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Lippia graveolens **and its activity against bacteria associated with bovine mastitis: Literature review**

Lippia graveolens y su actividad contra bacterias asociadas a mastitis bovina: Revisión bibliográfica

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ABSTRACT

Bovine mastitis is an infectious disease of the mammary gland caused by the invasion of pathogens, among them the bacterial etiology is one of the most important and the treatment of these infections has currently been complicated by the resistance generated by Gram positive bacteria and Gram negative to conventional antimicrobials. The objective of this research was to carry out a bibliographic review of *Lippia graveolens* and its activity against bacteria associated with bovine mastitis. Scientific reports on the phytochemical composition of wild oregano (*L. graveolens*) and the antibacterial activity against bacteria associated with bovine mastitis were consulted. The metabolites identified in *L. graveolens* with the highest reported antibacterial activity were naringenin, quercetin, luteolin as well as the terpenes thymol and carvacrol. *L. graveolens* contains secondary metabolites with reports of antibacterial activity, so it could be an alternative treatment against bacteria associated with bovine mastitis.

Keywords*:* *Lippia graveolens,* secondary metabolites, antibacterial activity, mastitis.

RESUMEN

La mastitis bovina es una enfermedad infectocontagiosa de la glándula mamaria causada por la invasión de patógenos. La etiología bacteriana de esta enfermedad es una de las más importantes y el tratamiento de estas infecciones actualmente es más complejo por la resistencia que han generado las bacterias a los antimicrobianos convencionales. El objetivo de la presente investigación fue realizar una revisión bibliográfica de *Lippia graveolens* y su actividad contra bacterias asociadas a mastitis bovina. Se consultaron los reportes científicos de composición fitoquímica del orégano silvestre (*L. graveolens)* y la actividad antibacteriana contra bacterias asociadas a mastitis bovina. Los metabolitos identificados en *L. graveolens* con mayor reporte de actividad antibacteriana fueron naringenina, quercetina, luteolina así como los terpenos timol y carvacrol. *L. graveolens* contiene metabolitos secundarios con reportes de

actividad antibacteriana por lo que podría ser una alternativa de tratamiento contra bacterias asociadas a mastitis bovina.
Palabras clave*:* *Lippia graveolens,* metabolitos secundarios, actividad antibacteriana, mastitis.

INTRODUCTION

Bovine mastitis is inflammation of the mammary gland caused by the invasion of pathogenic microorganisms that destroy milk-secreting tissues. More than 100 species associated with bovine mastitis have been reported in bacterial etiology (Sharun *et al.,* 2021; Morales *et al.,* 2023). The most common bacteria in cases of mastitis are: *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus uberis*, *Streptococcus dysgalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and coagulase-negative *Staphylococcus* (Pascu *et al.,* 2022; Morales *et al.,* 2023).

Mastitis is treated with chemical antimicrobials; however, their continuous and excessive use has led to the development of antimicrobial resistance, creating a global problem in animal and human health due to the interaction of bacteria from these two populations and the transfer of intergenic resistance (Galarza *et al.,* 2021; Wang *et al.,* 2021; Li *et al.*, 2023). Bacterial resistance leads to increased treatment costs and premature culling of animals, which has prompted the scientific community to search for new alternatives for the treatment of bovine mastitis (Kovačević *et al.,* 2022; Morales *et al.,* 2023).

Within the flora diversity, Mexican oregano (*Lippia graveolens*) is a plant of interest due to its phytochemical composition. This wild shrub has been used for culinary purposes and in traditional medicine to treat respiratory and digestive diseases, inflammation, headaches, and rheumatism (Bautista *et al.,* 2021). There are reports that demonstrate the antibacterial activity of *L. graveolens* using different methods of secondary metabolite extraction and concentrations at which antibacterial activity has been determined against various bacterial genera, including those associated with bovine mastitis (Bautista *et al.,* 2021; Cortés *et al.,* 2021; Kovačević *et al.,* 2022; Garcia *et al.,* 2022). The objective of this research was to conduct a literature review of *L. graveolens* and its activity against bacteria associated with bovine mastitis.

METHODOLOGY

To conduct this review, an exhaustive search was carried out in the following databases: PubMed, ScienceDirect, and Google Scholar, for studies published up to 2024. The following headings and keywords were used: *L. graveolens*, plant extracts, bovine mastitis, and antibacterial activity. Full-text documents were reviewed, and duplicate documents were removed. The exclusion criteria were inadequate methods and lack of access to the full text.

PLANT BOTANY

L. graveolens is a perennial shrub that grows to a height of two meters. It has exfoliating bark branches with opposite petiolate leaves that are oval-lanceolate in shape, with a rough, scabrous upper surface, glandular striae, densely hairy underside, obtuse apex, and variously crenate margin (Ocampo *et al.,* 2009). Flowering occurs during the rainy season (Bueno, 2014). Its inflorescence is indeterminate, subglobose spike-like, with white, zygomorphic corollas and small, 4 mm hermaphroditic flowers, in quantities of 2 to 20 flowers. It has small indehiscent capsule fruits with seeds without endosperm (Figure 1) (Ocampo *et al.,* 2009).

Figure 1. *Lippia graveolens* in Orizabita, Ixmiquilpan, Hidalgo, Mexico

The plant is wild and is found in the hills of temperate, arid, and semi-arid areas of Mexico. It adapts to altitudes between 1 400 and 2 300 meters, in stony soils with a sandy loam texture. It prefers a dry and semi-dry climate, with temperatures ranging from 20 to 24 °C and precipitation between 182 and 267 mm (Figure 1) (Martínez *et al.,* 2014). It is an aromatic plant used in cooking and herbal medicine for the treatment of digestive disorders. In Chihuahua, Durango, Tamaulipas, Coahuila, Jalisco, Zacatecas, Querétaro, Hidalgo, and Baja California, its foliage is collected for sale in local markets (Bueno, 2014).

COMPOSICIÓN FITOQUÍMICA PHYTOCHEMICAL COMPOSITION

The phytochemical characterization of *L. graveolens* from aqueous extracts, hydroalcoholic extracts, and essential oils shows differences in its phytochemical composition (González *et al.,* 2017; Bernal *et al.,* 2022). Extraction has been carried out using conventional techniques such as maceration with alcohols and water in different proportions, and by current technologies such as ultrasound-assisted extraction using eutectic solvents and supercritical fluid extraction using carbon dioxide as a solvent (Bernal *et al.,* 2023). The presence of metabolites differs depending on the extraction methods, as shown in Table 1, with phenolic compounds and monoterpenes standing out (González *et al*., 2017).

Table 1. Phytochemical compounds identified in plant extracts of *Lippia graveolens*

Extract	Extraction method	Solvent	Compounds	Reference
Aqueous	Ultrasound and supercritical fluid using CO_2	Choline chloride-ethylene glycol, choline chloride-glycerol, and choline chloride-lactic acid.	Caffeic, protocatechuic, and rosmarinic acids. Quercetin, luteolin, naringenin, eriodictyol, carvacrol	Garcia *et al.* (2022) González *et al.* (2017) Soto *et al*. (2019) Bernal *et al.*(2023)
Hexane	Maceration	Hexane	Thymol, m-cymene-8-ol, methyl salicylate, carvacrol, and linalool.	González *et al.*(2017)
Ethyl acetate	Maceration	Ethyl acetate	p-cymene, thymol, cirsimaritin, naringenin	
Ethanolic	Maceration	Ethanol Supercritical CO_2 modified with ethanol after steam distillation	Naringenin, taxifolin, eriodictyol, caffeic acid, luteolin, coumaric acid, quercetin 3 O-glucoside, 2-hydroxybenzoic acid, apigenin, quercetin, phloridzin, acacetin, sakuranetin, cirsimaritin, chrysoeriol.	Arias *et al.* (2023) Bernal *et al.* (2023) González *et al.* (2017)
Hydroalcoholic	Maceration	Methanol and Chloroform	Loganin, secologanin, secoxiloganin, dimethylsecologanoside, loganic acid, 8-epi-loganic acid, carioptosidic acid and its 6-O-p-coumaroyl and 6-O-caffeoyl derivatives,	Cortes *et al.* (2021) Picos *et al.* (2021) Leyva *et al.* (2016) Rastrelli *et al.* (1998) Lin *et al.* (2007)

		naringenin, pinocembrin, lapachenol and icterogenin, luteolin-7-O-glucoside, apigenin 7-O-glucoside, phloridzin, taxifolin, eriodictyol, scutellarein, luteolin, quercetin, and galangin.	
Essential oil	Hydro-distillation	Carvacrol, α-terpinyl acetate, m-cymene, thymol, β-pinene, and α-thujene, linalool, humulene Sesquiterpene: isocaryophyllene, γ-terpinene.	Hernández *et al.*(2009) Martínez *et al.* (2014) Nonato *et al.* (2022) Castillo *et al.* (2023)

In *L. graveolens*, the most abundant flavonoids are: quercetin, luteolin, naringenin, eriodictyol, luteolin, hesperidin, and phloridzin (Bernal *et al.,* 2023). The metabolites naringenin, quercetin, phloridzin, and cirsimaritin are chemical markers of the Lippia genus (Bernal *et al.,* 2022). The best flavonoid profile is obtained from methanolic leaf extract, in which three major iridoids have been found: carioptosidic acid with two derivatives: 6'-O-p-coumaroyl and 6'-O-caffeoyl, and seven minor iridoids: loganin, secologanin, secoxiloganin, dimethyl, secologanoside, loganic acid, 8-epi-loganic acid, and carioptoside (Rastrelli *et al.,* 1998; Lin *et al.,* 2007). Monoterpenes are the main components of essential oils of the *Lippia* genus (Cortés *et al.,* 2021; Bernal *et al.,* 2023). In water-, hexane-, and methyl acetate-based extracts and in hydrodistillation processes for obtaining essential oil, the presence of the following monoterpenes has been reported: thymol, carvacrol, limonene, b-caryophyllene, r-cymene, camphor, linalool, and a-pinene, which may vary according to the chemotype and extraction method (Calvo *et al.,* 2014; Garcia *et al.,* 2022). In this regard, Vernin (2001) reported that the essential oil of *L. graveolens* from Mexico and Central America has concentrations of 35 to 71% carvacrol and 5 to 7% thymol. Calvo *et al*. (2014) reported the presence of more than 70 compounds in its essential oils and identified three chemotypes of the plant: two phenolic (carvacrol and thymol) and one non-phenolic chemotype of oxygenated sesquiterpenes (β-caryophyllene, α-humulene, and caryophyllene oxide). Plant's habitat determines the oil composition, with the highest concentration of carvacrol obtained from plants growing in a semi-arid climate with thin, rocky soils (Torres *et al.,* 2022). However, there are reports of young plants growing in less arid conditions with deep soils, which provide a higher presence of thymol, and those growing in sub-humid climates have a higher amount of oxygenated sesquiterpenes (Llamas *et al.,* 2022).

METABOLITES AND ANTIBACTERIAL ACTIVITY

Terpenes

Carvacrol and thymol are most prevalent in *L. graveolens* (Calamaco *et al.,* 2023), and their concentration is affected by edaphic and climatic factors in the plant's habitat (Cortés *et al.,* 2021). Carvacrol (2-methyl-5-1-methylethylphenol) provides the characteristic aroma of oregano (Ultee *et al.,* 2000). It is synthesized from cymene via the mevalonate pathway and is a monoterpene that is insoluble in water and soluble in ethanol, carbon tetrachloride, and diethyl ether (Lee *et al.,* 2017). Its stereochemistry (Figure 2) of a single phenolic ring with three substituents of functional groups (Memar *et al.,* 2017) gives it antibacterial, antioxidant, anticancer, and anti-inflammatory properties (Tapia *et al.,* 2017).

Carvacrol **Thymol**

Figure 2. Terpenes reported in *Lippia graveolens*

In bacteria, carvacrol induces cell lysis by altering lipophilic compounds and hydrophobic parts of the cytoplasmic membrane, increasing cation permeability (H+ and K+), generating lipopolysaccharide efflux and reactive oxygen species production, inhibiting ATPase activity, microbial DNA replication, and energy synthesis, causing cell death (Gallegos *et al*, 2022). However, Ultee *et al.* (2000) reported that bacteria can adapt to carvacrol and modify the fatty acid composition of the membrane and reduce its permeability.

Thymol is an isomer of carvacrol (Figure 2). It is an aromatic substance with a white crystalline color, low solubility in water, and high solubility in organic solvents. It has a neutral pH but can have alkaline characteristics in aqueous solutions due to the deprotonation of phenol (Chizzola, 2013). It has bactericidal, fungicidal, insecticidal, nematicidal, and varroacidal activity (Gallegos *et al.,* 2022). Its antibacterial effect *in vitro* against *Escherichia coli*, *Salmonella spp*. and *S. aureus* has been reported at a concentration of 0.75 mg/mL (Shapira-Mimran 2007; Gallegos *et al.,* 2019). At concentrations of 1 and 2 % in oregano essential oil, it has greater antimicrobial activity against Gram-positive bacteria and less against Gram-negative bacteria (Du *et al.,* 2015;

Erazo *et al.,* 2017). *In vitro* studies on Gram-negative enterobacteria found greater antibacterial activity of thymol from Lippia berlandieri compared to other antimicrobials (Garcia *et al.,* 2022; Gracia *et al.,* 2022). The antibacterial mechanism of action is similar to that of carvacrol, binding to bacterial membranes in a hydrophobic manner via hydrogen bonds, affecting the outer and inner membranes, increasing permeability and the loss of potassium ions and intracellular ATP, causing cell death (Di Pasqua *et al.,* 2010).

Flavonoids

In *L. graveolens*, the flavonoids (Figure 3) with the highest reported biological activity are naringenin, quercetin, and luteolin (Lin *et al.,* 2007). Naringenin is a bioactive compound with hepatoprotective, antiatherogenic, anti-inflammatory, antimutagenic, anticarcinogenic, and antimicrobial activity (Ke *et al.,* 2017). In reaction with alkyl iodides, it forms O-alkyl compounds of naringenin with antibacterial potential against *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis* (Kozłowska *et al.,* 2019). A derivative of O-alkyl naringenin is sakuranetin (7-O-methylnaringenin), which has significant antimicrobial activity against Gram-negative and Gram-positive bacteria. Naringenin inhibits the growth of *Staphylococcus aureus* by affecting the cell membrane and fatty acid composition. In *Escherichia coli*, it acts on the genes associated with the biosynthesis of membrane fatty acids (Wang *et al.,* 2018).

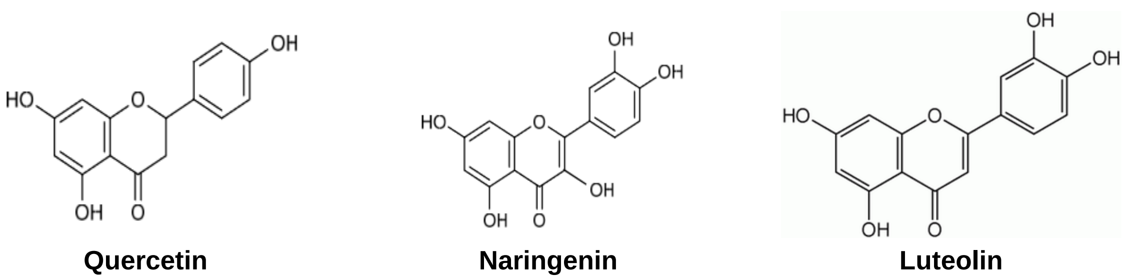

Figure 3. Flavonoids reported in *Lippia graveolens*

Quercetin is a flavonol based on the flavone structure nC6 (ring A)-C3 (ring C)-C6 (ring B). It has broad-spectrum antibacterial activity, breaks down the cell wall of bacteria, inhibits nucleic acid synthesis, and reduces enzyme activity (Wang *et al.,*2018). Specifically, in *Escherichia coli*, it alters the activity of adenosine triphosphate (Plaper *et al.,* 2003). According to Hooda *et al*. (2020), impregnating quercetin with silver nanoparticles inhibits the growth of bacteria: *Klebsiella pneumoniae* (ATCC[790603]), *Enterococcus faecalis* (ATCC[51299]), *Proteus vulgaris* (ATCC[426]), *Escherichia coli*

(ATCC[25922]), *Staphylococcus aureus* (ATCC[4330]), and *Pseudomonas aeruginosa* (ATCC[27853]).

Luteolin (3',4',5,7-tetrahydroxyflavone) is a polyphenol of the flavone family, with a molecular structure (C6-C3-C6) of two benzene rings and a third ring containing oxygen, and a double bond between carbons C2 and C3 (Figure 3). Its structure favors its biochemical and biological activity (Wu *et al.,* 2019). This flavonoid has various biological activities, such as antioxidant, anti-inflammatory, antimicrobial, anticarcinogenic, and hypoglycemic, hypolipidemic, hypotensive, and immunomodulatory effects (Wu *et al.,* 2019). In bacteria, luteolin affects the integrity of the cell wall and membrane, inhibiting nucleic acid synthesis and protein expression and interfering with energy metabolism (Guo *et al.,* 2022). In a study, Qian *et al.* (2021) found that luteolin impairs cell membrane morphology and affects biofilm formation in *Staphylococcus aureus* and *Escherichia coli*. In studies against *Trueperella pyogenes*, a minimum inhibitory concentration (MIC) of luteolin of 78 µg/mL was reported, and at half the MIC, susceptibility to methicillin- and macrolide-resistant *Staphylococcus increases*, providing an alternative treatment for resistant pathogens (Guo *et al.,* 2022).

ACTIVITY OF *Lippia spp.* AGAINST RESISTANT BACTERIA ASSOCIATED WITH BOVINE MASTITIS

There are reports of the antibacterial activity of *Lippia* spp. extracts on resistant bacteria such as *Streptococcus* spp., *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli* (Gupta *et al.,* 2020; Pinheiro *et al.,* 2022; Nonato *et al.,* 2022). The minimum inhibitory concentration in the evaluation of Lippia spp. extracts and metabolites on bacteria varies depending on the species evaluated, extraction methodology, and evaluation (Rani *et al.,* 2022; Nonato *et al.,* 2022; Suarez *et al.,* 2024).

In *Streptococcus* spp., an MIC of 67 mg/mL is reported for supercritical fluid from *L. graveolens*, while for metabolites: thymol, MICs of 0.31 to 8.0 mg/mL are reported, and for carvacrol, 0.31 to 9 mg/mL (Table 2). In *Staphylococcus* spp., the MIC for ethanolic extracts of *Lippia* spp. is reported to be 128 to 512 µg/mL, for essential oil 53.3 to 512 µg/mL, while for thymol it was 0.15 to 0. 75 µg/mL and carvacrol from 0.38 to 1.3 µg/mL (Dal Pozzo *et al.*, 2011; Rani *et al.,* 2022; Gallegos *et al.,* 2019; Nonato *et al.,* 2022).

In *Pseudomonas aeruginosa*, an MIC for ethanolic extracts of 128 to 512 µg/mL is reported, while for essential oils it is 0.37 to 80 µg/mL. In the case of *Escherichia coli*, the following MIC reports were found: ethanolic extracts (74.6 to 256 µg/mL), essential oils (0.37 to 426 µg/mL), thymol (0.15 to 0.38 µg/mL), and carvacrol (0.15 to 0.75 µg/mL). Essential oils and their compounds (carvacrol and thymol) have the highest antibacterial activity in resistant bacteria isolated from mastitis (Rani *et al.,* 2022; Nonato *et al.,* 2022; Suarez *et al.,* 2024). Pinheiro *et al.* (2022) mention that the essential oil has inhibitory and bactericidal action against strains of *Escherichia coli* and *Klebsiella pneumoniae*, but not against *Pseudomonas aeruginosa*, where its effectiveness is reduced by the formation of biofilm and the action of efflux pumps, intrinsic characteristics of this species. The combination of ethanolic extracts of *Lippia* spp. with antimicrobials reduces the MICs of amikacin, gentamicin, and cephalothin, but has an antagonistic effect with benzylpenicillin and other natural extracts (Nonato *et al.,* 2022). Currently, synergies between extracts and antimicrobials are being investigated to improve efficacy, reduce toxicity, and bacterial resistance (Garcia *et al.,* 2019; Pinheiro *et al.,* 2022; Nonato *et al.,* 2023; Suarez *et al.,* 2024).

Table 2. Antibacterial activity of *Lippia spp* and its metabolites against resistant pathogens associated with bovine mastitis

Bacteria	Extracts and compounds	Minimum Inhibitory Concentration (MIC)	Reference
Streptococcus spp.	Thymol Carvacrol	0.31-0.63 µL/mL 0.16-0.63 µL/mL	Gupta *et al.* (2020)
Streptococcus agalactiae	Supercritical fluid from L. graveolens	67 mg/mL	García *et al.* (2019)
	Thymol Carvacrol	8.0 mg/mL 9.0 mg/mL	Gupta *et al.* (2020)
Staphylococcus aureus	Ethanolic extract of L. alba Ethanolic extract of *L. sidoides* Ethanolic extract of *L. gracilis* Essential oil of *L. alba* Essential oil of *L. sidoides* Essential oil of *L. gracilis*	853 µg/mL 128 µg/mL 512 µg/mL 256 µg/mL 53.3 µg/mL 512 µg/mL	Nonato *et al.* (2022)
	Essential oil of *L. graveolens*	12 µL/mL	Suarez *et al.* (2024)
	Thymol Carvacrol	0.15-0.75 mg/mL 0.38-0.45 mg /mL	Gallegos *et al.* (2019) Rani *et al.* (2022)
Staphylococcus spp.	*L. graveolens* essential oil Thymol Carvacrol	1.6 mg /mL 0.4 a 0.5 mg/mL 0.8 a 1.3 mg/mL	Dal Pozzo *et al.* (2011)
Pseudomonas aeruginosa	Ethanolic extract of *L. alba* Ethanolic extract of *L. sidoides* Ethanolic extract of *L. gracilis* Essential oil of *L. alba* Essential oil of *L. sidoides* Essential oil of *L. gracilis*	213.3 µg/mL 128 µg/mL 512 µg/mL 1024 µg/mL 298.6 µg/mL 682 µg/mL	Nonato *et al.* (2022)

	Essential oil of *L. berlandieri*	80 µg/mL	Reyes *et al.* (2020)
	Essential oil of *L. origanoides*	2500 µg/mL	Pinheiro *et al.* (2022)
	Mixture of essential oils of *L. salvifolia*: *L. sidoides* (9:1)	0.37 µg/mL	Gupta *et al.* (2020)
Escherichia coli	Ethanolic extract of *L. origanoides*	5.0 µL	Castellanos *et al.* (2020)
	Ethanolic extract of *L. alba* Ethanolic extract of *L. sidoides* Ethanolic extract of *L. gracilis* Essential oil of *L. alba* Essential oil of *L. sidoides* Essential oil of *L. gracilis*	768 µg/mL 74.6 µg/mL 256 µg/mL 106.6 µg/mL 106.6 µg/mL 426.6 µg/mL	Nonato *et al.* (2022)
	L. origanoides essential oil	312 µg/mL	Pinheiro *et al.* (2022)
	L. berlandieri essential o	4 µg/mL	Bautista *et al.* (2021)
	Mixture of *L. salvifolia* essential oils: *L. sidoides* (9:1)	0.37 µg/mL	Gupta *et al.* (2020)
	Thymol Carvacrol	0.15-0.38 mg/mL 0.15-0.75 mg/mL	Gallegos *et al.* (2019) Rani *et al.* (2022)
Klebsiella pneumoniae	*L. origanoides* essential oil	312 µg/mL	Pinheiro *et al.* (2022)
	Thymol Carvacrol	0.75 mg/mL 0.75 mg/mL	Rani *et al.* (2022)

CONCLUSIONS

The main secondary metabolites of *L. graveolens* are flavonoids and monoterpenes, and their concentration varies according to the soil and climate conditions of the plant's habitat. Its antibacterial activity has been demonstrated against various bacterial genera of importance in health, including those associated with bovine mastitis. The greatest antibacterial activity of *L. graveolens* has been associated with thymol and carvacrol; however, activity has also been reported due to the presence of naringenin, quercetin, and luteolin. In the search for alternatives to combat resistant or multidrug-resistant bacteria associated with bovine mastitis, the secondary metabolites of *Lippia graveolens* represent an option for studying new treatments.

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Errata Erratum

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