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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 cork screw 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 García-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, anti-microbial 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 **(Bhunia, 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 deceased 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. **(Sebald 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. sputorum*, *C. fetus* and *C. jejuni* **(Veron and Chatelain, 1973)**.

Just during the 1980s, about 100 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 *Campylobacterales* 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. upsaliensis* 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* subspp. *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 *Doylei* 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 nitrate reductase (*nap*) locus (*nap*A and *nap*B genes), where *C. jejuni* subsp *Doylei* strains contained *nap*A 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. upsaliensis*, *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 (eg, *C. canadensis* and *C. insulaenigrae*) (2) spp. that have been incriminated with children and human diseases (eg, *C. showae*, *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. sputorum*, *C. fetus* and *C. hyointestinalis*) **(Miller and Parker, 2011 and Fitzgerald, 2015)**.

Among the genus *Campylobacter*, *C. iguaniorum*, *C. corcagiensis*, *C. troglodytis*, *C. volucris*, *C. avium*, *C. canadenses*, *C. subantarcticus* and *C. cuniculorum* are the only spp. that didn't cause animals or human diseases yet **(Fitzgerald, 2015)**.

MOLECULAR TAXONOMY OF *CAMPYLOBACTER* SPECIES

In 1960, 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 rRNA* 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 rRNA* **(Linton *et al*. 1996)**. However, because of similarity in *Campylobacter* spp. sequences; the *16S rRNA* gene sequence cannot be used for differentiation of genetically related spp. including *C. coli* and *C. jejuni* **(On, 2001)**.

Since the past ten years, there was a considerable decline in DNA 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 dependant on the *16S rRNA* sequences correlate with the whole-genome spp. trees **(Whitehouse *et al*. 2018)**.

BIOLOGICAL CHARACTERISTICS OF *CAMPYLOBACTER* SPECIES

Phenotypic and biochemical criteria of *Campylobacter* species

The members of genus *Campylobacter* are non-spore forming, small, slender, spirally 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 corkscrew appearance when seen by phase-contrast microscopy because of the existence of solitary unsheathed 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)**.

The ideal requirement for *Campylobacter* growth is the microaerophilic states of 3-10% CO_2, 3-15% O_2 and 85% N_2 **(Goni *et al*. 2017)**. However, some spp. (*C. rectus*, *C. concisus* and *C. curvus*) favor anaerobic states for development **(Kaakoush *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. upsaliensis* 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 catalase positive except for of *C. upsaliensis* **(Goni *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 hydrolyzes 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 **(Facciolà *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 **(Micciche *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)**.

Some *C. 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, *Campylobacter* become increasingly difficult to be cultured and the cells become coccoid. These bacteria can enter a viable but nonculturable (VBNC) form. Pre-enrichment as well as microaerobic growth condition and adding oxygen-quenching agents to

the growth media such as charcoal and hemin can improve the recovery *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 an expected 80% of human *Campylobacter* infection **(Silva *et al*. 2011; Epps *et al*. 2013 and Whiley *et al*. 2013)**. Thus, the gut mucosa of mammals and birds are considered the ideal site of bacterial multiplication and serve as a natural reservoir of *Campylobacter* spp. *Campylobacter* is a ubiquitous microorganism, which means that it can be found nearly everywhere as a commensal microorganism in the intestinal tract of different animals from the red kangaroos and Antarctic macaroni penguins to common housefly **(Llarena, 2015)**.

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. **(Cean *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 **(Gölz *et al*. 2014 and Skarp *et al*. 2016)**.

Campylobacter spp. might be transmitted to humans by utilizing food and water contaminated with theses bacteria 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. showae*, *C. mucosalis*, *C. helveticus*, *C. lari*, *C. upsaliensis*, *C. jejuni*, *C. fetus*, *C. concisus*, *C. coli*, *C. gracilis* and *C. sputorum* **(Chaban *et al*. 2010)**.

Wild animals, particularly birds, have an essential role as reservoirs for *Campylobacter* spp., spreading *Campylobacter* in the environment to different animals and humans **(Whiley *et al*. 2013)**. Regardless the significance of these reservoirs, food-producing animals are the essential sources for campylobacteriosis **(WHO, 2016)**.

Chicken is the most common reservoir of *Campylobacter* spp., therefore chicken carcasses and meat are the main vehicles for transmission of *Campylobacter* infection in human **(Skarp *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 coming in contact with *Campylobacter* infected animals including wild birds, poultry, other insects, household pets, feed, fecal dropping, 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 coprophagic 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 Ingresa-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, de-feathering, and scalding because of the meat exposure to the gut contents. Moreover, keeping the evisceration room temperature lower than 15ºC 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 retails usually through consumers processing and handling of contaminated raw chicken and its products. Thoroughly cooking of chickens before consumption can destruct 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)**.

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 campylobacteriosis, due to the bad 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 **(Elangro *et al*. 2012 and Mungai *et al*. 2015)**.

However, the *Campylobacter* transmission through contaminated raw fruit and vegetables is uncommon, it may be significant. Vegetables and fruits may get contaminated with *Campylobacter* spp. during distribution, packaging, processing, harvesting and production. Possible sources of contamination include dust, contact with infected animals, improper hygienic practices of the utensils, equipment and handlers, inadequately composted or natural manure, faeces, contaminated irrigation water and the survival or presence of the bacteria in the soil **(Verhoeff-Bakkenes *et al*. 2011)**.

Besides food, water can act as an important environmental reservoir for *Campylobacter* spp., due to high survival rate of *Campylobacter* in water. Practices such as swimming in natural waters as well as ingestion of contaminated water are important sources of human *Campylobacter* infection outbreaks **(Pitkänen, 2013 and Skarp *et al*. 2016)**.

Waterborne *Campylobacter* outbreaks can affect thousands of peoples, due to their need for potable water. Chlorination of water can be very effective against *Campylobacter* spp. Treatments of water need to take in their consideration the resistance of waterborne protozoa like *Tetrahymena pyriformis* that act as *C. jejuni* reservoirs **(Newell *et al*. 2011 and Sibanda *et al*. 2018)**.

The public health significance of human *Campylobacter* infection requires the identification of the seasonal patterns of human campylobacteriosis **(Friedrich *et al*. 2016)**. In temperate regions, seasonal peaks of campylobacteriosis are detected between July and August. These human campylobacteriosis peaks in the summer period are connected with high levels of chicken *Campylobacter* infection compared to winter, where insects are considered the regular vehicles of transmission between the food and the environment **(Sahin *et al*. 2015 and Skarp *et al*. 2016)**. The causes behind the seasonal patterns of human campylobacteriosis are not clear yet. However, climate, changes in human behavior and an increase in bacterial reservoirs can affect the shedding and spread of this microorganism. There is a high risk of spreading human *Campylobacter* infections between urban and rural areas **(Bronowski *et al*. 2014 and Williams *et al*. 2015)**.

ISOLATION AND IDENTIFICATION OF *CAMPYLOBACTER* SPECIES

No standard culture technique for *Campylobacter* spp. isolation is present and techniques used vary between research facilities. *Campylobacter* multiply more gradually than the other microbial flora in the intestine and need low oxygen levels. Therefore, it is hard to be isolated without utilizing selective media. 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 essential for clinical samples (stool 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 oxyrase 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 oxyrase enzyme **(Abeyta *et al*. 1997 and Galate and Bangde, 2015)**.

Many effective selective media for *Campylobacter* spp. isolation are available such as Butzler, modified charchoal cefoperazone deoxycholate (mCCDA) and Preston agars are equally effective **(Tran, 1998 and Galate and Bangde, 2015)**.

The most well-known selective agar utilized 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-generating sachets, envelopes or Campy packs to maintain microaerobic condition comprising of 10% CO2, 5% O2 and 85% N2 **(Levin, 2007 and Hu and Kopecko, 2018)**. The colonies of *Campylobacter* are typically gray, flat, irregular, and spreading in freshly prepared media. Selective culture is a fast, modest, and efficient technique for distinguishing *C. jejuni* and *C. coli*. After that, colonies suspected to be *Campylobacter* are cultured onto blood agar plates and the isolates are distinguished by motility, biochemical techniques and Gram's stain **(Galate and Bangde, 2015 and Hu and Kopecko, 2018)**.

Hippurate hydrolysis test is the most common conventional characterization procedure, which is utilized for distinguishing *C. coli* from *C. jejuni*, but this

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 condition. Biochemical techniques rely upon biochemical pathways and their interruption can cause false results and product failure. These outcomes give false *Campylobacter* spp. prevalence **(Yamazaki-Matsune *et al*. 2007 and Goni *et al*. 2017)**.

Denis *et al*. (1999) stated that biochemical tests give just 34% productivity contrasted with 100% for 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 *hip*O and *map*A genes for *C. jejuni* and the *gly*A and *ceu*E genes for *C. coli* **(Yamazaki-Matsune *et al*, 2007 and Goni *et al*. 2017)**.

A few molecular typing methods are essentially used for detection of intra- spp. differences (genetic diversity) 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 techniques for *Campylobacter* spp. including biotyping, 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 *fla*A-RFLP), 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* **(Silva *et al*. 2018a)**. The dosage for *Campylobacter* infection 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* causes a non-inflammatory 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 epidemiological and clinical features of the disease. Several genes have been identified as significant keys for the expression of pathogenicity. The *cadF* (adhesin gene), *fla*A (flagellin A gene), *dna*J, and *rac*R are pathogenic genes involved in colonization and adherence; *iam*A (invasion-associated gene A), *vir*B11 (virulence plasmid) and *cia*B are pathogenic genes responsible for invasion; *cgt*B and *wla*N (β-1,3-galactosyltransferases) are pathogenic genes involved in lipopolysaccharide production and *cdt*C, *cdt*B and *cdt*A, (cytolethal distending 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 surrounding gut environment. So, flagella 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 motion in the viscid mucus, which allow the *Campylobacter* to go to its colonization site in the internal intestinal mucosa (**Bhunia, 2018; 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 microorganism 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, CiaI, CiaC and CiaB **(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-basal body consists of (i) the cytoplasm 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, FlhB and FlhA), FliF, motor structures (MotB and MotA), motor switch proteins (FliY, FliN, FliM and FliG) and minor hook structures (FliM, FliK, FlgE, FlgH and FlgI). The extracellular filament is consisting of the minor flagellin subunit FlaB and the major subunits FlaA encoded by *fla*B and *fla*A 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 *flh*B, *flh*A, *fla*B and *fla*A prevents the FlaB or FlaA proteins production, which lead to the disruption motility, pathogenesis and invasion **(Yao *et al*. 2017; Bhunia, 2018 and García-Sánchez *et al*. 2018)**.

Chemotaxis

Chemotaxis is a normal reaction of the motile bacteria to be driven towards chemoattractants by the use of chemosensors. The chemosensors are two structures: methyl-accepting chemotaxis proteins (MCPs) and signal transduction pathway, which depends on histidine kinase and consists of chemotaxis proteins such as CheZ, CheY, CheW, CheR, CheB and CheA **(Bhunia, 2018)**. The flagellar proteins are regulated by chemosensing 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 mucus membrane can favor the intestinal colonization of *Campylobacter*. Moreover, there is other chemoattractant 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

colonization and essential for *Campylobacter* resistance to the intestinal expulsion and peristalsis **(Ganan *et al*. 2012 and Silva *et al*. 2018a)**.

Many adhesion proteins of *Campylobacter* spp. that present on the bacterial cell surface have been identified. CadF protein (37 kDa) is a protein presents on the outer membrane of *Campylobacter*, it regulates the adhesion of the bacterial cell by attaching to fibronectin, which is an extracellular glycoprotein present in the intestinal tract. This reaction stimulates a signaling pathway, which result in the activation of the Cdc42 and GTPases Rac1 that stimulate the bacterial cell to internalize through actin-mediated induced phagocytosis. Many researches have showed that mutation in this protein can prevent *Campylobacter* colonization **(Bhunia, 2018; García-Sánchez *et al*. 2018 and Silva *et al*. 2018a)**.

Additionally, other proteins have been detected in the adhesion mechanism like the surface-exposed lipoprotein, JlpA (42.3 kDa), fibronectin-like protein A; FlipA, *Campylobacter* adhesion protein A; CapA (autotransporter lipoprotein), and periplasmic binding protein; Peb3 (transport protein), Peb4 (chaperone—CadF transporter protein) and Peb1 (21 kDa protein). The JlpA attaches to the eukaryotic Hsp90 (90 kDa) and causes signal transduction in the host cells. The lipooligosaccharide (LOS) and lipopolysaccharide (LPS) are also contributed to serum resistance and bacterial adhesion **(Bolton, 2015; Bhunia, 2018 and Silva *et al*. 2018a)**.

Heat-shock proteins of *Campylobacter* spp., ClpB, DnaK, DnaJ and GroESL, help in the survival and thermotolerance of the bacteria in the poultry gut because the temperature of the intestinal tract is about 42 °C. Interestingly, DnaJ is the only heat-shock proteins, which have a direct role in the colonization of *Campylobacter* **(Bhunia, 2018)**.

Several studies stated that there is a relation between the degrees of *Campylobacter* adherence to the cultivated cell line and the intensity of campylobacteriosis in infected patients **(García-Sánchez *et al*. 2018)**.

Invasion

Campylobacter invasion ability is a significant factor in the pathogenesis. The clinical symptoms of acute campylobacteriosis are correlated with the invasion of epithelial cells. The flagellum has significant role during the invasion of host cell through helping the nonflagellar proteins secretion by its T3SS channel **(Bhunia, 2018)**. *Campylobacter* invasion antigens (Cia) are group of proteins, which have a vital role in the survival and invasion of host cells and they are delivered to the host cells cytosol through a flagellar T3SS. Therefore, mutations in the flagellar proteins lead to reduction of this invasion ability **(Barrero-Tobon and Hendrixson, 2012 and García-Sánchez *et al*. 2018)**.

Moreover, there are three Cia proteins; CiaI, which has a fundamental role in *Campylobacter* survival inside host cell, CiaC that is essential for maximal invasion of INT-407 cells and CiaB that is important for target cells adherence. In the recent years, a 4th protein, CiaD has been showed to have a key role in the host cells invasion **(Samuelson *et al*. 2013)**. Additionally, mutation in CiaB protein results in reduction of the invasion ability through minimizing the adherence and the possible invasion. Moreover, there are other proteins including FspA, VirK, HtrA (a chaperone protein), CeuE, IamA (invasion-associated protein A) and FlaC, which also play a role in the invasion of host cell, but the mechanisms are not fully known yet **(Bolton, 2015 and García-Sánchez *et al*. 2018)**. Moreover, some *Campylobacter* isolates have a plasmid with high molecular weight, pVir, which has been reported to be correlated to bloody diarrhea. pVir has been reported to have vital role in the invasion of host cell and it is encoded by *vir*B11 gene **(Same and Tamma, 2018)**.

Toxin production

After the internalization, *Campylobacter* enters a vacuole or a membrane-bound structure to escape the host immune system and survive inside the epithelial cell for long period of time until the conditions become favorable for cytotoxic response induction **(Rowe and Madden, 2014)**.

Campylobacter secretes many toxins and the main toxin is the cytolethal distending toxin (CDT), which encoded by a three gene operon (cdtABC). The CDT composed of three toxins with identical molecular weight, CdtB (29 kDa), CdtC (21 kDa) and CdtA (30 kDa). So, it is named a tripartite "AB2" toxin, where CdtB toxic subunit is the enzymatically active one, while the CdtC and CdtA comprise the "B2" subunit that have a role in binding to the receptor of the cell membrane and the CdtB internalization **(Bolton, 2015 and Bhunia, 2018)**.

The CdtB subunit is internalized in the nucleus after its translocation in cytoplasm of the host cell **(Silva *et al*. 2018a)**. Additionally, CdtB has a nuclease activity, which stimulates damage of DNA through double strand breaking. This will result in stopping the cycle of the cell, mainly in the mitosis G2/M transition stage, which affect the cell division and lead to distension of the cell and apoptotic cell death **(Koolman *et al*. 2016 and García-Sánchez *et al*. 2018)**.

The CDT is believed to cease the crypt cells maturation into effective villous epithelial cells; so, it stops the intestinal absorption for a short time and causes diarrhea. CDT is trypsin-sensitive and affected by heating (70 °C for 30 min). Moreover, *Campylobacter* have other toxins like hepatotoxin, pore-forming hemolysin, a shiga-like toxin, which disrupt the protein production and cholera-like enterotoxin that activates cAMP **(Bhunia, 2018)**.

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 *Campylobacter* in the host cells 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 secreated 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 include 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 *wla*N (β-1,3-galactosyltransfrase) and *cgt*B genes those mimics the myelin sheath of the nervous cells' ganglioside. When *Campylobacter* enter the host cells, an antibody is produced against the sialylated LOS 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-Barré 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)**. In *C. jejuni* genome sequencing, the *kps* genes were detected as genes responsible for capsule biosynthesis **(Zilbauer *et al*. 2008)**. Strains with the *ksp*M 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 *pgl* multigene locus found in *Campylobacter*. The surface proteins N-linked glycosylation are responsible for *Campylobacter* protection against gut proteases and avoiding 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 expression 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 *fla*A regulon, which have a key role in synthesis of *Campylobacter* flagella, is regulated by a signal transduction system composed of two components (FlgS/FlgR) **(Bhunia, 2018)**.

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 *rpo*S 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 stressors, 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 their exposure to several classes of antimicrobial agents. Between these antimicrobial agents, quinolones as enrofloxacin 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 competence and hypervariable 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 *gyr*A genes mutations), (iii) antimicrobial efflux pumps which actively eject the antimicrobial agents from the cell (e.g., multidrug efflux pumps, CmeABC), 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* antimicrobial resistance may be endogenous/ 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 antibiotics. So, it is an active method for these agents to be pumped extracellulary, consequently avoiding their accumulation inside the bacterial cell, which essential for the bacterial cell death **(Kurinčič *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)**.
CmeR is a transcription repressor protein, which modulates the expression of the cmeABC operon through the *cj0561c* 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 increased trends in *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 for treatment of patients suffering from campylobacteriosis **(EFSA, 2017)**. Thus, other antimicrobial agent has been required for treatment of human campylobacteriosis such as macrolides (azithromycin and/or erythromycin) and probably soon fluoroquinolones may become disused. 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 *gyr*A gene determining area of quinolone resistance **(Iovine, 2013; Shen *et al*. 2018 and Whitehouse *et al*. 2018)**.

Tetracyclines

Campylobacter resistances to tetracycline have been mediated by the protein of ribosomal protection; TetO that is encoded by the *tet*(O) gene. The *tet*O 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 *tet*O gene is found in the plasmid; but some *Campylobacter* isolates have a *tet*O 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, AphD and AphA) 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 *aph*A-3 gene. Moreover, other genes have also been identified in *Campylobacter* spp. such as genes conferring to kanamycin resistance (*aph*A-7 and *aph*A-1), streptothricin resistance (*sat*) and streptomycin resistance (*aad*E) **(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) efflux by CmeABC efflux pump and possibly others, (ii) methylation of the ribosome encoded by *erm*B gene, (iii) ribosomal proteins target mutations and (iv) mutation in the *23S rRNA* gene **(Bolinger and Kathariou, 2017)**. The ribosomal methylation pathway has been reported recently in one *avian C. coli* isolate in Spain. This was the first report about the *Campylobacter erm*B gene in Europe. This isolate had an elevated level of erythromycin resistance (MIC1024 mg/L) and the *erm*B gene was detected among a multidrug resistance island having five genes for antibiotic resistance. Additionally, this isolate was gentamicin susceptible, but it was resistant to streptomycin, tetracyclines, ciprofloxacin and nalidixic acid **(EFSA, 2017 and Shen *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 macrolide 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)**.
Campylobacter has another method for macrolide resistance includes an alteration in the permeability of the cell membrane mediated by the expression of the MOMP that is encoded by *por*A 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 MOMP make a small pore, which is selective for positively charged ion, in *C. coli* and *C. jejuni* this result in minimizing the

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* are usually resistant to many β-lactams antibiotics such as cephalosporins and penicillin **(Wieczorek 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 cecal 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 Gölz *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 acute watery 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 flabby 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 hyperendemic 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. **Koppenaal *et al*. (2017)** stated a *C. fetus* outbreak due to ingestion of products of unripen cheese, which made from contaminated raw sheep's milk. **Burakoff *et al*. (2018)** detected an outbreak of *C. jejuni* as a result of drinking contaminated unpasteurized milk. **Calciati *et al*. (2012)** reported a campylobacteriosis outbreak in 75 school children in Spain. Animals have been also identified as human campylobacteriosis sources due to the appearance of multidrug-resistant *Campylobacter* infections outbreak in several states that is related to the contact with infected puppies in a pet store. This outbreak occurred in 17 states in USA with 23 hospitalizations from 113 reported infected cases **(García-Sánchez *et al*. 2018 and CDC, 2018)**.

Globally, 166 million *Campylobacter* cases per year have been reported, but there is a great difference by the region. In region where surveillance programs for foodborne illness are well settled, the campylobacteriosis yearly rate is high. In New Zealand, 152.9 cases/ 100,000 populations were stated **(Ministry for Primary Industries, 2015)**. This was followed by Australia and Europe where 93.5 **(NNDSS, 2016)** 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, 2015 and García-Sánchez *et al*. 2018)**. In the developing nations the knowledge about the status of *Campylobacter* infection is obtained from research articles on *Campylobacter* isolation from different specimen **(Silva *et al*. 2018a)**.

PHYTOCHEMICALS AS INTERVENTION STRATEGIES USED TO REDUCE *CAMPYLOBACTER* SPECIES IN POULTRY PRODUCTION

Chickens are believed to be answerable for up to 80% of human *Campylobacter* infection. Therefore, intervention procedures have been developed for controlling *Campylobacter* in chickens at the farm level to minimize the products contamination and accordingly the incidence of human campylobacteriosis **(Upadhyay *et al*. 2019)**.

Since ancient times, phytochemicals have been utilized as food supplements, enhancers of flavor and natural preservatives in numerous cultures. Most of phytochemicals are produced in plants as secondary metabolites due to the interactions between plants and their surrounding environment. The phytochemicals do not participate with any principle metabolic procedures in plants, but they possibly increase the immunity and capacity of these plants to persist in stressful environment and pathogenic infection **(Upadhyay *et al*. 2017)**. Several phytochemicals possess important antimicrobial activities including beta-resorcylic acid (from Brazilian berries and wood), eugenol (from clove oil), trans-cinnamaldehyde (from cinnamon bark), caprylic acid (from coconut oil as medium-chain fatty acid), thymol and carvacrol (from oregano oil) **(Wagle *et al*. 2017a and Upadhyay *et al*. 2019)**.

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 bacterial cell wall and membrane integrity, which may cause a leakage of cellular contents and cell death **(Upadhyay *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 *Salmonella* species **(Mattson *et al*. 2011)**, *Listeria monocytogenes* **(Upadhyay *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 (*Syzgium aromaticum*/ *Eugenia caryophyllus*) **(Upadhyay *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 **(Micciche *et al*. 2019)**. Additionally, eugenol has exhibited an important antimicrobial action against foodborne microorganisms such as *Salmonella* spp. **(Upadhyay *et al*. 2013b)**, *Escherichia coli* **(Ghosh *et al*. 2013)**, *Listeria monocytogenes* **(Upadhyay *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 cytolethal distending toxins **(Upadhyay *et al*. 2017 and Wagle *et al*. 2017a)**. Eugenol and Beta-resorcylic acid are likewise 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)**.

CONCLUSION

Campylobacter spp., mainly *C. jejuni* have become the leading cause of bacterial foodborne enteritis worldwide. Human *Campylobacter* infection is caused by the consumption of contaminated poultry meat and meat products.

Over the last decade, many researches have been applied to study the biology, antimicrobial resistance, pathogenicity, virulence and epidemiology of *Campylobacter* spp. to found the ideal control strategies of these bacteria and thus reduce *Campylobacter* infection in humans. However, the lack of surveillance programs in developing countries making it difficult to control campylobacteriosis; therefore, efforts to survey and control these bacteria should be increased worldwide. There are various methods to control these pathogens, but recent researches prefer the use of phytochemicals such as beta resorcylic acid and eugenol due to their antimicrobial properties and their ability to down regulate the expression of several virulence genes, which lead to minimizing *C. jejuni* attachment and invasion to the epithelial cells in the gastro intestinal tract.

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