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Antiadhesive Effect of Plant Compounds in Bacteria

Orlando A. Abreu[1] and Guillermo Barreto[2]
[1]*Faculty of Chemistry, University of Camagüey,*
[2]*Faculty of Veterinary Scienses, University of Camagüey,*
Cuba

1. Introduction

Bacteria have been evolving in our planet for 3 500 – 4 000 million years; thus, based on chemical signals microbial communities have developed different systems to interact with their own colonies and with other species, even with host like plants or animals. Antibiotics release is one of the most outstanding microorganism behaviour. Microbial interaction in nature shows an unexpected performance, sublethal concentrations of antibiotics can modulate dynamic among microorganisms and it can achieve the activation of cooperation, self defence or motility mechanisms among microorganisms (Ratcliff & Denison, 2011).

Notwithstanding the arsenal of antibiotic drugs developed in last decades and, socioeconomic background of outbreaks or epidemic level of colibacilosis, tuberculosis, or cholera in Developing Countries, an underlying problem is challenging ahead: the eclosion of more virulent and resistant microbes. This is an unreliable phenomenon that stresses health care systems in countries and regions (von Baum & Reinhard Marre, 2005; Marcusson et al., 2009; Mediavilla et al., 2005; Wagenlehner & Naber, 2004).

One of the ways by which microbes avoid antibiotic products is by biofilm formation, a usually lipospolisacaride based microorganism aggregates that confer protection, it is a selective advantage for persistence under hostile environmental conditions; biofilm also promotes host colonization. Few decades ago there was a common misunderstanding of the microcosm, since 99% microbes in nature live in communities as biofilms and not in planktonic forms as they were usually cultured and studied (Barreto & Rodríguez, 2009, 2010).

Microorganism biofilm are systems that behave as a whole, determining what, when, and how to interact with the environment (physical or biological). This is mediated by the so called quorum-sensing (QS), a cell-to-cell communication mechanism in which the expression of certain genes in response to the presence of small signal molecules is coordinated (Defoirdt et al., 2011, Dobrindt & Hacker, 2008).

Urinary tract infections (UTIs) are a worldwide health problem, second only to infections of the respiratory tract. Sexual active women are the most susceptible population to UTI, but it is also frequent in elder people and catheterized patients. *Escherichia coli* is the prevalent etiological agent isolated in UTI (Johnson, 1997; 2003; Scholes et al., 2000; Svanborg &

Godaly, 1997; Zhang & Foxman, 2003). Chemotherapy is the main UTI conventional therapy, but antibioresistant strains are continuously emerging, for this reason, antibiotics therapy is sometimes inefficient, specially for β_lactamics, trimethoprim-sulfamethoxazole, and more recent drugs like fluoroquinolones (von Baum & Reinhard Marre, 2005; Drekonja & Johnson, 2008; Gupta et al.,1999; Hooton, 2003; Jadhav et al., 2011; Mediavilla et al., 2005; Storby, 2004; Wagenlehner & Naber, 2004).

In this never ending cycle, there is a race to develop different kinds of vaccines and effective new generation drugs. But it seems that immunologicals or antibiotics are not an exclusive criterion to deal with bacteria, some other subtle ways can be even more promising. If microorganism advantage adaptations are interfered, host abilities to overcome infection and restore itself will be increased.

This review deals with microbiological sciences related to the search of new antibacterial mechanisms, fimbriae as a virulence factor target, and the possibilities of using plant origin compounds as antiadhesive in bacterial attachment, particularly exposed by studies on uropathogenic *Escherichia coli*.

2. Uropathogenic *Escherichia coli* and virulence factors

Escherichia coli (Escherich, 1885 - *Enterobacteriaceae*) is a versatile bacteria that has become the most thoroughly studied organism in the planet (Barreto, 2007), it is a human and warm-blooded animal enteric comensal but, as a result of genetic fluidity of pathogenicity encoding genes, it could have different pathogenic behaviours (Dobrindt, 2005; Ahmed et al., 2008; Schubert et al., 2009); therefore, *E. coli* can become in a virulent bacteria adapted to different niches. Beside gastroenteritis, it can cause urinary tract infection, abdominal sepsis, septicaemia, and meningitis.

Eight virulence factors (VFs) armed pathovars have been described and classified as either diarrheagenic *E. coli*, enteropathogenic *E. coli* (EPEC), enterohemorrhagic *E. coli* (EHEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC) including Shigella, enteroaggregative *E. coli* (EAEC), and diffusely adherent *E. coli* (DAEC); or extraintestinal *E. coli* (ExPEC), uropathogenic *E. coli* (UPEC); and neonatal meningitis *E. coli* (NMEC) (Sasakawa & Hacker, 2006; Croxen & Finlay, 2010).

Uropathogenic *E. coli* is a facultative enteric bacterium, but if carrying some VFs, it can reach the lower urinary tract and cause cystitis or, travel further into the kidneys and cause pyelonephritis (Croxen & Finlay, 2010; Dobrindt & Hacker, 2008; Zhang & Foxman, 2003). UTI it is much more common in young women than men and female anatomy is determinant. It is estimated that 11 percent of women in U.S.A. are diagnosed for UTI every year, about half of all women have a UTI by their late twenties, 20-30 percent will have two or more infections, and 5 percent will suffer from recurrent UTI (Foxman et al., 2000; Zhang & Foxman, 2003).

It is a fact that comensal enteric bacteria must carry a subset of VFs, required in a hostile environment like the urinary tract, to be an ExPEC, and explore niches outside the gastrointestinal tract. Virulence factors provide mechanism by which bacteria survive at least for a period of time needed for each step of infection. Tropism in UPEC is remarkable; once it reaches the uroepithelium, it attaches to its surfaces impeding urinary mechanical clearance and starting colonization; then, it travels to the bladder and kidneys; haeminic

iron could be a gold medal in nephrones. However, UPEC needs a toolbox of VFs like: adhesins, alpha-haemolysin, cytotoxic necrotizing factor, and iron acquisition systems, to cause cystitis and pyelonephritis, which are associated with a number of symptoms such as: inflammation, haematuria, urohaemolitic syndrome, and renal scars; while subvert host unspecific immunity, provoke epithelial exfoliation and invade deeper cells (Gal-Mor & Finlay, 2006; Johnson, 1997, 2003; Kaper et al., 2004; Wiles et al., 2008).

Genetic expressions of VFs are coordinated by QS as a way to be effective in colonization and surviving at least of a reduct of bacterial cell in each infection step. In a recent review, Wu et al. (2008) classified VFs as follows:

- Membrane proteins, which play roles in adhesion, colonization, and invasions; promote adherence to host cell surfaces, are also responsible for resistance to antibiotics, and intercellular communication
- Polysaccharide capsules that surround the bacterial cell and have antiphagocytic properties
- Secretory proteins, such as toxin which can modify the host cell environment and are responsible for some host cell–bacteria interactions
- Cell wall and outer membrane components, such as lipopolysaccharide (LPS or endotoxin) and lipoteichoic acids
- Other virulence factors, such as biofilm forming proteins and siderophores

Virulence factors play a key role in adaptation and evolution. According to Jain et al. (2010), microbes either communal or individual ones provoke chronic or persistent infections, which are largely associated with populations of microbes, and have individual bacterial virulence traits associated with acute infections. VFs are encoded in large continuous blocks of virulence in genome, named pathogenicity associated islands (PAIs), and their expression can be regulated by the host and by environmental signals (Bergsten et al., 2005; Gal-Mor & Finlay, 2006; Johnson, 1997). Horizontal DNA transfer is mediated by plasmids, phages, and PAIs; this is one of the processes that generate bacterial and host genome evolution (Ahmed et al., 2008; Beauregard-Racine et al., 2011; Schubert et al., 2009; Tettelin et al., 2008; Zaneveld et al., 2008).

In *E. coli* pathotypes, several VFs are associated and could be expressed at the same time or not. In the last two decades, VFs research in molecular biology has advanced enough to explain different mechanisms of UPEC pathogenesis, and modern "omics" are focussed in relation to PAIs and UTI epidemiology; thus, aetiology of UTI is better understood, different purposes to disrupt VFs are supported, therapeutic guidelines can be much more successful, and new approaches on antimicrobials research are rendered (Ahmed et al., 2008; Dobrindt, 2005; Henderson et al., 2009; Johnson, 1997; Johnson & Russo, 2006; Westerlund-Wikström & Korhonen 2005; Zhang & Foxman, 2003). A lethal battery of VFs is responsible for the human food borne virulent *E. coli* 0157:H7 and the European recent lethal *E. coli* O104:H4, both strains produce hemolytic uremic syndrome.

2.1 Uropathogenic *E. coli* and fimbriae

Pili or fimbriae are hair-like polymeric (assembled from multiple subunits) proteinaceous appendages expressed on the outer surface of bacteria that enable pathogens to recognize host receptors, anchor, and begin infection; adhesion is produced by a bacterial adhesin

located at the tip of a pilus structure (Dodson et al., 2001; Johnson, 1997, 2003; Niemann et al., 2004). Fimbriae are determinant in early steps of colonization of most *E coli* pathovars. In UPEC are significant, they avoid lavage by the host, attaching to the urinary tract mucosa and triggering signals to start the disease process. This VF is associated to invasion, biofilm formation, cell motility, and transport of proteins and DNA across membranes (Gal- Mor & Finlay, 2006; Johnson, 2003; Kaper et al., 2004; Wiles et al., 2008).

If fimbriae-receptor interaction is not well established, UTI symptoms never occur; when bacterial persist in this condition the patient will have an asymptomatic bacteriuria (ABU). Adhesins have been termed as the most important determinant of pathogenicity (Le Bouguénec, 2005; Croxen & Finlay, 2010; Mulvey, 2002; Niemann et al., 2004; Sauer et al., 2000). The process of a UTI is viewed by Schilling et al. (2001) as a number of measures and counter-measures taken by the host and UPEC. The disease is triggered by fimbriae, inducing the host and bacterial cells signal pathways that involve different mutual responses. In the ''two-step'' model of UTI pathogenesis described by Bergsten et al. (2005), the first step is the activation of the innate response, and the second one is the effector phase involved in bacterial clearance, which depends on neutrophils and their ability to remove lingering inflammatory cells and bacteria. Electron microscopy shows hat this immunological response could be advantageous to bacteria, because it allow them to internalized and survive at the underlying bladder epithelium and creating a reservoir protected from immune surveillance and antibiotics. They remain in a quiescent state for several weeks before reemerging and provoking a recurrent acute infection (Caper et al., 2004; Lane & Mobley, 2007; Mulley et al., 2001; Mulley, 2002).

Uropathogenic *E. coli* type 1 fimbriae and type P fimbriae, are molecularly and epidemiologically well characterized. Both types of fimbriae are assembled in cell bacteria by a highly conserved periplasmatic chaperone and outer membrane usher proteins (Le Bouguénec, 2005; Waksman and Hultgren, 2009). Type 1 fimbriae are so far, the most common adhesin in non complicated low UTI (cystitis); while P fimbriae, encoded by *E. coli* pap (pyelonephritis-associated pilus) operon, adhere to kidney uroepithelium (Croxen and Finlay, 2010; Verger et al., 2007). Fimbriae can be classified according to their receptor-binding specific traits. Type 1 fimbriae mediate mannose-sensitive haemagglutination (MSHA), but P fimbriae are cause of mannose-resistant haemagglutination (MRHA) (Abraham et al. 1998; Johnson, 2003; Westerlund-Wikström and Korhonen, 2005).

Haemagglutination is an *E. coli* visual test to detect types 1 and P bacterial fimbriae, since some red blood cells (RBC) have carbohydrate residue receptors similar to adhesin uroepithelial receptors. When the adhesin of a bacterial cell suspension contacts the receptor of a RBC suspension, a surface reaction occurs and the RBC aggregate like macroscopic glomerules. Uroepithelial cells and oral cells can lead to an agglutination reaction too. Designation of P fimbriae is for the ability of these *E. coli* strains to agglutinate P blood antigens erythrocytes (Johnson, 1991).

Type 1 fimbriae consist in a 7 nm thick helical rod with a tip structure containing the adhesin FimH and two adaptor proteins, FimF and FimG. About 70 % of isolated UPEC encoded a variant of FimF adhesin that binds to monomannose residues. In addition to trimannose receptors, this affinity to monomannose receptors leads to tropism within uroepithelial cells (Johnson, 2003; Mulvey, 2002; Niemann et al., 2004; Verger et al., 2007). P fimbria is a 6.8 nm rod composed of repeating PapA subunits arranged in a right- handed

helical cylinder, with a distally located adhesin PapG on its tip. Receptors of P pili are globoseries of membrane glycolipids with a disaccharide galabiose (Gal-α (1-4)-Gal). There are three PapG alleles (I-III) which bind to different isoreceptors that differ in carbohydrate residues to the common Gal-α (1-4)-Gal core. PapG II binds mainly to globotetrasyl ceramide (GbO4) and it is associated with pyelonephritis symptoms like inflammation and uroepithelial exfoliation (Dodson et al., 2001; Johnson, 2003; Mulvey, 2002; Niemann et al., 2004; Westerlund-Wikström & Korhonen, 2005; Wullt, 2003;). It was demonstrated that class II adhesin is a prerequisite for acute pyelonephritis in primates; besides, in induced mixed infection with P fimbriated *E. coli* and not fimbriated strains it gives a competitive advantage to colonize bladder (Winberg et al., 1995).

The role of fimbriae as virulent factor in UTI pathogenesis has been thoroughly studied in the last thirty years, also confirming the special pathogenesis theory by means of modern methods (Beached, 1981; Johnson, 2001, 2003; Kaper et al., 2004; Verger et al., 2007; Wiles et al., 2008; Zhang & Foxman, 2003). See most of the review articles cited in this subchapter for details and graphics of VFs effects and UTI steps.

3. Experiences against fimbrial adhesion

Interference of VFs is an attractive approach to manage diseases due to bacterial infection. In the case of UPEC, fimbriae are an important target to prematurely neutralize them, before they spread within urinary tract, and if is not timely flushed out become in an asymptomatic bacteriruria. Beside UTI overcome, if this purpose is clinically effective, it is expected in these conditions that possibility of generating antibioresistance will be remote.

Fimbriae have been studied from different perspectives. Regarding enteropathogenic and uropathogenic *E. coli*, Barreto et al. (2001a) reviewed the following experimental attempts:

a. sublethal antibiotic concentrations: fimbrial adhesive ability of *E. coli* to attach to uroepithelium, enterocytes, and some erythrocytes could be decreased by a previous exposition to sublethal antibiotic concentrations of amphicillin, gentamycin, sulfonamides, trimethropim, and tetracycline, however, nalidixic acid can increase adhesion (Barreto et al., 1994; Hales & Aymes, 1985; Johnson, 1991; Padilla et al., 1991; Stenquist et al., 1987; Vosbeck et al., 1982). Sublethal amounts of gentamycin, chloramphenicol and kanamycin tested in *E. coli* G7 inhibit adhesiveness in this strain at 95%, 85%, 80% y 75%, respectively (Barreto et al., 1994). It was found that, in general, those antibiotics that inhibit protein synthesis also inhibit fimbrial expression at sublethal concentrations of either P fimbriae, or K88 and K99 fimbriae (Padilla et al., 1991; Barreto et al., 1994), without culture media influence (Barreto et al., 1995a, 1995b). But this is not the best option in therapy as it has the limitation of antibioresistance emergence (Barreto et al., 2000).
b. immunological methods (antifimbrial vaccines, monoclonal antibodies): Search for a vaccine that blocks *E. coli* fimbriae has been performed since the 1980´ and many results have been obtained, mainly in veterinary medicine. Several methods have been applied to obtain this products, attenuated strains, semipure antigenic extracts, and recombinant technology (Barreto et al., 2001a; Ofek et al., 2003; Campal et al. 2007, 2008). Fimbrial subunits vaccines are more efficient than conventional ones, since other non-protective cell components, or endotoxins that induce shock, vascular permeability,

and abortion in swine are not present (Kaper & Levine, 1988; Levine et al., 1993; Wong et al., 1995). In Cuba, the administration of VACOLI® vaccine to swine protect piglet by suckling in a 93 %, and in 98 % post-weaning (Wong et al., 1995).

A vaccine that induces an antibody response against FimH was tested in humans proving its effectiveness against an UPEC strain in mouse cystitis model (Langermann et al., 1997; Langermann & Ballou, 2003). A high level of protection against P fimbriae has been developed too in a primate model (Soderhall et al., 1997). Molecular microbiology of bacterial pathogenesis and new technologies show favorable expectations concerning discoveries of new vaccines against bacterial infectious diseases (Moingeon et al., 2003; Sasakawa & Hacker, 2006; Westerlund-Wikström & Korhonen, 2005). The wide fimbriae diversity encoded by enteric *E. coli*, and the selective pressure exerted by vaccination usually make bacteria population change toward fimbrial fenotypes not covered by the vaccine. On the other hand, adhesin diversity of enteropathogenic *E coli* is higher in human beings than in animals; antigenic diversity is the principal disadvantage for an UPEC P fimbriae vaccine (Barreto, 2007; Barreto & Campal, 2001; Barreto et al., 2001b).

c. medicinal plant extracts: it is exposing in next epigraph.

Some of these items were coincident with the strategies for UTI management mentioned by Reid (1999): prophylaxis by antibiotics, including natural peptides; vaccines, probiotics and others like avoiding spermicide and keeping a proper hygiene. In a review about anti-adhesion therapy for different bacterial germs, Ofek et al. (2003), referred to receptor analogs and adhesin analogs as anti-adhesive agents, dietary inhibitors of adhesion, adhesin-based vaccines, and host-derived anti-adhesins in innate immunity.

4. Medicinal plants extracts and virulence factors

In the last years, attention to medicinal plant research related to VFs inhibition as a target activity is increasing; several bioassays to evaluate VFs have been develop for several microorganisms, mainly bacteria and yeast. This is a valuable source of compounds to investigate new anti-virulence factors mechanisms of pathogenic microbes.

Different medicinal plant metabolites have antimicrobial activity (Cowan, 1999; Mahady, 2005). In traditional medicine systems of diverse cultures and regions, plants to treat urinary tract diseases are well known. Usually the same species are used for different purposes or medical conditions related to urinary system, i.e. as diuretic (most common), antilithic, and agents for cystitis or pyelonephritis treatment. However common people call all of them as "kidney diseases" or "urinary complaints".

Researches focused on adhesin-receptor medicinal plants interference are recent, since few studies have reported this action in plants, except those related *in vitro*, *in vivo*, and clinical trial of UPEC antiadhesion effects of cranberry fruit (*Vaccinium macrocarpon* Ait., *Ericaceae*). This is the only one commercial herbal product or food claimed as an antiadherent for UTI treatment. Besides, cranberry was among the top ten marketed herbal products in U.S. in the 1990´ (Siciliano, 1998).

In Cuba, first reports about plant extracts against fimbrial adhesion are those of Eucabev, an antidiarrheic drug for veterinary use, manufactured from *Eucaliptus* spp. (*Myrtaceae*) bark.

After using a decoction of *Eucaliptus* spp. bark to treat diarrheic syndrome in different animal species (Velázquez et al., 1991), and confirming no bactericide or bacteriostatic effect on ETEC at several concentrations (Barreto et al., 1993a), an antiadhesive mechanism of this plant was explored as antidiarrheic. Enteropathogenic *E. coli* strains G7 (08 K87, K88ab) and B44 (09 K30, K99) were tested as fimbrial antiadhesives by MSHA assay (Blanco & Blanco, 1993) or monoclonal antibodies assays. After exposure of each strain in media cultures with decoction, infusion, and water extract of *Eucaliptus saligna* and *E. citriodora*, fimbriae inhibition was found significant, 83,3% and 100%, respectively (Barreto et al., 1993b, 1993c; 1995a, 1995b; Barreto & Campal, 2001).

Similar experiments were carried out to screen P fimbriae-receptor interference in UPEC strains of medicinal plants traditionally used for urinary diseases. Wild *E coli* P^+ strains cultured or not with *Lepidium virginicum* (*Apiaceae*) and *Achyranthes aspera* (*Amaranthaceae*) extracts were tested by MRHA assay (Guerra et al., 1995; Prieto et al., 1995). Then, plant antiadhesin activity was determined by MRHA and anti-PapA monoclonal antiserum assays in *E. coli* ATCC 25922 to screen extracts of *A. aspera, L. virginicum, Ageratum conyzoides* (*Asteraceae*), *Zingiber officinale* (*Zingiberaceae*), *Curcuma longa* (*Zingiberaceae*) and *Costus speciosus* (*Costaceae*). Antiadhesive effect was detected in all plant species except *C. longa* extracts (Barreto et al., 2001). Besides, based on a previous study on K99 adhesin, effect of plant extracts on erythrocytes receptors was evaluated (Barreto et al., 1993b), finding activity in all plant species. Results of antiadhesin effect and Gal-Gal receptors are summarized in Table 1.

Plant	Extracts	Effect on fimbriae	Effect on receptors
A. aspera	ethanol 90%	-	-
	ethanol 20%	-	-
	decoction	-	+
L. virginicum	ethanol 90%	+	+
	ethanol 20%	-	-
	decoction	-	-
A. conyzoides	ethanol 90%	-	-
	ethanol 20%	-	-
	decoction	-	-
Z. officinale	ethanol 90%	-	-
	ethanol 20%	-	+
	decoction	-	-
C. longa	ethanol 90%	+	+
	ethanol 20%	+	+
	decoction	+	-
C. speciosus	ethanol 90%	+	+
	ethanol 20%	-	+
	decoction	+	-

Table 1. Effect of plant extracts on fimbrial expression and fimbrial receptors, from Barreto et al., (2001). (+ = positive adhesion - unaltered fimbriae or receptors; - = no adhesion -no expression of fimbriae or altered receptors).

Source	Microorganism	Effects on Virulence Factor	Reference
Vaccinium macrocarpon (*Ericaceae*)	See epigraph below		
Berberis aristata (*Berberidaceae*) berberine sulfate	UPEC	inhibit adhesion	Sun et al., 1988a
B. aristata berberine sulfate	*Streptococcus pyogenes*	inhibit adhesion to epithelial cells, fibronectin, and hexadecane	Sun et al., 1988b
Arctostophylos uva-ursi (*Ericaceae*) *Vaccinium vitis-idaea*	*E. coli*	enhance aggregation	Türi et al., 1999
Matricaria recutita (*Asteraceae*) *M. matricarioides*		block aggregation	
Psidium guajava (*Myrtaceae*) galactose-specific lectin	*E. coli* 0157:H7	inhibit adhesion to red cells	Coutiño et al., 2001
Azadirachta indica (*Meliaceae*)	*Streptococcus sanguis*	inhibit adhesion	Ofek et al., 2003
Camelia sinensis (*Theacae*) (green tea) (-) epicatechin gallate, (-) gallocatechin gallate	*P. gingivalis*		
(oolong tea) polyphenol	*S. mutans*, *S. sobranus*		
Galanthus nivalis (*Amaryllidaceae*) mannose-sensitive lectin	*E. coli*		
Gloipeltis furcata and *Gigartina teldi* (seaweeds) sulfated polysaccharides	*S. sobrinus*		
Humulus lupulus (*Urticaceae*) bract polyphenols	*S. mutans*		
Melaphis chinensis gallotannin	*S. sanguis*		
Persea americana (*Lauraceae*) tannins	*S. mutans*		
Andrographis paniculata (*Acanthaceae*)	*S. mutans*	inhibit adhesion	Limsong et al., 2004
Senna alata (*Cassia alata*) (*Caesalpinaeae*)			
C. sinensis			
Harrisonia perforata (*Simaroubaceae*)			
Punica granatum (*Punicaceae*)	*Staphylococcus aureus*	Staphylococcal enterotoxin A	Braga et al., 2005
Streblus asper (*Moraceae*) leaf	*Candida albicans*	inhibit adhesion to denture acrylic	Taweechaisupa-pong et al., 2006
Resveratrol (found in grapes seeds-*Vitis vinifera*) (*Vitaceae*)	*Proteus mirabilis*	Swarming, flagella, haemolysin and urease	Wang et al. 2006
Conocarpus erectus (*Combretaceae*)	*Chromobacterium violaceum* and *Agrobacterium tumefaciens*	quorum sensing-disrupting (QS-D)	Adonizio et al., 2006
Chamaecyce hypericifolia (*Euphorbiaceae*)			
Callistemon viminalis (*Myrtaceae*)			
Bucida burceras (*Combretaceae*),			
Tetrazygia bicolor (*Melastomataceae*)			
Quercus virginiana (*Fagaceae*).			
V. macrocarpon	*C. violaceum*	QS-D	Vattem et al., 2007
V. angustifolium			

Rubus idaeus (*Ericaceae*)			
R. eubatus			
Fragaria sp. (*Rosaceae*)			
Vitis sp.			
Origanum vulgare (*Lamiaceae*)			
Rosemarinus officinalis (*Lamiaceae*)			
Ocimum basilicum (*Lamiaceae*)			
Thymus sp. (*Lamiaceae*)			
Brassica oleracea (*Brassicaceae*)			
Curcuma longa (*Zingiberaceae*)			
Zingiber officinale (*Zingiberaceae*)			
Galla chinensis	*E. coli* (ETEC)	heat-labile enterotoxin	Chen et al., 2006
Z. officinale	*E. coli* (ETEC)	heat-labile enterotoxin	Chen et al., 2007a
Chaenomeles speciosa fruit (*Rosaceae*)	*E. coli* (ETEC)	heat-labile enterotoxin	Chen et al., 2007b
Pelargonium sidoides (*Geraniaceae*)	*Helicobacter pylori*	inhibit adhesion to intact human stomach tissue	Wittschier et al., 2007
P. sidoides (*Geraniaceae*)	*Streptococcus pyogenes*	HEp-2 cells and buccal epithelial cells	Conrad et al., 2007
V. angustifolium or *V. corymbosum* *V. myrtillus* *V. ovalifolium, V. ovatum, V. parvifolium*	*H. pylori* and *Streptococcus* spp.	adhesion	Yarnell & Abascal, 2008
C. sinensis	*S. mutans*		
Galla chinensis[1] methyl gallate (MG) and gallic acid (GA)	*S. mutans*	antibiofilm	Kang et al., 2008
Holarrhena antidysenterica (*Apocynaceae*)	EPEC	inhibit adhesion to enteric epithelial cells	Kavitha & Niranjali 2009
Glycyrrhiza glabra (*Fabaceae*)	*Porphyromonas gingivalis*	adhesion	Wittschier et al., 2009
G. glabra glycyrrhizin	*E. coli* (ETEC)	Heat-labile enterotoxin	Chen et al., 2009
Ibicella lutea (*Martyniaceae*) aereal part	*Proteus mirabilis*	swarming differentiation, hemagglutination and biofilm formation	Sosa, & Zunino et al., 2009
Dodonaea viscosa var. angustifolia (*Sapindaceae*)	*C. albicans*	adherence to oral epithelial cells	Patel et al., 2009
Aegle marmelos (*Rutaceae*) unripe fruit decoction	*E. coli* (EPEC), *E. coli* (EIEC) and *Shigella flexneri*	Adhesion to HEp-2 cell line, decrease production of heat labile toxin and its binding to ganglioside monosialic acid	Brijesh et al., 2009
P. guajava decoction	*E. coli* (EPEC), *E. coli* (EIEC) and *S. flexneri*	*idem.*	Birdi et al., 2010
P. sidoides root extract specific proanthocyanidins	*S. pyogenes*	anti-adhesion	Janecki et al., 2011

[1] Gall caused by aphids on *Rhus* spp. (*Anacardiaceae*)

Piper bredemeyeri (*Piperaceae*)	*C. violaceum*	QS-D	Olivero et al., 2011
P. brachypodom			
P. bogotence			
Terminalia catappa (*Combretaceae*) Tannin-rich fraction	*C. violaceum and Pseudomonas aeruginosa*	QS-D antibiofilm and LasA staphylolytic activity	Taganna et al., 2011
Delisea pulchra (red marine alga) Halogenated furanones	bacteria	QS-D	Defoirdt et al., 2011
Halobacillus salinus isolated from sea grass, phenetylamide metabolites	bacteria including *Vibryo harveyi*		
Compounds bacteria isolated from a marine alga *Colpomenia sinuosa*	bacteria		
Chamaecrista desvauxii (*Fabaceae*) Fruits	*Staphylococcus epidermidis*	antibiofilm	Trentin et al., 2011
Commiphora leptophloeos (*Burseraceae*) Stem bark			
Dioclea grandiflora (*Fabaceae*) Fruits			
Eugenia brejoensis (*Myrtaceae*) Leaves			
Libidibia ferrea var ferrea (*Caesalpinaeae*) Fruits			
Melocactus zehntneri (*Cactaceae*) Roots, Cephalium			
Myracrodruoun urundeuva (*Anacardiaceae*) Leaves, Branches, Stem bark			
Myroxylon peruiferum (*Fabaceae*) Leaves			
Parkinsonia aculeata (*Caesalpinaeae*) Leaves			
Piptadenia viridiflora (*Mimosoideae*) Branches, Fruits			
Pityrocarpa moniliformis (*Mimosoideae*) Leaves			
Polygala boliviensis (*Polygalaceae*) Leaves, Branches			
P. violacea Leaves, Roots			
Senna macranthera (*Caesalpinaeae*) Fruits			
S. splendida Branches			
Sida galheirensis (*Caesalpinaeae*) Leaves, Branches			
Euphorbia trigona (*Euphorbiaceae*) latex extracts	*P. mirabilis* and *P.aeruginosa*	swarming, antibiofilm rhamnolipid production inhibition of urease	Nashikkar et al., 2011
Lactuca indica (*Asteraceae*)	*E. coli*	inhibit effect on focus adhesin kinasa phosphorylation	Lüthjea et al., 2011

Table 2. Effect of natural products on microorganism virulence factor.

There is an increasing evidence that plant metabolites can inhibit different VFs expressions allowing host defense to overcome an infection; for instance, fimbrial adhesin interference in UTI, that is fundamental to avoid bacterial colonization, invasion, and then disease first symptoms. Results show this is a plausible mechanism by which maybe underestimated non-bacteriostatic/bactericides medicinal plants, traditionally used in treating "urinary complaints" are worthy.

Some studies of medicinal plants, food plants and seaweeds against different VFs on several Gram positive bacteria, Gram negative bacteria, and against *Candida albicans* are compiled in Table 2. Referring more than 60 plant species from diverse families, but there really are few species considering the potential of the world flora. Of particular interest is the evidence of activity of edible plants or seasoning plants like: *Camellia sinensis* (*Theacae*), *Psidium guajava* (*Myrtaceae*), *Vitas vinifera* (*Vitaceae*) and *Zingiber officinale* (*Zingiberaceae*), since daily ingestion as food of such plants could prevent infections. Ginger and *Curcuma* with antifimbrial UPEC activity (Table 1) are reported too as anti quorum sensing-disrupting. Most of summarized plants have traditional renown in microbial gastrointestinal disorders or urinary complaints treatment (Roig, 1974).

E. coli references are related to antiadhesion activity, or inhibition of toxins of enteric pathotypes; and in an early reference of Sun et al. (1988a), it is described the antiadhesive effects of berberine alkaloids inhibiting the expression of fimbrial subunits on UPEC. There are also studies on antiadhesion properties of certain plant extracts against oral and dental plaque forming bacteria.

In some studies, modern technology search for non-conventional antimicrobials is based on folk medicine (Birdi et al., 2010; Brijesh et al., 2009; Chen et al., 2007a, 2007b, 2009; Coutiño et al., 2001; Kavitha & Niranjali 2009;). In recent years, the increase in number of articles including new trends in VFs research, like biofilm inhibition or quorum sensing-disrupting is noticeable. Screening is reported for quorum sensing-disrupting in dietary plant (food or seasoning plant) (Vattem et al., 2007), in which all species were active. Taking into account ethnobotanic criteria, a quorum sensing-disrupting and antibiofilm effects of plants from Florida, USA, and Caatinga plants from Brazil, respectively, were screened (Adonizio et al., 2006; Trentin et al., 2011).

Several VFs can be neutralized by plant compounds. A broad field of research on this subject is ahead; science advances in phytochemistry, molecular microbiology, *in silico* designs, and "omics" providing new features that will end in VFs based new therapy strategies. Another point is that, like in other biological activities, ethnomedical knowledge-based criteria can afford success in the search for antivirulence factor novel drugs or herbal medicine (Abreu & Cuéllar, 2008).

4.1 Cranberry (*Vaccinium macrocarpon*) antiadhesive therapy leader

Cranberry is a fruit currently use widely as food and as medicine mainly for women in prophylaxis of ITU because of its antibacterial properties. Herein are present a bulk of information that allows stating that cranberry can be consider as a leader in the bacterial antiadhesive therapy.

4.2 Botany

Taxonomy: *Ericaceae* family, *Vaccinioideae* Subfamily, *Vaccinieae* Tribe; the genus comprises 450 species (Berazaín, 1992). Among the most common species used as medicine and food are *V. mirtillus* (blueberry), and *V. corymbosum* (highbush), *V. ashei* (rabbiteye) and *V. angustifolium* (lowbush). Description: *V. macrocarpon* is an evergreen trailing shrub, rhizomatous habits when young; pink, simple, axilar flowers. Ovary has four locules. Wind or insects are needed for pollination. Fruit is a shining red epigynous berry, ripening occurs 60-120 days after pollination. Distribution: east bogs in North America, from Newfoundland to Manitoba, south of Virginia, Ohio and north of Illinois.

4.3 Traditional use

Native people from North America cranberry use fruit as food in meat dishes and as medicine for erysipelas, tonsilitis, scarlatina sore throat, ulcers, pleuresy (leaves) (Moerman (2004); cancer and scurvy (Duke, 2007), and to treat cystitis and prevent UTI (Farnsworth, 2003).

4.4 Phytochemistry

V. macrocarpon is among the most phytochemically studied *Vaccinium* species (Abreu et al., 2008). Cranberry fruit mainly contains organic acids such as: citric, chlorogenic, malic, quinic and shiquimic acids (Duke, 1992; Jensen 2002); and polyphenols like flavonoids, and anthocyanic pigment glycosides of cyanidin and paeonidin (Abreu et al., 2008; Duke 1992). Polyphenolic compounds have been the most researched in *Vaccinium* spp. because of its antioxidant and anti-UTI activity, mainly in *V. macrocarpon* and *V. mirtillus* fruits.

Trimeric type A proanthocyanidines characterized in cranberry by Foo et al. (2000a), is of particular interest, since authors demonstrated it is the active compound in UPEC P fimbriae interference.

4.5 *In vitro* and *in vivo* antimicrobial activity

Almost all biological effects of cranberry fruit so far evaluated are antimicrobial activity. There are references of antivirus activity (Konowalchuk & Speirs, 1978), antifungal activity (Cipollini & Stiles, 1992; Marwan & Nagel, 1986) and antibacterial activity (Lee et al., 2000; Leitão et al. 2005; Marwan & Nagel, 1986). The last author reports no activity of cranberry juice (pH- 3, 5 and 6, 9) and cranberry proanthocyanidin-rich fractions against *E. coli* and other bacteria. Thus, cranberry use in UTI prevention or treatment is not due to bacteriostatic/bactericide activity; however, there is a great number of *in* vitro and *in vivo* research related to the antiadhesive effect of cranberry on UPEC P^+. Besides, there are reports of cranberry as a fimbrial antiadhesive in other bacteria (Moerman et al., 2003).

At the beginning of 20th century, antimicrobial cranberry studies were based on the possibility of acidification of urine or by excretion of hypoxic acid, a potent bacteriostatic associated to the fruit ingestion (Blatherwick, 1923; Moen, 1962); but other results questioned this mechanism (Fellers, 1933; Nickey, 1975). It is in the 1980' that research on bacterial adhesion began to be considered as a mechanism of action of cranberry in UTI (Schmidt & Sabot, 1989; Sabot, 1984; Safire et al., 1989); since then, dozen of articles have been reporting *in vitro*, *ex vivo*, and *in vivo* experiences of its antiadhesion activity. Among

models used were HARM and HASR in guinea pigs and human erythrocytes; uroepithelial cells, bladder cultured cell lines and laboratory animal models (Nowak & Schmitt, 2008). Using micro plate technology and turbidity assessment for testing the adherence of *Escherichia coli* P^+ to human uroepithelial cell line T24, Turner et al. (2005), developed a high-throughput assay to study *V. macrocarpon* extracts. A bioassay like this could also be use in the screening of extracts of plants used traditionally in urinary tract system diseases.

Certainty on cranberry antifimbrial effect was achieved by Ahuja et al. (1998) by means of electronic microscopy, no fimbrial expression or loose of them, and change in *E. coli* morphology were clear. More recently, isolated cranberry proanthocyanidins (PACs) at 60 µm/ml were tested on UPEC P^+ resulting in a potent antiadhesive activity (Foo et al., 2000a, 2000b, Howel et al., 2005).

Ex vivo studies on exposed UPEC strains in urine from healthy volunteers under different cranberry administration schedules, and several researches on humans have validated cranberry for UTI prevention. Prospective clinical trial in young women with recurrent UTI has demonstrated a protective effect. In a metaanalysis of human clinical trials, Jepson & Craig (2008) conclude that:

"There is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. Its effectiveness for other groups is less certain. (...) The evidence is inconclusive as to whether it is effective in older people (both men and women), and current evidence suggest that it is not effective in people with a neuropathic bladder. (...) Further properly designed studies with relevant outcomes are needed."

4.6 Proanthocyanidins

Proanthocyanidins (condensed tannins) are oligomeric and polymeric end products of the flavonoid biosynthetic pathway. They are present in the fruits, bark, leaves and seeds of many plants, where they provide protection against predation. They are charactehrized by their flavor and astringency in beverages like wine, tea, and fruit juices; and they have been used as leather tanning agents for a long time. An important property of this kind of tannins is their ability to bind proteins; hence they can inhibit enzymes and reduce protein availability in animal nutrition (Dixon et al., 2005; Miranda & Cuéllar, 2001). Like other plant polyphenol compounds, in recent years PACs have been biologically studied, mainly for their antioxidand activity (King et al., 2007). In general, their bioavailability is poor, since PACs high molecular weight difficult absorption, but this could be beneficial for gut health due to their effects on lipid oxidation, inflammation, immunity, and pathogenic bacterial adhesion (Reed & Howell, 2008).

Unusual A-type proanthocyanidins (B-type linkage is more common in plant kingdom), consisting primarily of epicatechin tetramers and pentamers (Fig. 1), with at least one A-type linkage has been elucidated in UPEC antiadhesive active fractions of cranberry. It is structurally characterized by a linkage between C2 of the upper unit (C ring), and the oxygen at C7 of the starter unit (A-ring), in addition to the linkage between C4 of the upper unit and positions 6 or 8 of the lower unit (Dixon et al., 2005; Foo et al., 2000b;. Howell et al., 2005). A-type linkage is a structural prerequisite for antiadhesion effects, since Howell et al., (2008) compared cranberry PACs with other B-type proanthocyanidins from commercial foods and not found *in vitro* or *ex vivo* activity.

Cranberry PACs decreases bacterial adhesion forces in UPEC (Pinzón-Arango et al, 2009) and influences *Streptococcus mutans* biofilms on saliva-coated apatitic surface and on dental caries development *in vivo* (Koo et al, 2010). Besides, cranberry PACs perform a cytotoxic activity in different cell lines (Singh et al., 2009).

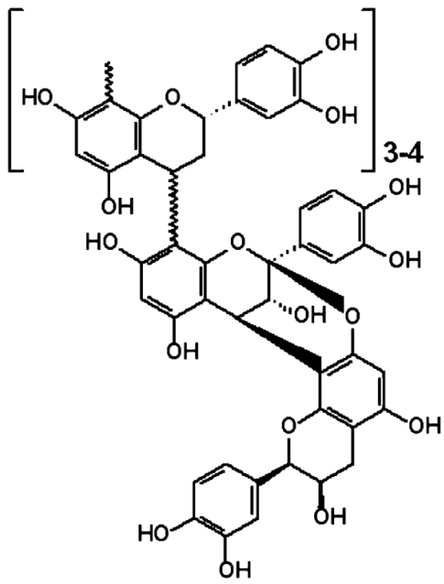

Fig. 1. Cranberry A-type proanthocyanidin.

5. Possible mechanism of plant antiadhesion effects

Chemical signal interactions between host and pathological microorganisms, or innocuous microorganisms have been recently understood, and seem to be very common in nature; in such magnitude, that plant origin product by host consumed could compete with microbes for specific receptors. These interactions are mediate by a complex dynamics of physico-chemical and biological parameters, in which time can also be a prominent variable. Quorum sensing coordinated the infection steps recognizing each critical moment of the process by biofilm bacterial density.

Mechanism of fimbrial adhesin inhibition can be related to different effects of plant metabolites such as: delection of genes encoding fimbrial subunits, enzymes or proteins associated to its transportation and allocation at the cell surface and cell receptor analogues that binds to adhesin subunits or nearby, impeding their interaction with receptors.

Antifimbrial activity at genetic level is similar to some antibiotics mechanism proposed at sublethal concentrations (Barreto et al., 1994; Padilla et al., 1991); besides *V. macrocarpon*, this mechanism had been proposed for berberine alkaloid (Sum et al., 1988).

Results on plant extracts blockade of adhesin-receptor interaction in RBC, suggest it can be mediated by glycoprotein (like lectins) with pectidic sequences similar to Pap G or Pap G-Pap F, or by compounds that subvert spatial configuration of Gal-Gal receptors. In both cases, structural analogues of adhesin-receptor interaction could also be interfered due to esteric constraints.

Thermodynamic approach of fimbriae interaction is another point of view, in which Liu et al. (2008), calculate the Gibbs free energy of adhesion changes by interfacial tensions on human kidney uroepithelial cells and fimbriated or not fimbriated *E. coli* strains treated three hours with cranberry juice extracts.

Interference of plant compounds in adhesin-receptor interaction should not promote microorganism antibioresistance, since at sublethal concentrations selection pressure is not established. Therefore, as effect is only exerted over pathogen VFs, it is not expected deleterious side effects on comensal microbiota as in chemotherapy usually occurs (candidiasis, colon disbacteriosis).

Synergy it is known among plant metabolites, in this case for instance, some plant species reported in table 1 and table 2, besides antiadhesion effects, have activity on further VFs, thus, the sum of those effects help to avoid or suppress infection. In UPEC, is traditionally reported diuretic effect in those plants (Roig, 1974), this activity can synergized too as anti-infective in UTI, increasing bacterial clearance.

6. Approach from nature in antibacterial research

Science development has explained several host-bacteria interactions and ways to rationally manage them. However, there is too much knowledge to acquire in this sense, but certainly these natural signalling mechanisms among microbes and their environment, including hosts, is rendering new clinical strategies and drug candidates. It is noteworthy how this kind of interaction is present in newborn mammals and during their span life. Food is something more than a mere matrix containing nutrients; starting from microbiota, human feeding has also coevolved with diverse biological niches.

Antiadhesive properties of human milk oligosaccharides in relation to pathogenic bacteria are remarkable. They show to be effective inhibitors of adhesion of gastric and uroepithelial bacterial pathogens *in vitro* and *in vivo*, and prevent diarrhoea in infants (Bavington & Page, 2005; Mårild et al., 2004; Ofek et al., 2003).

Carbohydrate compounds are usual in food stuff, but they are not only important to supply energy; recently, it is known that in several ways they are involved in a microorganism molecular mechanism of adhesion, invasion, and infection. Glycoproteins (lectins) and a broad range of non-nutrient components of food plants (phytochemicals) can also be active in this way.

Before vertebrates appeared, microorganisms and plants were part of the whole system of Nature. Plant phytochemicals are part of the pool of signals in food plant that deal with the microbe world. Plants that act against pathogens by a non-cidal mechanism are selected by Nature; but also culturally, humans have selected them as safe food plants, medicinal plants, or both at once. In the last decades, borders between food and medicine are disappearing, i.e. functional food. It is not surprising that most of them were always there, but now they are new products. Gastrointestinal tract and genito-urinary system are plenty of microorganism receptors and plant origin compounds receptors, thus dietary patterns or herbal products can probably promote a first barrier defence avoiding pathogen virulence factors like QS, fimbriae, or toxins.

Ethnobotany of antimicrobial food or medicinal plants can be corroborated by new antivirulence factor target techniques and other modern bioassays. Novel antimicrobial activities like antiadhesion effect could provide tools to eliminate or decrease virulence of infections that, in spite of quemotherapy advances, seem to become more inflexible microorganisms.

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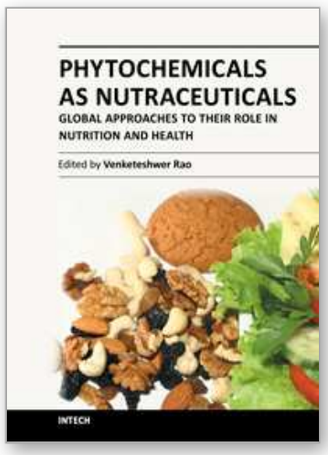

Phytochemicals as Nutraceuticals - Global Approaches to Their Role in Nutrition and Health

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Phytochemicals are biologically active compounds present in plants used for food and medicine. A great deal of interest has been generated recently in the isolation, characterization and biological activity of these phytochemicals. This book is in response to the need for more current and global scope of phytochemicals. It contains chapters written by internationally recognized authors. The topics covered in the book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The book has been planned to meet the needs of the researchers, health professionals, government regulatory agencies and industries. This book will serve as a standard reference book in this important and fast growing area of phytochemicals, human nutrition and health.

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Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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