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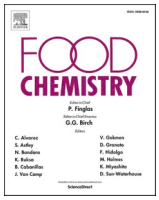

Review

The anti-campylobacter activity of eugenol and its potential for poultry meat safety: A review

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ABSTRACT

Poultry is one of the fastest growing industries due to advantages in land use, rapid production and advances in feed technology. The rising trend in the consumption of poultry meat over the last 50 years has also increased concerns about food safety. *Campylobacter jejuni* is the leading bacterial cause of gastroenteritis, the foremost cause of foodborne deaths. Despite significant progress in food safety methology, the genus *Campylobacter* remains a common foodborne pathogen in poultry. Increasing consumer demands for natural products require the discovery of new antimicrobials to ensure the safety of poultry meat. Recent studies have revealed that eugenol acts with antimicrobial activity on a wide variety of foodborne microorganisms. Eugenol is generally recognized as safe and is a promising preservative for the food industry. However, specific applications of eugenol need to be identified and validated to clarify the role of the food preservative in poultry meat safety.

1. Introduction

Food safety and healthy nutrition are key elements of food systems which have a significant impact on public health. The World Health Organization (WHO) underlines that healthy eating practices should be started early in life to reduce the risk of non-communicable diseases such as diabetes, heart diseases, stroke and cancer (World Health Organization, 2019). However, ensuring food safety is vital to achieving a healthy diet. Using the slogan "if it is not safe, it is not food", the Food and Agriculture Organization of the United Nations (FAO) has positioned safe food as a prerequisite for a healthy diet. Food safety risks pose a significant threat to the sustainability of public health, in both developed and developing countries. Additionally, the annual cost of unsafe food consumption is 110 billion dollars in low- and middle-income countries (Jaffee et al., 2018). Therefore, it is clear that food safety is crucial to sustaining both public health and economic development (Singh & Mondal, 2019).

To date, >250 foodborne diseases caused by infectious and non-infectious agents have been reported (Hoffmann & Scallan, 2017). In 2010, 600 million people had foodborne diseases and 420,000 foodborne deaths were reported. Moreover, it was stated that 40% of foodborne diseases occur in children under 5 years of age. It is reported that the most common causes of foodborne diseases are *Norovirus* and *Campylobacter*, and the most common cause of foodborne deaths is *Salmonella* (World Health Organization, 2015). Reportedly responsible for 25% of foodborne outbreaks and 30% of *Campylobacter* outbreaks, poultry meat is the main food-based contamination source of *Campylobacter* and *Salmonella* worldwide (Thames & Sukumaran, 2020).

Poultry production is one of the fastest growing livestock industries due to the advantage in minimal land use, rapid production and advances in feed technology (Kiilholma, 2007). Poultry meat consumption per capita has increased worldwide since 1960 and is projected to increase until 2030 (Bruinsma, 2017; Chai et al., 2017). Poultry meat is more in demand by consumers due to its lower risk of cardiovascular disease and cancer compared to red meat (Bruinsma, 2017; Kim et al., 2019). The increasing trend for poultry meat consumption has increased concerns of producers and public health professionals about food safety in the industry. Due to social media coverage, food safety risk awareness and concerns of consumers have also increased in recent years (Baron & Frattarolli, 2016; Rutsaert et al., 2013). However, consumers' perception of risk seems to be more related to avian influenza and chemical hazards (van Asselt et al., 2018). Several *Salmonella* and *Campylobacter* species are presented in the feathers, skin and digestive tract of live poultry. Modern poultry slaughter relies on automated equipment and processes, posing a challenge to avoid bacterial contamination in the slaughter line and contamination of poultry carcasses during slaughter is

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often inevitable (Tang et al., 2020).

It is well known that the most common bacterial cause of foodborne disease *is Campylobacter jejuni* and the main source of contamination for humans is chicken meat (Zbrun et al., 2020). This pathogen is considered the most significant cause of foodborne gastroenteritis in developed countries. It is also reported that *C. jejuni* causes autoimmune diseases such as Guillain Barre Syndrome, Miller Fischer Syndrome and Reactive Arthritis (Kaakoush et al., 2015). Despite high food safety standards and legislation in developed countries, *Campylobacter* infections remain a major public health problem. Therefore, it is essential to control microbiological quality, and develop effective decontamination strategies at all stages of the food chain, ''from farm to fork''.

At the pre-harvest stage antimicrobial drugs, e.g. fluoroquinolone against *Campylobacter*, have been widely used to improve growth and feed efficiency in poultry industry. However, excessive usage of antibiotics led to a wide range of antibiotic resistance in humans as well as in food-producing animals, leading decision makers to limit antibiotic usage as a growth promoter in healthy animals (Vose et al., 2000). After the United States Food and Drug Administration (FDA) banned the use of antibiotics in feedstuff in 2005, studies focusing on post-harvest decontamination methods have increased (Thames & Sukumaran, 2020). It is known that the most commonly used agents for post-harvest decontamination are chemical antimicrobials, however, consumer concerns about food products containing chemical antimicrobials are increasing and consumers mostly prefer products containing natural additives (Román et al., 2017). Essential oils are one of the promising natural antimicrobial agents offering an alternative to existing antimicrobials such as chlorine dioxide, cetylpyridinium chloride and ozone in the meat industry. The phenolic compounds of essential oil have been suggested as the main cause of antimicrobial activity (Ozogul et al., 2020). Eugenol, the main phenolic compound of clove essential oil, has become a focus of attention in the last 5 years due to its antimicrobial activity. Therefore, our study aims to review the anti-campylobacter activity of eugenol and its potential to increase the safety of poultry meat, in consideration of current studies.

2. Biological properties of eugenol

Eugenol ($C_{10}H_{12}O_2$; Fig. 1), a phenylpropanoid, is the main phenolic component of clove essential oil (bp: 254 °C; mp: −9 °C), obtained from the buds and leaves of *Eugenia caryophyllata* (Nejad et al., 2017; Caillol et al., 2021). Clove essential oil also contains minor components such as isoeugenol and methyl eugenol, which are natural derivatives of eugenol (Nurdjannah & Bermawie, 2012). Eugenol is a pale yellow liquid with an oily consistency and spicy aroma. It is a small molecule with the molecular weight of 164.2 g/mol. Eugenol has a weak acidic nature, is slightly soluble in water and well soluble in organic solvents such as alcohol, oils, ether and chloroform. According to the study of Fischer et al. (1990), eugenol was absorbed rapidly following oral administration and almost completely excreted through urine as eugenol conjugates within 24 h in healthy volunteers. Eugenol has low chemical stability because of its susceptibility to oxidation, heat and various chemical interactions. (Ulanowska & Olas, 2021). In recent years, the chemical interaction of eugenol with different proteins has attracted significant attention because of its pharmaceutical potential. Eugenol is known to interact with several proteins such as diabetes and hypertension-related enzymes, serum albumin and ion channels to affect their functional properties (Dubey et al., 2017).

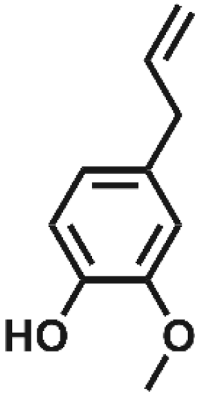

Fig. 1. Chemical structure of eugenol (Caillol et al., 2021). Chemical structure of eugenol, ($C_{10}H_{12}O_2$, 4-Allyl-2-methoxyphenol).

As reported in the literature, eugenol exhibits some health benefits such as antioxidant, anti-inflammatory, anticancer and analgesic activity (Ahmad et al., 2019; de Araújo-Lopes et al., 2018; Pisano et al., 2007). Additionally, eugenol also exhibits antibacterial, antifungal, antileishmanial and antigiardia activity (Shah et al., 2013; Darvishi et al., 2013; Machado et al., 2011; Ueda-Nakamura et al., 2006). Although its exact action mechanism is unknown, there are studies reporting synergistic interactions between eugenol and some antibiotics such as penicillin, cefotaxime and ciprofloxacin (Dhara & Tripathi, 2020; Hemaiswarya & Doble, 2009). The FDA has approved the use of clove oil as a flavoring agent for the food industry and as a natural analgesic and antiseptic in dentistry (Nejad et al., 2017). However, despite its significant biological activity, it has been emphasized that eugenol may cause adverse effects such as irritation and allergy. There are some case reports of aphthous stomatitis, contact dermatitis and burning mouth syndrome conected to the use of eugenol (Navarro-Triviño et al., 2019; White et al., 1999).

Clove oil may exhibit some changes in chemical structure and bioactivity, depending on the extraction method (Kapadiya et al., 2018). Steam distillation and hydrodistillation are the most commonly used, conventional methods for the extraction of clove oil. However, these methods have disadvantages such as long extraction times, high energy demand and thermal degradation. Recently, several advanced extraction methods, namely ''green extractions'', such as supercritical carbon dioxide (CO_2) extraction, micro-wave assisted extraction, ohmic heating assited extraction and ultrasound assisted extraction have been introduced; processes which ensure shorter processing times, reduce energy demand and high extraction yield (Khalil et al., 2017). Tunç and Koca (2019) have found that ohmic heating assisted hydrodistillation of clove oil provides higher eugenol yield and higher antimicrobial activity against gram-negative bacteria such as *Klebsiella pneumoniae* and *Escherichia coli* compared to conventional hydrodistillation. Similarly, the supercritical CO_2 extraction and ethanolic ultrasound assisted extraction methods from clove leaves had higher eugenol yields and higher antioxidant activity compared to conventional methods (Frohlich et al., 2019; Frohlich et al., 2022). Furthermore, supercritical CO_2 combined with ultrasound during the extraction of clove oil from clove buds increased the eugenol yield 13.5% relative to the supercritical CO_2 extraction method (Yang et al., 2014). The use of ultrasound assisted extraction in combination with the other advanced extraction methods to evaluate yield and bioactivity of eugenol is limited and needs to be further explore. The combination methods may provide a basis for future efficient extraction and industrial application of eugenol.

3. The proposed mechanism of antimicrobial action of eugenol

The antimicrobial activity of eugenol has been widely validated for decades and extensively studied in recent years (Miladi et al., 2017; Gowda et al., 2021; Mandras et al., 2021). The antimicrobial activity potential of eugenol is generally attributed to the free hydroxyl group (–OH) in its structure (da Silva et al., 2018). Although the mechanism of antimicrobial action has not been fully clarified, it is known that eugenol targets multiple mechanisms within the cell rather than relying on a specific mechanism. Previous studies have reported that eugenol exerts its antimicrobial action by increasing cell membrane permeability, decreasing intracellular ATP concentration, down-regulation of genes

related to the flagella system, stress response and biofilm formation (Olszewska et al., 2020; Qian et al., 2020; Wagle et al., 2019c). Hemaiswarya & Doble (2009) reported that 1 mM eugenol increased the membrane damage of *E. coli*, *Pseudomonas aeruginosa*, *Salmonella* Typhimurium and *Proteus vulgaris* by 50%. Liu et al. (2020) studied the effect of eugenol on *Listeria monocytogenes* motility and reported that 2 mM eugenol treatment significantly downregulated flagella-related genes. Furthermore, it has been stated that eugenol prevents biofilm formation of *S.* Typhimurium and *L. monocytogenes* at 0.66 and 0.5 mM concentrations, respectively (Purkait et al., 2020).

Some studies have reported that the aforementioned mechanism of action varies based on the concentration of essential oils. Nychas et al. (2003) reported that essential oils inhibit enzymes associated with energy production at low concentrations, while protein precipitation was observed at high concentrations. When assessing the antimicrobial activity, it is therefore essential to know the minimum inhibitory

Table 1
Current studies on the antimicrobial activity of eugenol against several microorganisms.

Microorganism	MIC value	MBC value	Effects	MIC determination method	Reference
Gram negative bacteria					
Escherichia coli	0.5 mg/mL		Inhibitory, anti-biofilm	Broth microdilution	(Olszewska et al., 2020)
Escherichia coli	2.0 mg/mL	4.0 mg/mL	Inhibitory, bactericidal	Broth microdilution	(Orlo et al., 2021)
Escherichia coli	0.312 mg/mL	0.312 mg/mL	Inhibitory, bactericidal	Disc diffusion	(Zhang et al., 2017a)
Escherichia coli		0.58–0.73 mg/mL	Bactericidal, anti-biofilm	Agar dilution	(Caballero-Prado et al., 2021)
Escherichia coli	0.007 mg/mL		Inhibitory, bactericidal*	Broth microdilution	(Dhara & Tripathi, 2020) (Xue et al., 2021)
Salmonella Enteritidis	0.5 mg/mL	1.0 mg/mL	Inhibitory, bactericidal	Broth microdilution	
Salmonella Typhimurium	0.625 mg/mL	0.625 mg/mL	Inhibitory, bactericidal	Disc diffusion	(Zhang et al., 2017a)
Salmonella Typhimurium	0.1–0.5 mg/mL	0.1–1.0 mg/mL	Bactericidal, anti-biofilm	Broth microdilution	(Miladi et al., 2017)
Salmonella Typhimurium	2.048 mg/mL		Inhibitory, anti-biofilm	Broth microdilution	(Liu et al., 2015)
Salmonella Typhimurium	0.075 mg/mL	0.082 mg/mL	Inhibitory, anti-biofilm	Broth microdilution	(Purkait et al., 2020)
Salmonella Typhimurium	0.07 mg/mL	0.06 mg/mL	Inhibitory, bactericidal*	Broth microdilution	(Guimarães et al., 2019)
Klebsiella pneumoniae	0.1–0.2 mg/mL		Inhibitory, anti-biofilm	Agar dilution	(Qian et al., 2020)
Klebsiella pneumoniae	0.002 mg/mL		Inhibitory, QS inhibitory	Disc diffusion	(Wang et al., 2019)
Klebsiella pneumoniae	0.004 mg/mL		Inhibitory, bactericidal*	Broth microdilution	(Dhara & Tripathi, 2020)
Pseudomonas aeruginosa	3.3 mg/mL		Inhibitory	Broth microdilution	(Hemaiswarya & Doble, 2009)
Pseudomonas aeruginosa	> 0.5 mg/mL		Inhibitory	Broth microdilution	(de Almeida et al., 2019)
Pseudomonas aeruginosa	0.15–0.3 mg/mL		Inhibitory, anti-biofilm	Broth microdilution	(Rathinam et al., 2017)
Aeromonas salmonicida	0.13–0.25 mg/mL	0.25–0.5 mg/mL	Inhibitory, bactericidal	Broth microdilution	(Hayatgheib et al., 2020)
Aeromonas hydrophila	0.025–0.2 mg/mL	0.05–0.2 mg/mL	Inhibitory, bactericidal	Disc diffusion	(Bandeira-Junior et al., 2018)
Enterobacter aerogenes	3.3 mg/mL		Inhibitory	Broth microdilution	(Hemaiswarya & Doble, 2009)
Citrobacter freundii	0.4 mg/mL	0.8 mg/mL	Inhibitory, bactericidal	Disc diffusion	(Bandeira-Junior et al., 2018)
Proteus vulgaris	3.3 mg/mL		Inhibitory	Broth microdilution	(Hemaiswarya & Doble, 2009)
Raoultella ornithinlytica	0.4 mg/mL	0.8 mg/mL	Inhibitory, bactericidal	Disc diffusion	(Bandeira-Junior et al., 2018)
Gram positive bacteria					(Wang et al., 2021)
Staphylococcus aureus	0.6 mg/mL	0.7 mg/mL	Inhibitory, bactericidal	Broth microdilution	
Staphylococcus aureus	1.0 mg/mL	2.0 mg/mL	Inhibitory, bactericidal	Broth microdilution	(Orlo et al., 2021)
Staphylococcus aureus	> 0.05 mg/mL		Inhibitory	Broth microdilution	(de Almeida et al., 2019)
Staphylococcus aureus	0.003		Inhibitory	Broth microdilution	(Guimarães et al., 2019)
Listeria monocytogenes	0.625 mg/mL	0.625 mg/mL	Inhibitory, bactericidal	Disc diffusion	(Zhang et al., 2017a)
Listeria monocytogenes	1.0 mg/mL	4.0 mg/mL	Inhibitory, bactericidal	Broth microdilution	(Xue et al., 2021)
Listeria monocytogenes	1.5 mg/mL	1.75 mg/mL	Inhibitory, bactericidal		(Shah et al., 2013)
Listeria monocytogenes	1.024 mg/mL		Inhibitory, anti-biofilm	Broth microdilution	(Liu et al., 2015)
Listeria monocytogenes	1.28 mg/mL		Inhibitory, anti-biofilm	Broth microdilution	(Liu et al., 2020)
Listeria monocytogenes	0.067 mg/mL	0.067 mg/mL	Inhibitory, anti-biofilm	Broth microdilution	(Purkait et al., 2020)
Clostridium perfringens			Inhibition of spore outgrowth		(Alanazi et al., 2018)
Enteroccoccus faecalis	> 0.05 mg/mL		Inhibition	Broth microdilution	(de Almeida et al., 2019)
Enteroccoccus faecalis	3.2 mg/mL		Inhibition	Broth dilution	(Gowda et al., 2021)
Bacillus spp.	0.5 mg/mL	0.68 mg/mL	Inhibitory, bactericidal	Broth microdilution	(Wang et al., 2021)
Streptoccocus mutans		1.6 mg/mL	Bactericidal		(Ribeiro et al., 2018)
Streptoccocus mutans	0.2 mg/mL		Inhibitory, anti-biofilm	Broth dilution	(Jafri et al., 2019)
Mycobacterium kansasii	0.06 mg/mL		Inhibitory	Resazurin microtiter assay	(de Almeida et al., 2019)
Mycobacterium spp.	> 0.25 mg/mL		Inhibitory	Resazurin microtiter assay	(de Almeida et al., 2019)
Fungi					
Candida albicans	0.1–0.4 mg/mL		Inhibitory, anti-biofilm	Broth dilution	(Jafri et al., 2019)
Candida albicans	1.96 mg/mL	3.92 mg/mL	Inhibitory, fungicidal	Broth microdilution	(Dąbrowska et al., 2021)
Candida albicans	0.5 mg/mL		Inhibitory	Broth microdilution	(Ahmad et al., 2015)
Candida krusei	0.12 mg/mL	0.25 mg/mL	Inhibitory, fungicidal	Broth microdilution	(Mandras et al., 2021)
Candida parapsilosis	0.06 mg/mL	0.12 mg/mL	Inhibitory, fungicidal	Broth microdilution	(Mandras et al., 2021)
Candida valida	0.06 mg/mL	0.12 mg/mL	Inhibitory, fungicidal	Broth microdilution	(Mandras et al., 2021)
Candida lusitaniae	0.12 mg/mL	0.12 mg/mL	Inhibitory, fungicidal	Broth microdilution	(Mandras et al., 2021)
Candida norvogensis	0.12 mg/mL	0.12 mg/mL	Inhibitory, fungicidal	Broth microdilution	(Mandras et al., 2021)
Saccharomyces cerevisiae	0.27–0.32 mg/mL		Inhibitory	Broth microdilution	(Darvishi et al., 2013)
Cryptococcus neoformans	0.125 mg/mL	0.5 mg/mL	Inhibitory, fungicidal	Broth microdilution	(Hassanpour et al., 2020)
Cryptococcus neoformans	0.06–0.25 mg/mL		Inhibitory, fungicidal*	Broth microdilution	(Alves et al., 2017)
Cryptococcus gatti	0.06–0.25 mg/mL		Inhibitory, fungicidal*	Broth microdilution	(Alves et al., 2017)

Note: MIC = minimum inhibitory concentration. MBC = minimum bactericidal concentration. QS = Quorum Sensing.
*-Bactericidal and fungicidal activity was assessed by time-kill assay.

concentration (MIC), which refers to the lowest antimicrobial concentration that visibly inhibits the growth of a microorganism. Besides, it may be clinically necessary to determine the minimum bactericidal concentration (MBC), which refers to the lowest antimicrobial concentration that kills 99.9% of bacteria (Orlo et al., 2021). Current studies on the antimicrobial activity and minimum inhibitory or minimum bactericidal concentrations of eugenol against some microorganisms are summarized in Table 1. Gram-negative bacteria are believed to be more resistant to antimicrobial molecules than gram-positive bacteria, due to the presence of additional protection provided by the outer membrane (Guimarães et al., 2019; Wang et al., 2021). However, literature findings have also revealed the high susceptibility of gram-negative bacteria to eugenol, as seen in Table 1. Some of the best bacterial susceptibilities have been observed against *K. pneumoniae* and *S.* Typhmurium (0.002 mg/mL and 0.007 mg/mL, respectively). Best antifungal activities have been observed against *Candida parapsilosis* and *Candida valida* (0.06 mg/mL in both).

4. General characteristics and survival mechanisms of the genus Campylobacter

There are 27 species and 8 subspecies assigned to the genus *Campylobacter* (Ngulukun, 2017). The genus *Campylobacter* are gram-negative, non-spore forming that exist as either curved or spiral shaped rods. Most of the *Campylobacter* species are motile with a single polar flagellum or bipolar flagella exhibiting a characteristic corkscrew-like motion (García-Sánchez et al., 2018). As a microaerophilic and capnophilic microorganism, the *Campylobacter* species require an atmosphere with low oxygen (3–6% O_2) and high CO_2 (2–10%) concentrations for optimal growth *in vitro* (Kaakoush et al., 2015). The temperature required for optimal growth is generally 37 °C, while it is 42 °C for thermophilic *Campylobacter* species (*C. jejuni*, *C. coli*, *C. lari* and *C. upsaliensis*) (García-Sánchez et al., 2018). It is suggested that the growth characteristics at high temperatures are due to adaptation to the avian digestive tract (Hermans et al., 2011). Among the thermophilic species, *C. jejuni* and *C. coli* are responsible for approximately 80–90% of *Campylobacter* infections in humans (European Food Safety Authority & European Center for Disease Prevention and Control, 2017).

The genus *Campylobacter* can neither ferment nor oxidize carbohydrates because they do not have the glycolytic enzyme 6-phosphofructokinase (Silva et al., 2018). Hence, they obtain energy mainly through the oxidation of amino acids or metabolites of the tricarboxylic acid cycle (García-Sánchez et al., 2018). While the genus *Campylobacter* lack lecitinase and lipase activities, catalase activity varies among species (Silva et al., 2018). Of all the thermophilic *Campylobacter* species, only *C. jejuni* can hydrolyze hippurate, thus the hippurate hydrolysis test is used for identification (Silva et al., 2011). Molecular methods such as multiplex-polymerase chain reaction (PCR) and sequencing are also used for identification (Vondrakova et al., 2014).

Some virulence factors encoded by genes associated with motility (*flaA*, *flaB*, *flhA*), chemotaxis (*cheA*, *cheB*, *cheR*, *cheW*, *cheY*, *cheZ*), adhesion (*cadF*, *jlpA*, *docA*, *racR*, *virB11*), invasion (*ciaB*, *ceuE*), toxin production (*cdtA*, *cdtB*, *cdtC*, *wlaN*), iron uptake system (*cfrA*, *fur*) and stress response (*katA*, *sodB*) have been identified for *Campylobacter* isolates (Koolman et al., 2015; Wieczorek et al., 2018; Hassan et al., 2019). Another important virulence factor is the sialylation of lipooligosaccharides (LOS) on the *Campylobacter* cell surface. Sialylated LOS resembles the ganglioside structure and this may cause autoimmune diseases such as Guillain Barre Syndrome (Kaakoush et al., 2015). Although they can develop some adaptive responses to stress factors such as heat, acidity and reactive oxygen species, *Campylobacter* species lack many of the adaptive response mechanisms of other foodborne pathogens (Bolton, 2015). However, *Campylobacter* species can form a biofilm and survive despite environmental stress factors (Wagle et al., 2019c).

5. *In vitro* assessment of the anti-campylobacter activity of eugenol

As seen in Table 1, there is substantial literature on the antimicrobial activity of eugenol against major human pathogens such as *P. aeruginosa*, *E. coli*, *Staphylococcus aureus* and *Candida albicans* (Rathinam et al., 2017; Dhara & Tripathi, 2020; Wang et al., 2021; Dąbrowska et al., 2021). Previous studies have reported the effects of eugenol on targeting microorganism viability as well as modulating various aspects of virulence (Ahmad et al., 2015; Wang et al., 2019). However, the genomic sequence of *C. jejuni* exhibits extreme variability. Remarkably, >8,000*C. jejuni* sequence types had been reported for registration by 2020 (Panzenhagen et al., 2021). *Campylobacter* has a natural ability to develop antimicrobial resistance thanks to its genomic plasticity (Iglesias-Torrens et al., 2018). In the last decade, ciprofloxacin- and tetracycline- resistant *Campylobacter* has been gradually increasing in the European population (European Food Safety Authority & European Center for Disease Prevention and Control, 2017). Recently, essential oils, either alone or in combination, have begun to be evaluated as a new alternative strategy against *Campylobacter* species (Bandeira-Junior et al., 2018; Upadhyay et al., 2017; Grilli et al., 2013), however, the literature data reporting the anti-campylobacter activity of eugenol is quite limited. *In vitro* studies which recorded the anti-campilobacter activity of eugenol, its natural derivatives, and clove oil are listed in Table 2.

Understanding the anti-campylobacter activity of eugenol is possible by determining the MIC value, which is the starting point of the research. Literature findings have indicated that the MIC of eugenol against *Campylobacter* species ranges from 0.05 to 1.28 mg/mL. Various laboratory methods are used to evaluate the *in vitro* activity of antimicrobial compounds. Several methods such as broth or agar dilution, well diffusion and disc diffusion are well known and basic methods (Caballero-Prado et al., 2021; Alves et al., 2017; Wang et al., 2019). It is underlined that the differences in MIC values are related to the laboratory method used in the research (Gahamanyi et al., 2020; Hassan et al., 2019). However, different MIC values of eugenol against *Campylobacter* species have mostly been determined using the broth dilution method (Rossi et al., 2007; Grilli et al., 2013; Kovács et al., 2016a). Dedieu et al. (2020) also found that the MIC value of eugenol was the same (0.25 mg/mL) in both the agar and the broth dilution methods. Possible reasons for differences in MIC values may be inoculum level, incubation time, antimicrobial resistance genes and presence of biofilm. Additionally, it may be clinically necessary to determine the MBC in order to understand the pharmacodynamic characteristic of a antimicrobial compound. If the MBC/MIC ratio is $\leq$ 4, the activity of antimicrobial compounds is considered bactericidal (Hayatgheib et al., 2020). Some researchers have therefore suggested the bactericidal potential of eugenol and clove oil against *Campylobacter* species (Kovács et al., 2016b; Dedieu et al., 2020; Gahamanyi et al., 2020). However, the bactericidal activity of eugenol should be confirmed by further studies using time-kill tests.

C. jejuni isolates have been confirmed as positive for most of the virulence genes associated with motility, adhesion, and invasion, worldwide (Panzenhagen et al., 2021). This probably causes researchers to focus more on *C. jejuni* among *Campylobacter* species in antimicrobial activity studies. The anti-campylobacter activity of eugenol has therefore been studied mostly against *C. jejuni* isolates. Friedman et al. (2002) previously reported that *C. jejuni* strains are highly sensitive to eugenol. The author also noted that eugenol was approximately 13 times more active against *C. jejuni* than isoeugenol, an isomer of eugenol (Friedman et al., 2002). The WHO lists antibiotic-resistant *Campylobacter* as one of the priority pathogens in the development of new treatment strategies (Tacconelli et al., 2018). In a study conducted by Gahamanyi et al. (2020), eugenol was noted to be effective against antibiotic-resistant *C. jejuni*. Some authors have reported synergistic interaction between eugenol and specific antibiotics as a possible strategy (Liu et al., 2015). To our knowledge, the anti-campylobacter activity of eugenol in

Table 2
In vitro studies on the efficacy of eugenol, eugenol derivatives and clove oil against *Campylobacter* spp.

Compound	Strain	Concentration	Key findings	Reference
Eugenol	C. jejuni (S1,S3,S4,S8)	0.0125% v/v	Down-regulation of motility, QS and stress response-related genes expression (↓*motA, motB, katA, luxS*)	(Wagle et al., 2019b)
Chitosan with eugenol	*C. jejuni* (S1,S3,S4,S8)	0.0125% v/v	Down-regulation of QS and stress response-related genes expression. Up-regulation of motility and adhesion-related genes expression (↓*katA, luxS*. ↑*cetA, jlpA*)	(Wagle et al., 2019b)
Eugenol	*C. jejuni* (S8)	0.01% v/v	Reducing the zone of motility, ability of adhesion and invasion into Caco-2 cells, cytotoxicity of Caco-2 cells by the pathogen. Down-regulation of colonization-related gene (↓ *racR)*	(Upadhyay et al., 2017)
Eugenol	*C. jejuni* (NCTC 11168)	0.01% v/v	Reducing the zone of motility, ability of adhesion and invasion into Caco-2 cells, cytotoxicity of Caco-2 cells by the pathogen Down-regulation of motility and cytotoxin production-related genes (↓*motA, cdtA*)	(Upadhyay et al., 2017)
Eugenol	*C. jejuni* (81–176)	0.01% v/v	Reducing the zone of motility, ability of adhesion and invasion into Caco-2 cells	(Upadhyay et al., 2017)
Eugenol	*C. jejuni* (106Cg,74Ctm,52Ccp,33Ccs)	0.062–0.125 mg/mL	Inhibition of bacterial invasion into chicken intestinal epithelial cells. Down-regulation of critical virulence genes (↓ *flaA, virB11, wlaN*)	(Ammar et al., 2020)
Eugenol	*C. jejuni* wild-type isolates	10, 20, 30 mM (corresponds to 0.17, 0.34, 0.5% v/v)	Bacterial load in chicken cecal contents inoculated with 10^5 CFU/mL was reduced to an undetectable level by eugenol treatment at 24 h	(Kollanoor-Johny et al., 2010)
Eugenol	*C. jejuni* (NCTC 11168)	15.22, 30.45, 60.90 mM (corresponds to 0.25, 0.50, 1.0% v/v)	Reducing the biofilm formation and inactivating the mature biofilms on polystyrene plates and stainless-steel coupons at 20 and 37 °C. Down-regulation of several genes critical for biofilm formation at SIC level (↓*flaA, flaB, flaG, flgA waaF, cosR, ahpC, luxS*) [SIC: 0.1 mg/mL, MBC:0.3 mg/mL]	(Wagle et al., 2019c)
Eugenol	*C. jejuni* (ATCC 33560, MT947450)		Inhibitory, bactericidal [MIC:0.05 mg/mL, MBC: 0.1 mg/mL]	(Gahamanyi et al., 2020)
Eugenol	*C. coli* (ATCC 33559, MT947451)		Inhibitory, bactericidal [MIC:0.1 mg/mL, MBC: 0.2 mg/mL]	(Gahamanyi et al., 2020)
Clove oil	*C. jejuni* (ATCC 33560, MT947450)		Inhibitory, bactericidal [MIC:0.05 mg/mL, MBC: 0.1 mg/mL]	(Gahamanyi et al., 2020)
Clove oil	*C. coli* (ATCC 33559, MT947451)		Inhibitory, bactericidal [MIC:0.1 mg/mL, MBC: 0.4 mg/mL]	(Gahamanyi et al., 2020)
Clove oil	*C. jejuni* (NCTC 11168, 81168, 81–176, RM1221)	0.025–6.4 mg/mL	Reducing the zone of motility at 0.33 mg/mL. Up-regulation of stress response-related genes expression. Down-regulation of flagellar secretion system and lipooligosaccharide production-related genes (↑*katA, groEL, groES, dnaK, fliA*. ↓*galE, flhB, porA*) [MIC:0.2 mg/mL, MBC:0.8 mg/mL]	(Kovács et al., 2016a)
Isoeugenol, Eugenol	*C. jejuni* (F38011, 81–176, 96C208,81176 CmeB-,96C208 CmeB-)		Inhibitory, Bactericidal [MIC:0.125 and 0.25 mg/mL for isoeugenol and eugenol respectively, MBC:0.25 mg/mL for both molecules]	(Dedieu et al., 2020)
Eugenol	*C. jejuni* mapA, C. coli ceuE		Inhibitory [MIC:0.5 mg/mL]	(Hassan et al., 2019)
Eugenol	*C. jejuni* (RM1046, RM1221, RM1230, RM1274)		Bactericidal [BA50:0.011–0.02% v/v]	(Friedman et al., 2002)
Eugenol	*C. jejuni* (ATCC 33291, 923/2010)	0.49–125 mM	Inhibitory [MIC:1.28 mg/mL (7.81 mM)]	(Grilli et al., 2013)
Clove oil	*C. jejuni* (NCTC 11168, 81–176, 2006–68)	0.25–128 μl/mL	Inhibitory and bactericidal [MIC:0.2 mg/mL, MBC:0.8 mg/mL]	(KKovács et al., 2016b)
Methylisoeugenol, Isoeugenol	*C. jejuni* (NCTC 11168)	0.03–1.0 mg/mL	Inhibitory [MIC:0.125 mg/mL]	(Rossi et al., 2007)
Methyleugenol, Eugenol	*C. jejuni* (NCTC 11168)	0.03–1.0 mg/mL	Inhibitory [MIC:0.25 mg/mL]	(Rossi et al., 2007)

Note: MIC = minimum inhibitory concentration, SIC: sub-inhibitory concentration, MBC = minimum bactericidal concentration, BA50: 50% of bactericidal activity, QS = quorum sensing.

combination with antibiotics has not been evaluated to date.

There is a strong correlation between *C. jejuni* strains isolated from broiler meat and *C. jejuni* strains isolated from campylobacteriosis patients (Duarte et al., 2019). Reducing colonization and invasion of the poultry digestive tract is critical to avoid contamination of poultry meat in hopes of thereby reducing human campylobacteriosis cases (Hermans et al., 2011). Eugenol has been reported to reduce *C. jejuni* colonization (<1 log CFU/mL) in the chicken digestive tract (Kollanoor-Johny et al., 2010). Ammar et al. (2020) reported that eugenol reduced the invasion of multi drug-resistant *C. jejuni* isolates into chicken intestinal cells by 29.16–31.94%. Human campylobacteriosis can be potentially controlled by reducing the adhesion and invasion of *C. jejuni* to intestinal epithelial cells. Upadhyay et al. (2017) reported that eugenol could limit the adhesion, invasion and colonization of *C. jejuni* to human intestinal epithelial cells (Caco-2) by decreasing the expression of virulence genes such as *motA*, *cdtA*, *racR*. Cell surface modifications, stress response and communication mechanisms between bacteria (quorum sensing) are prominent for maturation and biofilm formation in *C. jejuni* (Wagle et al., 2019b). Remarkably, critical genes associated with maturation, biofilm formation (*flaA*, *flaB*, *flaG*, *flgA*, *waaF*, *cosR*, *ahpC*) and quorum sensing (luxS) have been reported to be downregulated by eugenol treatment (Wagle et al., 2019c). However, further studies are needed to shed some light on the efficacy of eugenol on *C. jejuni* virulence factors.

6. Application problems of eugenol in the poultry meat food model

The antimicrobial activity of eugenol has mostly been determined *in vitro* using model broth systems. However, there is a need for identification and validation of specific applications of eugenol as a natural preservative to improve food safety. Intrinsic factors such as the fat, protein, water, salt and, antioxidant content of foods, as well as extrinsic

determinants such as packaging, temperature and, storage time can affect microbial susceptibility (Shaaban, 2020). For example, high fat and reduced water content in foods can limit the activity of essential oils against some microorganisms, as suggested by Burt (2004). As reported in the literature, the antimicrobial activity of essential oils is generally reduced by 30 to 100-fold in food model systems compared to *in vitro* systems (Siddiqua et al., 2015). The fact that nutrient content in foods are richer than microbiological media may favor the recovery of microorganisms (Burt, 2004). Conversely, the activity of several essential oils such as oregano, thyme and clove oil in the lettuce model was 10 times higher than that of broth media in the study conducted by Gutierrez et al. (2009). The authors believe that this finding is the result of the rich nutrient content of the broth media compared to lettuce media. Additionally, the antimicrobial activity of some essential oils may also differ among different types of food models. This may be the result of chemical bonding and intermolecular interactions between essential oil components and complex compounds such as phospholipids and whey proteins present in the matrix of some foods (Dehkordi et al., 2019).

It is known that essential oils containing lipophilic and volatile components are very sensitive to environmental factors such as heat, light, and oxygen, and therefore can easily degrade during storage. The degradation reactions reduce the antimicrobial activity of essential oils in the food system and it can also negatively affect the organoleptic properties of foods by causing discoloration and off-flavors (Cetin-Babaoglu et al., 2017; Siddiqua et al., 2015). Wagle et al. (2019b) observed that eugenol application (0.5, 1.0 and 2.0%) did not affect the lightness and redness of raw chicken wings. However, the authors underlined that refrigeration time (from 0 day through 7 days) has a significant effect on the yellowness of chicken wings treated with eugenol. Khare et al. (2014) reported that eugenol added to chicken noodles (0.1 g/100 g) uniquely reduced lipid oxidation and microbial growth. The authors also underlined that chicken noodles with added eugenol result in an odour more acceptable to consumers during storage compared to the untreated control. A preliminary sensory study by Mytle et al. (2006) established greater consumer acceptability of the sensory properties of clove oil at low concentration (1.0 v/v) compared to higher concentration (2.0 v/v) in chicken frankfurters. It is therefore crucial to increase the antimicrobial activity without significantly altering the sensory properties of the food.

Recently, researchers have focused on nanoparticles and nanoemulsions as a delivery vehicles to increase the antimicrobial activity of eugenol or clove oil and minimize their sensory properties in food systems. Findings from the literature have suggested that eugenol-loaded nanoparticles offer excellent chemical stability and antimicrobial activity potential (Wang et al., 2021; Oluoch et al., 2021; Xue et al., 2021). Similarly, clove/cinnamon essential oil nanoemulsion has exhibited higher antimicrobial activity against some foodborne pathogens such as *E. coli* and *S.* Typhimurium comparing to pure essential oils in the study of Zhang et al. (2017b). The authors also noted that the main flavor substances in a mushroom sauce to which nanoemulsion was added were similar compared to the untreated control group. However, the findings of Wagle et al. (2019a) suggested that eugenol nanoemulsions showed no additional activity on *C. jejuni* load and organoleptic properties when compared with the same dose of eugenol suspension (2.0% v/v) in chicken skin. Conflicting results regarding the efficacy of nanoemulsion may be related to emulsion characterization, essential oil and pathogen microorganism type (Ozogul et al., 2020).

Further to the above mentioned applications, new active packaging materials have recently been developed as a method of extending the shelf life of poultry meat. In this context, eugenol-loaded low density polyethylene (LDPE) film and eugenol grafted paper are considered a remarkable potential material for active packaging applications (Goni et al., 2016; Muratore et al., 2018). The instability of eugenol may reduce the effectiveness of active packaging applications and, nanotechnology based coatings are being attempted to avoid this issue when incorporating eugenol or clove oil into food packaging (Liu et al., 2021). Active packaging has the potential to be an outstanding alternative for the food industry, however, EU regulations on active packaging for food industry applications still have limitations (European Comission, 2009).

7. Antimicrobial and anti-campylobacter activity of eugenol applications in poultry meat

Poultry meat is one of the most perishable foods and has therefore a limited shelf life after harvest. Contamination of poultry meat with foodborne pathogens is a major concern and it is crucial to develop intervention strategies throughout the poultry meat chain to ensure food safety. Intervention strategies to ensure poultry meat safety generally target *Salmonella* and *Campylobacter* spp. (European Food Safety Authority & European Center for Disease Prevention and Control, 2017). The application of natural compounds such as essential oils to foods as a novel intervention strategy has attracted great interest from researchers. Eugenol, the main component of clove oil, is one of the most investigated natural compound for its significant antimicrobial activity. The efficacy of eugenol applications in the poultry meat model has been noted by recent studies, in addition to findings from *in vitro* studies (Alanazi et al., 2018; López-Romero et al., 2018; Nair et al., 2014). Besides eugenol, the activity of eugenol derivatives was evaluated against foodborne pathogens (Friedman et al., 2002; Hyldgaard et al., 2015). Despite limited actual data, the antimicrobial activity of eugenol, its natural derivatives and clove oil in poultry meat is summarized in Table 3.

Application methods of eugenol and clove oil in poultry meat model are mainly direct incorporation to a foods surface, synthetic or natural films and coating for active packaging as seen in Table 3. Antimicrobial activity of eugenol as a dip treatment for 1 min on *Salmonella*-inoculated turkey breast cutlets was evaluated by Nair et al (2014). The authors reported that eugenol treatments resulted in 0.7, 1.1, and 1.0 log CFU/g reductions of *Salmonella* at 1.0, 2.0, and 5.0% concentrations. Similar activity against Enterobacteriaceae and *Pseudomonas* spp. in chicken breast fillets stored for 13 days was also demonstrated by whey-based edible film incorporated with clove oil (Fernández-Pan et al., 2014). Both eugenol and clove oil can be incorporated with various natural polymers such as pectin, chitosan and synthetic polymers such as polyethylene to create stable films. Wagle et al. (2019b) reported that chitosan- and pectin-based edible film incorporating 2% eugenol reduced *C. jejuni* load by 3 log and 2 log CFU/sample in chicken wingettes stored at 4 °C for 7 days. The authors also suggested that a eugenol-chitosan combination significantly downregulated the expression of select genes encoding motility (*motA*) stress response (*katA*) and quorum sensing (*luxS*) in *C. jejuni*, thereby potentially limiting the survival of the bacteria in poultry. Additionally, clove oil infused into LDPE film as an active packaging has found effective against *S.* Typhimurium and *L. monocytogenes* in ground chicken for 21 days (Mulla et al., 2017). Literature findings have demonstrated the preservative potential of edible and active packaging as promising systems for poultry meat. However, more studies are needed to clarify the antimicrobial and anti-campylobacter activity of eugenol in poultry meat.

8. Toxicity and safety of eugenol

Despite all its significant biological activity, there are some *in vitro* studies focusing on eugenol toxicity. For instance, 1 mM eugenol exhibited a hepatotoxic effect during the 5-hours incubation period (Thompson et al., 1991). Absalan et al. (2016) found that 1 μg/mL eugenol had a significant cytotoxic effect in human adipose-derived mesenchymal stem cells. Similarly, cytotoxic effects on fibroblast MCR-5 strain were reported with 295.71 μg/mL eugenol treatment (Houdkova et al., 2017). There is to date no clinical study on the toxic effect of eugenol in humans, only a few case reports of acute toxicity in

Table 3
Antimicrobial activity of eugenol, eugenol derivatives and clove oil in poultry meat models.

Application	Source	Concentration	Species	Effects	Reference
Eugenol wash treatment	Chicken skin	2.0% (121.8 mM)	*C. jejuni*	> 2 log CFU/sample reduction for each application at 24 h (suspension, emulsion and nano-emulsion)	(Wagle et al., 2019a)
Eugenol coating with chitosan	Chicken wingettes	0.5, 1.0, 2.0%	*C. jejuni*	1–3 log CFU/sample reduction in bacterial load at 7 days in a dose-dependent manner	(Wagle et al., 2019b)
Eugenol coating with pectin	Chicken wingettes	0.5, 1.0, 2.0%	*C. jejuni*	1–2 log CFU/sample reduction in bacterial load at 7 days in a dose-dependent manner	(Wagle et al., 2019b)
Vacuum sealing with eugenol	Ground chicken meat	0.5, 1.0, 1,5, 2.0%	*Salmonella* spp.	Observed decimal reduction time (D-values) at 60 °C were 0.71 and 2.83 min in samples with added 1% of eugenol and without eugenol	(López-Romero et al., 2018)
Eugenol dip treatment	Turkey breast cutlets	0.5, 1.0. 2.0. 5.0%	*Salmonella* spp.	0.7, 1.1 and 1.0 log CFU/g reduction at 1.0%, 2.0% and 5.0% concentrations in bacterial load at 24 h	(Nair et al., 2014)
Incubation with isoeugenol	Turkey breast fillets	1.78 mg/mL (2xMIC)		No overall change in predominant microbiota or species diversity at 96 h in the food samples inoculated with *P. putida*.	(Hyldgaard et al., 2015)
Whey-based edible film incorporated with clove oil	Chicken breast fillets	10, 20 g/kg	*Pseudomonas* spp. Enterobacteriaceae	> 1 log CFU/g reduction in samples incorporated with 20 g/kg clove oil at 13 days.	(Fernández-Pan et al., 2014)
LLDPE film impregnated with clove oil	Minced chicken meat	0.5 g	*S.* Typhimurium *L. monocytogenes*	Significant growth inhibition was observed on day 5 of refrigerated storage and no further growth was detected during the 21 day storage period	(Mulla et al., 2017)
Cellulose-based film containing clove oil	Ground chicken meat	1.0, 2.0, 3.0%	*S. aureus, Bacillus cereus*	3–4 log CFU/g reduction in initial bacterial load of samples packaged with active film containing 3% clove oil in 7 days. Up to an additional 8 days increase in shelf life of samples packaged with active film.	(Muppalla et al., 2014)

Note: LLDPE = linear low density polyethylene.

the liver and nervous system after accidental ingestion of eugenol (Brown et al., 1992; Janes et al., 2005). However, some case reports have noted eugenol-related adverse effects including aphthous stomatitis, contact dermatitis, and burning mouth syndrome (Navarro-Triviño et al., 2019; White et al., 1999). Basically, current reports of toxicity and adverse effect are associated with high concentration.

Despite some concern about the carcinogenic potential of eugenol, there is limited evidence for carcinogenicity. Jaganathan et al. (2011) on the contrary reported that the growth of colon cancer cells (HCT-15 and HT-29) was significantly suppressed by 300 and 500 μM eugenol, respectively. Further, cell division arrest and apoptosis occurred in malignant melanoma cells with 0.5–2.5 μM eugenol treatment for 18 h (Ghosh et al., 2005). The International Agency for Research on Cancer (IARC) has listed eugenol as ''group 3 (not classifiable as to its carcinogenicity to humans)'' based on the evidence from animal studies (Sellamuthu, 2014). Eugenol has been approved by the FDA as "generally recognized as safe (GRAS)" and can be used as a food additive (Food and Drug Administration, 2002). Eugenol has also been approved as an active substance to be used in the formulation of plant protection products (European Food Safety Authority, 2016). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has proven that the maximum allowable daily intake of eugenol or clove oil for humans is 2.5 mg/kg body weight (Ulanowska & Olas, 2021).

9. Conclusion and future perspectives

Today, *C. jejuni* is the most common bacterial cause of gastroenteritis, which is the primary cause of foodborne deaths. Poultry meat is one of the most perishable foods and is responsible for approximately a quarter of foodborne illnesses. It is estimated that intervention strategies in poultry meat would significantly reduce foodborne illness and death worldwide. Despite significant progress in food safety, the genus *Campylobacter* remain common foodborne pathogens in poultry, and are thus a target for the development of intervention strategies. Eugenol is one of the promising natural preservatives emerging as an alternative approach to existing chemical antimicrobials in order to enhance the quality and safety of foods. Although eugenol exhibits high antimicrobial activity, some limitations of eugenol application have also been identified in poultry meat; namely that the structure of the food matrix and storage conditions may reduce the protection potential of eugenol. Furthermore, the application of eugenol in high concentrations can adversely affect the sensory properties of foods. However, novel nanotechnology based approaches and active packaging systems may be an effective strategy to improve the sensory quality and safety of poultry meat. Additionally, the investigation of advanced extraction technologies evaluating the bioactivity and yield of eugenol may provide a basis for specific applications of eugenol in the meat industry. Eugenol has significant potential to control foodborne outbreaks by reducing the *Campylobacter* load in the production process of poultry meat. Despite its promising bioactive nature, further investigations should focus more on the anti-campylobacter activity of eugenol and its protective potential in poultry meat.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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