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Review Article

# The Antibacterial Activity of Allium sativum, Thymus vulgaris, Origanum vulgare, Curcuma longa, Rosmarinus officinalis, and Cinnamomum species Against Various Antibiotic-Resistant Strains of Bacteria: A Literature Review

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**Objective. The purpose of this narrative review was to evaluate the antimicrobial activity of garlic (*Allium sativum*), thyme (*Thymus vulgaris*), oregano (*Origanum vulgare*), turmeric (*Curcuma longa*), rosemary (*Rosmarinus officinalis*) and cinnamon (*Cinnamomum* species) for the treatment of antibiotic-resistant strains of *Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli*, *Campylobacter jejuni,* and *Salmonella typhimurium*.**
**Methods. The scientific electronic database PubMed was utilized to review the current literature. The inclusion criteria consisted of academic journal articles that were available as free full-text studies published between 2007-2018.**
**Results. In total, 2,923 articles were found and 71 of those met the preset criteria. The literature review provided evidence that garlic (*Allium sativum*), thyme (*Thymus vulgaris*), oregano (*Origanum vulgare*), turmeric (*Curcuma longa*), rosemary (*Rosmarinus officinalis*) and cinnamon (*Cinnamomum* species) may be effective for the suppression of growth of antibiotic-resistant strains of *Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli*, *Campylobacter jejuni,* and *Salmonella typhimurium*.**
**Conclusion. Antibiotic-resistant strains of bacteria are a major issue in the healthcare field. Natural plant-based products may provide a benefit as an adjunct therapy or monotherapy for certain strains of bacteria that are antibiotic resistant.**

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## 1. Introduction

### *1.1. A Brief History of Antibiotic Resistance*

Sir Alexander Fleming discovered penicillin, which became the first antibiotic in 1928 (Ventola, 2015). This monumental moment in history has influenced the management of infectious diseases, saving countless lives. Antibiotics became the primary therapeutic method for treating individuals afflicted with severe communicable pathogens. Unfortunately, in the 1940s, bacteria that were resistant to the effects of penicillin began to emerge (Ventola, 2015). Consequently, research was conducted to identify new antibacterial agents to contend with antibiotic-resistant strains (Ventola, 2015). Unfortunately, in 1962, the first case of methicillin-resistant *Staphylococcus aureus* (MRSA) was confirmed, denoting an ever-growing public health issue of bacteria becoming resistant to antibiotics (Ventola, 2015).

### *1.2. Factors Contributing to Antibiotic Resistance*

Several factors have influenced the development of antibiotic-resistant microbes. One of the primary reasons bacteria are becoming resistant to antibiotics is overuse and inappropriate administration (Ventola, 2015). The misuse of antibiotics can eradicate the natural flora and create an environment favorable for bacteria resistant to antibiotics to propagate (Aslam et al., 2018). Antibiotics are one of the most commonly used medications, and it is estimated that antibiotic prescriptions are unwarranted in 30-50% of cases (Ventola, 2015). Another issue is the poor regulation of antibiotic products in various countries (Ventola, 2015). In many of these countries, antibiotics are not controlled and are available over the counter for anyone to purchase and use (Ventola, 2015). The utilization of antibiotics as growth stimulants in livestock has also compounded the development of antibiotic-resistant strains of bacteria (Ventola, 2015). Overpopulation and mass transit may be contributing factors to the development of antibiotic resistance (Aslam et al., 2018). Overpopulation provides additional growth mediums for bacteria, and mass transit around the world allows different strains of bacteria that would never have otherwise come in contact before to exchange genes (Aslam et al., 2018). Lastly,

inadequate sewage disposal systems can potentially allow antibiotic-resistant isolates to flourish (Aslam et al., 2018).

### *1.3. Statistics Related to Antibiotic Resistance*

The Centers for Disease Control and Prevention (CDC) released a statement in 2013 declaring that we are now in a "post-antibiotic era" (Ventola, 2015). According to the CDC, there are millions of cases of antibiotic-resistant infections in the US and thousands of deaths annually (Aslam et al., 2018). Although there have been many advances in medicine to prevent antibiotic-resistant microbes, at least 18 species of bacteria threaten human health, 12 of which are considered urgent threats (Ventola, 2015). These urgent threats have given rise to multidrug-resistant (MDR) bacteria, which are defined as bacteria that are resistant to one or more classes of pharmaceutical-grade antibacterial agents (CDC, 2015).

*S aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Campylobacteria jejuni,* and *Salmonella typhimurium* are bacterial strains with a greater tendency to be resistant to antibiotics or MDR and cause frequent infections in the US (Ventola, 2018). In the US, there are about 80,000 MRSA infections each year, with 11,000 deaths (Hanely et al., 2015). These infections result in over $83,000 in additional healthcare costs per patient (Sowash et al., 2014; Chu et al., 2005). *S pneumoniae* accounts for 2 million illnesses, 19,000 hospitalizations, and 23,000 deaths in the US annually, which causes about $91 million in medical expenses and an estimated $233 million in losses from reduced productivity and missed work (Kim et al., 2016). There are an estimated 6,000 infections with MDR *P aeruginosa* each year and 400 deaths in the US (CDC, 2021).

*E coli* causes 265,000 infections, 2,000 hospitalizations, and 60 deaths in the US per year (CDC, 2014; Frenzen et al., 2005). The financial burden due to *E coli*-related illnesses is $405 million, with $370 million due to premature death (Frenzen et al., 2005). *C jejuni* is the most frequent pathogen associated with food poisoning and is responsible for an estimated 1.3 million cases annually, costing the US almost $2 billion a year (USDA, 2019; CDC, 2022a; Johnson al., 2017). In the US, the economic burden of *Salmonella* infections roughly costs $3.6 billion and is responsible for 1.35 million infections annually (USDA, 2019; CDC, 2022b). Of those infections, about 26,500 are severe requiring hospitalization, and 2,420 result in death (CDC, 2022b).

With the emergence of a multitude of bacterial isolates that are resistant to antibiotics or MDR, the financial burden that these infections create, and the morbidity and mortality associated with the infections, it is necessary to pursue alternative agents that can act as therapeutic enhancers or replacements of the current modalities. Plants were the first antimicrobial agents utilized for infections in Ancient Egypt, Greece, and China (Ventola, 2018). There are a variety of botanicals that have exhibited potent bacteriostatic and bactericidal effects against a broad spectrum of bacteria (Ventola, 2018). In addition, plant products have been used as potential treatment strategies for eliminating MDR strains of bacteria (Ventola, 2018).

### *1.4. Herbal Treatment for Antibiotic-Resistant Bacteria*

In the US, there are several botanicals that are commonly used and may be capable of eradicating microbes resistant to antibiotics or MDR strains of bacteria. These herbs include garlic (*Allium sativum* (L.)), thyme (*Thymus vulgaris* subsp. aestivus (Reut. Ex Willk) A. Bolòs & O. Bolòs), oregano (*Origanum vulgare* subsp. Viridulum (Martrin-Donos) Nyman), turmeric (*Curcuma longa* (var. vanaharidra Velay., Pandrav. J.K. George & Varapr.)), rosemary (*Rosmarinus officinalis* var. serotinus (Loscos) Loscos), and cinnamon (*Cinnamomum verum* (J.Presl)). The nomenclature has been verified according to the latest revision of "World Flora Online". In addition to their antibacterial properties, these botanicals may have supplementary effects such as reducing prooxidants and inflammatory mediators associated with the pathogenicity of the microbe to attenuate symptoms in a living organism as well as acting as immunostimulants to assist with the elimination of the infection. Another consideration is that these plant extracts may enhance the activity of antibiotics, potentiating their effects.

## 2. Literature Review

The purpose of this literature review is to analyze and evaluate the currently available literature on the effectiveness of garlic (*A sativum*), thyme (*T vulgaris*), oregano (*O vulgare*), turmeric (*C longa*), rosemary (*R officinalis*), and cinnamon (*C verum*) as bacteriostatic and bactericidal agents against antibiotic-resistant and MDR strains of bacteria and find lapses in knowledge in the research.

## 3. Methods

A narrative review of the current literature was conducted in May of 2019 utilizing searches of the computerized database PubMed. The inclusion criteria for the review consisted of free full-text studies published between 2007-2018. The relevant keyword searches associated with garlic (*A sativum*), thyme (*T vulgaris*), oregano (*O vulgare*), turmeric (*C longa*), rosemary (*R officinalis*), cinnamon (*Cinnamomum species*), *S aureus*, *S pneumoniae*, *P aeruginosa*, *E coli*, *C jejuni,* and *S typhimurium* are specified in Table 1. PubMed was the only academic resource used. The narrative review analyzed experiments related to the growth inhibition of antibiotic-resistant strains of bacteria. Studies that did not meet the criteria of the particular keywords or did not discuss antibiotic-resistant strains were excluded. Studies that were abstracts only, meta-analysis studies, literature reviews, narrative reviews, commentary articles, research using herbal formulas or herbs in conjunction with drugs or other supplements, or were written in a language other than English were excluded.

| Botanical | Parts Used | Active Constituents | Pharmacological Activity | Traditional Uses |
|---|---|---|---|---|
| Garlic (*Allium sativum L.*) | Whole fresh or dried bulb, and oil | Allylalliin, ajoens, methylalliin, propenyl alliin, oligosufides, and vinyl dithiins | Antihyperlipidemic, antihypertensive, anticoagulant, antibacterial, antifungal, antiviral, anticarcinogenic, and immunostimulatory | Cardiovascular disease, hypertension, hyperlipidemia, diabetes, infectious disease, gastrointestinal colic, constipation, and dysmenorrhea |
| Thyme (*Thymus vulgaris*) | Dried leaves, fresh aerial parts of flowering plant, and oil extracted from the fresh flowering plant | Thymol, p-cymene, carvacrol, γ-terpinene, borneol, linalool, rosmarinic acid, luteolin, apigenin, naringenin, thymonine, eriodictyol, and thymusin | Antibacterial, antifungal, antiprotozoan, antioxidant, antiviral, spasmolytic, and expectorant | Upper respiratory tract infections, catarrh of the upper respiratory tract, asthma, gastritis, pruritus, pharyngitis, stomatitis, dyspepsia, and gastritis |
| Oregano (*Origanum vulgare*) | Fresh flowering herb, and oil extracted from fresh or dried leaves | Carvacrol, γ-terpinene, p-cymene, myrcene, thymol, α-pinene, linalool, naringin, germacrene D, and rosmaric acid | Antibacterial, anticarcinogenic, antifungal, antioxidant, antiparasitic, and expectorant | Upper respiratory tract infections, dyspepsia, dysmenorrhea, rheumatoid arthritis, and urinary tract infections |
| Turmeric (*Curcuma longa*), | Stewed and dried rhizome | α-atlantone, γ-atlantone, α-tumerone, β-tumerone, artumerone, curlone, curcumol, zingiberene, curcumin, demethoxy curcumin, bidemethoxy curcumin | Anticoagulant, anticarcinogenic, anti-inflammatory, antihyperlipidemic, antimicrobial, antioxidant, hepatoprotective, and estrogenic | Dyspepsia, loss of appetite, flatulence, upper respiratory tract infections, leprosy, nephritis, cystitis, intestinal colic, conjunctivitis, and constipation |
| Rosemary (*Rosmarinus officinalis*) | Stems, oil extracted from the leaves, flowering branches, and fresh aerial parts of the plant | Rosmarinic acid, rosmariquinone, rosmadial, rosmaridiphenol, carnosolic acid, isorosmanol, cirsimarin, diosmin, phegopolin, plantiginin, hesperidin, oleanolic acid, ursolic acid, 1,8-cineole, α-pinene, camphor, camphene, limonene, linalool, myrcene, verbenone, and α-terpineol | Antimicrobial, antiviral, anticoagulant, anticarcinogenic, anticonvulsant, spasmolytic, hepatoprotective, and choleretic | Hypertension, loss of appetite, rheumatic conditions, dyspepsia, dysmenorrhea, migraines, headaches, amenorrhea, poor memory, fatigue, dizziness, sciatica, intercostal neuralgias, and gastrointestinal disorders |
| Cinnamon (*Cinnamomum aromaticum*) | Dried flowers, whole or partly peeled bark, and the oil extracted from the bark | Cinnamaldehyde, weiterhin cinnamylacetate, cinnamic acid, coumarin, cinnamyl alcohol, cinnzeylanoles, cinncassiole A, and cinncassiole E | Antibacterial, antifungal, immunostimulant, antihistamine, and antiulcerogenic | Dyspepsia, loss of appetite, gastrointestinal colic, bloating, flatulence, diarrhea, amenorrhea, fatigue, enhancing immune function, and vomiting |

**Table 1.** Traditional Use of Botanicals

## 4. Results

A total of 2,923 articles were selected to be reviewed on PubMed. Of the academic materials available, only 71 publications met the inclusion criteria. Each of the 71 articles discussed the antibacterial effects of one of the chosen botanicals for an antibiotic-resistant strain of bacteria.

## 5. Discussion

As discussed previously, bacterial strains that are a public health issue in the US and are commonly resistant to antibiotics are *S aureus*, *S pneumoniae*, *P aeruginosa*, *E coli*, *C jejuni,* and *S typhimurium* (Ventola, 2018). Some antibiotics administered for these infections are penicillin, cephalosporins, monobactams, quinolones, tetracycline, macrolides, clindamycin, linezolid, rifampin, polymyxins, methicillin, gentamicin, sulfonamides, and vancomycin (Kapoor et al., 2017). The mechanisms of action of these antibacterial agents include interfering with the production of the cell wall or membrane, reducing folate synthesis, disrupting DNA or RNA replications, or impeding the generation of proteins (Kapoor et al., 2017). Although these antibiotics can impede the growth of bacteria, many bacteria are becoming resistant to them (Kapoor et al., 2017).

## 6. Antibiotic-Resistant Bacterial Strains

### *6.1. S aureus*

*S aureus* is a gram-positive, non-motile bacterium commensal to the human nares and skin (Kane et al., 2017). *S aureus* is the infectious agent in toxic shock syndrome and is capable of causing pneumonia, endocarditis, bacteremia, and skin infections (Kane et al., 2017). This microbe is a major concern in the healthcare setting, and in the community as it can become MRSA, which is considered a major threat by the CDC (CDC, 2022a, CDC, 2019a). *S aureus* can be

found colonized in the nasal mucosa and on the skin of 30-50% of the general population (Sowash, 2014). It is estimated that approximately 5% of patients in hospitals in the United States have MRSA colonized in their nasal mucosa and on their skin, which could cause an infection (Sowash et al., 2014; Chu et al., 2005). Infections caused by *S aureus* are especially prevalent in communities affected by the opioid epidemic due to intravenous drug use (CDC, 2019b).

An infection with *S aureus* occurs most frequently by bacteria colonized on the host's skin, within the nasal or oral cavity, the vagina, or the gastrointestinal (GI) tract (Liu, 2009). The pathogenesis of *S aureus* is associated with a multitude of virulence factors, which allow the bacteria to evade the immune system of the host. *S aureus* can adhere to and penetrate through the epithelial cells using a group of molecules called microbial surface components recognizing adhesive matrix molecules (Liu, 2009). Once the bacterium has colonized, *S aureus* secretes chemotaxis inhibitory protein, which impedes the ability of neutrophils to recognize chemotactic factors (Liu, 2009). Extracellular adherence protein interferes with the binding of neutrophils to endothelial adhesion molecule intracellular adhesion molecule-1, which down-regulates leukocyte adhesion, diapedesis, and the movement of white blood cells (WBC) from the circulation into the infected tissue (Liu, 2009).

In addition, staphylococcal superantigen-like molecules can further hinder neutrophil movement from the bloodstream into the infected tissue and chemotaxis, preventing leukocytes from entering the tissue to mount an attack against the pathogen (Thammavongsa, 2015). *S aureus* is also capable of producing hemolysins alpha and gamma, which induce inflammation and lyse neutrophils (Tomita, 1997). Another inflammatory toxin is Panton-Valentine leucocidin, which interacts with the mitochondrial membrane of host cells and induces apoptosis (Kane, 2018). Staphylococcal enterotoxins are a class of "superantigens" that have the ability to induce hyperstimulation of T cells by adhering to major histocompatibility complex (MHC) II, which can exacerbate inflammation (Kane, 2018). All of these mechanisms suppress the immune system of the host creating a favorable environment for an infection.

MRSA infections have become impervious to certain antibiotics, primarily penicillin, due to their two forms of β-lactam resistance (Kane, 2018). The first mechanism of resistance was the development of a penicillin-binding protein (Kane, 2018). This protein reduces the binding affinity of β-lactam compounds, specifically methicillin, for MRSA (Kane, 2018). The second method of resistance is more prevalent in MRSA. This process occurs via the activity of the enzyme β-lactamase, which inhibits the proteolytic activity of B-lactams (Kane, 2018). Prolonged intravenous administration of antibiotics such as daptomycin, vancomycin, gentamicin, and rifampin are the primary therapeutic agents currently utilized against MRSA and other antibiotic-resistant strains of *S aureus* (Kane, 2018). In addition to antibiotic treatment, botanicals may present another option available to control infections.

There were two studies identified in the narrative review related to the antimicrobial activity of garlic (*A sativum*) against antibiotic-resistant strains of *S aureus*. Both publications illustrated that garlic (*A sativum*) inhibited the growth of MRSA. The research by Viswanathan et al tested allicin, which is one of the primary phytochemicals in garlic (*A sativum*), and garlic (*A sativum*) oil against MRSA (Viswanathan, 2014). In their experiment, 500 mcg/ml and 1,000 mcg/ml extracts of allicin, and 10,000 mcg/ml and 50,000 mcg/ml of garlic (*A sativum*) oil were utilized (Viswanathan, 2014). The zone of inhibition (ZOI) was measured at 25±2.52 mm, 31.33±1.53 mm, 8.67±1.53 mm, and 16.67±2.31 mm for the 500 mcg/ml and 1,000 mcg/ml extracts of allicin and 10,000 mcg/ml and 50,000 mcg/ml of garlic (*A sativum*) oil respectively (Viswanathan, 2014). The other study by Woods-Panzaru et al compared the bacteriostatic activity of garlic (*A sativum*) to 5 mcg disks of Ciprofloxacin (Woods-Panzaru, 2009). These investigators found that the fresh undiluted extracts of garlic (*A sativum*) produced a ZOI of 25 mm while Ciprofloxacin had a ZOI of 19 mm (Woods-Panzaru, 2009). Unfortunately, the dosage of garlic (*A sativum*) was not specified.

In the two articles discussing the efficacy of garlic (*A sativum*) for its antibacterial effects against MRSA, there were several extracts tested, and all the extracts tested demonstrated positive effects for growth inhibition against MRSA. The results from Viswanathan et al suggest that isolating allicin from garlic (*A sativum*) may be more effective than utilizing garlic (*A sativum*) oil as a monotherapy. However, the undiluted garlic (*A sativum*) extract in the study by Woods-Panzaru et al produced a ZOI similar to that of allicin as a monotherapy. Additional studies are required to determine the form of the extract with the greatest potential to impede the replication of MRSA, the minimum inhibitory concentration (MIC), and the minimum bactericidal concentration (MBC). In addition, even though the information on garlic (*A sativum*) for the eradication of MRSA is marginal, in the study by Woods-Panzaru et al, the activity of garlic (*A sativum*) was more pronounced than the antibiotic Ciprofloxacin, which indicates that garlic (*A sativum*) could be a viable alternative.

In the narrative review, five articles discussed the antibacterial activity of thyme (*T vulgaris*) for antibiotic-resistant strains of *S aureus*. Four of the studies demonstrated a reduction in cellular replication (Dahiya, 2012; Wang, 2016; Mehreen, 2016; Mahboubi, 2014). The one academic article that failed to show growth inhibition was by Subbu Lakshmi et al (Subbu, 2016). However, the concentration of thyme (*T vulgaris*) administered was unclear. Dahiya et al compared hexane, chloroform, methanol, and ethanol extracts against MRSA and two other antibiotic-resistant strains of *S aureus*. All of the dilutions were effective against one of the antibiotic-resistant strains (Dahiya, 2012). However, the methanol and ethanol extracts were effective against MRSA, and only the ethanol formula was effective against the second antibiotic-resistant strain (Dahiya, 2012). The ethanol dilution had a MIC of 1,560 mcg/ml and 6,250 mcg/ml against antibiotic-resistant isolates and 3,120 mcg/ml for MRSA, while the methanol extract had a MIC of 3,120 mcg/ml for the first antibiotic-resistant strain and 6,250 mcg/ml for MRSA (Dahiya, 2012). The MIC for Mahboubi et al was 12,500 mcg/ml (Mahboubi, 2014). Mehreen et al experimented with three strains of MRSA that were MDR. They recorded the MIC for two of the isolates at 15.63 mcg/ml and 31.25 mcg/ml for the third strain (Mehreen, 2016). The study by Wang et al extracted thymol and used it as a monotherapy for the elimination of MRSA. In their research, the MIC and MBC of thymol as monotherapy were 200 mcg/ml (Wang, 2016).

The ZOI for the hexane, chloroform, methanol, and ethanol extracts were 12±0.2 mm, 8.20±0.4 mm, 12±0.15 mm, and 17±0.2 mm, respectively, for the first antibiotic-resistant strain (Dahiya, 2012). The ZOI for MRSA was 11.83±0.1 mm and 13.76±0.2 mm for the methanol and ethanol dilutions, respectively, and the ZOI of the ethanol formula was 7.03±0.05 mm for the second antibiotic-resistant isolate (Dahiya, 2012). The data by Mahboubi et al reflect a ZOI for MRSA at concentrations of 12,500 mcg/ml, 25,000 mcg/ml,

50,000 mcg/ml, 100,000 mcg/m, and 200,000 mcg/ml to be 20±0 mm, 25.5±0.5 mm, 22±0 mm, 24.5±0.5 mm, and 28.5±0.5 mm respectively (Mahboubi, 2014). For the three strains in the study by Mehreen et al, the ZOI was measured at 22 mm for the first two MDR bacteria and 25 mm for the third (Mehreen, 2016). Wang et al did not specify the exact ZOI but noted that it was over 20 mm (Wang, 2016).

Although there are only five studies evaluating the antimicrobial activity of thyme (*T vulgaris*) for antibiotic-resistant strains of *S aureus*, multiple antibiotic-resistant isolates and MRSA were compared. The MIC values in the research differed greatly. However, this is most likely dependent on the strain and extract used. Mahboubi et al had a higher MIC value but also had a more pronounced ZOI. The data collected from this research indicates that thyme (*T vulgaris*) may be effective in inhibiting the growth of multiple strains of MRSA and antibiotic-resistant *S aureus*. Further investigations should be conducted.

In the narrative review, there were two studies assessing the antibacterial activity of oregano (*O vulgare*) for the eradication of MRSA. Oregano (*O vulgare*) inhibited the replication of MRSA in both experiments (Dahiya, 2012; Mehreen, 2016). The first study by Mehreen et al administered oregano (*O vulgare*) to three strains of MDR MRSA. Oregano (*O vulgare*) impeded the growth of all three strains. The MIC for the first and third isolates were 7.81 mcg/ml and 15.62 mcg/ml for the second strain. The ZOI for the first and third strains was 22 mm and 20 mm for the second isolate (Mehreen, 2016).

The other article evaluated the effects of different extracts of oregano *(O vulgare)* against two MDR strains of *S aureus* and MRSA. This study used formulas with hexane, chloroform, methanol, and ethanol. However, the MIC was only found for the methanol and ethanol extracts. The methanol extract inhibited the growth of the first and second MDR strains and MRSA at 6,250 mcg/ml, 3,120 mcg/ml, and 6,250 mcg/ml, respectively (Dahiya, 2012). The ethanol extract suppressed the proliferation of the first and second MDR isolates and MRSA by 6,250 mcg/ml, 3,120 mcg/ml, and 3,120 mcg/ml, respectively (Dahiya, 2012). All dilutions were bacteriostatic against the first MDR strain with ZOI of 9.90±0.55 mm, 10±0.2 mm, 12±0.03 mm, and 11±0.8 mm for hexane, chloroform, methanol, and ethanol, respectively (Dahiya, 2012). The extracts all impeded the growth of the second MDR bacteria as well, with a ZOI of 14±0.17 mm, 6.9±0.1 mm, 15.06±0.05 mm, and 13±0.2 mm for the hexane, chloroform, methanol, and ethanol dilutions respectively (Dahiya, 2012). Only the methanol and ethanol formulations attenuated the reproduction of MRSA with ZOI of 12.03±0.1 mm and 14.9±0.05 mm, respectively (Dahiya, 2012).

Although there were only two publications discussing the activity of oregano (*O vulgare*) for the mitigation of the growth of antibiotic-resistant strains of *S aureus*, four strains of MRSA and two MDR strains were tested utilizing several different extracts. Oregano (*O vulgare*) reduced the growth of all the bacteria analyzed. The MIC and ZOI varied between the two experiments, which may have been due to the utilization of different strains. The dilutions in the study by Mehreen et al were prepared using hexane, methanol, and aqueous extracts, which could be the possible difference. In addition, the dilutions may have been more concentrated as the MIC is lower and the ZOI is higher. More studies are required to determine the appropriate dosage of oregano (*O vulgare*) for the eradication of MRSA and MDR strains of *S aureus*, but the initial research is promising.

In the narrative review, there were three studies evaluating the antibacterial effects of turmeric (*C longa*) for the elimination of MRSA. The research showed turmeric (*C longa*) generated bacteriostatic effects in two of the studies (Marasini, 2015; Singh, 2017). In the experiment conducted by Kong et al, nematodes were infected with MRSA (Kong, 2014). At a dosage of 200 mcg/ml, turmeric (*C longa*) did not cure the infection (Kong, 2014). In contrast to Kong et al, Marasini et al utilized an extract of turmeric (*C longa*) and found it effective in recording a MIC at 6,250 mcg/ml (Marasini, 2015). In the experiment by Singh et al, curcumin, which is the primary antimicrobial component, was used as a monotherapy. The MIC for curcumin against MRSA ranged from 175-300 mcg/ml (Singh, 2017). The dosage range varied depending on the solvent. Unfortunately, the MIC for each solvent was not specified. The reason that turmeric (*C longa*) was not effective in the study by Kong et al may be due to an inadequate amount of curcumin being administered to an infected organism. Curcumin is the primary antimicrobial component of this botanical, and a dosage of 200 mcg/ml of the whole plant extract may not have contained enough curcumin to elicit effects as Singh et al used 175-300 mcg/ml of curcumin as a monotherapy, which inhibited the growth of MRSA. Consequently, a higher concentration of curcumin may be required to treat a living organism.

In the narrative review, three studies showed that rosemary (*R officinalis*) inhibited the growth of MRSA and other antibiotic-resistant strains of *S aureus*. Dahiya et al studied dilutions of hexane, chloroform, methanol, and ethanol against MRSA and two MDR isolates. The methanol and ethanol extracts impeded the growth of all strains, and the chloroform extract reduced the replication of the second MDR isolate (Dahiya, 2012). However, the MIC was only listed for the methanol and ethanol extracts for the two MDR strains and MRSA. The values were 3,120 mcg/ml for all isolates except the ethanol extract, which was 6,250 mcg/ml for the first MDR bacterium (Dahiya, 2012). The article by Luís et al did not measure the MIC but recorded a ZOI of 17.27±1.88 mm (Luís, 2017). The ZOI for the methanol extract against the first and second MDR strains and MRSA were 15±0.3 mm, 12.03±0.05 mm, and 14±0.7 mm, respectively, while the ethanol dilution produced a ZOI of 14±0.8 mm, 14.93±0.9 mm, and 14±0.9 mm respectively (Dahiya, 2012). The chloroform extract had a ZOI of 6±0.15 mm against the second MDR strain of S aureus (Dahiya, 2012). The research conducted by Ekambaram et al isolated rosmarinic acid and administered it as a monotherapy against MRSA. The MIC was not assessed. However, at 2,000 mcg/ml, 4,000 mcg/ml, 6,000 mcg/ml, and 8,000 mcg/ml, rosmarinic acid suppressed bacterial growth by 11.6±0.4 mm, 14.2±0.2 mm, 17.6±0.2 mm, and 20.0±0.4 mm respectively (Ekambaram, 2016).

In the narrative review, there were four studies evaluating the activity of cinnamon (*Cinnamomum species*) against MRSA and antibiotic-resistant strains of *S aureus*. All the academic articles reported the inhibitory activity of cinnamon (*Cinnamomum species*) against MRSA antibiotic-resistant isolates (Mehreen, 2016; Perumal Samy, 2013; Mandal, 2011; Naveed, 2013). The studies by Mandal et al and Mehreen et al assessed the antimicrobial effects against MRSA. The research published by Mandal et al evaluated the effects of cinnamon (*C zeylanicum* Blume) against twelve strains of MRSA. Cinnamon (*C zeylanicum*) was found to be effective in suppressing the growth of all strains of MRSA (Mandal, 2011). Unfortunately, the individual test results for each strain were not provided. However, the MIC ranged from 64-256 mcg/ml (Mandal, 2011). The MIC for cinnamon (*C zeylanicum*) in the data collected by Mehreen et al was 7.81 mcg/ml, 125 mcg/ml, and 250 mcg/ml for each of the three isolates of MRSA (Mehreen, 2016). The MBC for cinnamon (*C zeylanicum*) was 200-250 mcg/ml for MRSA (Mandal, 2011). The ZOI

for all isolates in the experiment by Mandal et al ranged from 22-27 mm (Mandal, 2011). The ZOI was comparable in the study by Mehreen et al at 20 mm, 22 mm, and 25 mm for each of the three strains (Mehreen, 2016).

For the two MDR strains of *S aureus*, the MIC was measured at 7.8 mcg/ml for cinnamon (*C zeylanicum*) and 4,800±0.96 mcg/ml for cinnamon (*C verum*) in the studies by Perumal Samy et al and Naveed et al respectively (Perumal Samy, 2013; Naveed, 2013). The ZOI produced by cinnamon (*C zeylanicum*) was analogous to that observed in the previous studies at 22 mm (Perumal Samy, 2013). In the data assembled by Naveed et al, cinnamaldehyde extracted from cinnamon (*C verum*) was compared to a standard of cinnamaldehyde essential oil. The reference compound had a ZOI of 23.16±0.60 mm, and the tested extract was 23.5±0.28 mm, indicating that these compounds were capable of generating equivalent effects (Naveed, 2013).

The information from these studies demonstrates the effectiveness of cinnamon (*Cinnamomum species*) against MRSA and MDR strains of *S aureus*. Both cinnamon (*C zeylanicum*) and cinnamon (*C verum*) were shown to impede the growth of this bacterium. However, the antibacterial activity of cinnamon (*C zeylanicum*) was more comprehensively analyzed, especially in the experiment by Mandal et al, who tested twelve strains of MRSA. This evidence strongly supports the potential use of cinnamon (*C zeylanicum*) as an adjunct or substitute for the treatment of MRSA. More research is necessary to determine the bacteriostatic effects of cinnamon (*C verum*).

### *6.2. S pneumoniae*

*S pneumoniae* is a gram-positive bacterium capable of aerobic and anaerobic metabolism (Kim, 2016). Antibiotic-resistant *S pneumoniae* causes pneumococcal and meningococcal infections (Kim, 2016; CDC, 2021). This pathogen is the leading cause of community-acquired pneumonia, meningitis, and bacteriemia (Kim, 2016). The first cases of antimicrobial-resistant pneumococcal infections were documented in 1912 (Kim, 2016).

*S pneumoniae* possesses many virulence factors that contribute to its pathogenicity. The cell wall of the bacteria contains a layer of polysaccharides that possess antiphagocytic activity (Brooks, 2018). This allows the bacteria to evade neutrophils and disrupts phagocytosis and the complement cascade (Brooks, 2018). The infectious nature of *S pneumoniae* is facilitated primarily by cell surface proteins and other structures (Keller, 2016). Surface protein A and choline-binding protein A (CbpA) promote the colonization of *S pneumoniae* by assisting with its adherence to the surface of the cell (Keller, 2016). Surface protein A also blocks the complement cascade (Keller, 2016). In addition, CbpA impairs the function of immunoglobulin A, which impedes the activity of the immune system (Keller, 2016). Neuraminidase is another protein that assists with the adherence of the cell during colonization and stimulates the growth of the bacterium (Brooks, 2018). Lipoteichoic acid initiates inflammatory activity in the host tissue (Brooks, 2018). The biofilm protein prevents immune cells from recognizing *S pneumoniae* as foreign, allowing it to persist in the body (Brooks, 2018). Lastly, pili protein down-regulates phagocytic activity preventing bacteria from being engulfed by immune cells (Brooks, 2018).

*S pneumoniae* has been found to be resistant to penicillin, erythromycin, and trimethoprim-sulfamethoxazole (Kim, 2016). Penicillin targets peptidoglycan in the cell wall in gram-positive bacteria binding to the active site of transpeptidase, which prevents the cross-linking of the cell wall, interfering with synthesis (Kim, 2016). Research indicates that mutations in the gene encoding transpeptidase reduce the binding affinity of penicillin, resulting in antibiotic resistance (Kim, 2016). Antibiotic-resistant strains of *S pneumonia* are more prevalent in individuals that are immunocompromised (Kim, 2016). Treatment of MDR strains consists of macrolides, which down-regulate virulence factors and reduce inflammation (Kim, 2016). However, possible mutations that encode genes for ribosomal RNA can lead to antibiotic resistance to macrolides (Kim, 2016). Other antibiotics that have been administered are different forms of penicillin, ampicillin, cephalosporin, clindamycin, cefdinir, or cefuroxime (Kim, 2016). A vaccine for *S pneumoniae* was developed and introduced in the US in 2010 (CDC, 2022c). According to the CDC, utilization of the vaccine can prevent the spread of strains that are antibiotic-resistant (CDC, 2022c).

The narrative review revealed only one study examining the effects of garlic (*A sativum*) for the elimination of MDR *S pneumoniae*. For this research, allicin was extracted from garlic (*A sativum*) and tested against four strains of MDR *S pneumoniae*. The data showed that this herb had the ability to attenuate the growth of all four isolates of this MDR bacterium (Reiter, 2017). The MIC of allicin was 64 mcg/ml for all strains tested (Reiter, 2017). The MBC was 128 mcg/ml for three of the MDR isolates and 64 mcg/ml for the last strain (Reiter, 2017). Unfortunately, the ZOI was not available in this study. This article provides some preliminary information suggesting that allicin extracted from garlic (*A sativum*) may suppress the growth of MDR strains of *S pneumoniae*. However, additional research is necessary to determine the exact antibacterial activity especially studies investigating ZOI.

There was one article discussing the effects of thyme (*T vulgaris*) on MDR *S pneumoniae*. The MIC was measured by the broth dilution method at 110 mcg/ml, and the MBC was 220 mcg/ml (Ács, 2018). As there is no direct contact between the essential oils with *S pneumoniae*, a vapor phase test was used to detect the bacteriostatic effects of thyme (*T vulgaris*). In this test, a culture was grown on a Petri dish with sheep's blood, and the essential oil of thyme (*T vulgaris*) was placed on a filter paper disc that was attached to a separating wall of the Petri dish, which was then incubated for two days at 37°C. There was a 2 mm distance between the culture and the disc. The vapor phase test had a MIC of 75 mcl (Ács, 2018). There are minimal amounts of research related to the use of thyme (*T vulgaris*) for the elimination of *S pneumoniae*. More research should be conducted in order to determine its efficacy as an antimicrobial against antibiotic-resistant strains of *S pneumoniae*.

There was one publication evaluating the activity of rosemary (*R officinalis*) against MDR *S pneumoniae*. In the article, rosemary (*R officinalis*) had a ZOI of 8 mm at 100 mcg/ml (Perumal Samy, 2013). However, there was not a MIC listed. Due to the minimal quantity of information related to the antibacterial effects of rosemary (*R officinalis*) for antibiotic-resistant strains of *S pneumoniae,* more experiments should be conducted to determine the true nature of the herb for its treatment.

Two research papers investigated the antibacterial activity of cinnamon (*Cinnamomum species*) against MDR *S pneumoniae*. In both studies, cinnamon (*C zeylanicum*) mitigated the growth of the MDR bacterium (Perumal Samy, 2013; Ács, 2018). The first study by Ács et al established the MIC to be 60 mcg/ml and the MBC to be 130 mcg/ml (Ács, 2018). In a vapor phase test, cinnamon (*C zeylanicum*) inhibited growth at 75 mcl (Ács, 2018). In the second study, a ZOI of 7 mm was shown against MDR *S pneumoniae* (Perumal Samy, 2013). Unfortunately, a MIC was not determined.

Based on the results of these data, it would appear as if cinnamon (*C zeylanicum*) may be useful as an antibacterial agent for the treatment of *S pneumoniae*. However, additional trials are required before definite conclusions can be drawn. There were no articles available discussing the antibacterial activity of oregano (*O vulgare*) or turmeric (*C longa*) for MDR strains of *S pneumoniae*.

### *6.3. P aeruginosa*

*P aeruginosa* is a gram-negative bacillus (Shortrdige, 2019). It is classified as an opportunistic pathogen afflicting individuals with impaired immune function (Elsen, 2013). *P aeruginosa* is associated with the development of hospital-acquired infections in the US and is termed MDR as it is often resistant to at least three or more antibiotics (Shortridge, 2019). Hospital-acquired infections can become septic or cause pneumonia (Moradali, 2017). These infections are one of the most prevalent factors associated with an increased mortality rate in patients with cystic fibrosis and patients requiring a ventilator (Moradali, 2017). The primary population that is susceptible to illness from *P aeruginosa* are individuals hospitalized with burns or after surgery or in patients requiring the use of a catheter (CDC, 2019c).

One feature of *P aeruginosa* that allows it to become resistant to antibiotics is its large genome, which gives the bacteria the ability to regulate its genes and adapt to a multitude of different environments, increasing its probability of survival (Moradali, 2017). This is due primarily to its metabolic capacity to utilize a variety of substrates as energy sources (Moradali, 2017). Another virulence factor that allows *P aeruginosa* to develop resistance to antibiotics is quorum sensing (LaSarre, 2013). Quorum sensing is the process of cellular communication with specific chemical signals to synchronize a response throughout a population of bacteria (LaSarre, 2013). Regulation of the genes associated with quorum sensing may allow for the colonization and protection of the bacteria (LaSarre, 2013). Quorum sensing gene regulation may be correlated with the progression of acute infections to severe chronic ones (Venturi, 2006).

Another virulence factor is the production and release of pyocyanins (Hall, 2016). Pyocyanins potentiate the production of superoxide and hydrogen peroxide radicals contributing to oxidative stress by inhibiting the activity of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) in the organism (Hall, 2016). This increases intracellular oxidative damage and cytotoxicity, which increases mucous secretion in the respiratory tract creating a favorable environment for the colonization of the bacterium (Hall, 2016).

*P aeruginosa* has adopted several antibiotic-resistant mechanisms. These mechanisms can be classified as intrinsic, acquired, and adaptive (Pang, 2019). Blair et al state that intrinsic resistance of bacteria to antibiotics can occur by preventing the entry of the antibiotic into the bacterium or expelling the antibiotic after it enters through the efflux pump (Blair, 2015). Acquired resistance mechanisms occur through either mutation of the genome or during the transfer of genetic components or plasmids (Davies, 2010; Khaledi, 2016). Mutations in the OprD gene have been shown to upregulate resistance by increasing the number of efflux pumps available to eliminate antibiotics or produce β-lactamase enzymes allowing the bacterium to evade antibiotics (Moradali, 2017). The gene mutation for β-lactamase enzymes that occurs in the presence of antibiotics is associated with adaptive resistance to that antibiotic (Martin, 2018a). MDR *P aeruginosa* is treated with piperacillin, piperacillin with tazobactam, cephalosporins, carbapenems, ciprofloxacin, gentamicin, tobramycin, and polymyxin (Yayan, 2015). However, a few strains have developed resistance to some of these drugs (Yayan, 2015). In addition, synthetic pyocins can act as quorum-sensing inhibitors, which can reduce the virulence of MDR *P aeruginosa* (Curran, 2018).

In the narrative review, there were four articles evaluating the efficacy of garlic (*A sativum*) against MDR strains of *P aeruginosa*. In all of the studies, garlic (*A sativum*) reduced the growth of MDR strains of *P aeruginosa* (Subba, 2016; Karuppiah, 2012; Gull, 2012; Kulikova, 2018). The first study by Karuppiah et al measured the MIC at 58.5 mcg/ml (Karuppiah, 2012). In the research by Gull et al, aqueous, ethanol, and methanol dilutions were assessed. The MIC for the aqueous, ethanol, and methanol extracts were 200 mcg/ml, 300 mcg/ml, and 800 mcg/ml, respectively (Gull, 2012). The article by Kulikova et al found a MIC for allicin at 60 mcg/ml and an MBC of 1,000 mcg/ml (Kulikova, 2018). The investigation conducted by Subbu Lakshmi et al stated that garlic (*A sativum*) inhibited the growth of *P aeruginosa*, but the MIC, MBC, and ZOI were not listed (Subba, 2016).

The ZOI was determined at different dosages in the experiment by Karuppiah et al. These investigators recorded a ZOI of 7.5±0.5 mm, 9±0.6 mm, and 11.5±0.48 mm at dosages of 50 mcg/ml, 100 mcg/ml, and 200 mcg/ml respectively (Karuppiah, 2012). The ZOI in the trial by Gull et al was 15.6±0.54 mm, 14±0.47 mm, and 11±0 mm for the aqueous, ethanol, and methanol extracts, respectively (Gull, 2012). Unfortunately, the dosage used was not specified. Lastly, at 2,000 mcg/ml, the ZOI for the study by Kulikova et al was 10 mm (Kulikova, 2018).

The data supporting the administration of garlic (*A sativum*) for the treatment of MDR strains of *P aeruginosa* is marginal. However, in each of the studies, garlic (*A sativum*) or key constituents found in garlic (*A sativum*) produced antibacterial effects. The MIC varies according to the research. However, this seems dependent on the extract that is being used. The inhibitory activity appears to be dose-dependent, which is illustrated in the article by Karuppiah et al. In this case, allicin as a monotherapy was not as effective as the extract of garlic (*A sativum*) in the other experiments. This may be due to the strain of bacteria, or the dilution used in the study.

There were two studies that investigated the effects of thyme (*T vulgaris*) against MDR strains of *P aeruginosa*. In the study by Kavanaugh et al, thyme (*T vulgaris*) impeded the growth of the bacterial biofilm, promoting cell death (Kavanaugh, 2012). Unfortunately, the ZOI was not provided with the results. In addition, planktonic cells were used as the growth medium for the determination of the MIC and MBC. Unfortunately, thyme (*T vulgaris*) did not interfere with the proliferation of the bacteria on this medium, indicating that its primary mechanism of action against MDR *P aeruginosa* is the disruption of the biofilm (Kavanaugh, 2012). The data collected by Subbu Lakshmi et al illustrated an inhibition of growth, but an exact ZOI, MIC, MBC, or mechanism was not identified (Subbu, 2016). Unfortunately, the amount of research regarding the bacteriostatic activity of thyme (*T vulgaris*) for the elimination of *P aeruginosa* is minuscule and requires many more experiments to determine its true antibacterial effects. However, one important aspect of the research by Kavanaugh et al was the disruption of the synthesis of the biofilm. The biofilm is a polymer of polysaccharides, proteins, and extracellular DNA that is produced by the bacteria, which increases their resistance to disinfectants, antibiotics, and phagocytic activity (Høiby, 2011). Consequently, this mechanism of action may reduce the pathogenicity of the bacterium.

Three studies analyzed the antibacterial effects of oregano (*O vulgare*) against MDR *P aeruginosa*. Bacteriostatic effects were demonstrated in two of the studies (Mehreen, 2016; Lu, 2018; Obaidat, 2011). The research by Obaidat et al utilized carvacrol as a monotherapy. Growth inhibition did occur, but it was considered insignificant at dosages of 500 mcg/ml, 800 mcg/ml, 1,100 mcg/ml, 1,400 mcg/ml, 1,700 mcg/ml and 2,000 mcg/ml (Obaidat, 2011). The trial by Lu et al tested oregano (*O vulgare*) against three strains of MDR *P aeruginosa*. The MIC for two of the isolates was 560 mcg/ml and 640 mcg/ml for the remaining strain (Lu, 2018). The experiment by Mehreen et al established the MIC at 7.81 mcg/ml (Mehreen, 2016). Lu et al found that the MBC for two of the MDR strains of *P aeruginosa* was 750 mcg/ml and 1,000 mcg/ml for the third MDR isolate (Lu, 2018). In addition, Lu et al created a lesion in female rats and infected the wound with MDR strains of *P aeruginosa*, which were treated with oregano (*O vulgare*) at doses of 5,000 mcg/ml or 10,000 mcg/ml (Lu, 2018). The results showed that each dose significantly reduced the replication of the MDR strains of the microbe in the infected laceration of the rats by 8.6 and 24.6 times, respectively (Lu, 2018). Mehreen et al measured the ZOI of the extract at 20 mm (Mehreen, 2016).

There is a limited amount of data available to determine if oregano (*O vulgare*) is effective for the treatment of MDR *P aeruginosa*. However, two of the three studies demonstrate attenuation of the viability of the bacteria, and oil of oregano (*O vulgare*) did mitigate an infection of MDR *P aeruginosa* in a living organism in the article by Lu et al. The one study that did not reduce growth used carvacrol as a monotherapy, which may indicate that it is not the component that generates antibacterial effects against MDR *P aeruginosa*. The effects may be produced by other constituents such as thymol or γ-terpinene. More research needs to be conducted to establish the constituents capable of eradicating MDR *P aeruginosa*, but some evidence exists that the oil itself may be an effective modality.

One study examined the antibacterial effects of turmeric (*C longa*) for MDR P aeruginosa. Unfortunately, the MIC and MBC were not included in the results section. The article did provide the ZOI at 23 mm, which indicates potent inhibitory effects (Rath, 2014). However, the concentration was not specified, and a single article is not sufficient to determine the efficacy of turmeric (*C longa*) for the treatment of MDR *P aeruginosa*, especially since the MIC was not provided.

Two studies assessed the antibacterial effects of rosemary (*R officinalis*) against MDR P aeruginosa. The experiment conducted by Ibraheem Qabaha demonstrated that rosemary (*R officinalis*) inhibited the growth of MDR *P aeruginosa* by 9.7±1.2 mm, 13.3±1.5 mm, and 16.0±1 mm at dosages of 6,000 mcg/well, 12,500 mcg/well and 25,000 mcg/well, respectively (Qabaha, 2013). The study by Perumal Samy et al did not show inhibitory effects against the MDR strain of the bacteria (Perumal Samy, 2013). However, the dosage administered was 100 mcg/ml, which was much lower than the dosage utilized in Ibraheem Qabaha's research. The low dosage is the most probable reason no effects were observed. MIC and MBC were not provided in either study. More research is required to determine the efficacy of rosemary (*R officinalis*) against MDR *P aeruginosa*.

In the narrative review, there were eight studies examining the antibacterial activity of cinnamon (*Cinnamomum species*) against MDR P aeruginosa. Cinnamon (*Cinnamomum species*) inhibited the growth of MDR P aeruginosa in five of the articles (Mehreen, 2016; Perumal Samy, 2013; Kavanaugh, 2012; Rath, 2014; Utchariyakiat, 2016; Voukeng, 2012; Seukep, 2013; Juarez, 2017). The research conducted by Utchariyakiat et al tested twenty strains of MDR P aeruginosa. The oil from the bark of cinnamon (*C zeylanicum*) inhibited the growth of all twenty strains (Utchariyakiat, 2016). The MIC and MBC were recorded as percent volume per volume (v/v). The MIC percent v/v ranged from 0.0562% to 0.225%, and the MBC ranged from 0.1125% to 1.8% (Utchariyakiat, 2016). Unfortunately, the ZOI was not provided.

Kavanaugh et al found that cassia oil extracted from the bark of cinnamon (*C aromaticum Zoll*) suppressed the proliferation of MDR *P aeruginosa* at 0.2% v/v, while cinnamaldehyde had a MIC at 0.1% v/v and MBC at 0.2% v/v (Kavanaugh, 2012). The investigators recorded that cassia oil had an MBC comparable to that of the MIC but did not list it (Kavanaugh, 2012). An additional experiment by Juarez et al demonstrated that cinnamaldehyde produced bacteriostatic and bactericidal effects (Juarez, 2017). However, the exact mg/ml dosage of the MIC and MBC responsible for these effects is unclear, and a ZOI is not provided. Rath et al and Mehreen et al recorded the MIC at 1,510 mcg/ml and 125 mcg/ml with a ZOI of 25 mm and 20 mm, respectively (Mehreen, 2016; Rath, 2014). Rath et al measured the MBC at 3,410 mcg/ml (Rath, 2014). The three articles with an absence of antibacterial effects were Voukeng et al, Seukep et al and Perumal Samy et al (Perumal Samy, 2013; Voukeng, 2012; Seukep, 2013). Voukeng et al and Seukep et al administered cinnamon (*C zeylanicum*) at a dosage of 1,024 mcg/ml, and Perumal Samy et al used 100 mcg/ml (Perumal Samy, 2013; Voukeng, 2012; Seukep, 2013).

The research conducted advocates the use of cinnamon (*Cinnamomum species*) for the treatment of MDR strains of P aeruginosa. Although three studies found cinnamon (*C zeylanicum*) ineffective, the type of extract that was utilized may have been the issue. Mehreem et al used n-hexane, methanol, and aqueous extracts and found that only the n-hexane and aqueous extracts had antimicrobial activity. Utchariyakiat et al administered an ethanol extract, which demonstrated antibacterial effects. Rath et al, Voukeng et al, Seukep et al, and Perumal Samy et al all used methanol extracts. However, the dosages utilized by Rath et al were much higher than those in the other experiments, which may signify that the concentration of cinnamon (*C zeylanicum*) administered in those studies was inadequate to impede microbial growth. The experiment by Utchariyakiat provides substantial evidence that cinnamon (*C zeylanicum*) could be utilized as an adjunct or substitute for antibiotics for MDR strains of *P aeruginosa* as it was effective against 20 different MDR isolates.

### *6.4. E coli*

*E coli* are a group of gram-negative, anaerobic, pathogenic bacilli capable of causing disease (Lim, 2010). This bacterium typically induces a diarrheal disease but can cause a urinary tract infection, pneumonia, or hemolytic uremic syndrome resulting in kidney failure (CDC, 2014). One of the virulent pathological strains is enterohemorrhagic *E coli*, which can synthesize and release Shiga toxins (CDC, 2014). The Shiga toxin is a major contributor to morbidity and mortality (CDC, 2014).

Shiga toxin 2 released from *E coli* colonized in the gastrointestinal tract can enter the circulatory system eliciting cytotoxic effects against cells in the vasculature, kidney, and brain (Berdasco, 2019). In particular, Shiga toxin 2 can perpetuate inflammation of astrocytes in the hippocampus region of the brain (Berdasco, 2019). An additional effect of Shiga toxin is the downregulation of the expression of genes associated with the myelin sheath of oligodendrocytic cells, which could interfere with cellular communication (Berdasco, 2019).

The Shiga toxin can create a myriad of negative physiological effects. It can initiate a stress response and reduce protein synthesis (Lee, 2019). The Shiga toxin can stimulate innate and cell-mediated immunity inducing a pro-inflammatory process, which can lead to sensitization of cells (Lee, 2019). This cascade of events can increase the susceptibility of the human host to further inflammatory mediators, potentially increasing the risk of morbidity and mortality (Lee, 2019).

According to Majeed et al, the antibiotic resistance of *E coli* may be through mutations, intrinsic mechanisms, or acquired through genetic transfer (Majeed, 2019). Data shows that strains of *E coli* that produce Shiga toxins 1 and 2 can be resistant to antibiotics (Mukherjee, 2017). However, strains that secrete Shiga toxin 1 have a greater potential to be resistant to antibiotics (Mukherjee, 2017). Mutations in the genome can accumulate, altering the portions of the DNA that are targeted by the antibiotic, rendering it ineffective (Song, 2009). An intrinsic mechanism of resistance is the synthesis of efflux pumps capable of eliminating the antibiotic (Song, 2009).

An acquired factor that has assisted in the antibiotic resistance of *E coli* is the development of a protein known as Extended-Spectrum β-lactamase (ESβL) (Majeed, 2019). The production of this protein is due to the ability of *E coli* to exchange genes with other microbes that encode for EsβL (Majeed, 2019). This protein allows *E coli* to breakdown broad spectrum antibiotics such as cephalosporins via hydroxylation (Majeed, 2019). Antibiotic-resistant strains of *E coli* are treated with nitrofurantoin drugs, which have been shown to have a resistance rate of 7.3% (Olorunmola, 2013). Other antibiotics that *E coli* may be susceptible to are fluoroquinolones, ciprofloxacin, and norfloxacin (Olorunmola, 2013). Ceftazidime and cefotaxime administered in conjunction with clavulanic acid were effective against EsβL-producing *E coli* Rasheed, 2014).

In the narrative review, five publications investigated the bacteriostatic and bactericidal effects of garlic (*A sativum*) on MDR *E coli* (Subbu, 2016; Karuppiah, 2012; Gull, 2012; Rahman, 2011; Amber, 2018). Four of the studies showed that garlic (*A sativum*) reduced the growth of MDR *E coli* (Subbu, 2016; Karuppiah, 2012; Gull, 2012; Amber, 2018). Amber et al measured the MIC of the primary constituents of garlic (*A sativum*). These investigators found a MIC for the methanolic extracts of alkaloids, flavonoids, saponins, and the whole extract to be 25,000 mcg/ml, 50,000 mcg/ml, 50,000 mcg/ml, and 12,500-25,000 mcg/ml respectively (Amber, 2018). Karuppiah et al recorded the MIC of an ethanol extract of the cloves at 65.5 mcg/ml (Karuppiah, 2012). Gull et al utilized the aqueous, ethanol, and methanol extracts discussed above. The aqueous, ethanol, and methanol extracts had MIC values of 100 mcg/ml, 300 mcg/ml, and 200 mcg/ml, respectively (Gull, 2012). Amber et al determined the MBC to be 50,000 mcg/ml, greater than 50,000 mcg/ml, and less than 50 mcg/ml for alkaloids and flavonoids, saponins, and the whole extract, respectively (Amber, 2018).

In the research conducted by Karuppiah et al, antibacterial effects of garlic (*A sativum*) were dose-dependent with a ZOI at 10.5±0.21 mm, 15±0.4 mm, 17±0.58 mm, and 18.5±0.29 mm at 25 mcg/ml, 50 mcg/ml, 100 mcg/ml, and 200 mcg/ml respectively (Karuppiah, 2012). The experiment by Gull et al had a ZOI of 14.3±0.54 mm, 11.6±0.27 mm, and 12±0 mm for the aqueous, ethanol, and methanol extract at the MIC, respectively (Gull, 2012). The dosage that produced these ZOI was not provided. At 50,000 mcg/ml, Amber et al determined that the ZOI was 18±1 mm, 13±1 mm, 13.3±2.3 mm, and 19±1 mm for the dilutions of alkaloids, flavonoids, saponins, and the herbal extract, respectively (Amber, 2018). The research by Subbu Lakshmi et al stated that garlic (*A sativum*) was effective in reducing the growth of *E coli*, but the MIC, MBC, and ZOI were not listed (Subbu, 2016). The concentration of garlic (*A sativum*) that failed to inhibit growth was 2 mcg/disc (Rahman, 2011).

There are a few studies that illustrate that garlic (*A sativum*) could be administered for the treatment of MDR *E coli*. The MIC does vary depending on the experiment. This is probably due to the types of dilutions that are being used. In the study by Amber et al, key constituents were isolated and used, but the researchers used a crude extract, which had a lower MIC and higher ZOI. This may indicate that using the whole herb is more effective than using an individual component. As shown in the studies by Kaurppiah et al and Gull et al, the whole herb extract was capable of inhibiting the growth of MDR strains of *E coli*. In these experiments, the MIC was lower, which may have been caused by the different dilutions created. The one study that found that garlic (*A sativum*) was ineffective as an antimicrobial against MDR *E coil* used a dosage of 2 mcg/disc, which is much lower than the MIC in the other studies indicating that it may have been insufficient to elicit bacteriostatic effects. Additional research should clarify the required MIC and MBC.

The antibacterial effects of thyme (*T vulgaris*) against MDR *E coli* were determined by three studies. In two out of the three studies, thyme (*T vulgaris*) attenuated the growth of *E coli* (Mehreen, 2016; Subbu, 2016; Mansouri, 2018). Subbu Lakshmi et al found thyme (*T vulgaris*) ineffective, but the dosage that was used was not clear (Subbu, 2016). The data collected by Mehreen et al demonstrated that this botanical had a MIC of 31.25 mcg/ml and a ZOI of 21 mm (Subbu, 2016). The article composed by Mansouri et al provides an extensive amount of data elucidating the efficacy of thyme (*T vulgaris*) for the elimination of MDR *E coli* (Mansouri, 2018). In their study, forty strains of MDR *E coli* that were impervious to twenty-one antibiotics were evaluated. The pure extract and a 15% diluted extract were examined. Both extracts suppressed the proliferation of all forty strains of MDR *E coli* (Mansouri, 2018). Only the MIC was measured for the pure extract, with values ranging from 70 mcg/ml to 930 mcg/ml, with a mean of 310 mcg/ml and an average of 323 mcg/ml (Mansouri, 2018). On average, the pure essential and the diluted oils produced analogous effects. The ZOI was over 18 mm for every sample tested, indicating a large degree of growth inhibition (Mansouri, 2018). The ZOI ranged from 18.66±0.152 mm to 39.33±0.585 mm for the pure essential oil with an average of 26.75±0.426 mm and 19.13±1.021 mm to 37.26±0.404 mm for the 15% diluted extract with an average ZOI of 26.65±0.542 mm (Mansouri, 2018). Although there are only three studies related to the antibacterial nature of thyme (*T vulgaris*) against MDR *E coli*, the immense amount of data obtained in the research by Mansouri et al exponentially indicates its potential use as a bacteriostatic agent.

There were three studies exploring the activity of oregano (*O vulgare*) for the elimination of MDR *E coli*. Oregano (*O vulgare*) inhibited the growth of MDR *E coli* in all the studies examined (Mehreen, 2016; Khan, 2017; Pașca, 2017). The studies by Mehreen et al and Pasca et al administered whole herb extracts while Khan et al managed the bacterial replication with carvacrol. The MIC for the plant extract was 15.63 mcg/ml for Mehreen et al (Mehreen, 2016). The MIC and MBC for the extract tested by Pasca et al was 90 mcg/ml (Pașca, 2017). Monotherapy with carvacrol had a MIC of 450 mcg/ml (Khan, 2017). The ZOI was 15.63 mm in the research by Mehreen et al (Mehreen, 2016). Pașca et al measured the ZOI for two MDR isolates of *E coil* at 12.0 mm and 12.5 mm (Pașca, 2017).

The information related to the activity of oregano (*O vulgare*) against antibiotic-resistant strains of *E coli* is marginal. However, the three studies that were conducted show that it produced

bacteriostatic and bactericidal effects whether used as an extract or individual constituent. Additional data should be collected to elucidate the effects of oregano (*O vulgare*) on MDR *E coli*. There were three experiments used to determine the inhibitory activity of turmeric (*C longa*) for MDR *E coli*. In two of the three studies, turmeric (*C longa*) generated antibacterial activity (Marasini, 2015; Rath, 2014; Das, 2012). According to Rath et al, the MIC of this botanical was 1,510 mcg/ml, the MBC was 3,410 mcg/ml, and the ZOI 26 mm (Rath, 2014). Das et al did not provide a MIC or MBC. However, 10 mcl of the oil was placed on a disc and produced a 12 mm ZOI for MDR *E coli* (Das, 2012). The experiment conducted by Marasini et al noted that turmeric (*C longa*) did not possess inhibitory activity. Unfortunately, the investigators did not list the concentration used (Marsini, 2015).

With the limited amount of information obtained from these studies, the activity of turmeric (*C longa*) against *E coli* cannot be distinguished. Two of the experiments promote the use of turmeric (*C longa*), while one failed to produce antibacterial effects. Since the dosage was not given in the study, it is impossible to determine if it was adequate. The strain could have had an impact as well. Marasini et al was the only study that used a β-lactamase-producing bacterium. Consequently, more research is necessary.

In the narrative review, four research papers analyzed the effects of rosemary (*R officinalis*) on the eradication of MDR and antibiotic-resistant strains of *E coil*. In all four studies, rosemary (*R officinalis*) suppressed the replication of MDR and antibiotic-resistant *E coli* (Dahiya, 2012; Qabaha, 2013; Sienkiewicz, 2013; Hussain, 2010). Hussain et al determined that the MIC for the essential oil extract and 1,8-cineol, which is a major component of the essential oil composing approximately 38.5% ± 1.1%, to be 1,720±0.04 mcg/ml and 1,800±0.08 mcg/ml respectively (Hussain, 2010). Dahiya et al tested hexane, chloroform, methanol, and ethanol dilutions against three MDR isolates of *E coil*. Methanol and ethanol extracts impeded growth with a MIC of 1,560 mcg/ml for one of the strains and 12,500 mcg/ml for the other two isolates (Dahiya, 2012). The hexane and chloroform formulations did not have an inhibitory effect (Dahiya, 2012).

Sienkiewicz et al evaluated the effects of rosemary (*R officinalis*) against thirty-two clinical species of MDR *E coli* obtained from the abdominal cavity, bronchia, lesions, urine, blood, and catheters of infected patients (Sienkiewicz, 2013). This botanical reduced bacterial proliferation of all thirty-two MDR strains with MIC values ranging from 18.5 mcl/ml to 19.75 mcl/ml, 18.25 mcl/ml to 20 mcg/ml, 19 to 20 mcl/ml, and 18.25 mcl/ml to 19.75 mcl/ml for samples extracted from the abdominal cavity, wounds, the bronchia and urine, blood, and catheters respectively (Sienkiewicz, 2013). The study by Qabaha et al did not establish a MIC. However, the ZOI at 12,500 mcg/ml and 25,000 mcg/ml were 9±1.7 mm and 14.7±1.5 mm, respectively (Qabaha, 2013). Hussain et al found the ZOI of the essential oil and 1,8-cineol to be 12.8±0.5 mm and 9.0±0.3 mm, respectively (Hussain, 2010). The trial by Dahiya et al resulted in ZOI measurements of 14±0.30 mm, 10±0.05 mm, and 11±0.15 mm for the methanol extract and 10±0.10 mm, 9±0.05 mm, and 10±0.10 mm for the ethanol extract against the MDR isolates of *E coli* (Dahiya, 2012).

The extensive amount of research related to the antibacterial effects of rosemary (*R officinalis*) indicates that it could be an effective adjunct or substitute for the treatment of antibiotic-resistant strains of *E coli*. The article by Sienkiewicz et al provides the greatest amount of information as thirty-two strains of MDR *E coli* that were extracted from infected patients were used. As this study isolated MDR strains of *E coli* from a clinical setting, it highly advocates for the use of rosemary (*R officinalis*) as a potential antibacterial agent.

There were seven studies evaluating the antibacterial activity of cinnamon (*Cinnamomum species*) for *E coil*. All the studies found that cinnamon (*C zeylanicum*) and cinnamon (*C verum*) suppressed the growth of antibiotic and MDR species of E coli (Mehreen, 2016; Naveed, 2013; Rath, 2014; Voukeng, 2012; Seukep, 2013; Khan, 2009; Njimoh, 2015). The form of cinnamon (*Cinnamomum species*) used in all the studies except Naveed et al was cinnamon (*C zeylanicum*). Naveed et al created extracts using cinnamon (*C verum*). Voukeng et al and Seukep et al tested the herbal extract against three strains of antibiotic-resistant *E coli*. The results of these experiments were similar. Voukeng et al measured the MIC for the two strains at 512 mcg/ml and one strain at 1,024 mcg/ml, while Seukep et al recorded the MIC for all three strains at 512 mcg/ml (Voukeng, 2012; Seukep, 2013). Rath et al, Njimoh et al, Mehreen et al and Naveed et al recorded MIC at 3,410 mcg/ml, 62 mcg/ml, 250 mcg/ml and 3,800±0.96 mcg/ml respectively (Mehreen, 2016; Naveed, 2013; Rath, 2014; Njimoh, 2015).

Khan et al investigated MDR nosocomial and community-acquired *E coli* infections. There were twenty-six strains of MDR *E coli* examined. The researchers found MIC values at 3,130 mcg/ml and 6,250 mcg/ml for MDR nosocomial strains and 195 mcg/ml and 780 mcg/ml for MDR community-acquired strains (Khan, 2009). In the article published by Seukep et al bactericidal effects were not observed in two of the three antibiotic-resistant strains. However, in the third strain, the MBC was 512 mcg/ml (Seukep, 2013). Rath et al and Njimoh et al established that the MBC was 4,270 mcg/ml and 185 mcg/ml (Rath, 2014; Njimoh, 2015). Khan et al found the MBC for seven of the MDR nosocomial strains at 6,250 mcg/ml and 12,500 mcg/ml for three of the MDR nosocomial strains and 1,560 mcg/ml for eleven of the MDR community-acquired strains and 3,130 mcg/ml for five of the MDR community-acquired isolates (Khan, 2009).

The ZOI measured was 21 mm, 14 mm, and 22 mm for Rath et al, Njimoh et al, and Mehreen et al respectively (Mehreen, 2016; Rath, 2014; Njimoh, 2015). Khan et al did not provide the approximate ZOI but listed the range of the ZOI for all ten of the MDR nosocomial strains as 16-25 mm (Khan, 2009). For thirteen of the MRD community-acquired strains, the ZOI was 5-15 mm, and for two of the strains, the ZOI measured 26-35 mm (Khan, 2009). There was one strain of MDR community-acquired *E coli* that cinnamon (*C zeylanicum*) was considered ineffective against with a ZOI less than 5 mm (Khan, 2009). However, it should be noted that both a MIC and MBC were produced against this strain. Unfortunately, the dosage used to measure the ZOI was not given, so it may not have been high enough for that particular strain. In the article by Naveed et al, the whole herb extract of cinnamon (*C verum*) was effective to eradicate MDR *E coli* in a broth dilution (Naveed, 2013). However, when cinnamaldehyde was extracted and used as a monotherapy, it did not impede the growth of the bacteria (Njimoh, 2015). Unfortunately, the dosage that cinnamaldehyde was administered was not clarified, so a low dose may have accounted for the absence of activity.

There is an abundance of data available pertaining to the bacteriostatic and bactericidal effects of cinnamon (*Cinnamomum species*) for the treatment of MDR infections of *E coli*. All the published research demonstrated that cinnamon (*Cinnamomum species*) was effective in suppressing the growth of MDR strains of *E coli*. Khan et al provided the most significant information for the treatment of infections related to MDR *E coli* as they studied twenty-six different nosocomial and community-acquired isolates

and found cinnamon (*Cinnamomum species*) to be effective against them all. The range of the MIC may have been due to the differences in the strain of MDR *E coli* that was utilized in the study. As demonstrated in the experiment by Khan et al, the MIC for the community-acquired strains was generally lower.

### 6.5. C jejuni

*C jejuni* is a gram-negative, helical-shaped bacterium that does not produce spores and is classified as a microaerophilic bacterium that usually causes campylobacteriosis (Nakagawa, 2017; Silva, 2011). However, in rare cases, an infection with *C jejuni* can result in Guillain-Barré syndrome as a sequela (Nyati, 2013). It is estimated that *C jejuni* is implicated as the pathological agent in 90% of illnesses that affect humans and is the most common cause of GI illnesses around the world (CDC, 2022a; Johnson, 2017).

The data related to the virulence of *C jejuni* is limited. However, the pathogenicity of this microbe may be due to its motility, toxins, and ability to colonize, utilize iron and elude immune cells (Lluque, 2017). The flagellum is one of the primary factors that enhances the motility of the bacterium allowing it to adhere to and invade the WBC of the host (Lluque, 2017). A second function of the flagellum is to introduce proteins onto the surface of the outer membrane or inoculate these proteins directly into the host cell, which can assist with the development of an infection (Lluque, 2017). In addition, there are several proteins on the outer membrane of this pathogen that assist with its binding to the host cell allowing it to infiltrate (Neddermann, 2019). One toxin that can exacerbate an infection is the cytolethal distending toxin, which increases intercellular pressure, causing swelling of cells leading to cell death and exacerbating inflammation (Lluque, 2017).

*C jejuni* possesses virulence factors as well that enhance its ability to invade the intestinal epithelial cells of the host. Of these, one significant factor is the serine protease high-temperature requirement A (HtrA) protein (Neddermann, 2019). This protein enables bacteria to tolerate changes in heat (Neddermann, 2019). In addition, the HtrA protein promotes the movement of the bacterium through the epithelial layer of cells by dissolving various cell-cell adhesion proteins, which promotes the transient expansion of cellular junctions, enhancing pathogenicity (Neddermann, 2019).

A possible mechanism associated with antibiotic resistance of *C jejuni* is a substitution mutation of amino acids affecting DNA-gyrase and topoisomerase IV (Lluque, 2017). Alterations of genes may also occur through the direct transfer of genetic material with other bacteria, increasing the probability of resistance (Johnson, 2017; Lluque, 2017). Modifications in the uptake of certain antibiotics have occurred as a result of resistance as well (Lluque, 2017). In a majority of cases, infections with *C jejuni* are self-limiting, lasting about 2 to 5 days (CDC, 2022a). A potential treatment strategy to reduce the incidence of *C jejuni* infections is to vaccinate chickens prior to slaughter to eliminate the bacterium and prevent foodborne transmission (Johnson, 2017). Azithromycin, ciprofloxacin, and a combination of amoxicillin and clavulanic acid have been utilized to treat antibiotic-resistant strains of the bacteria (Schiaffino, 2019).

In the narrative review, there was one journal article discussing the antimicrobial nature of rosemary (*R officinalis*) against antibiotic-resistant *C jejuni*. In this experiment, multiple forms of rosemary (*R officinalis*) were assessed. The plant extracts had varying levels of carnosic and rosmarinic acid. The dilutions were V40 with 40% carnosic acid, V70 with 70% carnosic acid, and A40 with 40% rosmarinic acid (Klančnik, 2012). In addition, carnosic and rosmarinic acid were tested as monotherapies (Klančnik, 2012). The plant-based antimicrobials had MIC values of 78 mcg/ml, 156 mcg/ml, 78 mcg/ml, 156 mcg/ml, and 313 mcg/ml for the carnosic acid, rosmarinic acid, V40, V70, and A40 extracts, respectively (Klančnik, 2012). Unfortunately, the ZOI was not tested.

From the data, it would appear as if rosemary (*R officinalis*) or its active constituents may possess bacteriostatic properties for antibiotic-resistant strains of *C jejuni*. However, the most effective component cannot be determined. Carnosic acid had the lowest MIC as a monotherapy and in the 40% extract, but the 70% dilution, which should have had the smallest MIC, had the same MIC as rosmarinic acid as a monotherapy. With the discrepancies in the results of the extracts, the primary agent that has the greatest potential to reduce the growth of antibiotic-resistant bacteria is not clear. More research is required to determine the extent of the activity of rosemary (*R officinalis*) against antibiotic-resistant strains of *C jejuni*. The narrative review failed to reveal the antibacterial activity of garlic (*A sativum*), thyme (*T vulgaris*), oregano (*O vulgare*), turmeric (*C longa*), and cinnamon (*Cinnamomum species*) against antibiotic-resistant strains of *C jejuni*. This indicates there is a major gap in the literature related to the potential benefit of these botanicals for the elimination of infections caused by antibiotic-resistant *C jejuni*. Experiments need to be conducted to acquire this vital information.

### 6.6. S typhimurium

*S typhimurium* is a flagellated, gram-negative, facultative, anaerobic bacillus that possesses multiple virulence factors to aid in its ability to infect a host (Akoachere, 2009). *S typhimurium* is a serotype of *S enterica* and is capable of causing salmonellosis, which manifests as a fever with abdominal pain, headache, and diarrhea and can contribute to the morbidity and mortality of humans (Akoachere, 2009). It is estimated that the mortality rate is 10-20% without treatment but less than 1% with the administration of antibiotics (Fàbrega, 2013). However, a major issue is the emergence of MDR strains of *S typhimurium*, which could increase the risk of mortality from infection with this bacterium (Akoachere, 2009; Fàbrega, 2013).

The primary means of transmission of this bacterium is contaminated, improperly cooked meat products (Akoachere, 2009). The flagella of *S typhimurium* propel the bacteria through the intestinal lumen, and the fimbriae allow it to attach and colonize within the intestinal tract utilizing its extracellular matrix glycoprotein laminin (Gart, 2016). Once attached to the intestinal lining, *S typhimurium* utilizes *Salmonella* pathogenicity islands 1 and 2 to inject secretory proteins into the host cells allowing for an infection (Gart, 2016). This bacterium has the ability to disrupt the activity of NADPH oxidase, inhibiting phagocytic free radical production, allowing it to avoid macrophage-mediated destruction (Gart, 2016).

MDR species of *S typhimurium* were first identified in the early 1980s (Crump, 2015). Serotypes of this bacterium may be immune to fluoroquinolone, ampicillin, streptomycin, sulfonamides, cephalosporins, ceftriaxone, chloramphenicol, trimethoprim-sulfamethoxazole and tetracycline (Crump, 2015). The primary mechanism of antibiotic resistance is gene mutation (Crump, 2015). An alteration of the genes that encode the folic acid pathway can increase its resistance to certain antibiotics (Crump, 2015). *S typhimurium* secretes β-lactamase enzymes that prevent denaturing of the bacteria (Crump, 2015). Modification of DNA gyrase and topoisomerase IV reduces the susceptibility of *S typhimurium* to quinolone antibiotics (Crump, 2015). The majority of

infections with *S typhimurium* are self-limiting and will resolve in five to seven days with rest and fluids (CDC, 2022d). However, antibiotic administration has been shown to drastically reduce the rate of morbidity and mortality (Fàbrega, 2013). Ciprofloxacin has been utilized as a monotherapy or in conjunction with levofloxacin, ofloxacin, and norfloxacin for the treatment of *S typhimurium*-resistant strains (Wang, 2019). In addition, third-generation cephalosporins or azithromycin have demonstrated efficacy in treatment (CDC, 2022d).

Only one study exists evaluating the antibacterial effects of turmeric (*C longa*) against MDR *S typhimurium* (Marasini, 2015). Turmeric (*C longa*) was not found to be an effective inhibitor of the growth of *S typhimurium* by the agar well diffusion method (Marasini, 2015). Unfortunately, the concentration of turmeric (*C longa*) utilized in this study was not specified. Additional studies should be conducted.

There was one research article investigating the antibacterial effects of cinnamon (*Cinnamomum species*) against MDR *S typhimurium*. The MIC for cinnamon (*C zeylanicum*) was 1,560 mcg/ml and the MBC was 3,130 mcg/ml (Khan, 2009). The exact ZOI was not indicated. However, the ZOI listed in the results was between 26-35 mm (Khan, 2009). More studies need to be conducted to determine the extent of bacteriostatic and bactericidal activity of cinnamon (*Cinnamomum species*) against MDR *S typhimurium*.

There is not much data available for the administration of botanicals for the treatment of antibiotic-resistant strains of *S typhimurium* and there was no research related to the antibacterial activity of garlic (*A sativum*), thyme (*T vulgaris*), oregano (*O vulgare*) or rosemary (*R officinalis*) against antibiotic-resistant strains of *S typhimurium* found in the review. Consequently, there is a gap in the literature related to data of this nature. Studies should be conducted to elucidate the potential benefits of these botanicals for the eradication of this antibiotic-resistant bacterium.

## 7. Natural Medicine Approach to Bacterial Infections

### *7.1. Overview of Plant Medicine Treatment of Bacterial Infections*

The first antimicrobial agents deployed in Ancient Egypt, Greece, and China consisted of plant components (Ventola, 2015). Numerous herbs have exhibited potent bacteriostatic and bactericidal effects against a broad spectrum of bacteria (Ventola, 2015). Additionally, plant products have been used as potential treatment strategies for eliminating MDR strains of bacteria (Ventola, 2015). This was demonstrated in many cases throughout the narrative review. Unfortunately, the research discussed above provides a limited amount of information related to the mechanism of action of the botanicals for the inhibition of the growth of these microbes.

### *7.2. Garlic (A sativum)*

Garlic (*A sativum*) has been utilized for centuries for the treatment of infectious diseases, especially in Ancient China and India (Rivlin, 2001). This herb is considered to be a broad-spectrum antimicrobial agent (Li, 2015). There are a few research studies elucidating the antibacterial mechanism of garlic (*A sativum*), which is centered around an organosulfur chemical known as allicin (Lu, 2011). Allicin is the main bacteriostatic component of garlic (*A sativum* (Lu, 2011). Organosulfur compounds can diffuse through the membrane of bacteria and impede sulfhydryl groups of enzymes, preventing the growth of the microbial cell (Lu, 2011). A study by Lu et al illustrated these antimicrobial effects. In this study, the investigators found that increasing the exposure of *P aeruginosa* to higher concentrations of sulfur-containing compounds from garlic (*A sativum*) potentiated its bacteriostatic effects (Lu, 2011).

Another possible mechanism for antibacterial activity is acting as a quorum-sensing inhibitor (Høiby, 2011). Quorum sensing is a trait of strains of both gram-positive and gram-negative bacteria and has been demonstrated by MDR strains of *P aeruginosa* (Miller, 2001). The ability of garlic (*A sativum*) to disrupt quorum sensing activity can interfere with the release of chemical signals used for communication impairing the physiological activity of the microbe, which could prevent the colonization of the bacteria or the formation of biofilm (Miller, 2001). This may have been the reason that garlic was able to impede the growth of the MDR *P aeruginosa* as demonstrated in the narrative review. In the study by Kavanaugh et al, thyme (*T vulgaris*) suppressed the growth of *P aeruginosa* by this mechanism (Kavanaugh, 2012). *S pneumoniae* has the ability to produce a biofilm as well, which could account for the inhibitory activity that garlic (*A sativum*) displayed for this organism. Consequently, by hindering quorum sensing, garlic (*A sativum*) can extirpate biofilms reducing the virulence of certain bacteria (Høiby, 2011).

### *7.3. Thyme (T vulgaris)*

Thyme (*T vulgaris*) is an herb cultivated from the Mediterranean region that has been utilized historically for gram-positive and gram-negative bacteria (Ocaña, 2012). It is considered a broad-spectrum, strong bactericidal agent (Ocaña, 2012; Nzeako, 2006). Thymol, carvacrol, eugenol, aliphatic phenols, flavonoids, and saponins are the secondary metabolites found in thyme (*T vulgaris*) that are capable of inhibiting the growth of bacteria (Nzeako, 2006; Fachini-Queiroz, 2012). However, the activity of thymol and carvacrol are the main phytochemicals that have been the primary focus of most studies. The primary mechanism of action of thymol is the lysis of the cytoplasmic membrane of gram-positive and gram-negative bacteria by adhering to and deteriorating the membrane proteins through hydrophobic and hydrophilic interactions (Boskovic, 2015; Gonelimali, 2018; Liu, 2017). This causes lipopolysaccharides to be released, increasing membrane permeability, which allows uncontrolled ATP diffusion across the membrane preventing the bacterium from harnessing energy (Boskovic, 2015).

In addition, thymol and carvacrol have been implicated as agents capable of inducing abnormalities in cell membrane potentials (Nagoor, 2017). This may be the case as it was shown to inhibit the growth of MDR *E coli* as a monotherapy in the narrative review but did not prevent the replication of MDR *P aeruginosa*. Thymol can initiate atypical depolarizations, while carvacrol can alter the permeability of the cell membrane allowing potassium ions to diffuse across the membrane unregulated (Boskovic, 2015; Nagoor, 2017). The irregular depolarizations and unrestricted movement of potassium ions could disrupt the membrane potential (Boskovic, 2015; Nagoor, 2017). Consequently, the combination of carvacrol and thymol may have been necessary for the eradication of MDR *P aeruginosa*. Carvacrol also has the ability to diminish the levels of intracellular ATP, hindering energy production and impairing the physiological functions of the bacteria (Boskovic, 2015; Nagoor, 2017).

### 7.4. Oregano (O vulgare)

There were several articles discussing the antibacterial activity of oregano (*O vulgare*) in the narrative review. Unfortunately, none of the studies explained its mechanism for impeding the growth of the MDR strains of bacteria. Oregano (*O vulgare*) is another herb cultivated in the Mediterranean region (Fournomiti, 2015). The antimicrobial constituents found in oregano (*O vulgare*) are predominately thymol and carvacrol (Fournomiti, 2015). However, this herb contains monoterpenoid metabolites that have a minor antimicrobial effect (Fournomiti, 2015). It is a broad-spectrum antibacterial agent (Bryce, 2016). The mechanisms of action of thymol and carvacrol in oregano (*O vulgare*) are analogous to those observed in thyme (*T vulgaris*) (Boskovic, 2015). In addition, one terpenoid known as γ-terpinene can disrupt the function of the cell wall and membrane, inducing the leakage of intracellular proteins and lipids, resulting in cell death (Oyedemi, 2009). Oregano (*O vulgare*) as a whole extract inhibited the efflux pump of an antibiotic-resistant strain of *S pneumoniae*, which causes an accumulation of toxins within the cell, inducing cell death (Ghafari, 2018).

### 7.5. Turmeric (C longa)

The literature review revealed a small amount of information pertaining to the antimicrobial effects of turmeric (*C longa*), which seems to be an oversight as turmeric (*C longa*) has been used medicinally in Ayurvedic medicine since 250 BCE (Tyagi, 2015). Although the activity of curcumin was not assessed in the narrative review, it is the secondary metabolite that is responsible for the antibacterial properties of this herb (Tyagi, 2015). It is considered to be a broad-spectrum antimicrobial agent.[116] One potential mechanism of curcumin is the interference with bacterial adherence to extracellular matrix proteins of the host cell preventing colonization (Tyagi, 2015). Another target of this metabolite is the cytoskeletal protein FtsZ (Teow, 2016). Curcumin inhibits the formation of FtsZ, which impedes the synthesis of the cell wall prohibiting cellular proliferation (Teow, 2016). Analogous to garlic (*A sativum*), curcumin is capable of disrupting quorum sensing and biofilm formation, reducing the virulence of bacteria, which could indicate that it is effective against strains of MDR *S pneumoniae* and MDR *P aeruginosa* (Teow, 2016). Unfortunately, no experiments testing the MIC or ZOI for turmeric (*C longa*) against these microbes were performed. Curcumin can deteriorate the cell membrane increasing permeability and contributing to the leakage of the cell contents reducing the viability of the cell (Tyagi, 2015). Lastly, turmeric (*C longa*) diminished the secretion of α-hemolysin by MDR *S aureus*, reducing its pathogenicity (Teow, 2016).

### 7.6. Rosemary (R officinalis)

Another herb cultivated in the Mediterranean region is rosemary (*R officinalis*) which was featured in this review was rosemary (*R officinalis*), which has bactericidal effects against Gram-positive and Gram-negative bacteria (Santoyo, 2005). The components of rosemary that may impede the growth of these microbes are rosmarinic acid, 1,8-cineol, rosmaridiphenol, carnosol, epirosmanol, carnisic acid, rosmanol, and isoromanol (Hussain, 2010; Nieto, 2018). The effects of rosmarinic acid, carnisic acid, and 1,8-cineol were found to inhibit the growth of MDR E coli and MDR *C jejuni*, yet the investigators did not discuss a potential mechanism of action for the growth suppression that was observed.

Consequently, reducing the replication of the MDR-resistant bacterium in the narrative review may have been attributed to multiple active constituents. These phytochemicals can disrupt the activity of cell membrane proteins and contribute to the leakage of intracellular material (Nieto, 2018). Alterations in the cellular function of the bacteria have been observed as well (Nieto, 2018). Abnormalities in cellular metabolism, DNA replication, the ability to transport electrons, and the fatty acid composition have occurred, which can compromise the capacity of the bacterium to survive (Nieto, 2018). In addition, rosemary (*R officinalis*) can interfere with the formation of the bacterial biofilm, which may explain its antimicrobial effects against MDR *S pneumoniae* and MDR *P aeruginosa* (Jardak, 2017). This reduces the ability of the microbe to adhere to, colonize and proliferate (Jardak, 2017). Destruction of the biofilm can reduce the pathogenicity of the bacteria and attenuate antibiotic resistance as well (Jardak, 2017).

### 7.7. Cinnamon (Cinnamomum species)

The last botanical evaluated in the narrative review was cinnamon (*Cinnamomum species*). As with turmeric (*C longa*), this is a major gap in the research as the first recorded use of cinnamon (*Cinnamomum species*) was around 2800 BCE in Ancient China, indicating that it has been used medicinally for thousands of years (Kawatra, 2015). There are several species of cinnamon (*Cinnamomum species*), but cinnamon (*C zeylanicum*), cinnamon (*C verum*), and cinnamon (*C aromaticum*) are the most prevalent (Kawatra, 2015). Cinnamon (*C cassia* (L.) D. Don) is used for medicinal purposes in China, while cinnamon (*C zeylanicum*) is classically used in Mexico and Sri Lanka (Kawatra, 2015). Since there are multiple species of cinnamon administered for therapeutic purposes, the narrative review encompassed the genus of cinnamon (*Cinnamomum species*) rather than a specific genus and species.

Cinnamon (*Cinnamomum species*) is considered a broad-spectrum antibacterial agent against Gram-positive and Gram-negative bacteria (Nabavi, 2015; Ooi, 2006). Although there were numerous studies demonstrating the efficacy of cinnamon (*Cinnamomum species*) as a bacteriostatic and bactericidal agent, none of the research described a mechanism of action. Eugenol and cinnamaldehyde are the major components responsible for their antimicrobial properties and may have been responsible for the growth inhibition exhibited in the narrative review (Nabavi, 2015). Eugenol, cinnamaldehyde, and oil from the bark initiate an antibacterial effect by suppressing the formation of the biofilm of the bacteria, which impedes its ability to colonize and proliferate, which may explain the effectiveness of cinnamon (*Cinnamomum species*) for MDR *S pneumoniae,* and MDR *P aeruginosa* (Nabavi, 2015). Although the mechanism was not discussed, cinnamaldehyde as a monotherapy impaired the replication of MDR *P aeruginosa* and MDR *S aureus*. However, it may have prevented the growth of MDR *S aureus* by a different mechanism, and it was not found to be effective alone against MDR *E coli*.

The phytochemicals of the botanical can interact with the cell membrane changing the lipid profile and increasing its permeability, impairing the membrane porins of MDR strains of bacteria (Vasconcelos, 2018). In addition, damage to the cell membrane contributes to the leakage of potassium ions and a collapse of the membrane potential, which impedes the functionality of the cell (Bouhdid, 2010). Lastly, interference with various chemical reactions related to energy conservation, active transport, and pH homeostasis can occur through the inhibition of ATPase activity leading to metabolic defects resulting in cell death (Vasconcelos, 2018; Bouhdid, 2010).

## 8. Antibiotic Herb Interactions

As conventional medicine in the US is primarily based on pharmaceuticals, the interaction of each botanical with antibiotics is crucial to ensure the proper treatment of an infection. Certain phytochemicals may enhance or impede the activity of antibiotics. Promoting the activity of antibiotics may produce additional bacteriostatic or bactericidal effects to eliminate MDR strains of bacteria.

### *8.1. Garlic (A sativum) Antibiotic Interaction*

Garlic (*A sativum*) may generate synergistic effects with antibiotics. A study by Li et al found that fresh garlic (*A sativum*) extract was effective as a monotherapy for eradicating MRSA and MDR *P. aeruginosa* (Li, 2015). In addition, garlic promoted the therapeutic effects of several antibiotics against these antibiotic-resistant strains (Li, 2015). Another study showed that garlic (*A sativum*) enhanced the activity of cefoxitin, oxacillin, and piperacillin against MRSA and cefoxitin, levofloxacin, ceftriaxone, cefazolin, and ampicillin against *P aeruginosa* (Li, 2015). Niels et al showed that the combination of garlic (*A. sativum*) and tobramycin produced bactericidal effects against *P aeruginosa* (Høiby, 2011). Lastly, the coadministration of garlic (*A sativum*) and ciprofloxacin produces antibacterial effects (Sohn, 2009).

### *8.2. Thyme (T vulgaris) Antibiotic Interaction*

There is not much information on the potential benefit of administering thyme (*T vulgaris*) in conjunction with certain antibiotics to enhance their antimicrobial activity. Thyme (*T vulgaris*) amplified the effects of tetracycline, ampicillin, and cloranfenicol against MDR *P. aeruginosa* (Nascimento, 2000). It was shown to potentiate the effects of penicillin and nitrofurantoin (Chouhan, 2017). Lastly, synergism has been demonstrated between thyme (*T vulgaris*) and ciprofloxacin, amphotericin B, ethambutol, isoniazid, and cefotaxime against various strains of bacteria (Rahgozar, 2018; van Vuuren, 2009; Benameur, 2018).

### *8.3. Oregano (O vulgare) Antibiotic Interaction*

A few research studies have found that oregano (*O vulgare*) can amplify the activity of antibiotics. An experiment conducted by Si et al revealed potent synergistic bactericidal effects of oregano (*O vulgare*) essential oil when administered in combination with a variety of antibiotics (Si, 2008). Apportioning oregano (*O vulgare*) in conjunction with polymyxin, amoxicillin, lincomycin, doxycycline, fluoroquinolones, and maquindox florfenicol generated a substantial increase in antibacterial activity (Si, 2008). The coadministration of these medications with oregano (*O vulgare*) lowered the minimum inhibitory concentration necessary for each antibiotic against MDR *E coli* (Si, 2008). Oregano (*O vulgare*) enhanced the inhibitory effects of ciprofloxacin and ethidium bromide by increasing their uptake in an antibiotic-resistant isolate of *S pneumoniae* (Subbu, 2016). In addition, carvacrol and thymol propagated the antibacterial properties of tetracycline against MDR *S aureus* (Cirino, 2014).

### *8.4. Turmeric (C longa) Antibiotic Interaction*

Synergism between turmeric (*C longa*) and antibiotics has been efficacious against Gram-positive and Gram-negative strains of bacteria (Tyagi, 2015). One study indicated that adjunct therapy enhanced the antibacterial effects of cefixime, vancomycin, and tetracycline (Tyagi, 2015). In a study by Kali et al, curcumin was found to potentiate the effects of penicillin, erythromycin, ciprofloxacin, ampicillin, ceftriaxone, cefepime, gentamicin, amikacin, imipenem, and meropenem (Kali, 2016). It should be noted that the increases in sensitivity of antibiotic-resistant strains of bacteria to ampicillin, imipenem, and meropenem were minimal (Kali, 2016). However, the coadministration of ampicillin and curcumin produced bactericidal activity against antibiotic-resistant strains of *S aureus*, *E coli*, *Bacillus subtilis*, *P aeruginosa*, and *Corynebacterium diphtheriae* (Alihosseini, 2016). The zone of inhibition of norfloxacin was significantly increased with the addition of turmeric (*C longa*) against a broad spectrum of aerobic and anaerobic bacteria (Dua, 2013). The combination of an extract of turmeric (*C longa*) with cefaclor, cefodizime, and cefotaxime for the treatment of Gram-negative and Gram-positive bacteria that caused diarrhea significantly lowered the minimum inhibitory concentration and minimum bactericidal concentration (Sasidharan, 2014).

### *8.5. Rosemary (R officinalis) Antibiotic Interaction*

There are a limited number of studies evaluating the benefits of using rosemary (*R officinalis*) in conjunction with antibiotics. The coadministration of rosemary (*R officinalis*) with vancomycin, ofloxacin, and amoxicillin enhanced their antibacterial effects (Ekambaram, 2016). In a study by van Vuuren et al, rosemary (*R officinalis*) potentiated the effects of ciprofloxacin against K pneumoniae (van Vuuren, 2009). However, it reduced the effectiveness of ciprofloxacin against *S aureus* (van Vuuren, 2009). Another study by Hosseiny et al showed that rosemary (*R officinalis*) strengthened the activity of ceftazidime, imipenem, aztreonam, and ciprofloxacin by 12-33.3% for the elimination of *P aeruginosa* (El Hosseiny, 2015). Although the amount of research is minimal, there are a few studies that promote the use of rosemary (*R officinalis*) with antibiotics. More investigations are necessary as this botanical did reduce the effects of ciprofloxacin against *S aureus*.

### *8.6. Cinnamon (Cinnamomum species) Antibiotic Interaction*

Cumulative effects have been demonstrated between cinnamon (*Cinnamomum species*) species and several antibiotics. Cinnamon (*Cinnamomum species*) bark potentiated the effects of piperacillin against β-lactam resistance *E coli* species (Nabavi, 2015). The effects of amikacin and gentamicin were bolstered by cinnamon (*Cinnamomum species*) for the elimination of *Acinetobacter* species (Guerra, 2012). Oil from the bark and cinnamaldehyde enhanced the inhibitory activity of colistin on MDR *P aeruginosa* by 16.7% and 10%, respectively (Utchariyakiat, 2016). Synergy occurred between cinnamon (*Cinnamomum species*) oil and doxycycline when used against several Gram-negative strains of bacteria (Goc, 2016). One study by Roshan et al found that cinnamaldehyde amplified the effects of vancomycin and metronidazole (Roshan, 2017).

Although additive effects are typically seen between cinnamon (Cinnamomum species) and antibiotics, a study by Sawicki et al observed that cinnamaldehyde neither increased nor decreased the activity of ethambutol, isoniazid, rifampicin, ciprofloxacin, or streptomycin for the treatment of *Mycobacterium tuberculosis* (Sawicki, 2018). The absence of synergism is potentially strain-specific or from using an herbal component, as Atki et al determined that the essential oil of cinnamon (*Cinnamomum species*) augmented the activity of streptomycin against *E coli, S aureus,* and *P aeruginosa* (El Atki, 2019). In addition, Atki et al

concluded that the essential oil enhanced the activity of ampicillin and chloramphenicol against S aureus and chloramphenicol against *E coil*, yet the combination of cinnamon (*Cinnamomum species*) and ampicillin had neither antagonism nor synergism for *E coli* or *P aeruginosa*, and cinnamon (*Cinnamomum species*) did not affect the bacteriostatic activity of chloramphenicol against *P aeruginosa* (El Atki, 2019).

These studies demonstrate that garlic (*A sativum*), thyme (*T vulgaris*), oregano (*Origanum vulgare*), turmeric (*Curcuma longa*), rosemary (*Rosmarinus officinalis*), and cinnamon (*Cinnamomum species*) may be administered as potential adjuncts with antibiotics for the treatment of bacterial infections. In the majority of cases, these botanicals reinforce their antibacterial properties and enhance their effects. This may be especially beneficial in the case of antibiotic-resistant strains of bacteria.

## 9. Additional Benefits of Using Botanicals for Infections

### *9.1. Bacteria-Induced Inflammatory Reactions*

The pathophysiology associated with an infection creates an inflammatory state. *S aureus* has the ability to release hemolysins that inflict damage on the tissue and lyses neutrophils, Panton-Valentine leucocidin erodes the mitochondrial cells, and enterotoxins promote hyperactivity of T cells, intensifying inflammation and inducing apoptosis (Kane, 2018; Liu, 2009; Tomita, 1997). Lipoteichoic acid is released from *S pneumoniae,* deteriorating host cells, and activating the inflammatory cascade (Brooks, 2018). *P aeruginosa* secretes pyocyanins that increase oxidative stress by inhibiting antioxidant enzyme capacity contributing to inflammation (Hall, 2016). The Shiga toxin from *E coli* can augment the inflammatory process by activating the innate and cell-mediated immune systems (Berdasco, 2019). *C jejuni* contains the cytolethal distending toxin in its outer membrane that exacerbates the inflammatory state (Lluque, 2017).

The pro-inflammatory effects generated by this bacterium can increase the risk of morbidity and mortality from an infection (Berdasco, 2019). The concept of utilizing an anti-inflammatory agent to reduce the pathogenicity of infection is illustrated by the utilization of oral corticosteroids (Martin, 2018). Oral corticosteroids are administered to reduce the inflammation created by the pathogen (Martin, 2018). In the narrative review, the research focuses on the activity of the botanical on the bacteria under controlled conditions on a growth medium, which does not take into account the positive effects the herb may have on the body during an infection.

### *9.2. Anti-inflammatory Effects of Herbs*

Each of the herbs in the narrative review can reduce the levels of the proinflammatory mediators such as interleukin (IL)-6, tumor necrosis factor-$\alpha$, and inflammatory cytokines (Ocaña, 2012; Arreola, 2015; Leyva-López, 2017; Jagetia, 2007; Habtemariam, 2016; Qu, 2019). Thyme (*T vulgaris*), oregano (*O vulgare*), turmeric (*C longa*), rosemary (*R officinalis*), and cinnamon (*Cinnamomum species*) can diminish the activity of IL-1$\beta$ and thyme (*T vulgaris*), and oregano (*O vulgare*) can augment the production of anti-inflammatory IL-10 (Ocaña, 2012; Leyva-López, 2017; Jagetia, 2007; Habtemariam, 2016; Kim, 2019). Additionally, turmeric (*C longa*), rosemary (*R officinalis*), and cinnamon (*Cinnamomum species*) can reduce the synthesis of the inflammatory mediator IL-8 (Jagetia, 2007; Habtemariam, 2016; Kim, 2019).

Each botanical has phytochemicals that can further reduce inflammation by decreasing the expression of nuclear factor-κB, which is a transcription factor associated with the arachidonic acid cascade and the production of proinflammatory thromboxanes, prostaglandins, and leukotrienes (Nagoor, 2017; Arreola, 2015; Jagetia, 2007; Habtemariam, 2016; Kim, 2019; Cheng, 2018). Thyme (*T vulgaris*), oregano (*O vulgare*), turmeric (*C longa*), rosemary (*R officinalis*), and cinnamon (*Cinnamomum species*) have direct inhibitory effects on cyclooxygenase activity, further reducing inflammation related to the arachidonic acid cascade (Leyva-López, 2017; Habtemariam, 2016; Qu, 2019; Cheng, 2018; PDR, 2007). Turmeric (*C longa*) can hinder the effects of phospholipase, which is an enzyme that synthesizes arachidonic acid, downregulating its production (PDR, 2007). Turmeric (*Curcuma longa*) and rosemary (*R officinalis*) have been shown to disrupt 5-lipoxygenase, which is the enzyme responsible for the production of inflammatory leukotrienes generated along the arachidonic acid pathway (Habtemariam, 2016; Chainani-Wu, 2003). Consequently, the anti-inflammatory properties of these botanicals may mitigate symptomatology associated with an infection as well as amplify the effects of antibiotics (Martin, 2018). Although there were few studies exemplifying the effectiveness of the botanicals for the elimination of *C jejuni*, reducing inflammation associated with its pathogenicity may decrease the intensity of the infection.

### *9.3. Antioxidant Activity of Herbs*

All of the botanicals discussed above possess antioxidant activity. Antioxidant activity can attenuate free radical-related damage and inflammation associated with an infection and the immune response (Martin, 2018). Phagocytes use prooxidants during respiratory bursts to destroy invading pathogens (Martin, 2018). Unfortunately, a consequence of a respiratory burst is an increase in the levels of oxidative stress (Martin, 2018). In addition, elevating oxidative stress promotes the release of glucocorticoids (Martin, 2018). Higher levels of respiratory burst, oxidative stress, and glucocorticoid release can result in dysfunction of the antioxidant defense system (Martin, 2018). Since increasing oxidative stress is a virulence factor that certain bacterium such as *P aeruginosa* use to create a favorable environment to infect the host, reducing prooxidant levels and damage would be essential for eradicating the microbe. Administering each botanical may improve antioxidant status and prevent impairment of the antioxidant defense system, ultimately assisting with the elimination of the pathogen.

Garlic (*A sativum*), thyme (*T vulgaris*), oregano (*O vulgare*), turmeric (*C longa*), rosemary (*R officinalis*), and cinnamon (*Cinnamomum species*) can increase antioxidant status by up-regulating SOD, CAT, and GPx (Arreola, 2015; Leyva-López, 2017; Rašković, 2015; Agliassa, 2018; Park, 2015; Hewlings, 2017; Selmi, 2017; El-Demerdash, 2016; Niknezhad, 2019). This is of particular importance as *P aeruginosa* down-regulates these enzymes to increase oxidative stress. Oregano (*O vulgare*) and rosemary (*R officinalis*) have the ability to enhance glutathione transferase activity as well (Park, 2015; El-Demerdash, 2016). In addition, turmeric (*C longa*) can decrease the activity of xanthine oxidase due to tissue damage, which reduces the generation of hydrogen peroxide (Hewlings, 2017).

Reducing the levels of prooxidants could attenuate tissue damage and decrease inflammation. Eliminating free radicals may decrease the severity of the infection. As antibiotics target the bacterium itself, this therapeutic activity may be invaluable for attenuating the symptoms.

### *9.4. Interactions Between Bacteria and the Immune System*

Certain bacteria are able to infiltrate the body and colonize through virulence factors that suppress immune function. *S aureus* causes dysfunction of neutrophils and MHC II and the movement of WBCs (Liu, 2009). *S pneumoniae* is capable of evading neutrophils, inhibiting phagocytosis, impairing the function of immunoglobulin A and reducing the ability of the immune system to recognize it (Books, 2018; Keller, 2016). *C jejuni* uses its flagellum to invade the WBCs of the host, which inactivates the WBC (Lluque, 2017). *S typhimurium* prevents NADPH oxidase activity impeding the ability of macrophages to eradicate the bacterium (Gart, 2016).

### *9.5. Immunostimulatory Effects of Herbs*

Each of these herbal extracts may have the potential to boost the immune system. Enhancing the immune response may increase the natural defenses of the body to expel the infectious agent. The research on the immunostimulatory effects of rosemary (*R officinalis*) and cinnamon (*Cinnamomum species*) is limited, but there is some evidence that they potentiate the innate immune system (Braun, 2010; Abdel-Tawwab, 2018). Garlic (*A sativum*), thyme (*T vulgaris*), oregano (*O vulgare*), and turmeric (*C longa*) can increase the proliferation of T lymphocytes, especially CD8 t cells, which are involved with the protection of the body from pathogenic invaders (Nagoor, 2017; Arreola, 2015; Walter, 2004; Bose, 2015).

Additionally, thyme (*T vulgaris*), oregano (*O vulgare*), and turmeric (*C longa*) increase the activity of CD4 t cells (Nagoor, 2017; Walter, 2004; Bose, 2015). Garlic (*A sativum*) is capable of promoting the activation of macrophages and stimulating the generation of natural killer cells and dendrites, optimizing phagocytic activity (Arreola, 2015). Oregano (*O vulgare*) and turmeric (*C longa*) can also augment the production of natural killer cells, and turmeric (*C longa*) enhances the synthesis of WBC and the activity of macrophages (Walter, 2004; Bose, 2015). Thyme (*T vulgaris*) can up-regulate the gene expression of interferon-γ, which is crucial for the function of both innate and adaptive immunity against pathogenic microbes (Nagoor, 2017). In addition, thyme (*T vulgaris*) accelerates the propagation of immunoglobulins, IL-12, which promotes the proliferation and function of T lymphocytes, and the activity of MHC-II, which helps with the identification of foreign proteins (Nagoor, 2017). Oregano (*O vulgare*) can also potentiate the effects of MHC-II (Walter, 2004).

## 10. Limitations

There were several limitations to this study. One of the limitations was that studies were only chosen between the dates of January 2007 to December 2018. However, due to the extensive amount of research articles that were filtered through the inclusion and exclusion process, this was necessary. Increasing the dates of the study may have increased the articles available for review. As it was, there were only 71 studies that met the inclusion criteria. Of the 71 articles, not all of them included the MIC or ZOI, and there were very few articles available on antibiotic-resistant *S pneumoniae, C jejuni,* and *S typhimurium*. This is a major lapse in the research. Unfortunately, due to the limited amount of information on the administration of these botanicals for antibiotic-resistant strains of bacteria, it is difficult to draw accurate conclusions. More research needs to be conducted.

Another limitation was that articles that did not specify if the bacteria were resistant to antibiotics were excluded. Consequently, a number of articles that could have been using antibiotic-resistant strains of bacteria may have been excluded. Additionally, there were several studies using a combination of botanicals or botanicals with medications that could have shown antibacterial effects against antibiotic-resistant strains of bacteria that were excluded. Lastly, there were several publications that used other strains of antibiotic-resistant bacteria that were not one of the six that were chosen. Consequently, these botanicals may have been effective in suppressing the growth of other antibiotic-resistant strains of bacteria not included in this study.

## 11. Conclusion

Antibiotic-resistant strains of bacteria are a major medical issue in the United States, accounting for a large number of infections resulting in hospitalization and possibly death. These infections may also present a financial burden on individuals, the healthcare system, and society. Using natural herbs either as a monotherapy or in combination with antibiotics may enhance the efficacy of the treatment of MDR infections. The preliminary studies conducted demonstrate the potential benefit of using botanical extracts for the treatment of MDR strains of bacteria. However, additional research is necessary before conclusions can be drawn.

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