Cinnamon, Clove and Cumin against Urinary Tract Infections

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Spices are aromatic plants widely used in Mexico to flavor, color, or preserve food. In particular, the Food and Drug Administration (FDA) Organization defined *spices* as: “whole, broken or ground aromatic vegetable substances, whose significant function in food is to flavor rather than to nourish”. Most of the beneficial health properties of spices are mediated through the direct action of their phytochemicals, especially polyphenols or polyphenol degradation products. These phytochemicals have broad antioxidant properties and target specific receptors or enzymes involved in various anti-inflammatory pathways or immune responses. Phenolic acids and flavonoids, especially flavones and flavonoids, are spices’ predominant class of polyphenols. Furthermore, the antimicrobial properties of spices are attributed to their unique volatile oils and oleoresins. Because spices are obtained from aromatic plants and herbs, they are generally considered safe (GRAS).

Keywords: cinnamon ; cloves ; cumin ; urinary tract infections ; antimicrobial activity

1. Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections. Worldwide, in 2019, it was estimated that 404.61 million cases and 236,790 deaths were associated with UTIs [1]. Regarding Mexico, the picture is similar, UTIs are one of the most common pathologies, and approximately 4 million cases are reported each year, and it is the third most common cause of morbidity [2]. UTIs can affect both males and females, but the prevalence is higher in females (>70%) due to the very close presence of the urethra to the anus and the gastrointestinal colonization of pathogens in the vagina [3]. UTIs are an inflammatory response of the urothelium to bacterial infection, and it involves pyelonephritis (kidney infection), urethritis (ureters infection), cystitis (bladder infection), and prostatitis [3]. UTIs are caused by bacteria, viruses, and yeast, although bacteria cause more than 85% of infections. Among the bacteria most commonly associated with UTIs are *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae, Enterococcus faecalis, Pseudomonas aeruginosa, Proteus mirabilis, Acinetobacter baumannii*, and *Staphylococcus saprophyticus* [4]. It is worth mentioning that UTIs are considered established when the pathogen can enter the urinary tract system and reach more than 10^5 colony/mL in the urine [4]. *E. coli* and *Enterococcus* spp. are the most frequent bacteria in UTIs. Both bacteria are present in the gastrointestinal habitat, which favors acquiring resistance genes from other commensal organisms [5]. Bacterial resistance and recurrence are due to the misuse and abuse of antibiotics and the adherence capacity of uropathogens that allows them to internalize in target cells, forming biofilm [2][6][7]. Furthermore, catheters are estimated to be one of the most common causes of healthcare-associated infection, as it is known that bacteria can form biofilms on catheters, making the control of bacterial biofilm formation an urgent need [8][9].

2. Cinnamon

The trees and shrubs of the Cinnamomum genus belong to the Lauraceae family and contain around 300 species worldwide. The most common are *C. burmanni, C. camphora, C. cassia, C. osmophloeum, C. verum,* and *C. zeylanicum* [10][11][12][13]. The fruit, leaf, and bark of the cinnamon tree contain bioactive compounds such as cinnamyl acetate, coumarin, eugenol, eucalyptol, *trans*-cinnamaldehyde, L-borneol, caryophyllene oxide, benzoic acid, linalool, caffeic acid, and camphor [11][13][14][15]. Cinnamon leaves and the bark have been reported to have antioxidant activity [12]. However, the peeled and dried bark is a popular spice used as a condiment and flavoring agent in desserts, spicy sweets, tea, liqueurs, cereals, bread, fruit, and chocolates. Mexico is the biggest importer of *C. zeylanicum*, also known as true cinnamon [16], and it is also used in chocolate production and sweet and savory dishes. Moreover, cinnamon is used in traditional medicine worldwide due to its antimicrobial, antifungal, nematicidal, antipyretic, insecticidal, antioxidant, and antidiabetic properties [11][12][14][17][18][19]. Although cinnamon is recognized as a safe spice, with a tolerable daily intake of 0.1 mg/kg/day, adverse effects such as stomach and bowel disorders and allergic reactions have been described [16][20].

The solvents used to extract the bioactive compounds of cinnamon are water, methanol, ethanol, and chloroform [15]. Hydrodistillation, steam distillation, Soxhlet extraction, and maceration are the most common methods to prepare cinnamon extract oils from leaf, fruit, and bark. Nevertheless, novel extraction methods such as supercritical fluid, assisted by microwave radiation, superheated water, supercritical carbon dioxide (CO_2), or ultrasounds have been developed [15][17][21]. The essential oils (EOs) are obtained from bark through hydrodistillation, steam distillation, and supercritical fluid extraction techniques. EOs extracted contain *trans*-cinnamaldehyde, eugenol, cinnamyl acetate, camphor, and linalool, representing about 85% of the total oil composition [17][22]. However, *trans*-cinnamaldehyde is an unstable compound that can be oxidized to cinnamic acid when exposed to air, losing the acrolein group, which is responsible for antimicrobial activity. Nevertheless, the other bioactive compounds in cinnamon EO have antimicrobial activity and synergistic or additive effects with *trans*-cinnamaldehyde [11][23][24].

The bioactive compounds in cinnamon EO, such as *trans*-cinnamaldehyde, pass through bacteria cell walls, altering the permeability and integrity of the membrane and, consequently, causing loss of transporting proteins, metabolites, and ions which leads to cytoplasmic coagulation and denaturation of proteins [11][25][26][27]. Moreover, *trans*-cinnamaldehyde downregulated the F1F0-ATPase complex, inducing the depletion of intracellular adenosine triphosphate (ATP) synthesis and growth rate. Furthermore, *trans*-cinnamaldehyde causes energy deprivation, amino acid decarboxylation activity inhibition within the cells, and cell death [11][26]. The antimicrobial activity of cinnamon bark extracts is shown in **Table 1**.

It has been described that the EO of *C. cassia* obtained by hydrodistillation has a minimum inhibitory concentration (MIC) against bacterial strains collected from patients with UTIs, such as *E. coli* in the range of 0.30 to 2.50 mg/mL, *P. aeruginosa* to 2.5 to 5.0 mg/mL, *P. mirabilis* 0.30 to 1.25 mg/mL, and *K. pneumoniae* to 0.16 to 31 mg/mL. In addition, this EO has inhibition zones around 12 to 39 mm for Gram-negative bacteria strains [28].

Moreover, cinnamon bark oil (*C. zeylanicum*) has inhibitory and bactericidal activity against *P. aeruginosa* and its multidrug-resistant strains isolated from patients with UTIs. The MIC and minimal bactericidal concentrations (MBC) values are in the range of 0.1125 to 0.225% (v/v) and 0.1125 to 1.8%, respectively. Moreover, cinnamon bark oil has a synergistic interaction with some antibiotics. The main bioactive compounds identified in this cinnamon bark oil are *trans*-cinnamaldehyde and eugenol. However, *trans*-cinnamaldehyde possessed better antimicrobial activity to reduce 6 log CFU/mL to this pathogen [27].

In addition, ethanolic extract of *C. zeylanicum* could inhibit the growth of colonies of *E. coli*, *P. aeruginosa*, and *K. pneumoniae* obtained from urine samples of patients with UTIs. The results indicate that the mean zone of inhibition against the pathogens mentioned before is 11.72 mm, 20.16 mm, and 25.50 mm, respectively. This inhibition zone is similar to norfloxacin, a common antibiotic for treating UTIs. Although *trans*-cinnamaldehyde has been identified as the bioactive antimicrobial compound in the cinnamon extract, it was found that the zone of inhibition of *trans*-cinnamaldehyde against *P. aeruginosa* (14.82 mm) and *K. pneumoniae* (18.45 mm) was lower than the of the whole extract, while against *E. coli* (24.39 mm), the zone of inhibition was higher compared to cinnamon extract against [29]. As mentioned above, this compound could have antimicrobial activity and be enhanced by other bioactive compounds in the cinnamon extract. Because of this, the isolated bioactive compound *trans*-cinnamaldehyde was used in a uropathogenic *E. coli* colonization in C57BL/6 female mice to reproduce a UTI. Female mice were supplemented in the feed with *trans*-cinnamaldehyde at 0.1, 0.2, and 0.4% for 14 days. On day 10, mice were infected with *E. coli* through transurethral inoculation. It is observed that *trans*-cinnamaldehyde reduced pathogen populations in the bladder and urethra in a concentration-dependent manner [30].

Moreover, it is described that aqueous *C. zeylanicum* extract (0.1 g/mL) has antimicrobial activity against isolated pathogens isolated from the urine of patients with UTIs such as *E. coli*, *K. pneumoniae*, *S. aureus*, *Enterobacter spp*, *P. aeruginosa*, *S. typhi*, and *S. flexneri*.

Furthermore, this aqueous cinnamon extract has moderate antifungal activity against *Aspergillus niger* and *Candida albicans* compared to ketoconazole. Nevertheless, due to the significant extraction of *trans*-cinnamaldehyde, the EO cinnamon extract has more antifungal activity than the aqueous extract [26]. Finally, the EO of cinnamon has MIC and MCB values of 0.125% and 0.25%, respectively, against *K. pneumoniae* isolated from patient urine samples and has good efficacy against this biofilm produced by this Gram-negative bacterium [31].

Table 1. Antimicrobial activity of cinnamon bark extracts.

Cinnamon Specie	Type of Extract	Phytochemicals	Uropathogen	MIC	MBC	Diameter of the Inhibition Zone (mm)	Ref.
C. cassia	Essential oil	*trans*-cinnamaldehyde, cinnamic acid, eugenol, benzaldehyde	*E. coli*	26–35 mg/mL	ND	26–38	[28]
			P. aeuruginosa	12–19 mg/mL	ND	12–19	
			P. mirabilis	30–39 mg/mL	ND	30–39	
			K. pneumoniae	27–32 mg/mL	ND	27–32	
C. zeylanicum	Essential oil	*trans*-cinnamaldehyde, cinnamic acid, eugenol, benzaldehyde	*P. aeuruginosa*	0.11–0.2%	0.1125–1.8%	ND	[27]
NS	Essential oil	*trans*-cinnamaldehyde, cinnamic acid, eugenol, benzaldehyde	*E. coli*	1 mg/mL	4 mg/mL	19.2	[25]
			S. aureus	1 mg/mL	2 mg/mL	28.7	
C. verum	Essential oil	*trans*-cinnamaldehyde, cinnamic acid, eugenol	*K. pneumoniae*	0.125%	0.25%	ND	[31]
C. zeylanicum	Ethanolic extract	Tannins, Flavonoids, anthraquinones, saponins	*E. coli*	ND	ND	11.72	[29]
			K. pneumoniae	ND	ND	25.50	
			P. aeuruginosa	ND	ND	23.25	
C. verum	Ethanolic extract	Tannins, Flavonoids, anthraquinones, saponins	*P. aeuruginosa*	10 mg/mL	20 mg/mL	12.3	[32]
			K. pneumoniae	20 mg/mL	40 mg/mL	15.3	
			S. aureus	10 mg/mL	20 mg/mL	12.5	
	Dichloromethane extract	Flavonoids, anthraquinones, alkaloids, saponins	*P. aeuruginosa*	20 mg/mL	40 mg/mL	10.0	
			K. pneumoniae	20 mg/mL	40 mg/mL	12.3	
			S. aureus	5 mg/mL	10 mg/mL	11.5	
	Hexane extract	Tannins, alkaloids, flavonoids, anthraquinones, saponins	*P. aeuruginosa*	10 mg/mL	20 mg/mL	10.5	
			K. pneumoniae	20 mg/mL	20 mg/mL	14.5	
			S. aureus	5 mg/mL	10 mg/mL	15.0	

ND: not determined; NS: not specified in the article. MIC: minimum inhibitory concentration; MBC: minimum bactericidal concentration.

3. Clove

Clove (*Syzygium aromaticum, syn. Eugenia caryophyllata*) is a plant used for centuries as a food preservative and for many medicinal purposes. It belongs to the family of Myrtaceae, the subfamily Myrtoideae, and the tribe Syzygieae [33]. It is native to Maluku Island in Indonesia. However, today it is cultivated in various parts of the world, especially in countries with tropical and subtropical environments, such as Indonesia, Sri Lanka, India, Tanzania, Malaysia, Madagascar, and Pakistan [18]. Its dried buttons (flowers that have not yet opened) are called cloves or gyrofles and are used as a spice in kitchens worldwide [34]. In Mexican cuisine, cloves are widely used to season sweet and salty foods. In salty stews, it is

included whole or ground in moles, marinades, and other dishes. As for desserts, it is used above all in fruit syrups such as guava candy.

Cloves are a valuable source of phenolic compounds such as glycosides, flavonoids (kaempferol and quercetin), saponins, tannins, and EOs. Gallic acid is the phenolic acid with the highest concentration (783.50 mg/100 g fresh weight), although researchers also find caffeic, ferulic, and salicylic acids in smaller quantities [35]. However, the main bioactive component of cloves is eugenol [2-methoxy-4-(2-propenyl) phenol], an allyl chain substituted guaiac that is a member of the allylbenzene class of chemical compounds [36], and is present in concentrations ranging from 9381.70 to 14,650.00 mg/100 g fresh plant weight [35].

In medicine, various therapeutic properties have been attributed to clove, including antifungal, antibacterial, antiviral, anti-inflammatory, antioxidant, hepatoprotective, antistress, antidiabetic, antinociceptive, anesthetic, and even anticancer activities [34]. Clove has also been widely used to treat UTIs due to its wide range of antimicrobial activities against Gram-positive and Gram-negative bacteria [37][38][39][40][41]. **Table 2** shows the antimicrobial activity of the different clove extracts.

Among the most used clove extracts to treat UTIs is clove oil, an aromatic oil extracted from the buds and leaves of *S. aromaticum* trees. It is traditionally obtained by hydrodistillation, steam distillation, or solvent extraction. These processes are inexpensive but can induce thermal degradation, hydrolysis, and water solubilization of some fragrance components [42][43]. Some authors have also carried out clove oil extraction with CO_2, which offers significant advantages over traditional methods. For example, the higher percentage of eugenol active antioxidant ingredients and a shorter extraction time, among others [42].

Clove oil has been highly successful against the bacteria responsible for UTIs. For example, it has been reported that after 8 h of treatment with clove oil, the population of *E. coli* and *S. aureus* is reduced by 99.999% and 99.9999%, respectively [38]. Additionally, in a study conducted with 60 clinical isolates from the urine of UTIs patients, clove EO was found to be more effective against *E. coli* strains than against *K. pneumoniae* strains. This is because the growth inhibition of *E. coli* was 24.5 (22.75–28) mm, while for *K. pneumoniae* it was only 22 (20–24) mm [37]. In fact, clove oil has been reported to kill *E. coli* resistant to recommended antibiotics [44].

The efficacy of EOs differs from one type of oil to another and from the target bacteria, depending on their structure (Gram-positive and Gram-negative bacteria) [45][46]. However, in a study comparing clove oil with cinnamon, bell pepper, thyme, oregano, and rosemary oils, clove oil was reported to be the most effective in inhibiting the growth of *S. typhi*, *S. aureus*, and *P. aeruginosa* [47]. Furthermore, it has been observed that mixing clove oil vapor with cinnamon oil vapor antagonistically inhibits the growth of *E. coli*. In contrast, both oils exerted a synergistic effect for inhibiting *Listeria monocytogeneses*, *Bacillus cereus*, and *Yersinia enterocolitica*, when the maximum inhibition concentrations are used [48].

So far, there are few studies on the antibacterial mechanism of clove oil, especially at the molecular level. However, previous studies report that clove oil could be destroying the integrity of cell membranes, which triggers the egress of biological macromolecules and intracellular enzymes and interferes with protein synthesis [49][50]. Clove oil may also affect bacteria by slowing respiratory metabolism. Clove oil treatment has decreased the intracellular ATP of *E. coli* and *S. aureus* by up to 76.23% and 71.55%, respectively. In addition, in this same study, a decrease in nucleic acids was observed, indicating that clove oil affects the permeability of the cell membrane [38]. In another study on *L. monocytogeneses*, clove oil was reported to reduce the activity of three key enzymes (isocitrate dehydrogenase, citrate synthase, and α-ketoglutarate dehydrogenase) in the citric acid cycle pathway, affecting the content of metabolites in the pathway. In addition, it has been shown that eugenol, the main component of clove oil, can change the structure of DNA through the formation of eugenol-DNA chimeras [38].

Another preparation that has been used against UTIs is the phytochemical extraction of the clove spice, which can be carried out by aqueous-ethanolic maceration. Previous studies have shown that 80% ethanol effectively extracts most bioactive phytochemical compounds, especially flavonoids [51]. In fact, a study comparing extraction with different solvents in spices reported that the 80% ethanol extraction method has the highest inhibition towards Gram-negative and Gram-positive bacteria [52].

To prepare the ethanolic extract of cloves, the spices are washed with sterile water and subsequently dried at 40 °C. Then, the clove is ground with a blender to a fine powder. Finally, a maceration with 80% ethanol is carried out, and the filtrate is concentrated using a rotary evaporator [53][54].

A recent study demonstrated that ethanolic extract of clove (2000 µg) exhibited broad-spectrum inhibition against Gram-negative and Gram-positive UTIs-causing pathogens: *P. mirabilis* (19.7 mm), *Staphylococcus epidermidis* (18 mm), *S.*

aureus (14.7 mm), *E. coli* (12.7 mm), *K. pneumoniae* (12.3 mm) (depending on the size of the inhibition halo) [54]. Interestingly, the comparison between ethanolic clove extract and commercial clove EO revealed that the former demonstrated more potent antimicrobial and antioxidant properties at a similar concentration of eugenol. However, Gas Chromatography/Mass Spectrometry (GC/MS) indicates that the ethanolic extract has a lower concentration of eugenol than the EO, suggesting that eugenol is not the only compound responsible for the antimicrobial effect observed for the ethanolic extract [54].

In another study where 221 Gram-negative bacteria were isolated and the production of b-lactamases, enzymes responsible for resistance to b-lactam antibiotics, was analyzed, it was reported that the ethanolic extract of cloves was effective against all Gram-negative isolates. However, the best antibacterial activity was shown against *P. mirabilis* species with an inhibition halo of 19 mm. Likewise, it was found that the ethanolic extract of cloves has a different antibacterial potential depending on the Gram-negative uropathogenic [39].

In another study, aqueous and ethanolic extracts of clove, cinnamon, and garlic were prepared and tested for their antibacterial efficacy against isolated *E. coli*. Clove extracts were shown to have one of the best antibacterial activities against UTIs strains according to their mean values of the zone of inhibition (13.33 mm). The combined effect of 10% plant extracts with antibiotics such as resistance drugs ampicillin, imipenem, ciprofloxacin, norfloxacin, and nalidixic acid was also tested and showed a pattern of susceptibility with increasing inhibition zone diameter in three UTIs strains [5]. Therefore, researchers could say that the use of ethanolic clove extract to treat UTIs could be complementary to the use of antibiotics due to its additive effect with them.

There are no studies on the antibacterial mechanism of the ethanolic extract of clove, although it could be suspected that it acts the same or similar to the EO. Until now, the antibacterial activity of the ethanolic extract has only been attributed to its antioxidant properties. A recent study reported that the EC_{50} of DPPH (1,1-diphenyl-2-picrylhydrazyl), ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), and reducing power assay for the ethanolic extract content of clove was 0.037 mg/mL, 0.68 mg/mL, and 0.44 mg/mL, respectively [54].

Finally, it is essential to mention that the consumption of cloves has been declared safe for humans. Clove crude EO is classified as generally considered safe (GRAS) by the US Food and Drug Administration [55]. Acute and chronic toxicity studies with clove oil conclude that there are no adverse effects in albino rats [56]. Additionally, an aqueous extract of dried clove buds (known as ‘Clovinol’), rich in polyphenols, was found to be safe in rats [57]. Furthermore, eugenol is rapidly absorbed, metabolized in the liver, and eliminated within 24 h when consumed orally [58]. However, eugenol can be toxic in children under two years of age in relatively small amounts (5–10 mL) [59]. Additionally, if cloves are consumed or used excessively topically or by an allergic person may experience side effects. For example, oral intake of cloves may cause lactic acidosis, nausea, numbness, dizziness, or tiredness [60]. Furthermore, it can lead to liver problems associated with stomach pain, clay-colored stools, dark urine, and sometimes jaundice [61]. If applied topically, it could cause itchy rashes with mild skin irritation, swollen or bleeding gums, erection problems, and delayed ejaculation [60]. Previously, the World Health Organization (WHO) set the daily human intake of clove oil at 2.5 mg/kg body weight for humans [62].

In short, clove extracts can be used to develop a new antimicrobial drug that is the need of the hour. However, more research is required on the mechanisms of action, identification, and characterization of bioactive molecules, particularly their antibacterial activities in vivo against human pathogens.

Table 2. Antimicrobial activity of *S. aromaticum* extracts.

Type of Extract	Phytochemicals	Uropathogen	MIC	MBC	Diameter of the Inhibition Zone (mm)	Ref.
Clove oil	Eugenol, β-caryophyllene, vanillin, crategolic acid, bicornin, galotanic acid, methyl salicylate eugenin, kaempferol, ramnetin and eugenitin, oleanolic acid, stigmasterol, campesterol, and various sesquiterpenes	*E. coli*	0.5 mg/mL	0.5 mg/mL	ND	[38]
		S. aureus	0.5 mg/mL	0.5 mg/mL	ND	

Type of Extract	Phytochemicals	Uropathogen	MIC	MBC	Diameter of the Inhibition Zone (mm)	Ref.
Clove oil	Eugenol, β-caryophyllene, vanillin, crategolic acid, bicornin, galotanic acid, methyl salicylate eugenin, kaempferol, ramnetin and eugenitin, oleanolic acid, stigmasterol, campesterol, and various sesquiterpenes	*A. baumanni*	ND	ND	28	[63]
		P. aeruginosa	ND	ND	17	
		E. faecalis	ND	ND	25	
		S. aureus	ND	ND	20	
Clove oil	Eugenol, β-caryophyllene, vanillin, crategolic acid, bicornin, galotanic acid, methyl salicylate eugenin, kaempferol, ramnetin and eugenitin, oleanolic acid, stigmasterol, campesterol, and various sesquiterpenes	*E. coli* isolated from UTIs patients	2.1 to 3.1 mg/mL	3.1 to 4.2 mg/mL	ND	[44]
		Antibiotic-resistant *E. coli*	2.6 mg/mL	3.7 mg/mL	ND	
Clove oil	Eugenol, β-caryophyllene, vanillin, crategolic acid, bicornin, galotanic acid, methyl salicylate eugenin, kaempferol, ramnetin and eugenitin, oleanolic acid, stigmasterol, campesterol, and various sesquiterpenes	*E. coli* isolated from UTIs patients	5.5 µL/mL and 0.55 µL/mL *	ND	24.5 mm	[37]
		K. pneumoniae isolated from UTIs patients	5.5 µL/mL and 0.55 µL/mL *	ND	22 mm	
Ethanolic extract	Eugenol, glycosides, flavonoids, saponins, tannins, and essential oils.	*S. aureus*	5 mg/mL	10 mg/mL	11.4	[64]
		P. aeruginosa	5 mg/mL	12.5 mg/mL	9.2	
Ethanolic extract	Eugenol, glycosides, flavonoids, saponins, tannins, and essential oils.	*E. coli*	0.39 mg/mL	0.19 mg/mL	17	[39]
		K. pneumoniae	0.78 mg/mL	0.39 mg/ml	16	
		Enterobacter species	0.78 mg/mL	0.39 mg/mL	17	
		Citrobacter Species	0.39 mg/mL	0.19 mg/mL	18	
		P. mirabilis	0.39 mg/mL	0.19 mg/mL	19	
		P. aeruginosa	1.56 mg/mL	0.78 mg/mL	14	
		A. baumanni	0.78 mg/mL	0.39 mg/mL	18	
Ethanolic extract	Eugenol, glycosides, flavonoids, saponins, tannins, and essential oils.	*P. mirabilis*	ND	ND	19.7	[54]
		S. epidermidis	ND	ND	18	
		K. pneumoniae	ND	ND	12.3	
		E. coli	ND	ND	12.7	
		S. aureus	ND	ND	14.7	

* Depending on the strain. ND: not determined; MIC: minimum inhibitory concentration; MBC: minimum bactericidal concentration.

4. Cumin

Cumin (*Cuminum cyminum L.*) is an aromatic plant that belongs to the Apiaceae family, Apioideae subfamily, Scandiceae tribe, and Daucinae subtribe [65]. It has a branched and ribbed stem, leaves divided into filaments and strongly lobed, small white or pink flowers, and ovate or spindle-shaped fruits, light brown or light grey. The seeds are ovoid, and two

grains are connected in one body; one side is raised and ribbed, and the other is flat, brown in color, fragrant in odor, and pungent in taste [66]. The seeds are mainly used as a seasoning or flavoring agent for different culinary purposes [67]. The seed's EO is used in abundance to make soups, stews, sausages, cheeses, pickles, curries, meats, and chutneys. Furthermore, the seeds are widely used in the perfume industry due to their intense aroma [68]. Additionally, it is used in medical preparations such as toothpaste, mouthwashes, and soaps [67].

Today, cumin is produced in countries such as Chile, Mexico, Syria, Egypt, Morocco, Turkey, Iran, Tajikistan, Uzbekistan, and China, where India accounts for 70% of world production and 90% of consumption [69]. Particularly in Mexico, it was popularized by the Spanish, who traditionally used it to make blood sausage and other dishes, and it quickly became part of the local cuisine due to its spicy flavor [70].

Cumin seed contains 22.27 to 23.80% total lipids and 2.4 to 5.0% EO (volatile). It also has organic acids such as aspartic, benzoic, citric, malic, propionic, tartaric, ascorbic, maleic, oxalic, and fumaric acids, phenols such as salicylic, cinnamic, gallic, p-hydroxybenzoic acid, hydroquinone, resorcinol and flavonoids such as rutin, quercetin, and coumarin [69][71][72]. Limonene, α- and β-pinene, 1, 8-cineole, *o*-and *p*-cymene, α- and γ-terpinene, safranal, and linalool are compounds that are also found in cumin seed. However, cuminaldehyde, cymene, and terpenoids are the main bioactive components, although the EO, in addition to cuminaldehyde, also has paracymene [66][69].

Cumin has different preparations. The most used is the EO extracted from the seeds with the hydrodistillation method. For extraction with this method, the dried and macerated seeds are placed in a distillation apparatus with distilled water for three to four hours. The oil is then extracted and stored in dark vials until use [73][74][75]. The main components of cumin can also be extracted using different solvents such as methanol, acetone, butanol, alcohol, and even water [75][76][77].

In medicine, cumin extracts have been used as an antiseptic, antispasmodic, anticancer, and treatment for digestive disorders, colic, and dyspeptic headaches [78]. In addition, *Cuminum cyminum* seeds have been shown to possess significant biological properties, such as antibacterial and antifungal activity [75]. Cumin has played an important role in UTIs due to its antimicrobial activity against Gram-positive and Gram-negative bacteria [74][75][77]. **Table 3** shows the antimicrobial activity of the different cumin extracts.

Table 3. Antimicrobial activity of *Cuminum cyminum* extracts.

Type of Extract	Phytochemicals	Uropathogen	MIC	MBC	Diameter of the Inhibition Zone (mm)	Ref.
Essential oil	**Cuminaldehyde, α-thujene, α,β-pinene, *p*-cymene, γ-terpinene, cumin oils**	***K. pneumoniae***	**0.8–3.5 µg/mL**	**ND**	**ND**	[74]
Essential oil	**Cuminaldehyde, α-thujene, α,β-pinene, *p*-cymene, γ-terpinene, cumin oils**	***E. coli***	**10–50 ppm and 100–250 ppm ***	**ND**	**ND**	[73]

Type of Extract	Phytochemicals	Uropathogen	MIC	MBC	Diameter of the Inhibition Zone (mm)	Ref.
Essential oil	Cuminaldehyde, α-thujene, α,β-pinene, *p*-cymene, γ-terpinene, cumin oils	*E. coli*	0.25 mg/mL	0.5 mg/mL	23	[75]
		K. pneumoniae	0.25 mg/mL	0.5 mg/mL	22	
		p. aeruginosa	0.25 mg/mL	0.5 mg/mL	20	
		S. agalactiae	0.25 mg/mL	0.5 mg/mL	21	
		group A *streptococci*	0.015 mg/mL	0.03 mg/mL	20	
		E. faecalis	0.125 mg/mL	0.25 mg/mL	20	
		S.epidermidis	0.25 mg/mL	0.5 mg/mL	10	
		S. aureus	ND	ND	7	
		S. saprophyticus	0.25 mg/mL	0.5 mg/mL	20	
Essential oil	Cuminaldehyde, α-thujene, α,β-pinene, *p*-cymene, γ-terpinene, cumin oils	*S. aureus*	1161 µg/mL	ND	45	[52]
		P. aeruginosa	84.97 µg/mL	ND	8	
		K. pneumoniae	204.87 µg/mL	ND	12	
		E. coli	7.219 µg/mL	ND	52	
Ethanolic extract	ND	*E. coli*	0.125 mg/mL	0.25 mg/mL	22	[75]
		K. pneumoniae	0.125 mg/mL	0.25 mg/mL	22	
		P. aeruginosa	0.25 mg/mL	0.5 mg/mL	20	
		S. agalactiae	ND	ND	7	
		group A *streptococci*	0.125 mg/mL	0.25 mg/mL	23	
		E. faecalis	0.125 mg/mL	0.25 mg/mL	23	
		S. epidermidis	0.125 mg/mL	0.25 mg/mL	25	
		S. aureus	0.125 mg/mL	0.25 mg/mL	20	
		S. saprophyticus	0.25 mg/mL	0.5 mg/mL	23	
Aqueous-ethanolic (30/70) extract	Carbohydrates, flavonoids, protein, alkaloids, phenols	*E. coli*	ND	ND	26	[77]
		K. pneumonia	ND	ND	22	
		S. saprophyticus	ND	ND	25	
		P. mirabilis	ND	ND	21.5	

* Depending on the isolated strain; ND: not determined; MIC: minimum inhibitory concentration; MBC: minimum bactericidal concentration.

Cumin EO has potent antimicrobial activity even against strains of *E. coli* resistant to multiple drugs, including tetracycline, erythromycin, amoxicillin, ceftazidime, and cefixime. A study carried out on 12 strains of *E. coli* isolated from the urine of

patients hospitalized with UTIs showed that cumin EO had a differential inhibitory effect between the different isolates. Approximately 24.9% of *E. coli* isolates showed low MICs (<50 ppm), while 41.6% had moderate MICs (100 ppm), and 16.6% of the isolates had high MICs (250 ppm) [73]. Likewise, another study observed that cumin oil and methanolic extract have better antibacterial activity in uropathogenic isolates than amoxicillin; however, this did not happen with other antibiotics. The EO and the methanolic extract were tested against *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. agalactiae*, group A *streptococci*, *E. faecalis*, *S. epidermidis*, *S. aureus*, and *S. saprophyticus*, isolated from samples of 95 UTIs patients, but without malignant diseases, diabetes and immunosuppression [75]. In another study carried out in 2016, the effect of cumin oil was compared with chamomile and clove oil. Cumin oil was found to inhibit most bacteria. Furthermore, it was more effective when used with some antibiotics, suggesting that it could be an adjunctive treatment [52].

The mechanism by which cumin EO exerts its antibacterial effects remains unclear. However, it has been reported to cause cell wall damage or changes in outer membrane proteins; these effects could be attributed to the molecular characteristics of the aldehydes present [74][79][80]. It should be noted that bacterial DNA degradation is not a proven antibacterial mechanism for cumin EO. It was previously reported that cumin AE could not induce DNA degradation of the R plasmid of clinical isolates of *K. pneumoniae* [74]. In addition, the aqueous-ethanolic extract (30/70) of cumin has been reported to have significant antibacterial and antioxidant activities [77].

Finally, researchers must consider that cumin use has side effects, including contact dermatitis, respiratory reactions, and liver cancer (above dietary levels) [81]. Patients with stomach ulcers, liver disorders, and pregnant or lactating women should use cumin with caution. Patients should also be aware of the use of drugs similar to cumin, including antibiotics, anticancer drugs, antifungals, anti-inflammatory drugs, antioxidants, anticonvulsants, cholesterol, and lipid-lowering drugs, estrogen and gastrointestinal drugs, pesticides, iron, morphine, opioids, osteoporosis agents, analgesics and phytoestrogens [66].

In summary, cumin extracts can be used as antibiotics against UTIs-inducing pathogens, even those resistant to drugs. However, it is important to continue updating the information on cumin in combination with antibiotics to enhance the inhibitory effect of uropathogens and study the possible mechanisms behind this protection.

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