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REVIEW ARTICLE

Use of Polyphenols for the Control of Chicken Meat Borne Zoonotic *Campylobacter jejuni* Serotypes O1/44, O2, and O4 complex

Bekzhan I. Barbol[1] and Abdullah F. Alsayeqh*[2]

[1]Laboratory of General Parasitology, Institute of Zoology, Almaty 050060, Kazakhstan
Faculty of Biology and Biotechnology, Al-Farabi Kazakh National University, Almaty 050040, Kazakhstan.
[2]Department of Veterinary Preventive Medicine, College of Veterinary Medicine, Qassim University, Buraidah, Saudi Arabia.
*Corresponding author: a.alsayeqh@qu.edu.sa

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A B S T R A C T

Campylobacteriosis is a major food-borne zoonotic disease which is caused by the *Campylobacter* species. *Campylobacter jejuni* is the most prevalent species causing infections in humans. To meet protein requirements, humans primarily consume poultry meat. *C. jejuni* serotypes O1/44, O2, and O4 complex are frequently present in chickens which are the primary source of food-borne zoonotic campylobacteriosis. The pathogenic bacteria spread in commercial poultry farms from one bird to another by horizontal route of transmission. *C. jejuni* enters the human body through contaminated food (chiefly chicken meat) and proliferates in the gastrointestinal tract. Antimicrobial resistance is a significant challenge today. To overcome antibiotic resistance, scientists are now focusing on alternative strategies for the control of Campylobacteriosis. Polyphenols are naturally occurring botanical compounds which have multiple medicinal properties. These properties include antioxidants, anti-inflammatory, anti-carcinogenic, anti-mutagenic, cardio-protective, anti-diabetic, and neuro-protective activities. Polyphenols, with their wide range of therapeutic properties, are a focus for scientists in developing potent drugs to control campylobacteriosis. In this review, we will discuss the pathogenesis of *C. jejuni* for a better understanding of controlling the infection and the detailed mechanisms of the action of different polyphenols.

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INTRODUCTION

Campylobacter jejuni is a Gram-negative, ubiquitous bacterium that belongs to the family *Campylobacteraceae* (Ammar *et al.*, 2021). *C. jejuni* was first described by Escherich when he isolated the bacteria from the colon of a dead child (Olson *et al.*, 2008). When microscopically examined, the bacterium was also found in the stool of children who were suffering from diarrhea (Kumar *et al.*, 2022). Campylobacters are helical or spiral in shape and they are non-spore-forming bacteria (Huang and Garcia, 2022). Other characteristics of this bacterium are that they are microaerophilic (less demanding free oxygen), motile, non-fermenting, and have a single flagellum at one or both ends (Li *et al.*, 2020). The optimum temperature range for the growth of *C. jejuni* is 37-42°C and they are oxidase-positive (having the ability to produce cytochrome c oxidase enzyme). It is infamous for the proliferation of the food-borne zoonotic disease 'campylobacteriosis' in humans and animals, including small and large ruminants, farm animals, and many other warm-blooded species (Abebe *et al.*, 2020). Campylobacteriosis is the most frequently reported food-borne zoonotic disease since 2005 (Schirone and Visciano, 2021; Myintzaw *et al.*, 2023). *C. jejuni* pathogens also have the ability to survive the critical conditions of the gut of the organism (Lopes *et al.*, 2021; Al Hakeem *et al.*, 2022). *C. jejuni* is transmitted to humans by the means of consumption of contaminated food chiefly meat (Ben Romdhane and Merle, 2021). Now-a-days poultry farming is at a peak level in the whole world, as production in 2023 was 142 million metric tons of poultry meat. The high demand for poultry meat increases food-borne illness risk. *C. jejuni* spreads horizontally through fecal ingestion (Rapp *et al.*, 2020; Al Hakeem *et al.*, 2022). Bird-to-bird transmission is

reported in broilers by fecal shedding and ingestion contaminated with *C. jejuni* (Kanwal *et al.*, 2023). However, vertical transmission is still controversial as pathogens have been seen in birds of age 2-3 weeks (Sadek *et al.*, 2023). Infected individuals typically face inflammation of the small intestine (enteritis) characterized by fever, diarrhea, abdominal pain, and malaise (discomfort) (Cohen, 2022). It causes severe diarrhea in children of less than 5-years of age and causes fatality in 1 out of 9 individuals (Ryoo, 2021). Campylobacteriosis is estimated to cause contamination in 1 out of 10 individuals annually across the globe (Myintzaw *et al.*, 2023). However, the rate of the infection is quite high in developing countries while it is endemic in low- and middle-income countries (Endtz, 2020). The infection rate of campylobacteriosis chiefly depends on multiple serotypes of *C. jejuni*.

Many serotypes of *C. jejuni* are responsible for the transmission of the disease in humans (Heimesaat *et al.*, 2021). Since a large portion of people eat chicken, we are particularly concerned about the presence of the poultry pathogenic serotypes O1/44, O2, and O4 complex in chicken meat (Møller Nielsen *et al.*, 1997). These serotypes of *C. jejuni* are responsible for the transmission of campylobacteriosis from the meat of chicken to consumers (humans). The prevalence rate of previously discussed serotypes of *C. jejuni* is relatively higher in commercial poultry farms, while the horizontal route is considered the primary source of infection in birds (Huang *et al.*, 2009). Strict biosecurity can prevent the pathogenic bacteria from entering the poultry farm, but once they enter the farm premises, control of *C. jejuni* would be a challenging task (Newell *et al.*, 2011; Davies and Wales, 2019). Antibiotics are the first choice of treatment when the disease enters the premises of a poultry shed.

Multiple antibacterial drugs are being used for the control and treatment of campylobacteriosis infection (Dai *et al.*, 2020). Antibiotics are added to poultry water and feed to control the disease and lower the infection rate (Hofacre *et al.*, 2013). Antibiotics target multiple stages of *C. jejuni* life cycle in the gastrointestinal tract of the birds (Hermans *et al.*, 2011). Antibacterials have both camplylobactericidal and campylobacteriostatic effects, but the major drawback of using antibiotics in poultry is the drug residues that remain in the flesh of birds and can be transmitted to the consumer (Ghimpețeanu *et al.*, 2022; Zampara *et al.*, 2023). Parasites are developing resistance against various antimicrobial drugs.

Drug resistance is the primary problem of the modern era, as resistance to multiple chemical drugs is increasing day by day (Church and McKillip, 2021; Liu *et al*., 2023; Ullah *et al.*, 2023). Drug resistance against campylobacteriosis leads to various problems, i.e., severe economic losses, the transmission of the disease, and resource wastage (Ali and Alsayeqh, 2022). Scientists are now focusing on alternative treatment strategies for campylobacteriosis to avoid antibiotic resistance and other problems (Abd El-Hack *et al.*, 2021). These alternatives include prebiotics, probiotics, peptides, immunogens, vitamins, and plant-based preparations. Among all the alternative strategies, plant-based compounds are the most effective because of their diverse biological and health properties (Hassan *et al.*, 2023; Özüiçli *et al.*, 2023; Adeli *et al.*, 2024). Different parts of the plants have been in use for the treatment of multiple problems for centuries (Ahmad *et al.*, 2022; Mubashir *et al.*, 2022; Aljohani, 2023; Hussain *et al.*, 2023; Velázquez-Antunez *et al*., 2023). Now in this modern era, we have focused on the single compound of the part of the plant despite using the whole part (Al-Hoshani *et al.*, 2023; Eltaly *et al.*, 2023; Mohammad *et al.*, 2023). Multiple botanical compounds have been tested for the control of parasites in poultry and have proven effective (Ahmad *et al.*, 2023; Batool *et al.*, 2023; Rehman *et al.*, 2023). For the development of alternative strategies to control the spread of food-borne zoonotic campylobacteriosis, we must know the mechanism of the pathogenicity of *C. jejuni* in the host cells.

MATERIALS AND METHODS

This review used Google Scholar (www.scolar.google.com) as the primary source of information. Furthermore, ResearchGate (www.researchgate.com), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and ScienceDirect (http://www.sciencedirect.com/) were used as secondary search engines. Keywords used are "Polyphenols", "*Campylobacter jejuni*", "Food-borne zoonotic diseases of poultry", "Campylobacteriosis", "*C. jejuni*", "Use of Polyphenols for the control of *C. jejuni*", and "Plants used for the control of *C. jejuni*". This is a qualitative review, so no statistical comparison was performed, and the results are not quantified.

Pathogenesis of *C. jejuni*: The fecal-oral route is the primary pathway of the transmission of *C. jejuni* between poultry birds (Hermans *et al.*, 2012). A very small dose of *C. jejuni* is adequate for successful colonization in birds (Al Hakeem *et al.*, 2022). Pathogenesis in humans starts with the ingestion of contaminated food/chicken (Saeed *et al.*, 2021). After the entrance of the pathogenic *C. jejuni* into the host body, it gets attached to the epithelial cells or mucous membranes with the help of flagella (tiny tails that help the bacteria to move) (Kemper and Hensel, 2023). *C. jejuni* consists of 1 or 2 polar flagella which aid in movement and infection (Henderson *et al.*, 2020). C*ampylobacters* have flagellum in order to cause the disease (Lopes *et al.*, 2021). The flagellum aids the bacterium to overcome the peristaltic movement of the gut of the host (Ishikawa *et al.*, 2020). It also makes the bacterium able to enter the mucous membranes and invade the epithelial cells/membrane (Cao *et al.*, 2022).

After the invasion, *C. jejuni* faces very harsh conditions of the human body, including the immune response of the body and acidic environment of the stomach (Kim *et al.*, 2021). *Campylobacter* multidrug efflux pump assists *C. jejuni* to overcome the toxic compounds i.e., heavy metals, bile salts, and antimicrobials (Sangave, 2020). *C. jejuni* starts to colonize the small intestine of the host after surviving all the harsh conditions of the body (Cayrou *et al.*, 2021). It consumes the nutrients of the gastrointestinal tract to conquer the resistance of colonizing (Khan *et al.*, 2021). *C. jejuni* invades and destroys the epithelial cells of the gastrointestinal tract and produces enterotoxins (Rogers *et al.*, 2023). Detailed pathogenesis is shown in Fig. 1.

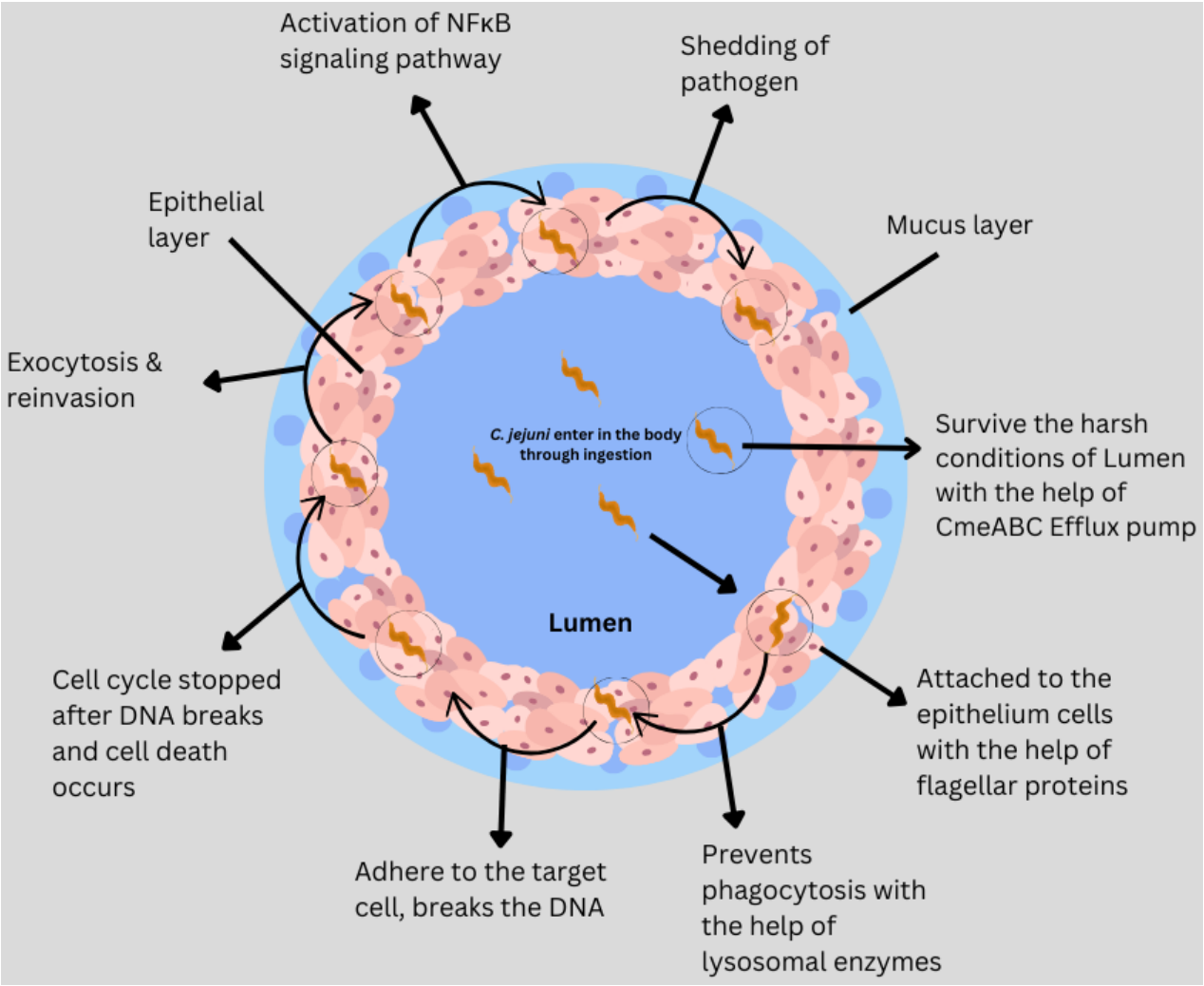

Fig. 1: Pathogenesis of *C. jejuni* in human's Gastrointestinal tract.

Production of enterotoxins is chiefly responsible for the diarrhea in the patients (Lobo de Sá *et al.*, 2021). However, the production of toxins is quite variable between different stains of *C. jejuni* (Elmi *et al.*, 2021). Pathogens of *C. jejuni* are able to produce biofilms for their survival in the harsh environment of the human gastrointestinal tract (Elgamoudi and Korolik, 2021). Biofilms are an essential part of *C. jejuni* bacterium in order to provide nutritional access to pathogens (Tram *et al.*, 2020). The pathogenesis of *C. jejuni* can be prevented by disrupting the formation of biofilms (Elgamoudi *et al.*, 2020).

Use of Polyphenols for the control and prevention of campylobacteriosis: Polyphenols are naturally occurring plant compounds that belong to a major family of phenols (Tuladhar *et al.*, 2021). Polyphenols are chemical compounds that have more than one hydroxyl group attached to the aromatic ring (Šamec *et al.*, 2021). The simplest chemical structures of some polyphenols that are being used for the control of *C. jeuni* are given in Fig. 2. They have been widely used for multiple purposes, especially for health benefits (Yan *et al.*, 2020). Polyphenols have excellent antimicrobial properties which enable them to be used as food preservatives (Martinengo *et al.*, 2021). They have a wide range of biological activities, including anti-oxidative, anti-inflammatory, anti-carcinogenic, anti-mutagenic, cardio-protective, anti-diabetic, and neuro-protective properties (Ahmed *et al.*, 2021). With such a wide range of biological properties, polyphenols can be used to control *C. jejuni* at different pathogenesis stages and to prevent the proliferation of campylobacteriosis (Klančnik *et al.*, 2021; Kamelan Kafi *et al.*, 2022). Detailed mechanisms of the action of different polyphenols and their use against *C. jejuni* are given below.

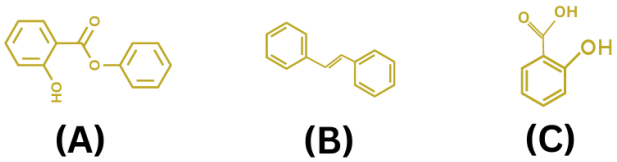

Fig. 2: Simplest chemical structures of polyphenols (A) Flavonoids (B) Stilbenes (C) Phenolic acids.

Flavonoids: Flavonoids is a Latin word which means yellow in color, this is because of their yellow color naturally occurring appearance (Patil and Murumkar, 2024). Flavonoids are the naturally occurring plant compounds that belong to the family polyphenols (Dias *et al.*, 2021). The simplest chemical structure of flavonoids contains one heterocyclic ring attached with 2 phenyl rings (Çetinkaya *et al.*, 2022). Flavonoids are chiefly present in glycoside-bound and free aglycone forms in

plants (Olech *et al.*, 2020). The most consumed form in the diet is glycosidic bound form of the flavonoids (Xie *et al.*, 2022). Flavonoids are infamous for their multiple medicinal activities that make them able to be used as a cure to treat multiple diseases (Ullah *et al.*, 2020a). The biological activities of the flavonoids include anti-oxidative, antibacterial, antiviral, anti-inflammatory, and anticancer properties (Mondal and Rahaman, 2020; Rupasinghe, 2020; Wen *et al.*, 2021).

Multiple compounds of flavonoids have been studied against the control of the highly zoonotic food-borne campylobacteriosis (Oh and Jeon, 2015b; Ibrahim *et al.*, 2020; Ullah *et al.*, 2020b; Kamelan Kafi *et al.*, 2022; Kunčič *et al.*, 2022). Mechanisms of action of different compounds of the flavonoids have also been studied and proven effective. Multidrug efflux pumps (MEP) are the membrane proteins that are responsible for the removal of multiple antibacterial drugs from the cell (Fig. 3) (Ramalingam *et al.*, 2024). MEP is directly influenced by the CmeABC gene of the *C. jejuni* bacterium (Sharifi *et al.*, 2021). Flavonoids can reduce the gene expression of CmeABC which will disturb the efflux mechanism and ultimately death of the pathogenic cell occurs (Waditzer and Bucar, 2021).

Another mechanism of flavonoid compounds has also been reported to change the permeability of the cell membrane of *C. jejuni* (Ibrahim *et al.*, 2020) (Table 1). Alteration in the membrane permeability of the cell results in the imbalance of ions in the cell, resulting in the loss of energy in the cell (Wiczew *et al.*, 2021). Multiple studies have reported the positive effects of flavonoids when used against *C. jejuni* for the control of food-borne zoonotic campylobacteriosis (Klančnik *et al.*, 2019; Upadhyay *et al.*, 2019; Pan *et al.*, 2020; Ullah *et al.*, 2020b; Elgamoudi and Korolik, 2021; Menikheim *et al.*, 2024). Flavonoids can be used to make more effective commercial drugs for the control of campylobacteriosis (Klančnik *et al.*, 2012; Abd El-Hack *et al.*, 2021).

Stilbenes: Stilbenes are the Class of naturally occurring polyphenols in various parts of multiple plant species (Teka *et al.*, 2022). Stilbenes are well known for their multiple medicinal properties, including antifungal, antibacterial, antiviral, anticancer, cardioprotective, neuroprotective, and antioxidant activities (Tushar, 2022; Duta-Bratu *et al.*, 2023). They also take part in cell proliferation mechanisms, cell signaling pathways, estrogen receptor agonist activities, controlling the glycogenic levels in diabetic patients, and apoptosis of the cell (Huang *et al.*, 2020; Blahova *et al.*, 2021; Shahwan *et al.*, 2022).

Multiple research studies have reported that stilbenes are used for the control of food-borne zoonotic campylobacteriosis (Duarte *et al.*, 2015; Mingo *et al.*, 2016; Možina *et al.*, 2018b, a; Silva *et al.*, 2018; Kalogianni *et al.*, 2020; Heimesaat *et al.*, 2023; Menikheim *et al.*, 2024). Stilbenes cause loss of the charge difference between the plasma membrane of a muscle cell or nerve cell, which will result in the depolarization of the cell (R Neves *et al.*, 2012; Cebova and Pechanova, 2020). Pathogenic cells gain nutritional values through ion channels (Bortner and Cidlowski, 2020). When cell depolarization occurs, ion channels become unable to exchange the ionic concentration along with the nutrients (Dreyer, 2021). Ions are the principal components that maintain the integrity of the cell. An imbalance in the ions present in the cells causes loss in the structural integrity of the cell (Matuz-Mares *et al.*, 2022). Stilbenes alter the membrane permeability of the cell, which makes the cell unable to maintain its ion concentration as described earlier (Serreli *et al.*, 2020).

Keeping in view all the beneficial aspects of stilbenes against the control of *C. jejuni* pathogens, we may conclude that stilbenes have a very good potential to control campylobacteriosis. Stilbenes and their multiple compounds can be used to make potent drugs that can control the proliferation of the *C. jejuni* bacterium (Mattio *et al.*, 2020). However, the safety of the drugs must be investigated with multiple experimental strategies.

Phenolic acids: Phenolic acids, also known as phenolcarboxylic acids, are naturally occurring aromatic acids of phenolic compounds. Phenolic acids, along with flavonoids constitute the major group of polyphenols (Mutha *et al.*, 2021). Phenolic acids contain a phenol ring with an attached carboxylic acid (functional group) (Chen *et al.*, 2020). The simplest structure of the phenolic acids is given in Fig. 2. The Highest phenolic acid contents can be obtained from the dried fruit as they have maximum concentrations of phenolic acids (Özcan *et al.*, 2021). Phenolic acids are well known for their multiple beneficial properties in improving the health of the individual (Bento-Silva *et al.*, 2020). They have anti-inflammatory, anti-microbial, antioxidant, and immune modulator properties (Akanbong *et al.*, 2021; Kiokias and Oreopoulou, 2021).

Phenolic acids have become the center of attraction for many scientists because of their various health properties (Saleem *et al.*, 2022; Sehrawat *et al.*, 2022; Shahrajabian and Sun, 2023). Multiple scientists have reported that phenolic acids have a very potent activity for the control of *C. jejuni* (Puupponen-Pimiä *et al.*, 2005; Gañan *et al.*, 2009; Oh and Jeon, 2015b; Sima *et al.*, 2018; Kamelan Kafi *et al.*, 2022; Pham *et al.*, 2023). Biofilm production is an excellent strategy for the pathogenic bacteria for the survival in the host organisms (Kumar *et al.*, 2017). Biofilm is a community of microorganisms that attaches to the surface of the living organism with the help of self-produced extracellular polymeric substances (Khan *et al.*, 2017). Phenolic acids have been reported to destroy the biofilm produced by the *C. jejuni* pathogens (Puupponen-Pimiä *et al.*, 2005; Dávila-Aviña *et al.*, 2020). Survival of the pathogens of *C. jejuni* would be very difficult when phenolic acids damage their biofilm (Corcionivoschi *et al.*, 2023). Phenolic acids disrupt the cell membrane of *C. jejuni* and also damage the cell protein and intracellular enzymes (Barbosa *et al.*, 2020). Safety index of the phenolic acids must be considered in formulating new effective drugs for the control of *C. jejuni* and prevent campylobacteriosis.

Other polyphenolic compounds: There are multiple other polyphenolic compounds that are effective against *C. jejuni* (Bensch *et al.*, 2011; Oh and Jeon, 2015a; Kamelan Kafi *et al.*, 2022; Mehdizadeh *et al.*, 2022). Among all other compounds, tannins, and curcumins are the most important, as they have shown antibacterial

Table 1: Mechanisms of action of different polyphenolic compounds and their results

Sr. no.	Polyphenolic Class	Compound used	Source of Compound	Mechanism of Action	Results	References
1	Flavonoid	Galangin	Propolis	They alter the cell membrane permeability of *C. jejuni* which causes an ionic imbalance in the cell.	Inhibits the growth of *C. jejuni.* The highest sensitivity percentage among *C. jejuni* strains observed was 68.8%. The MIC[1] of galagin range from 0.250-0.125mg/mL.	(Campana *et al.*, 2009; Ramalingam *et al.*, 2024)
		Taxifolin	-	Reduces the gene expression of CmeABC multidrug efflux pump and also reduces the membrane permeability.	Inhibits *C. jejuni* growth in the intestine of humans and prevents proliferation. The membrane permeability was significantly increased at the concentration of 1µg mL^{-1}.	(Oh and Jeon, 2015b; Sharifi *et al.*, 2021)
		Various compounds of flavonoids have been used	Extracted from the leaves of *Adenanthera pavonine* and *Annona squamosa*		Prevents the proliferation of *C. jejuni* and is effective against the control of campylobacteriosis. Compounds of *A. pavonine* exhibited the inhibition growth at 62.5-125µg mL^{-1}. Compounds of *A. squamosa* showed the inhibition growth at 62.5-500µg mL^{-1}.	(Dholvitayakhun *et al.*, 2012)
		Combination of different flavonoids	Extracted from *Glycyrrhiza*		Promotes the growth of broiler birds and reduces the load of *C. jejuni* in feces. The cecal samples were observed by using real time qPCR & culturing and *C. jejuni* reduction count was detected 2.28 and 2.58 log^{10} CFU/g, respectively.	(Ibrahim *et al.*, 2020)
		Dihydromyricetin	-		DHM at the concentration of 50µg/mL exhibits the 24% growth inhibition of *C. jejuni.*	(Wrońska *et al.*, 2022)
		Multiple flavonoid compounds	*R. rosea* roots and rhizomes		Flavonoids extracted from *R. rosea* had shown great potential against the inhibition of AI-2[2] mediated signaling in *C. jejuni.* Bioluminescence reduction rates were observed from 54-91%.	(Kunčič *et al.*, 2022)
		Mixture of multiple flavonoid compounds	White sorghum		Total flavonoid compounds were effective against the control of *C. jejuni* pathogens. 6.25% of MIC was observed in this experiment while the inhibition zone was 7.8±0.3mm. It also showed an IC_{50} concentration of 34.6µg/mL.	(Hamad *et al.*, 2023)
		Epicatechin gallate	Winemaking waste		Exhibited potential activity against the pathogens of *C. jejuni.* MIC between 40 and 160 mg GAE/L[3].	(Mingo *et al.*, 2016)
		Silymarin	-	They down-express the gyrB and 16s rRNA gene of *C. jejuni*	Potent activity against *C. jejuni* pathogens has been seen in the experiment. MIC and MBC were 512µg/mL.	(Kareem *et al.*, 2020)
2	Phenolic acids	Gallic acid	-	They stop the proliferation of biofilms, resulting in the death of the pathogens. However, gallic acid also alters the membrane permeability of the cell.	Membrane permeability was highly increased at the concentration of 0.5 µg mL^{-1}.	(Oh and Jeon, 2015b; Dávila-Aviña *et al.*, 2020)
		Gallic acid, pyrogallol, cinnamic acid, ellagic acid, naringin, vanillic acid, and chyrsin	Extracted from *Ferula gummosa*		Reduces the population of *C. jejuni* pathogens in the ileum of mice. The phenolic-rich fraction encapsulated had shown the efficiency of 83.7% with a particle size of 314.6nm.	(Kamelan Kafi *et al.*, 2022)
		Phenolic acid glycosides	Extracted from the plant *Lavandula angustifolia*	*Lavandula* preparation reduced the motility of *C. jejuni* by 50% which have significant effect on the formation of Biofilms.	The growth of *C. jejuni* pathogens was arrested. MIC vary from 0.2mg/mL to 1mg/mL.	(Ramić *et al.*, 2021; Pham *et al.*, 2023)
		Oleuropein	Olive oil	Oleuropein is a source of hydroxytyrosol which inhibits	Inhibition of *C. jejuni* has been detected when the of	(Kamelan Kafi *et al.*, 2022; Silvan *et*

				the growth of *C. jejuni* and prevents its transmission through the food chain	hydroxytyrosol was 0.1-0.25mg/mL.	*al.*, 2022)
		Galllic acid	-	Disrupts the cell membrane of the pathogen and damages the cell protein and intracellular enzyme of *C. jejuni.*	Maximum inhibition of *C. jejuni* was observed when the gallic acid was mixed with lactic acid. However, gallic acid alone also showed effective results for the control of the pathogen.	(Sima *et al.*, 2018; Lee *et al.*, 2023)
3.	Stilbenes	Pterostilbene and Pinosylvin	-	Causes depolarization of the cell membrane and also changes the permeability of the cell membrane of *C. jejuni*	Pinosylvin has been proven effective against *C. jejuni* and it has shown bactericidal activities in the experiment. MIC values were 16–64 µg/mL.	(Silva *et al.*, 2015; Cebova and Pechanova, 2020)
		Resveratrol	-		Both bacteriostatic and bactericidal effects have been observed. MIC of resveratrol against *C. jejuni* was 100µg/mL.	(Duarte *et al.*, 2015)
		Resveratrol	Winemaking waste		It showed promising activity for the inhibition of pathogenic bacteria. MIC between 40 and 160 mg GAE/L.	(Mingo *et al.*, 2016)
		Synthetic Resveratrol			The experiment showed potent activity against campylobacteriosis in mice. MIC value of 456.5mg/L was observed.	(Heimesaat *et al.*, 2020)
		Multiple compounds of stilbenes	*Rheum officinalis*		Showed effective results when multiple natural compounds were mixed and used against *C. jejuni.* MIC of the purified compound was 31.25µg/mL.	(Yosri *et al.*, 2020)
4.	Other compounds	Curcumin	*Curcuma longa*	Curcumins suppressed the NFκB signaling pathway activated by *C. jejuni*	Effective results have been observed when curcumins were used against *C. jejuni.* MIC was 87µM with a pH of 7.4.	(Lobo de Sá *et al.*, 2019b; Li *et al.*, 2022)
		Curcumin	-	It inhibits the anti-inflammatory effects by disturbing the DNA binding. Disturbing the DNA binding results in the failure of cell division process.	Curcumin showcased potential antibacterial activity against *C. jejuni* pathogens. MIC and MBC concentrations were 256µg/mL and 512µg/mL, respectively.	(Kareem *et al.*, 2020)
		Tannins	Chestnut, mimosa, and quebracho extracts	Inhibits the extracellular microbial enzymes	Extracts rich in hydrolysable and condensed tannins inhibited the growth of *C. jejuni.*	(Anderson *et al.*, 2012)

[1]MIC (Minimal Inhibitory Concentration). [2]AI-2 signaling refers to Autoinducer-2 which is responsible for the communication between species of the pathogen.[3]GAE/L (Gallic acid extract per Liter)

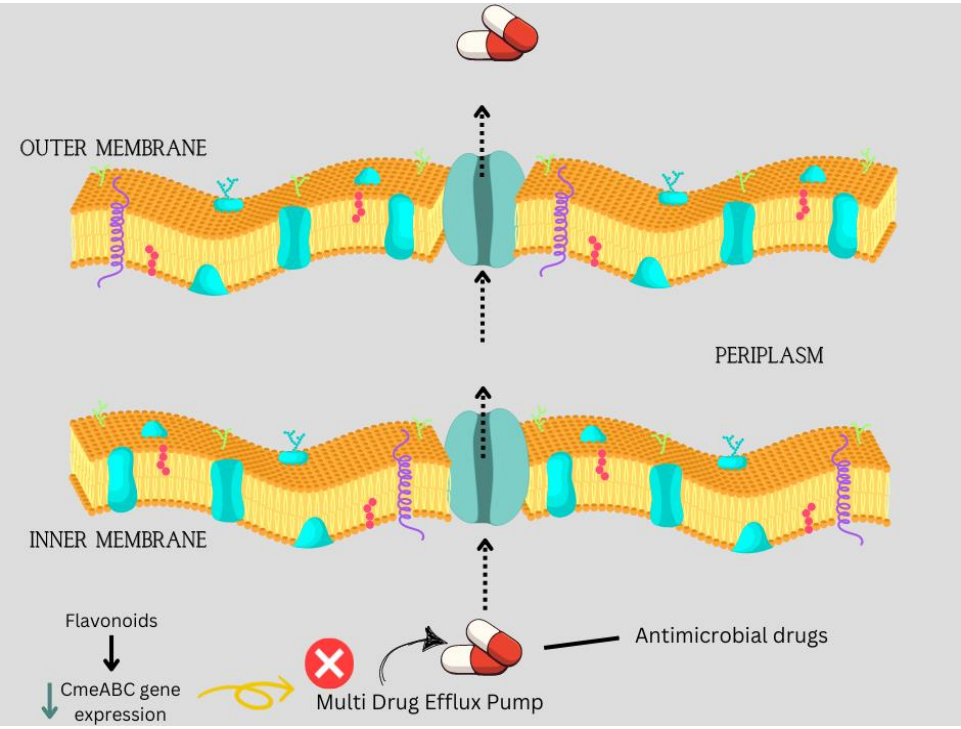

Fig. 3: Mechanism of Flavonoids in Inhibiting the Multi-Drug Efflux Pump.

activities in various studies (Redondo *et al.*, 2014; Lobo de Sá *et al.*, 2019a; Kareem *et al.*, 2020; Heimesaat *et al.*, 2024). Tannins have a potent effect on the extracellular enzymes of *C. jujuni* (Anderson *et al.*, 2012; Dholvitayakhun *et al.*, 2012). All the cellular activities slow down or totally inhibited when the enzymes are not working (Morrison, 1982; Wang *et al.*, 2020). Without any enzyme activity, cellular growth and survival is a challenging task so; by inhibiting the enzymes of the pathogens, we can control the proliferation of the infection (Raheem *et al.*, 2021; Tu *et al.*, 2022). Curcumins also have exhibited potential against the control of food-borne zoonotic campylobacteriosis (Morsy *et al.*, 2023). Curcumins inhibit the anti-inflammatory effects by disturbing DNA binding (Memarzia *et al.*, 2021; Zhang *et al.*, 2022; Jamil *et al.*, 2023). Disturbing the DNA binding results in the failure of the cell division process (Wilhelm *et al.*, 2020). Another mechanism of action of curcumins is also reported that they suppress the NFκB signaling pathway (Liczbiński *et al.*, 2020; Li *et al.*, 2022). NFκB signaling pathway induces the pro-inflammatory genes which are responsible for encoding the chemokines and cytokines (Singh and Singh, 2020; Su *et al.*, 2021). It also plays a very important role in activation, survival, and differentiation of the inflammatory T-cells and innate immune cells (An *et al.*, 2021; Barnabei *et al.*, 2021; Liu *et al.*, 2022).

Conclusions: Campylobacteriosis is a highly zoonotic food-borne disease caused by *Campylobacter* species, chiefly *C. jejuni*. It is transmitted to humans through contaminated food (chicken mainly). Because of the increasing antibacterial resistance, scientists focused on the use of alternative strategies to control the proliferation of *C. jejuni* and avoid campylobacteriosis. Multiple compounds of polyphenols are found to have potential against the pathogenic bacterium, i.e., *C. jejuni*. These compounds can inhibit the growth of *C. jejuni* through multiple mechanisms of action. Naturally occurring compounds of polyphenols can be used to synthesize more potent drugs. However, the safety index of these drugs must be ensured by further research experiments.

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