi,* one of the species whose compounds have already been identified, is popularly known as Job's tear and has been used to treat various diseases, such as rheumatic diseases, neuralgia and female endocrine disorders, as it has anti-inflammatory, antitumor, antiallergic, and antimicrobial properties. The objective of this study was to evaluate the synergism of polar extract of *Coix lacryma-jobi* and antibiotics (ciprofloxacin, chloramphenicol and gentamicin) against the bacterium Pseudomonas aeruginosa. The material was collected in a vacant lot, it was dried in a forced air oven and ground in a blender and subjected to extraction in organic solvent ethyl acetate, over 28 days occasional agitations were made, then the bottle was reserved at room temperature for solvent evaporation. The extract was tested along with specific antibiotics for *P. aeruginosa*. It was concluded that the extract of the leaves of *C. lacryma-jobi* has an inhibitory effect against the strain of *Pseudomonas aeruginosa* tested. There was synergism between the leaf extract and gentamicin increasing its antimicrobial activity. It was also observed that the strain showed high tolerance to chloramphenicol, and that it inhibited the effect of *C. lacryma-jobi* extract. Further tests, especially in vivo, are suggested to evaluate the efficacy or otherwise of using the antibiotic gentamicin together with *C. lacryma-jobi* extract, and to better understand the antagonistic effect demonstrated to chloramphenicol.

Keywords: *P. aeruginosa*. *Coix lacryma-jobi*. Medicinal Plants.

Resumo

Há uma grande variedade de plantas com princípios ativos com atividade antimicrobiana. *Coix lacryma-jobi*, uma das espécies cujos compostos já foram identificados, é conhecida popularmente

como lágrima de Jó e tem sido utilizado para tratar diversas doenças, como doenças reumáticas, neuralgia e distúrbios endócrinos femininos, pois a mesma possui propriedades anti-inflamatórias, antitumoral, antialérgica, e efeitos antimicrobianos. O objetivo do trabalho foi avaliar o sinergismo do extrato polar de *Coix lacryma-jobi* e antibióticos (ciprofloxacino, cloranfenicol e gentamicina) contra a bactéria *Pseudomonas aeruginosa.* O material foi coletado em um terreno baldio, o mesmo foi seco em estufa de ar forçado e moído em liquidificador e submetido à extração em solvente orgânico acetato de etila, ao longo de 28 dias foram feitas agitações ocasionais, em seguida, o frasco foi reservado em temperatura ambiente para evaporação do solvente. O extrato foi testado juntamente com antibióticos específicos para *P. aeruginosa*. Concluiu-se que o extrato das folhas de *C. lacryma-jobi* apresenta efeito inibitório contra a cepa de *Pseudomonas aeruginosa* testada. Houve sinergismo entre o extrato das folhas e gentamicina aumentando sua atividade antimicrobiana. Pôde-se observar ainda, que a cepa apresentou alta tolerância ao cloranfenicol, e que inibiu o efeito do extrato de *C. lacryma-jobi*. Sugerem-se mais testes, principalmente in vivo, para que possa ser avaliada a eficácia ou não da utilização do antibiótico gentamicina juntamente com o extrato de *C. lacryma-jobi*, e para uma maior compreensão do efeito antagônico demonstrado ao cloranfenicol.

Palavras-chave: *P. aeruginosa*. *Coix lacryma-jobi.* Plantas Medicinais.

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1 Introduction

Whether due to cultural aspects or the ease of access, it is known that around 80% of the world population resorts to the use of medicinal plants as alternatives and/or adjuncts in various disease treatments (WHO, 2021). In Brazil, since 2006, phytotherapy has been considered a complementary or alternative therapy to improve health and is widely promoted within the public healthcare system (Brasil, 2006).

According to Qadri *et al*. (2022), the use of plant extracts as antimicrobial agents offers little opportunity for microbial resistance, as they possess pharmacological compositions of high complexity. Their antimicrobial activity is commonly linked to multiple mechanisms of action, which hinders microbial adaptation and targeted selection.

Dos Santos *et al*. (2019) state that the use of extracts derived from phytotherapy in the healthcare field is increasing due to the ongoing search for new drugs with high efficacy and low toxicity.

The medicinal plant *Coix lacryma-jobi* (Poaceae), popularly known as Job's Tears or Rosary Tears, originates from India and Myanmar and is currently widely distributed in tropical and warm temperate regions (Soni *et al*., 2023). It can be found throughout the Americas, Africa, and Oceania, as well as in northeastern India, southern China, Myanmar, the Philippines, Indonesia, Vietnam, Papua New Guinea, Bhutan, China, Cambodia, Thailand, Laos, Japan, Korea, Malaysia, and was also introduced to Honduras, Ecuador, and Brazil (Shouliang; Phillips, 2006; Zuloaga *et al*., 2003).

This species exhibits anti-inflammatory, antioxidant, antitumor, antiallergic, and antimicrobial properties (Acharya *et al*., 2024; Chung *et al*., 2011; Yu *et al*., 2011). Its antimicrobial effect is well

described against *Pseudomonas aeruginosa*, an opportunistic pathogen responsible for nosocomial infections (Dutra *et al*., 2023).

Pseudomonas aeruginosa is considered one of the most common hospital pathogens and is frequently isolated from patients with ventilator-associated pneumonia. It has low membrane permeability, which prevents certain antibiotics from penetrating, rendering them ineffective (Breidenstein; De La Fuente-Núñez; Hancock, 2011; Dutra *et al*., 2023; Hidron *et al*., 2008;).

Natural extracts that increase membrane permeability in *P. aeruginosa* may enhance the antimicrobial effect of commercial antibiotics, thereby increasing their efficacy and reducing the likelihood of directional selection for resistant strains (Álvarez-Martinez *et al*., 2021; Caldeira *et al*., 2015).

The objective of this study was to evaluate the synergism between the polar extract of *Coix lacryma-jobi* and antibiotics (ciprofloxacin, chloramphenicol, and gentamicin) against *Pseudomonas aeruginosa*.

2 Material and Methods

The collections were carried out in the city of Guarapuava, Paraná, on September 28th, 2018, at 9:00 a.m., in a vacant lot near the Carro Quebrado river in the Bairro dos Estados (Lat: -25.382094 Long: -51.479908). The botanical material was taken for identification to the botany laboratory at the Universidade do Centro-Oeste (Unicentro), under the care of Dr. Tania Maria de Moura, who identified it as *Coix lacryma-jobi*. The procedures were conducted in the laboratories of the Centro Universitário Campo Real.

The material, previously dried and ground in a blender, underwent extraction from different parts of the plant (leaves, stems, roots, and seeds), which were separated into portions of 50 g for stem, leaf, and seed, and 25.5 g for root. These portions were then placed into amber bottles and submerged in 70% ethyl acetate (Gomes; Almeida, 2020).

The bottles were sealed and kept under agitation for 28 days. After this period, they were opened and left at room temperature inside a fume hood to allow for solvent evaporation. During this time, the bottles were weighed daily until no further weight variation was observed in three consecutive measurements. The liquid was then filtered using filter paper and stored in a separating funnel, from which the supernatant was collected and used for microbial activity tests. For this study, the extract obtained from the plant's leaves was used.

The strain used — *Pseudomonas aeruginosa* (NEWP 0027) — was kindly provided by the laboratories of Centro Universitário Campo Real from previous projects. The bacteria were maintained on Mueller Hinton agar in a bacteriological incubator at 35°C for 24 hours to prepare the inoculum.

For antimicrobial tests, a single colony was suspended in saline to adjust turbidity according to the 0.5 McFarland standard. Then, 25 µL of the standardized bacterial suspension was inoculated on Mueller Hinton agar and spread using a Drigalsky loop.

The antibiogram model followed the Bacteria from Environment and Health Collection (CBAS) laboratory protocol at Instituto Oswaldo Cruz, Fundação Oswaldo Cruz (Fiocruz).

Mueller-Hinton agar was prepared using 23 mL per plate, and the test was performed in quintuplicate. The agar was poured into all plates, which were then sealed with PVC film. Plates were stored for five days in an incubator at 25 °C and then for an additional two days at 37 °C to check for possible fungal or bacterial contamination.

The plates were stored in a refrigerator until use and were removed about 30 minutes prior to testing to reach room temperature.

Next, using a properly flamed and cooled platinum bacteriological loop, a fresh colony (18–24 h) was suspended in sterile saline solution (0.85% NaCl) until reaching turbidity equivalent to 0.5 on the McFarland scale ($1x10^6$ CFU/mL), using a reference tube with 0.5 McFarland standard as comparison.

A sterile swab was then immersed in the bacterial suspension, pressed against the inner wall of the tube to remove excess liquid, and gently spread across the agar surface in five directions to ensure full plate coverage.

Once the agar surface dried, sterile tweezers (previously flamed and cooled) were used to place the test disks on the inoculated medium. A slight pressure was applied to ensure proper disks adherence.

To prepare the disks containing the *Coix lacryma-jobi* extract, sterile blank disks were used, and 10 µL of the extract was applied to each. For the synergism test, antibiotic disks (as previously described) were used, and 10 µL of the extract was added directly to those disks.

The plates with the disks were incubated in a bacteriological incubator at 37°C for 18 to 24 hours. Inhibition zones were measured using a caliper.

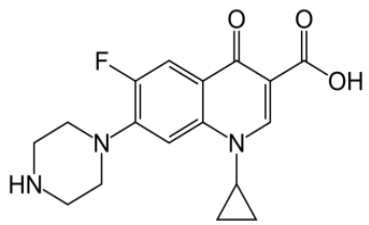
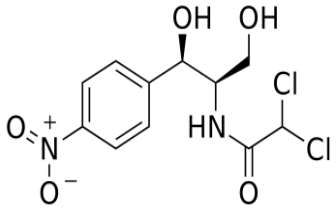
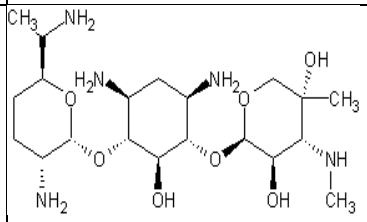
The data were tabulated in Excel software, and a paired t-test was performed between the values of the antibiotics alone and in combination with the extract using XLSTAT software to verify the existence of statistically significant differences ($p < 0.05$).

3 Results and Discussion

Among the antibiotics tested, only ciprofloxacin (*monopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid*) (Figure 1) showed high efficacy against the *Pseudomonas aeruginosa* strain (Figure 2). This antibiotic belongs to the group of quinolone

antibacterials, has a broad spectrum of action, and is effective *in vitro* against virtually all Gram-negative pathogens, including *Pseudomonas aeruginosa*.

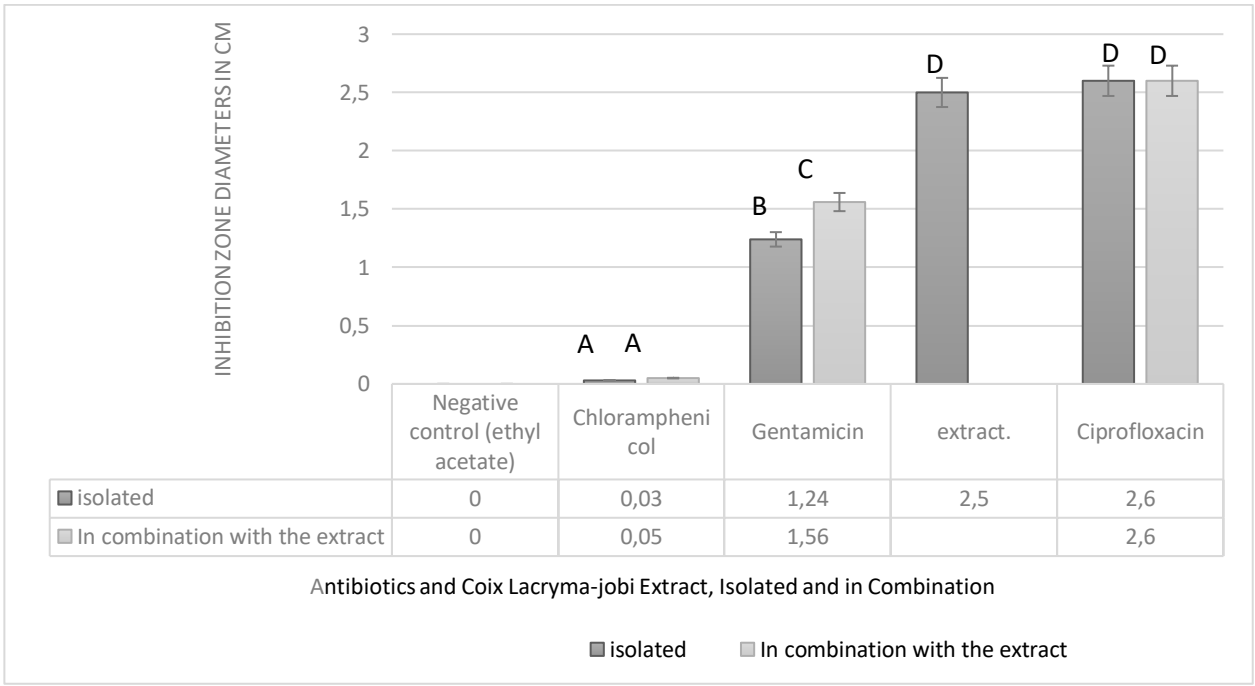
Figure 1 - Molecular Structures of the Antibiotics Used in This Experiment

Ciprofloxacin	Chloramphenicol	Gentamicin
		

Source: research data.

The *in vitro* tests conducted using the *Coix lacryma-jobi* extract and the antibiotics showed no synergistic effect between the two. Chloramphenicol did not exhibit a significant level of antimicrobial activity against the tested strain (Figure 2), nor did it show any synergistic effect.

Figure 2 - Average Inhibition Zones Formed Against *Pseudomonas aeruginosa*



Source: research data.

It is also effective against Gram-positive microorganisms, such as *Staphylococcus* and *Streptococcus* species. The main ciprofloxacin mechanism of action is to inhibit DNA replication by blocking the A subunit of DNA gyrase (topoisomerase II and topoisomerase IV), and it also has an additional effect on substances in bacterial cell walls (Shariati *et al*., 2022).

Especially against Gram-negative bacteria, due to its structural formula (Figure 1), ciprofloxacin is effective against beta-lactamase-producing bacteria (Millanao *et al*., 2021). In the present experiment, no synergistic or antagonistic interaction with *Coix lacryma-jobi* oil was observed for this antibiotic (Figure 2).

According to Andriole (1999) and Millanao *et al*. (2021), quinolones rarely exhibit synergism or antagonism with other agents due to their molecular structure, which features highly stable ring systems (Figure 1).

The figure exhibits the average inhibition zones for: the control group; chloramphenicol alone and combined with the extract; gentamicin alone and combined with the extract; the extract alone; and ciprofloxacin both alone and in combination. Identical letters indicate no statistically significant difference (paired t-test, 0.05 confidence interval).

Chloramphenicol is a broad-spectrum antimicrobial agent that acts against both Gram-negative and Gram-positive bacteria (Balbi, 2004; Del Fiol; Avallone, 2005; Singhal *et al*., 2023). It is a protein synthesis-inhibiting antibiotic that blocks the 50S subunit of the bacterial ribosome, hindering ribosome movement along the mRNA, possibly by inhibiting peptidyl transferase, the enzyme responsible for elongating the peptide chain (Jardetzky, 1963; Balbi, 2004; De Fariña; Poletto, 2010). According to Oliveira *et al*. (2006), among Gram-negative strains, *Pseudomonas aeruginosa* stands out for its high resistance to chloramphenicol, which supports our results.

According to Lorusso *et al*. (2022), the genome of this bacterium is relatively large (5.5–7 Mbp) compared to other sequenced bacteria. This indicates that the genome of *P. aeruginosa* encodes a large proportion of regulatory enzymes crucial for metabolism, transport, and efflux of organic compounds, which contributes to its intrinsic resistance to antibiotics and high adaptability to environmental changes. These efflux pumps are trimeric complexes that function as drug/proton antiporters, catalyzing the extrusion of specific substrates from the periplasm through the outer membrane. They are composed of three different proteins: a periplasmic adaptor protein, commonly known as a periplasmic membrane fusion protein (PMFP), such as MexA, MexX, MexC, or MexE; a resistance-nodulation-cell division transporter (RNDt), such as MexB, MexY, MexD, or MexF; and an outer membrane factor (OMF) forming a channel, such as OprM, OprJ, or OprN (Lorusso *et al*., 2022).

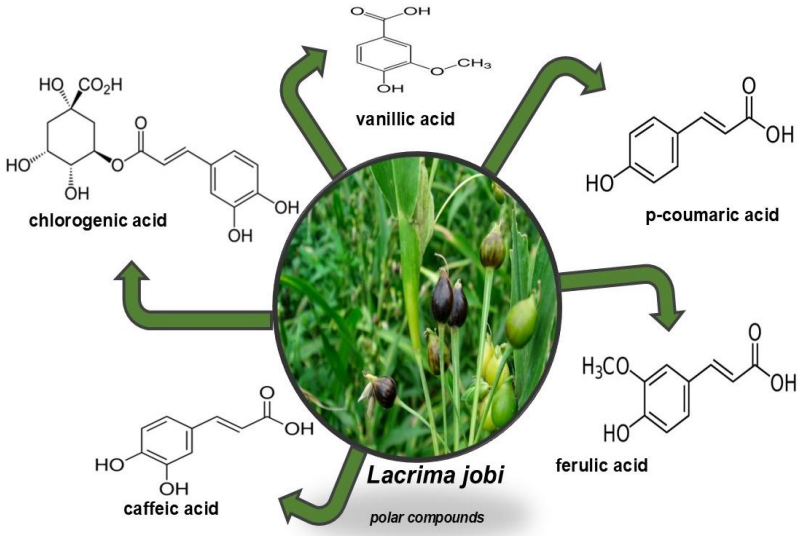
In our experiment, no synergism was observed with the *Coix lacryma-jobi* oil. However, antagonism occurred — the antibiotic inhibited the oil effect . We infer that the efflux pumps activated by the presence of chloramphenicol may also have inhibited the effect of the compounds present in the extract; however, this was not specifically evaluated.

Gentamicin has high activity against most Gram-negative bacilli (Baggio, 2010; Karunarathna *et al*., 2024). In this experiment, it produced an average inhibition zone of 12.4 mm (Figure 2), which

was lower than the activity presented by ciprofloxacin. According to Germoni, Bremer, Lamont (2016), *Pseudomonas aeruginosa* may secrete large amounts of alginate during chronic infections, which has been associated with high antibiotic resistance. It is possible that the limited activity of gentamicin against the tested strain is related to this characteristic.

The *Coix lacryma-jobi* extract showed antimicrobial efficacy comparable to that of ciprofloxacin, with no statistically significant differences between their mean inhibition zones. According to Chhabra and Gupta (2015), *Coix lacryma-jobi* extract contains several compounds with antimicrobial activity. Antimicrobials are chemical substances capable of inhibiting microbial growth or inducing microbial death (Seija; Vignoli, 2006).

Figure 3 - Chemical Compounds Extracted from the Polar Fraction of *Coix lacryma-jobi*, Adapted from Chhabra and Gupta (2015)



Source: research data.

Among these compounds, the polar ones already described for *Coix lacryma-jobi* include chlorogenic acid, a phenolic compound extracted from the plant that has recently gained significant attention as a potential antimicrobial agent. The antimicrobial activity of this compound has been reported against *Escherichia coli* O157:H7, *Listeria innocua*, and the fungi *Penicillium chrysogenum* and *Candida albicans* (Muthuswamy; Rupasinghe, 2007).

An investigation into the mode of action of chlorogenic acid indicated that the acid significantly increased the plasma membrane permeability, resulting in the loss of barrier function and even inducing mild cytoplasmic leakage. Cytoplasmic content leakage was also observed through electron micrographs (Lou *et al*., 2011). It has also been described that the compound induces a reduction in intracellular ATP levels, the release of cellular components into the extracellular environment, a

decrease in pH, and hyperpolarization of the cell membrane, as observed in Staphylococcus aureus. Electron microscopy further showed that the S. aureus cell membrane was damaged by chlorogenic acid, which also exhibits high reactivity against the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical (Libardi, 2010).

Another compound found in the plant is vanillic acid, which, according to Zheng *et al*. (2005), shows antibacterial activity and is one of the main ingredients in antimicrobial food additives and certain antibacterial herbs. The author reported that vanillic acid inhibited the bacterial enoyl-acyl reductase enzyme (FabI), an essential component of bacterial fatty acid biosynthesis, and that the antibacterial action of vanillic acid is mediated through the inhibition of fatty acid synthesis.

Caffeic acid, also present in the species, is a phytocompound with strong antimicrobial activity, including activity against the DPPH radical. According to Fu *et al*. (2010), *Bacillus subtilis*, *Pseudomonas fluorescens*, *Aspergillus niger*, *Candida albicans*, and *Trichophyton rubrum* showed considerable sensitivity to caffeic acid.

Ferulic acid is capable of neutralizing free radicals and enhancing the activity of enzymes responsible for inhibiting these radicals. Regarding antimicrobial properties, this compound exhibits significant activity against *Enterococcus* and vancomycin-resistant *E. faecalis*, as well as planktonic *Staphylococcus aureus*, with a MIC < 8 μg/mL, and inhibits bacterial biofilm formation by *S. aureus* with a MBEC < 8 μg/mL—64 and 128 times more potent than ofloxacin and vancomycin, respectively.

p-Coumaric acid also shows antimicrobial potential, and literature reports reveal that p-coumaric acid and its derivatives possess a broad spectrum of biological activities, including antimicrobial properties (Khatkar *et al*., 2017).

The results of this study demonstrated that gentamicin exhibited a synergistic effect when combined with the *Coix lacryma-jobi* extract.

As previously described, *Pseudomonas aeruginosa* can secrete large amounts of alginate, which is possibly the reason for gentamicin low activity against the tested strain. The slight increase in antimicrobial activity demonstrated in our experiment when combined with the extract may be due to the action of chlorogenic acid. According to Zhao *et al*. (2010), this bioactive compound is unstable under environmental conditions and tends to bind with amine-containing compounds, such as gentamicin.

In addition to this possible explanation, the mechanism of action of this acid and other acids extracted from the plant appears to be directly related to lipid degradation beneath the alginate layer. Alginate is a polysaccharide—more specifically, a polyuronide—composed of two base monomers, β-D-mannuronic acid and α-L-guluronic acid, connected by glycosidic bonds between their carbon atoms 1 and 4. These polymer chains are linear and consist essentially of three types of blocks of

varying lengths: blocks composed solely of guluronic acid, blocks composed solely of mannuronic acid, and blocks alternating between the two monomers. This composition does not prevent the passage of fatty acids such as those extracted from *Coix lacryma-jobi*, which could be a possible explanation for the results observed in the present experiment.

4 Conclusion

The leaf extract of *Coix lacryma-jobi* demonstrated inhibitory effects against the tested *Pseudomonas aeruginosa* strain. A synergistic effect was observed between the *C. lacryma-jobi* leaf extract and gentamicin, enhancing its antimicrobial activity. It was also noted that the strain exhibited high tolerance to chloramphenicol, which inhibited the effect of the *C. lacryma-jobi* leaf extract. Further studies, especially *in vivo*, are recommended to assess the efficacy of using gentamicin in combination with *C. lacryma-jobi* leaf extract, as well as to gain a deeper understanding of the antagonistic effect observed between chloramphenicol and the *C. lacryma-jobi* leaf extract.

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