CAMPYLOBACTER AS A MAJOR FOODBORNE PATHOGEN: A REVIEW OF ITS CHARACTERISTICS, PATHOGENESIS, ANTIMICROBIAL RESISTANCE AND CONTROL

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ABSTRACT

Campylobacter, mainly Campylobacter jejuni is viewed as one of the most well-known reasons of foodborne bacterial diarrheal sickness in people around the globe. The genus Campylobacter contains 39 species (spp.) and 16 sub spp. Campylobacter is microaerophilic, Gram negative, spiral-shaped rod with characteristic corkscrew motility. It is colonizing the digestive system of numerous wild and household animals and birds, particularly chickens. Intestinal colonization brings about transporter/carrier healthy animals. Consequently, the utilization of contaminated meat, especially chicken meat is the primary source of campylobacteriosis in humans and chickens are responsible for an expected 80% of human campylobacter infection. Interestingly, in contrast with the most recent published reviews that cover specific aspects of campylobacter/campylobacteriosis, this review targets the taxonomy, biological characteristics, identification and habitat of Campylobacter spp. Moreover, it discusses the pathogenesis, resistance to antimicrobial agents and public health significance of Campylobacter spp. Finally, it focuses on the phytochemicals as intervention strategies used to reduce Campylobacter spp.in poultry production.

Keywords: Campylobacter, Campylobacter jejuni, foodborne, campylobacteriosis, poultry, phytochemicals, virulence

INTRODUCTION

Attention to the public health significance of Campylobacter infection has advanced over a century. Campylobacteriosis of extraordinary general wellbeing significance is Campylobacter enteritis caused mainly by Campylobacter jejuni (C. jejuni) and Campylobacter coli (C. coli), but to a lesser extent (Goni et al. 2017 and Garcia-Sánchez et al. 2018). C. jejuni has become the most common recognized reason of foodborne bacterial gastroenteritis in people in developed countries (EFSA-ECDC, 2009; CDC, 2014 and Whitehouse et al. 2018). Campylobacteriosis is a self-limited disease and antimicrobial treatment is not indicated for the most part. Notwithstanding, under explicit clinical conditions antimicrobial treatment might be fundamental, but treatment might be convoluted because the development of antimicrobial resistant Campylobacter strains as a result of the common utilization of antimicrobial agents in agriculture and veterinary medicine (Goni, 2018 and Silva et al. 2018a).

For the consumer’s safety, it is important to characterize the pathogenicity markers in strains that are recognized in food. C. jejuni has a few putative virulence genes, which have perceived to be liable for the pathogenicity expression (Bolton, 2015 and García-Sánchez et al. 2018).

Genotyping of Campylobacter spp. has been developed for studying the genetic variety and the link between the isolates from various origins to control human or animal health problems (Malakauskas et al. 2017).

Chickens are recognized as the primary reservoir of thermotolerant Campylobacter spp. and they are the main source of human campylobacter infection. Therefore, intervention procedures for controlling Campylobacter in chickens have been created to diminish product contamination and subsequently the rate of Campylobacter diseases in human (Upadhyay et al. 2019). With expanding the consumer requests for safe and natural products with negligible preservatives, important researches are being conducted to investigate the capability of natural antimicrobials for example, phytochemicals for controlling C. jejuni in chickens (Wagle et al. 2017a and Wagle et al. 2019). Thus, this review shed light on all important issues related to Campylobacter spp. including (i) the history, taxonomy and biological characteristics (ii) isolation, identification and natural habitat (iii) pathogenesis, virulence factors and resistance to antimicrobial agents and (iv) public health significance of Campylobacter spp. and (v) phytochemicals as intervention strategies used to reduce Campylobacter in poultry production.

HISTORICAL EMERGENCE OF CAMPYLOBACTER SPECIES

The genus Campylobacter comprises a huge and various group of bacteria. In 1886, Campylobacter was primary documented by Theodor Escherich which stated the appearance of nonculturable helical-shaped bacteria in smears of the mucosa of the large intestine related with diarrhea in children de nauseated of what he called "Cholera infantum”. The primary isolation of campylobacters (a vibrio-like bacterium) was made from the uterus of aborted sheep in 1906 (Kist, 1986). In 1912, a similar pathogen was isolated from fetus of aborted cow and called Vibrio fetus (Smith and Taylor, 1919). Fifteen years later, another vibrio pathogen was found in faeces of cattle suffering from diarrhea and later called Vibrio jejuni (Jones et al. 1931). In 1944, Vibrio coli was isolated from diarrheic pigs (Doyle, 1948).

Campylobacter was considered as a cause of animal illness for over 40 years, except only in 1938 when Campylobacter spp. were incriminated in foodborne disease outbreak. A Vibrio jejuni like pathogen was detected in the blood of 13 victims of an outbreak due to the ingestion of contaminated milk and this outbreak caused acute diarrheal illness in 357 inmates in Illinois state institutions in the United States (Levy, 1946).

In 1963, due to their specific characteristics for example low DNA base composition (low G+C content), microaerophilic development and nonfermentative metabolism, these microorganisms were moved into the recently made genus Campylobacter to recognize these bacteria from the Vibrio spp. (Sehald and Veron, 1963 and Silva et al. 2011). The genus's name means bended/ curved which derived from the Greek expression "kampyo’s” (Keener et al. 2004 and Silva et al. 2018a).

The first proper description of the genus Campylobacter was given by the American bacteriologist Elisabeth King, which was committed to find the proper techniques to isolate these bacteria from faeces because she believed that the prevalence of Campylobacter was more than the few reported cases (Butzler, 2004 and García-Sánchez et al. 2018).

In the early 1970s, a special filtration method was developed for identification of Campylobacter in veterinary medicine, which allowed Butzler to detect these
bacteria from stools of human patients suffering from high body temperature and diarrhea (Butzler et al. 1973). But, the primary advance toward the isolation of Campylobacter was accomplished by incorporation of specific antimicrobial agents to the basal media including trimethoprim, polymyxin B and vancomycin (Skirrow, 1977).

In 1973, a detailed research on the microaerophilic vibrio-like organism's taxonomy was done by Veron and Chatelain and they found that the genus Campylobacter had 4 separate spp. including C. coli, C. sporum, C. fetus and C. jejuni (Veron and Chatelain, 1973). Just during the following years subsequent to its primary detection, C. jejuni was recognized as one of the most well-known reasons of foodborne bacterial enteritis in human worldwide (García-Sánchez et al. 2018).

**NOMENCLATURE AND CLASSIFICATION OF CAMPYLOBACTER SPECIES**

The genus Campylobacter has a place within the phylum Proteobacteria, the class Epsilonproteobacteria, the order Campylobacteridae and the family Campylobacteraceae. The genus Campylobacter taxonomy is in continues variation from its origin because of the re-classification of certain spp. into different genera or the discovery of new spp. (Silva et al 2018a).

As of now, the genus Campylobacter contains at least 39 spp. and 16 sub spp. with valid published names (http://www.bacterio.net/campylobacter.html, accessed 08 August 2019). Twelve spp. of the genus Campylobacter are viewed as pathogenic bacteria such as C. lari, C. curvus, C. coli, C. concisus, C. fetus, C. upsalensis and C. jejuni. Disease caused by Campylobacter might cause gastroenteritis; but, C. jejuni has additionally been incriminated in systemic infections (Bhunia, 2018). C. coli and C. jejuni subsp. jejuni are commonly related to human campylobacteriosis representing up to 90% of the outbreaks and sporadic campylobacteriosis cases (Debruyne et al. 2008; Llarena, 2015 and Llarena et al. 2015).

Additionally, C. jejuni consists of 2 sub spp.; C. jejuni subsp Doyley and C. jejuni subsp jejuni. However, the C. jejuni subsp doylei pathogenic role is unknown yet, but it was detected in blood samples of infected children (Llarena, 2015 and Llarena et al. 2015). These two sub spp. varies biochemically and they can be differentiated by polymerase chain reactions (PCR) on the basis of the nitrates reductase (nap) locus (napA and napB genes), where C. jejuni subsp Doyley strains contains napA deletions of 2761 bp (Miller et al. 2007 and García-Sánchez et al. 2018). C. jejuni sub spp. jejuni will hereafter be referred to as C. jejuni.

A system for typing Campylobacter spp. depending on the heat-stable lipopolysaccharide (LPS) O-antigenic components has differentiated C. coli, C. lari and C. jejuni into 60 serotypes, although another typing system dependent on heat-labile antigen has detected 100 serotypes of these bacteria (Bhunia, 2018). Moreover, Miller and Parker reported that C. lari, C. upsalensis, C. jejuni and C. coli are related genetically and are referred to as the thermotolerant campylobacters, due to their growth at 42°C. These four Campylobacter spp. considered the principle spp. of public health and clinical significance. The remaining spp. of the genus Campylobacter form 3 general groups: (1) spp. that have not been associated with human disease and are not detected in water or food, (2) C. jejuni spp. that have been incriminated with children and human diseases (e.g. C. shewae, C. rectus, C. curvus and C. concisus) and (3) spp. that have been associated with disease in livestock animals and infrequently causes human illness (e.g. C. sporum, C. fetus and C. homintestinalis) (Miller and Parker, 2011 and Fitzgerald, 2015).

Among the genus Campylobacter, C. iguanidum, C. corriganii, C. tropidostis, C. volucris, C. avium, C. canadenesi, C. subantaeutesicus and C. cuniculorum are the only spp. that didn’t cause animals or human diseases yet (Fitzgerald, 2015).

**MOLECULAR TAXONOMY OF CAMPYLOBACTER SPECIES**

In 1980, several studies have reported that the gold standard technique for delineation of the bacterial spp. is the whole-genome DNA-DNA hybridization. In 1980, the bacterial phylogeny has been studied depending on the degree of the ribosomal genes’ similarities. The bacterial classification schemes have been developed, revised and became more popular (Debruyne et al. 2008).

In 1990, DNA sequencing became more common, therefore the molecular taxonomy researches and the molecular diagnosis of the bacteria including members of the genus Campylobacter have been increasingly used basing on the sequence similarity of 16S rDNA gene (Debruyne et al. 2008 and Whitehouse et al. 2018).

The most common regions of DNA used for classification and differentiation of the bacteria such as Campylobacter spp. are the ribosomal genes, mainly 16S rDNA (Linton et al. 1996). However, because of similarity in Campylobacter spp. sequences, the 16S rDNA gene sequence cannot be used for differentiation of genetically related spp. included C. coli and C. jejuni (On, 2001). Furthermore, the cost of whole-genome sequencing cost due to the advancement of many next-generation sequencing (NGS) techniques, which lead to the development of more robust phylogenetic trees by the whole-genome sequencing (WGS) utilization. Generally, for most of the published researches; the phylogenetic trees dependent on the 16S rDNA sequences correlate with the whole-genome spp. trees (Whitehouse et al. 2018).

**BIOLGICAL CHARACTERISTICS OF CAMPYLOBACTER SPECIES**

Phenotypic and biochemical criteria of Campylobacter species

The members of genus Campylobacter are non-sporulating, forming, small, slender, slightly curved Gram-negative bacilli. The size of a Campylobacter bacterium is 0.2–0.9 μm in width and 0.5 to 5.0 μm in length. Campylobacter could be present in chains or in pairs, showing up as gull-winged or S- shape appearance. The gull-wing gives them a darting motility. The motility of the genus Campylobacter is distinctively fast and darting in corank screw appearance when seen by phase-contrast microscopy because of the existence of solitary or branched polar flagella at one or both ends of the bacterial cell. Among every single known spp., C. gracilis is the only nonmotile spp., while C. showae shows up as straight bacilli due to the appearance of numerous flagella (Goni et al. 2017 and Silva et al 2018a).

Campylobacter spp. are successful foodborne bacteria and they require complex growth requirements which make them quite fastidious microorganisms (Bhunia, 2018). Campylobacters are mainly microaerophilic and they need limited oxygen, but these bacteria can be killed by normal atmospheric levels of oxygen (approximately 20%). These criteria lead to difficult diagnosis of campylobacteriosis cases (Hu and Kopecko, 2018). Moreover, C. jejuni is the most well-known of the genus due to the appearance of numerous flagella (Hu and Kopecko, 2018). Twelve spp. of the genus Campylobacter is the microphagelos of species of 3–10% CO₂, 3–15% O₂ and 85% N₂ (Goni et al. 2017). However, some spp. (C. rectus, C. concisus and C. curvus) favor anaerobic states for development (Kaaoksh et al. 2015 and García-Sánchez et al. 2018).

All campylobacters develop at 37°C and cannot develop under 30°C, but thermophilic campylobacters comprise C. lari, C. coli, C. upsalensis and C. jejuni can develop at 42°C. The ideal pH for the development of Campylobacter spp. is 5.5 - 8.0, while pH values over 9 and beneath 5 are deadly for the bacterium (Silva et al 2018b).

Campylobacter cannot ferment or oxidize sugars for energy, but instead it utilizes amino acids and tricarboxylic acid cycle (TCA) intermediates and it is resistance to bile (Llarena, 2015 and Llarena et al. 2015).

The thermophilic campylobacters reduce selenite, are oxidase positive and indole-negative. When exposed to urease test, thermophilic campylobacters are negative except for C. lari. Thermophilic campylobacters are cathylase positive except for C. upsulensis (Kaaoksh et al. 2017).

Campylobacter spp. identification is difficult because of the fastidious development requirements and metabolic inactivity. The hydrolysis of sodium hippurate is a biochemical technique routinely utilized in discrimination between C. coli and C. jejuni. Even though, some strains of C. jejuni can give negative responses, C. jejuni can hydrolyze sodium hippurate, but C. coli cannot hydrolyze the hippurate. Lately, molecular discrimination for example multiplex PCR is additionally needed to recognize Campylobacter spp. on the basis of variant genes (Vondrakova et al 2014 and García-Sánchez et al. 2018).

**Physiology of Campylobacter species**

Campylobacter spp. can be killed by high temperatures reached in frying, cooking and pasteurization, but they can survive in sun-sheltered moist environment at 4°C (Llarena, 2015 and Llarena et al. 2015). Moreover, these bacteria can survive for many weeks at 4°C in water, but they survive at temperatures more than 15°C for only a few days. Campylobacters can survive at 20°C for 2-5 months, but they can suffer from a great fall in the number of viable bacteria due to thawing and freezing. Some spp. of the genus Campylobacter can survive in uncooked, salted meat if the primary contamination level due to their ability to survive at 4°C for several weeks in 2% sodium chloride solution (Hu and Kopecko, 2018). Campylobacters don’t have gene for cold shock protein, so they can't survive at temperatures below 30°C. Additionally, they cannot survive in water activity below 0.987 (Faciolia et al. 2017). In spite of the disappearance of cold shock gene in C. jejuni isolates, these bacteria can survive and form biofilms at 13°C with the largest surface area in comparison with those formed at 42°, 37° and 20°C (Mielich et al. 2019).

Campylobacter spp. are more liable to be affected with stress conditions including radiation, disinfectants, acidity, freezing, heat, desiccation and drying than other pathogenic foodborne bacteria. This finding suggests that Campylobacter spp. are survived better in vivo than in vitro (Silva et al 2018a).

The idea jejuni can survive under extreme environmental and aerobic conditions due to biofilm production, which facilitate its spread in the environment of food production and antimicrobial resistance (Platts-mills and Kosek, 2014 and Silva et al 2018b).

Under prolonged cultivation and during stress conditions, C. jejuni can transform from a vegetative cell to a prespore that is viable but nonculturable (VBNC) form. Pre-enrichment as well as microaerobic growth condition and adding oxygen-quinquening agents to
the growth media such as charcoal and hemin can improve the recovery of Campylobacter spp. (Hu and Kopecko, 2018).

**NATURAL HABITAT OF CAMPYLOBACTER SPECIES**

Campylobacter spp. are commonly found in the gut of different domestic animals for example, swine, sheep, cattle, cats and dogs and also the poultry caecum. Avian spp. especially, poultry has become the most well-known reservoir of Campylobacter spp. as a result of their high body temperature and they are responsible for more than half of human Campylobacteriosis, due to the human's hygienic practices during milking which can result in milk fecal contamination. The Campylobacter incidence in dairy cow may be seasonal with a summer peak, while human Campylobacter infection outbreaks because of the contaminated milk consumption increases in the spring and fall (Elango et al. 2012 and Mungai et al. 2015).

Additionally, defrosting and storing chickens without hygienic precautions may increase the cross-contamination between foods by contact with dripping water from the defrosted meat (FSA, 2012; Hue et al. 2010 and Silva et al. 2018b).

Interestingly, unpasteurized milk is another potential vehicle for human infection when raw milk is typically refrigerated at

**Thermotolerant Campylobacter spp. (C. lari, C. jejuni and C. coli)** are linked to the chicken intestine and to illness due to contaminated food, but in relation to the public health importance C. jejuni is believed to be the predominant spp. (Cea et al. 2015 and Ugarte-Ruiz et al. 2018).

Few researches have reported that C. jejuni colonization of chicken intestinal tract may cause negative health implications. Therefore, Campylobacter is considered a commensal microorganism in the poultry intestine (Thibodeau et al. 2015 and Abd El Hamid et al. 2019). Human campylobacteriosis can be caused by ingestion of raw or undercooked chicken meat contaminated with only few Campylobacter cells. The high genetic diversity and the wide range of hosts of Campylobacter spp. are making the attribution and tracing of the original source of infection difficult (Götz et al. 2014 and Sharph et al. 2016).

Campylobacter spp. might be transmitted to humans by utilizing food and water contaminated with these pathogens, by handling, or by coming in contact with carrier animals (fecal-oral way). Household pets are another possible transmission method for Campylobacter infection (Pintar et al. 2015). Despite the few studies available on the incidence of Campylobacter spp. in cats and dogs, these animals can be reservoir of several Campylobacter spp. such as C. houae, C. mucosalis, C. helveticus, C. lari, C. upsaliensis, C. jejuni, C. fetus, C. concisus, C. coli, C. gracilis and C. spatori (Chaban et al. 2010).

Wild animals, particularly birds, have an essential role as reservoirs for Campylobacter spp., therefore chicken carcasses and meat are the main vehicles for transmission of Campylobacter infection in human (Sharph et al. 2016). Many researches have been coordinated to detect Campylobacter origins and transmission methods to poultry with the major objective to identify the best intervention techniques to minimize the quantity of chicken flocks infected with Campylobacter spp. (Cox et al. 2012).

The usual source of poultry contamination with Campylobacter spp. is the horizontal transmission. Poultry can get infected with Campylobacter spp. through the ingestion of water contaminated with this bacterium and also through contact with feces from infected animals including wild birds, poultry, other insects, household pets, feed, fecal droppings, farm equipment and vehicles (Hazeleger et al. 2008; Ellis-Iversen et al. 2009; Cox et al. 2012 and Georgiev et al. 2017).

Campylobacter spp. can spread rapidly in poultry flocks, mainly because of the coprophagous behavior of these animals and the high population density in breeding (Man, 2011 and Humphrey et al. 2014). Bird to bird transmission usually occurs in farms. Once infected, poultry remain infected until slaughter (van Gerwe et al. 2009 and Ingrasa-Capaccioni et al. 2015).

Moreover, the vertical transmission of chicken is still controversial. Some researchers reported that Campylobacter spp. can’t be transmitted through the egg shell (Fonseca et al. 2014). Interestingly, chickens maternal anti-Campylobacter antibodies disappeared after the 3rd week of life, thus they usually become infected after the 4th week of life (Humphrey et al. 2007). However, the vertical transmission is still a possible transmission method (Silva et al. 2018b).

Lamb, beef, pork and poultry meat and its products may become contaminated with Campylobacter spp. during slaughtering and its subsequent steps, because the microorganism found in the intestinal tract of infected animal can spread to their viscera, meat cuts and carcasses. In the chicken processing line, the stages with the highest contamination levels for are evisceration, plucking, defathering, and scalding because of the meat exposure to the gut contents. Moreover, Campylobacter spp. can survive in flesh at temperatures lower than 15°C which can minimize the risk of contamination with these bacteria (Hue et al. 2010 and Ridley et al. 2011).

Additionally, water chillers are another source for carcass cross-contamination originating from various batches of animals (Melero et al. 2012 and García-Sánchez et al. 2017).

Moreover, cross-contamination with Campylobacter spp. can occur in the post-marketing stages at home and in public areas like restaurants and retail stores usually through consumers processing and handling of contaminated raw chicken and its products. Thoroughly cooking of chickens before consumption can destroy the microorganism cell. On the other hand, raw chickens and ready-to-eat food cross-contamination can happen as a result of bad hygienic practices of consumers such as cleaning raw chicken with water, which can lead to the contamination of kitchen utensils and other ready-to-eat food (FSA, 2012).

The most well-known selective agar used for isolation of Campylobacter is modified charcoal cefoperazone deoxycholate agar (mCCDA). The petri dishes are incubated at 42°C/37°C for 2 days in anaerobic jars with gas enrichment techniques used vary between research facilities. No standard culture technique for Campylobacter spp. is available and enrichment steps are not typical for clinical specimens (Chon et al. 2014; Goni et al. 2017 and Hu and Kopecko, 2018).

A few enrichment broths have been defined to promote the growth of Campylobacter such as Preston broth, Bolton broth, Campylobacter enrichment broth, and Campy-thio (Baylis et al. 2000; Fitzgerald, 2015 and Galate and Bangde, 2015). The oxygen enzyme addition to the selective broths plays a fundamental role in minimizing the oxygen levels and improving Campylobacter spp. isolation from naturally contaminated specimens, but a blood free enrichment broth does not contain the oxynzyme (Abeyta et al. 1997 and Galate and Bangde, 2015).

**ISOLATION AND IDENTIFICATION OF CAMPYLOBACTER SPECIES**

No standard culture technique for Campylobacter spp. isolation and techniques used vary between research facilities. Campylobacter multiply more gradually than the other microbial flora in the intestine and need low oxygen concentration (thioleth) to grow. Moreover, in aerobiosis, it is impossible to grow Campylobacter spp. and other pathogenic Campylobacter strains like Tetrathillum because they are anaerobic. Additionally, enrichment techniques are important for food, environmental specimens and old stool specimens where the quantity of Campylobacter is low. However, an enrichment step is not typical for clinical samples (stool specimens) (Chon et al. 2014; Goni et al. 2017 and Hu and Kopecko, 2018).
technique may produce false negative results (Van Dyke et al. 2010). A few replacement and quick techniques have been documented for distinguishing Campylobacter spp. Polymerase chain reaction (PCR) is the best strategy for confirmation of Campylobacter spp., because the phenotypic responses are frequently atypical and hard to be read (Galate and Bangde, 2015).

Many studies reported the Campylobacter spp. detection by the use of culture-based techniques; however, these techniques have minimal bacterial recovery rates and they possibly underestimate the Campylobacter count in a given specimen, due to Campylobacter requirements for fastidious and complex growth conditions. Biochemical techniques rely upon biochemical pathways and their interruption can cause false results and product failure. These outcomes give false Campylobacter spp. prevalence (Yamazaki-Matsuene et al. 2007 and Goni et al. 2017).

Denis et al. (1999) stated that biochemical tests give just 34% productivity compared with the PCR assay. This methodology has essentially expanded the frequency of C. jejuni detection (8.1% against 5.3%) (Humphries and Linscott, 2015 and Goni et al. 2017). For surveillance of antimicrobial resistance and epidemiological purposes, identification of Campylobacter spp. has become significant (Galate and Bangde, 2015). Therefore, many methodologies have been reported such as the conventional PCR assays, which utilized for identification of different genes such as 23S rRNA gene for Genus Campylobacter, the hioP and mapa genes for C. jejuni and the gA and creaE genes for C. coli (Yamazaki-Matsuene et al. 2007 and Goni et al. 2017).

A few molecular typing methods are essentially used for detection of intra-spp. diversity (species, strain, and biotype) among foodborne bacterial pathogens such as Campylobacter, to improve the comprehension of the epidemiology of these bacteria to start powerful control measures and to study the genetic relationship between the isolates of different sources (Hu and Kopecko, 2018).

The collective effort to meet this need during the most recent 30 years have led to different typing methods for Campylobacter. Conventional Campylobacter serotyping, phage typing, gene-sequencing, multilocus enzyme electrophoresis typing (MLEE), repetitive sequence-based polymerase chain reaction (rep-PCR) which amplifies small DNA segments of the bacterial chromosome, pulsed-field gel electrophoresis (PFGE), fragment length polymorphism by amplification and restriction of specific genes (such as flaA-FLP), amplified fragment length polymorphism (AFLP), metabolic markers, whole genome sequencing (WGS), antimicrobial-resistance profiling and multilocus sequence typing (MLST) (Llarena et al. 2015 and Hu and Kopecko, 2018).

Interestingly, no golden standard genotyping method exists; but the perfect genetic typing technique (for attribution of sources) could be founded on the markers of the genome which give us clues about the host (genes that are associated with the animal reservoir), and inform us about the pathways (Llarena et al. 2015).

**PATHOGENESIS AND VIRULENCE FACTORS OF CAMPYLOBACTER SPECIES**

Campylobacter has a complex and not completely known mechanisms for survival to conquer the host barriers and to cause sicknesses in humans, interestingly studies on pathogenesis of Campylobacter are usually made with C. jejuni. Therefore, the usage for Campylobacter genomics is believed to be 350-10,000 cells and the infective dose is frequently correlated to the attack intensity. Campylobacter infections are most common in immunocompromised, elder people and children (Epps et al. 2013; Bolton, 2015 and Bhunia, 2018). After the consumption of contaminated water or food, Campylobacter needs to go through the gastric acid barrier of the stomach and the highly alkaline secretions from the bile duct in the upper small intestine (Hu and Kopecko, 2018). Interruption of the gastric acid barrier permits the pathogenic microflora like Campylobacter to survive and flourish. Thus, people with diminished gastric acidity such as those accepting antacid and inhibitors of proton pump can be at a high risk of campylobacteriosis (Same and Tamma, 2018).

Severe inflammation and cell damage are well established when Campylobacter attacks the distal ileum and colon epithelial cells after its arrival to the lower gastrointestinal tract; though in chickens, the cecum is the essential colonization site for Campylobacter (Meade et al. 2009). In developed countries, C. jejuni causes an invasive, inflammatory disease. However; in developing countries, Campylobacter enteritis causes a non-inflamatory watery diarrheal disease (Hu and Kopecko, 2018).

It is believed that host colonization, adhesion and invasion by Campylobacter needs chemotaxis and motility. Iron acquisition, resistance to gastric acids and bile salts and oxidative stress defense are important for growth and survival. Bacterial toxins mediate inflammatory responses and tissue damage (Galate and Bangde, 2015).

Many putative survival and virulence factors are believed to be significant for pathogenesis and induction of gastroenteritis by Campylobacter spp. The molecular mechanism of Campylobacter infection is believed to be affected by the bacterial pathogenicity factors of the disease. Several genes have been identified as significant keys for the expression of pathogenicity. The cadF (adhesin gene), flaA (flagellin A gene), dnaJ, and racR are pathogenic genes involved in colonization and adherence; lamA (invasion-associated gene A), virB11 (virulence plasmid) and cibA are pathogenic genes responsible for invasion; cgb and wlaN (β-1,3-galactosyltransferases) are pathogenic genes involved in lipopolysaccharide production and cadC, cadB and cadA, (cytotoxid distension toxins C, B, and A) are pathogenic virulence genes significant for the cytotoxin production expression (Bolton, 2015; Zhang et al. 2016 and García-Sánchez et al. 2018).

**Motility**

Motility is significant for Campylobacter to avoid harsh environmental conditions and genes associated with motility are mostly upregulated under stressful environments. The motility of bacteria needs flagella and a chemosensory system, which guides the flagella movement according to the nutrients available. Campylobacter jejuni has a characteristic flagellum that are significant pathogenic factors that are required for the movement of the bacterium towards the epithelium surface, colonization, adhesion and invasion of the host epithelial cells. Campylobacter has characteristic helical shaped polar flagella at both or one end of the bacterial cell, which is responsible for the corkscrew torque impulsive movement in the viscous mucus, which allow the Campylobacter to go to its colonization site in the intestinal mucosa (Bhunia, 2015; García-Sánchez et al. 2018 and Silva et al. 2018a).

Additionally, the flagellum also has type III secretion systems (T3SS), which have a role in transporting nonflagellar proteins important for bacterial host interaction and pathogenesis. The T3SS are macromolecular complex component that permit Gram-negative microorganisms to produce proteins through the outer and inner membranes in the absence of periplasmic intermediate, which serve as a molecular syringe. Many proteins can be transported through the flagellum like FspA, FlaC, CiuA, CiuC and CiuB (Neal-McKinney and Kronkel, 2012 and García-Sánchez et al. 2018).

Flagellins of Campylobacter can't stimulate proinflammatory cytokines, this feature permit Campylobacter to escape the host immune responses distinguishing it from many foodborne microorganisms such as Salmonella (Same and Tamma, 2018).

The flagellum composed of a helical shaped structure of the flagellin proteins, which include a hook–basal body and the extracellular filamentous structure. The hook-based body consists of (i) the cytoplast with a base implanted in it and the cellular internal membrane, (ii) the hook, which is localized in the surface and (iii) the periplasmic rod and its correlated ring components. The periplasmic rod is attached to the motor proteins, which provide energy for the flagellum movement. This system contains several proteins with various roles (Bolton, 2015; Bhunia, 2018 and García-Sánchez et al. 2018).

The hook– basal body is consisting of proteins such as the T3SS proteins (FliR, FliQ, FliP, FliO, FliB and FliA), FliF, motor structures (MotB and MotA), motor switch proteins (FliY, FliN, FliM and FliG) and minor hook structures (FliM, FliK, FliG, FliH and FliG). The extracellular filament is consisting of the minor flagellin subunit FliB and the major subunits FlaA encoded by flaA and flaB genes, respectively that can be used for genotyping of Campylobacter spp. (Bolton, 2015 and Bhunia, 2018).

Additionally, CheY is another significant protein that is a response regulator essential for the turnover of the flagella. The mutation in essential genes like cheR, cheA, cheY, cheW, cheV, cheR, cheB and cheA (Bhunia, 2018). The flagellar proteins are regulated by chemosensory proteins, which regulate the bacterium directional movement that drive the bacteria to move towards the favorable environmental conditions and avoid unfavorable ones (Rowe and Madden, 2014).

Campylobacter motility towards glycoproteins and mucins on the surface of the host cell membrane can favor the intestinal colonization of Campylobacter. Moreover, there is other chemotactrant such as succinate, lactate, malate, formate, serine, pyruvate, glutamate, cysteine, asparagine, aspartate, α-ketoglutarate, acceptors and donors of electrons, other metabolic substrates and amino acids (Bolton, 2015; Bhunia, 2018 and Silva et al. 2018a).

**Adhesion**

After bacteria have passed the mucosal layer, they bind to the gut epithelial cells. Adhesion to the epithelial cells is a complex mechanism, where adhesions on the microorganism cell surface attach to the receptors of the host cells resulting in specific and irreversible binding. This cellular adherence of the gut is prior to
Iron acquisition

The capability of Campylobacter to take iron from transferrin in the host serum and lactoferrin from the mucosa is significant for pathogenesis and persistence of campylobacteriosis. The bacterial adherence and the effective colonization of the intestinal mucosa including many receptors on the cell membrane, regulators and transporter proteins (Hermans et al., 2011; Bolton, 2015 and Bhunia, 2018). Campylobacter cannot produce siderophores, but it uses enterochelin, ferrichrome and siderophores secreted by other microorganisms to obtain iron. Thus, Campylobacter will have a competitive advantage taking into account the several genes involved in regulation of iron acquisition and homeostasis despite its small DNA. Moreover, there are two important regulator proteins for iron uptakes including PerR (peroxide stress regulator) and fur (ferric uptake regulator) (Miller et al. 2009; Bhunia, 2018 and García-Sánchez et al. 2018).

Carbohydrate structures

Four various categories of carbohydrate structures like N- and O-linked glycans, capsular polysaccharides (CPS) and LOS can be established on the Campylobacter cell surface. The LOS molecule is a significant virulence factor associated with the immunological symptoms. It is composed of lipid A and a core oligosaccharide and it has been related to various activities such as protection from killing by complement-mediated, invasion, host cell adhesion and immune evasion. Adding a sialyl group to the LOS molecule will maximize the invasive ability and minimize the Campylobacter strains immunogenicity (Bolton, 2015 and García-Sánchez et al. 2018). Campylobacter sialylated LOS, which have the ability to mimic the human antigens, such as swi6 (β-1,3-galactosyltransferase) and cgb genes those mimics the myelin sheath of the nervous cells’ ganglioside. When Campylobacter enter the host cells, an antibody is produced against the sialylated LOSs by the host immune system. These antibodies can cause nerve cell demyelination, blockage of nerve impulse and progressive weakness in the muscles of the respiratory system and limbs, which lead to the emergence of Miller Fisher syndrome and Guillain-Barre syndrome (GBS). Most GBS patients had campylobacteriosis with strains have LOS belonging to the locus class A (Revez and Hänninen, 2012 and García-Sánchez et al. 2018).

Additionally, CPS have been reported to have several functions including contribution to the gut virulence, formation of biofilm and protection of Campylobacter from harsh environmental conditions such as maximize its resistance to desiccation (Nachamkin et al. 2008 and García-Sánchez et al. 2018). Moreover, different polysaccharide groups (CPS), with capsular gene sequences, the kps genes were detected as genes responsible for capsule biosynthesis (Zibauer et al. 2008). Strains with the kspM gene mutants that encode a protein responsible for capsular polysaccharide transport will minimize Campylobacter invasiveness, colonization and decrease its resistance to human serum (Bolton, 2015 and Silva et al. 2018a). Concerning glycosylation of protein, Campylobacter is the main microorganism that has both N- and O- linked systems (Jeon et al. 2010). Moreover, the Campylobacter N-linked glycosylation system plays a key role in post-translational modification of more than 60 periplasmic proteins such as flagellin and it is encoded by the pgj multigene locus found in Campylobacter. The surface proteins N-linked glycosylation are responsible for Campylobacter pathogenesis, most gut colonization and the effective immune system of the host. On the other hand, O-linked glycosylation has a significant role in flagellar glycosylation and only limited to the flagellin subunits (Bolton, 2015 and García-Sánchez et al. 2018).

Regulation of virulence genes

Colonization and thermotolerance in the intestinal tract are regulated by regulatory system composed two components including a response regulator (RR) and a histidine kinase (HPK) sensor. The RR is phosphorylated by HPK and responsible for the regulation of the response of RacR, CheY and other proteins those are important for thermotolerance at 37°–42°C and colonization. Moreover, the acquisition of iron is regulated by PerR and Fur proteins. Additionally, the flaA regulon, which have a key role in synthesis of Campylobacter flagella, is regulated by a signal transduction system composed of two components (G)flbA and GflB (Kuhn, 2016). 7.8 Campylobacter survival in stress environment

The foodborne microorganisms are exposed to stressful environment both inside and outside of the host organism. The expression of stress response mechanisms by the foodborne pathogens has a significant role in their persistence in different habitat (Silva et al. 2018a).

Unlike other foodborne pathogens, Campylobacter doesn’t possess several adaptive responses to stressful environment. These bacteria do not have the rpoS gene, which is a sigma factor in the stationary stage that encodes for the RpoS (sigma 38) global regulator that is associated with virulence genes and the transcription of stress response (Silva et al. 2018a). However, Campylobacter have few adaptive responses for reactive oxygen spp., acid tolerance and heat shock that permit them to persist in the stressful environmental conditions (Bolton, 2015 and Dasti et al. 2010). Despite lack of many stress response...
mechanisms, fastidious growth requirements and its sensibility to environmental stresses, these bacteria can cause a public health hazard due to its persistence in the food chain (Silva et al., 2018a).

**RESISTANCE OF CAMPYLOBACTER SPECIES TO ANTIMICROBIAL AGENTS**

Bacterial resistances are mainly caused because of the aimless utilization of the antibiotic agents in human disease treatment as well as its exaggerated use in animal production (Silva et al., 2018a). Recently, the emergence of antimicrobial resistance in *C. coli* and *C. jejuni* originating from food of animal origin has become a critical public health problem worldwide (EFSA, 2017).

Campylobacteriosis is characterized by a self-limited diarrhea; in this way, antimicrobial therapy is not usually recommended. But antimicrobial therapy is required in case of serious infection, which may be systemic or prolonged. *Campylobacter* is a zoonotic pathogen; subsequently, *Campylobacter* resistant strains will cause serious problems because the most well-known antimicrobial agents would be useless against campylobacteriosis (Bhunia, 2018).

*Campylobacter* is a commensal bacterium in the intestine of different domestic animals and this led to its exposure to several classes of antimicrobial agents. Between these antimicrobial agents, quinolones as ciprofloxacin or ciprofloxacin is believed to be associated with causing high resistance rates in food products and farms; so, the US Food and Drug Administration (FDA) has restricted fluoroquinolones utilization in USA chicken industry as a growth supplement (Bhunia, 2018 and Same and Tamma, 2018). Additionally, the natural course of infection and the genomic structure of *Campylobacter* lead to an extensive genomic diversity which may be another cause of antibiotic resistances (Goni et al., 2017 and García-Sánchez et al., 2018).

*Campylobacter* is resistant innately to vancomycin, nafcillin, trimethoprim, sulfamethoxazole, oxacillin and cloxacillin. But, different kinds of resistance may be an outcome of the use of antibiotics in animal and human treatment (Llarena, 2015 and Llarena et al., 2015). Four main methods are implicated in *Campylobacter* resistance to antibiotics including (i) production of enzymes that modify or inactivate antimicrobial agents (e.g., β-lactamase), (ii) changing the antibiotic recipient and/or its expression (e.g., 23S rRNA or gyrA genes mutations), (iii) antimicrobial efflux pumps which actively eject the antimicrobial agents from the cell (e.g., multidrug efflux pumps, CmeABC, and CmeD), and (iv) minimize the antimicrobial permeability, so the antimicrobial cannot reach its target due to unique membrane structures (i.e., the major outer membrane porin expression or MOMP) (Luangtongkum et al. 2010 and García-Sánchez et al., 2018).

Finally, *Campylobacter* has a chromosomal region, inherited to the bacterium, or exogenous by genetic transfer from other microorganisms or mutation. *Campylobacter* have many mechanisms for resistance making it resistant to the main classes of antibiotics including: aminoglycosides, tetracyclines, quinolones, macrolides and β-lactams (Shen et al., 2018; Silva et al., 2018a and Whitehouse et al., 2018).

**Multidrug efflux pump system**

The *Campylobacter* multidrug efflux (CME) pump usually mediates *Campylobacter* resistance to heavy metals, bile salts and a wide range of other antimicrobials. So, it is an active method for these agents to be pumped extracellularly, consequently avoiding their accumulation inside the bacterial cell, which essential for the bacterial cell death (Kurinčíč et al., 2012). The CME pump is encoded by the cmeABC operon that is composed of a periplasmic fusion protein; CmeB a protein on the outer membrane, CmeC an efflux transporter on the inner membrane that belongs to the superfamily of resistance-nodulation-cell division and CmeA that bridges CmeC and CmeB (Bolton, 2015 and García-Sánchez et al., 2018).

CmeB is a transcription repressor protein, which modulates the expression of the cmeABC operon through the cjo656c gene inhibition. The CME pump has a fundamental role in *C. jejuni* intrinsic resistance to variety of structurally unrelated antibiotics (Bolton, 2015 and Whitehouse et al., 2018). Several studies have demonstrated the significant contribution of this efflux system in the antimicrobial resistance to ampicillin, macrolides, tetracycline and quinolones (Iovine, 2013 and Silva et al., 2018a).

**Quinolones**

The European Food Safety Authority (EFSA) stated that Norway and Denmark are the only European state members, which have very high ciprofloxacin resistance levels. Five member states stated that 90% of the total *C. jejuni* fluoroquinolone resistance. Moreover, 11 out of 17 member states countries showed high levels of *C. coli* ciprofloxacin resistance (80-100%) with 2 reporting countries have increased trends during the period from 2013-2015 (EFSA, 2017). According to the high level of fluoroquinolones acquired resistance, they should not be used in food animals treatment as antibiotics. The alteration of the cmeABC operon expression was identified as an alteration in the permeability of the cell membrane mediated by the expression of the MOMP that is encoded by porA gene. Porins are proteins in the external membrane of Gram-negative microorganisms, which made pores across the membrane that permit the hydrophilic molecules passive diffusion like several antimicrobial agents. The alteration of the MOMP porA gene is associated with negative charged ion, in *C. coli* and *C. jejuni* result in minimizing the probably soon fluoroquinolones may become disqualified. Several researches have showed a correlation between the increased resistance of *Campylobacter* isolates among chicken and human and the fluoroquinolone use in poultry industry (Luangtongkum et al. 2010; Shen et al. 2018 and García-Sánchez et al., 2018).

*Campylobacter* quinolones resistance is mediated by the CmeABC efflux pump and also through a single point mutation in the gyrA gene determining area of quinolone resistance (Iovine, 2013; Shen et al. 2018 and Whitehouse et al., 2018).

**Tetracyclines**

*Campylobacter* resists to tetracycline have been mediated by the protein of ribosomal protection; TetO that is encoded by the tetR(O) gene. The tetR gene is common in *C. coli* and *C. jejuni*. The TetO protein identifies the bacterial ribosome open A site and attach to it to cause conformational changes, which lead to the detachment of tetracycline molecule from the ribosome (Luangtongkum et al. 2010 and García-Sánchez et al., 2018).

*Campylobacter* tetracycline resistance has two methods including: (i) multidrug efflux pump system and (ii) changing the ribosomal target of tetracycline. Usually the tetR gene is found in the plasmid; but some *Campylobacter* isolates have a tetR gene detected on the chromosome (Iovine, 2013 and Whitehouse et al., 2018).

**Aminoglycosides**

Aminoglycosides antimicrobial agents include streptomycin, tobramycin, neomycin, amikacin, kanamycin and gentamicin. There are two mechanisms for aminoglycosides to maintain their antimicrobial activities: (i) proofreading interference which lead to dysfunctional proteins due to using wrong amino acids and (ii) interference with the early peptide chain translocation from the ribosomal A site to the P site, which result in its premature end (Iovine, 2013 and Yao et al., 2017).

*Campylobacter jejuni* aminoglycoside resistance is mainly occurred through aminoglycoside-changing enzymes (Sat, aacA AaDE, ApH and ApA) that are encoded by plasmids genes. Moreover, the efflux pump system contribution is not fully understood yet (Iovine, 2013 and García-Sánchez et al., 2018). The first report of *Campylobacter* resistance to aminoglycosides was in *C. coli* and has been mediated by a 3’-aminoglycoside phosphotransferase that is encoded by the aphA-3 gene. Moreover, other genes have also been identified in *Campylobacter* spp. such as genes conferring to kanamycin resistance (aphA-7 and aphA-1), streptothricin resistance (sat) and streptomycin resistance (aadE) (Silva et al., 2018a and Whitehouse et al., 2018).

**Macrolides**

European food safety authority (EFSA) studies reported that *Campylobacter* resistance to macrolides has been increased in the last years and it is found usually at high levels in several European Union members. Historically, the incidence of *C. jejuni* macrolides resistance has been low, but there are many methods for *Campylobacter* to acquire macrolides resistance (EFSA, 2017).

*Campylobacter* has four main mechanisms for macrolides resistances including: (i) production and possible antimicrobial efflux by CmeABC efflux pump and possibly others, (ii) methylation of the ribosome mediated by a 3′-aminoglycoside phosphotransferase that is encoded by the aphA-3 gene. Moreover, other genes have also been identified in *Campylobacter* spp. such as genes conferring to kanamycin resistance (aphA-7 and aphA-1), streptothricin resistance (sat) and streptomycin resistance (aadE) (Silva et al., 2018a and Whitehouse et al., 2018).

*Macrolides* are modifiers of the ribosomal subunit B23S protein, which make the ribosome unable to synthesize proteins. The 23S rRNA is a part of a small ribosome subunit, which is essential for translation initiation by acting on the 50S ribosomal subunit and disrupting the bacterial synthesis of the bacteria, which result in bacterial conformational changes and premature termination of the peptide chain elongation. Additionally, the *Campylobacter* 23S rRNA gene has three chromosome copies. In erythromycin resistant *Campylobacter* strains, all copies have mutations related to ribosome resistance (Wieczorek and Osek, 2013 and García-Sánchez et al., 2018). Moreover, the synergy between mutations and the CmeABC efflux pump system has fundamental role in ketolides (telithromycin) and macrolides (tylosin, azithromycin clarithromycin and erythromycin) resistance in *C. coli* and *C. jejuni* (Luangtongkum et al. 2010; Shen et al. 2018 and García-Sánchez et al., 2018).

Macrolides inhibit the bacterial ribosome protein synthesis by acting on the 50S ribosomal subunit and disrupting the protein synthesis of the bacteria, which result in ribosomal conformational changes and premature termination of the peptide chain elongation. Additionally, the *Campylobacter* 23S rRNA gene has three chromosome copies. In erythromycin resistant *Campylobacter* strains, all copies have mutations related to ribosome resistance (Wieczorek and Osek, 2013 and García-Sánchez et al., 2018). Moreover, the synergy between mutations and the CmeABC efflux pump system has fundamental role in ketolides (telithromycin) and macrolides (tylosin, azithromycin clarithromycin and erythromycin) resistance in *C. coli* and *C. jejuni* (Luangtongkum et al. 2010; Shen et al. 2018 and García-Sánchez et al., 2018).
passage of most antimicrobial agents with a negative charge or those which have a molecular weight more than 360 kDa (Iovine, 2013 and Silva et al. 2018a).

β-lactams

β-lactams resistance in Campylobacter spp. is usually mediated by β-lactamases enzymes, which breakdown the β-lactams structure. Additionally, some Campylobacter strains have other mechanisms for β-lactams resistance such as cation-selective MOMP and efflux pump system (Iovine, 2013). Campylobacter and Salmonella spp. are β-lactamase producers and penicillin (Wiezorek and Osek, 2013; Silva et al. 2018a and Whitehouse et al. 2018).

PUBLIC HEALTH SIGNIFICANCE OF CAMPYLOBACTER SPECIES

The human Campylobacter infection of incredible public health importance is Campylobacter gastroenteritis caused mainly by C. jejuni and sometimes by C. coli. Chickens are distinguished as the principle reservoirs of thermophilic Campylobacter spp. Furthermore, chickens are answerable for an expected 80% of Campylobacter infection in human. Chickens are believed to be asymptomatic carriers (Goni et al. 2017 and García-Sánchez et al. 2018).

Campylobacter spp. can colonize large proportion of poultry flocks. An European Union baseline research stated that campylobacter was detected in 75.8% of broiler carcasses, 71.2% of eecal contents of broiler batches were also contaminated with campylobacter (FSA, 2012) and there was a 61.3% prevalence rate of Campylobacter in samples of chicken skin at the retail level, 18.6% of which had Campylobacter counts more than 1000 CFU/g (PHE, 2017 and Gótz et al. 2018).

Despite, campylobacteriosis severity rate is low (0.03%), the quantity of human Campylobacter infection cases is elevated. Interestingly, human Campylobacter infection is the third most common reason of mortality between the foodborne microorganisms and death can occurs in immunocompromised patients suffering from liver diseases, cancer and acquired immunodeficiency syndrome (AIDS) (EFSA, 2017; Bhunia, 2018 and García-Sánchez et al. 2018).

Campylobacteriosis are mainly self-limiting and sporadic. Gastroenteritis caused by Campylobacter is distinguished by high body temperature, vomiting, weight loss, abdominal pain/cramps, headache and sometimes bloody diarrhea (CDC, 2014 and Skarp et al. 2016).

Additionally, Campylobacter can cause post infectious immune disorders like Guillain Barré syndrome (GBS), which is a nervous system disorder distinguished by an advanced weakness and floppy paralysis in the extremities and it may cause paralysis in the respiratory muscles, reactive arthritis (inflammation of joints) and Miller Fisher syndrome (MFS) which is characterized by coulometer weakness (areflexia and ataxia) and the vision problem (ophthalmoplegia) (Bhunia, 2018 and Whitehouse et al. 2018).

In developing countries, campylobacteriosis is hyper-endemic and the Campylobacter infection is symptomatic and occurs almost exclusively and repeatedly in young children and infants. Subsequent infections can be asymptomatic, which make the symptomatic infection rare in adults or older children (Same and Tamma, 2018).

Campylobacteriosis is usually sporadic, but there were many reported outbreaks. Kompantas et al. (2017) and 59.8% (European Centre for Disease Prevention and Control, 2016) cases/ 100,000 populations were reported. In USA, 14 cases/100,000 populations were stated yearly (CDC, 2017); however, in Canada, 23 cases/100,000 populations were reported in 2015 (Public Health Agency of Canada, 2017; Silva et al. 2018a and Whitehouse et al. 2018).

Interestingly, there is a significant difference in the epidemiology of campylobacteriosis between developed and developing nations. In developing countries, Campylobacter is not the most common cause of the bacterial foodborne illness, because in the developing nations there aren't national programs for surveillance of Campylobacter infection, thus the state of Campylobacter infection is difficult to be evaluated in these countries (WHO, 2013 and Garcia-Sanchez et al. 2018). Moreover, recent researches have demonstrated that beta-resorcylic acid and eugenol can change microbial virulence in C. jejuni by minimizing principle foodborne microorganisms such as Salmonella spp. (Ubdayh et al. 2013b), Escherichia coli O157:H7 (Baskaran et al. 2013) and C. jejuni (Wagle et al. 2017b) in food products.

Conclusion

Recently, a great expansion in the consumer preference towards natural products has been reported. Therefore, several scientists concentrated on utilizing products from plant origin as an alteration to antimicrobial agents in food from animal origin. Several phytochemicals have an antimicrobial efficacy by disrupting the outer cell wall and membrane integrity, which may cause a leakage of cellular contents and cell death (Ubdayh et al. 2019).

Beta-resorcylic acid (2, 4 dihydroxybenzoic acid) is a polyphenolic complex which is broadly distributed as a secondary metabolite between the angiosperms for plants protection from microbial infection and it is also utilized as food additives and flavoring agent. It is classified under “Everything Added to Food in the United States” by the US-FDA (EAFUS; Cas no. 89-86-1) (Food and Drug Administration, 2013 and Wagle et al. 2017a). Former researches have indicated that beta-resorcylic acid is efficient in minimizing principle foodborne microorganisms such as Salmonellae species (Mattson et al. 2011). Listeria monocytogenes (Ubdayh et al. 2013a), Escherichia coli O157:H7 (Baskaran et al. 2013) and C. jejuni (Wagle et al. 2017b) in food products.

Eugenol is another polyphenol compound that is the significant antimicrobial component found in the oil of cloves (Syzygium aromaticum/ Eugenia Caryophyllus) (Ubdayh et al. 2017 and Wagle et al. 2019) and it is additionally attractive to consumers as a substitution for the antimicrobial agents, since it is considered acceptable for organic and non-conventional uses (Miechiche et al. 2019). Additionally, eugenol has exhibited an important antimicrobial action against foodborne microorganisms such as Salmonella spp. (Ubdayh et al. 2013b), Escherichia coli (Ghosh et al. 2013), Listeria monocytogenes (Ubdayh et al. 2015) and C. jejuni (Wagle et al. 2019).

Moreover, recent researches have demonstrated that beta-resorcylic acid and eugenol can change microbial virulence in C. jejuni by minimizing C. jejuni attachment and invasion to the epithelial cells in the intestinal tract and by changing the expression of virulence factors such as motility and cytotoxicity distending toxins (Ubdayh et al. 2017 and Wagle et al. 2017a). Eugenol and its derivatives are a well classified by the FDA as GRAS (generally recognized as safe) with fast biodegradation in the environment and minimal cytotoxicity, which making them safe and efficient replacement to the antimicrobial agents (Food and Drug Administration, 2012 and 2013 and Wagle et al. 2019).

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