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ANTI-ADHESION THERAPY: A POTENTIAL ALTERNATE APPROACH TO OVERCOME DRUG RESISTANCE AMONG INFECTIOUS MICROORGANISMS

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ABSTRACT

Pathogenesis of the infectious microorganisms begins with the adhesion and subsequent colonization on the different organ surfaces, made possible due to the presence of protein/polysaccharide at the surfaces of the pathogen which are called adhesins. The emergence of drug resistant bacteria in the recent past encourage searching for novel means to treat most dreadful diseases. The present article reviews the potential alternative approach to treat various infectious diseases and strategies to overcome drug resistance among infectious microorganisms using anti-adhesins such as carbohydrate lectins, cranberry extract, bromelain from fruit or stem of pineapple, receptor analogues, adhesion analogs and other dietary inhibitors.

Keywords*:* Anti-adhesins, Cranberry, lectins, proanthocyanidins, Anti-L-selectin antibody.

INTRODUCTION

In the recent past, repeated emergence of drug resistant bacteria forced researchers to investigate for novel means of fighting bacterial infections. An alternative approach is the use of agents that interfere with the ability of the microorganisms to adhere onto the tissues. Adhesins are cell-surface components or appendages of bacteria that facilitate to bind on to the specific receptors on epithelial cell membranes of the host. Most fimbriae of Gram negative bacteria function as adhesins, but in many cases it is a minor subunit protein at the tip of the fimbriae that is the actual adhesin. In Gram-positive bacteria, a protein or polysaccharide surface layer serves as the specific adhesin. Adherence is often an essential

step in pathogenesis and therefore these are the attractive candidates for the preparation of vaccines [1]. Adhesins are found on the stiff hair, like submicroscopic structure known as fimbriae (Pili) that form bonds with a host cell receptor site. Distinct adhesins located on the cell surface of pathogens mediate attachment to complementary glycoprotein or glycolipids on the host tissue [34].

Anti-adhesins are the substance which reduces contact between host tissue and pathogens either by prevention or reversal of adhesion of the infectious agent. Recently various substances, such as fruits, dietary constituents, adhesion analogs, have been used for anti-adhesion therapy [23]. Anti-adhesins play an important role in reducing the colonization of pathogenic organisms on to surface for gastrointestinal, urinogenital, respiratory tracts and thereby preventing subsequent infection. Anti-adhesion therapies intended to prevent biofilm formation or the rate of colonization, on different organ surfaces [37, 2, 4, 44].

There are many types of anti-adhesins, derived from various sources, which may include; carbohydrate lectins, receptor analogues, adhesion analogous, dietary inhibitors (Dietary constituents) and Anti-L-selectin antibody, which will be discussed in the further section.

PREPARATION OF ANTI-ADHESINS

Different types of anti-adhesins may be prepared using various methods, some of which are included in the following.

Preperation of N-Acetyl D-Lactosamine specific lectins

The tubers of *Arisaema intermedium* contains lectin which could be purified by affinity chromatography using asialofetuin linked porous amino activated silica beads [32]. The filtered homogenate needs to be centrifuged (30 min/4°C). The clean supernatant can be dialyzed against 0.001M PBS (pH 7.2/4° C) to remove low molecular weight substances which would interfere with lectin activity. Further purification could be done by affinity chromatography. The bound lectins should be eluted with 0.1M HCl buffer (pH 2.5) and immediately with 2M tris buffer, pH 8.8 [15]. The obtained lectin can be further purified by electrophoresis, gel exclusion and ion exchange chromatography. The protein, carbohydrate content, and stability need to be determined. The purified lectin can be later used for the anti-adhesion therapy.

Preperation of *Piper betle* and *Psidium guajava* extracts

100 ml stocks of *Piper betle* and *Psidium guajava* extracts were dried to obtain 200 mg of dried pellet and sonicated to break up the pellet and centrifuged (10.000 rpm/10 min) to obtain clear suspension of the extract. The debris could be discarded to eliminate any interference in the reading of the optical density and supernatant could be used for the treatment of dental plaque [29].

Bromelain a crude extract from the fruit or stem of Pineapple

The fruit or stem of pineapple plant (*Ananas comosus* linn.) yield a group of protein digesting enzymes referred to as bromelain. It is nontoxic compound with therapeutic value, which reduces the inflammation to the patient with arthritis. Bromelain could be extracted from the fresh pineapple, washing it with 0.1% hydrogen peroxide solutions, peeled off, cut into small pieces and weighed. Juice needs to be collected from the fresh pineapple stem part by homogenization, in the presence of sodium acetate buffer solution and filtered. Benzoic acid/sodium benzoate can be added as a preservative at a concentration of 1 gm/kg of stem. The crude extract used as source of bromelain [3].

LC-MS analysis of Cranberry juice concentrate

Cranberry juice can be extracted with ethyl acetate (1:6) and evaporated and reconstituted with 500 µl of 80% methanol. LC-MS analyses for the ethyl acetate extract of the cranberry juice could be performed. In addition HPLC have been performed on reversed-phase pre-equilibrated with 10 M ammonium acetate. Separations were effected by a linear gradient starting with acetonitrile concentration 5%/0-15 min; 80%/16 min; 5% and stopped at 20 min. Further analysis can be done by mass spectrometer using electrospray ionization in the negative mode. LC-MS analyses of the ethyl acetate extract showed several molecular ions corresponding to proanthocyanidins, anthocyanins, flavonoids and organic acids. Flavonoids and anthocyanins exist predominantly in conjugated form with various sugars (pentose and hexoses), which may significantly influence its bioavailability and absorption [28].

Characterization of Cranberry drink

The juice extract of North American cranberry plant, *Vaccinium macrocarpon* of 250 ml of the drink included 25 % cranberry juice from sweetened dried cranberries, with 40 g constitutes protein, carbohydrates, fat, fiber, sodium, sugars (fructose, glucose, sucrose), acids (quinic, citric, malic, benzoic, ascorbic acid,) and different phenolic compounds

including proanthocyanidin (PAC) and determined using dimethylaminocinnamaldehyde method [7]. Further, PAC constitute a group of flavones ranging from dimers to polymers, while monomeric flavonoids (such as catechin and epicatechin) are not considered PAC as there are differences in the linkages (A- or B- type) between the monomeric units. Analyses of the proanthocyanidin fraction isolated from cranberries (*Vaccinium macrocarpon*) indicated the presence of a mixture of epicatechin oligomers of various molecular weights with activity associated with A-type linkages. The cranberry drinks and sweetened dried cranberries contained typically 80 mg cranberry proanthocyanidins per serving which was characterized [8].

USAGE OF ANTI-ADHESINS IN URINARY TRACT INFECTION

Urinary tract infections (UTI) are common, painful and disruptive disease of urinary tract occurs most often in women [6]. Eleven percent female in the United States, reports at least one UTI in a year [9]. The pathogen responsible for over 80% of all UTI was *Escherichia coli* [18].

The potential for cranberry juice to inhibit bacterial adherence was demonstrated using 77 isolates of *E. coli* adherence to uroepithelial cells obtained from women with no history of UTI. Further, adherence inhibition was assessed using 33% of freshly prepared cranberry juice and *in-vitro* studies suggested that cranberry juice contained factors that inhibited adherence of *E. coli* to epithetical cells, by interfering with a surface component of the bacteria [37].

UTI preventive effects have been documented in commercially available cranberry-lingonberry juice concentrate. In a six month of the study, 50 women drinking 50 ml of the cranberry-lingonberry juice concentrate experienced 20% absolute risk reduction in developing UTI against the control group. Further, 25ml of pure unsweetened cranberry juice and concentrated tablets of similar strength reduced the UTI by 12% compared to placebo [18]. Further, distinct groups of compound from cranberries have been characterized as condensed proanthocynidins and demonstrated anti-adherence activity on the p-fabricated *E. coli* associated with UTI at concentration as low as 10-50 mg/ml [12]. Commonly recommended amount of cranberry for UTI prevention is daily consumption of 300 ml of cranberry juice cocktail containing 36 mg proanthocyanidins which clinically reduced bacteriuria and pyuria [1].

The usages of cranberry juice in reducing biofilm formation on uroepithelial cells have also been reported [31]. Consumption of 250 ml of water in addition to normal diet at breakfast, lunch time, and dinner time for seven days was practiced and ninth day, for a further seven days each patient was given 250 ml of cranberry juice at the meal times, and urine analysis report suggested that cranberry juice intake caused a significant reduction in biofilm load and substantial decrease in the infection rates when taken before infection sets in [31].

USAGE OF CRANBERRY JUICE CONCENTRATES IN URINARY BLADDER CANCER

The chemopreventive efficacies of cranberry juice concentrate in an experimental model for urinary bladder cancer have been evaluated using female rats. The experimental animal received N-butyl-N-4-hydroxy butyl- nitrosamine, for a period of eight weeks. Cranberry juice concentrate was administered each day. A dose dependent preventive effect of cranberry treatment was observed with reduced number urinary bladder cancers of 38% against controls group [28]. Further, quercetin and its methylated derivative detected in the urine samples and thus the components of cranberries were observed to be reducing the intensity of urinary bladder carcinogenesis.

USAGE OF ANTI-ADHESINS IN DENTAL INFECTIONS

Dental plaque harbours bacteria and other microorganisms that serve as precursor to a number of human diseases, including dental caries and periodontal disease. Gram negative anaerobic bacteria that exhibit interspecies adhesion or co-aggregation expressed by the bacterial colonies in dental plaque allow them to withstand the mechanical forces, and salivary flow that would normally displace the bacteria from the mouth [21]. High molecular weight non-dialyzable material (NDM) extracted from cranberry juice, disrupted the coaggregation of bacterial species up to 70% segregation and found to be effective in inhibiting coaggregation [44].

In an another study, the ability of lectin from *Talisia esculenta*, and protein from *Labramia bojeri* seeds observed to inhibit adherence of microorganisms and the minimum inhibitory concentration of these proteins were determined with *Streptococcus mutans, S. sobrinus, S. S. sanguinis, S. mitis* and *S. oralis* responsible for dental carries. The results suggested that the use of anti-adhesive agents such as lectin, could disengage mutant streptococci from dental biofilm or interfere with their adhesion without affecting their viability [25]. Further, two acid lectins from mulberry leaves, found to agglutinate the pathogenic bacteria

Pseudomonas syringae pv mori, in addition to *Griffonia simplicifolia* lectins, *Canavalia ensiformis*, wheat germ agglutinin, peanut lectin[21]. Lectin such as soyabean agglutinin *Dolicus biflorus* was also reacting with Streptococci, and propose to affect this bacteria by interacting with N-acetyl D-galactosamine residues in their external structures [14].

Several plant seed lectins such as, glucose-mannose chains found to be very effective in preventing the *Streptococcus* adherence on tooth surface and also exhibited distinct biological activities. Thus, these lectins would be useful for anti-adhesion therapy and even it would reduce the biofilm formation on tooth surfaces [44].

USAGE OF ANTI-ADHESINS IN GASTROINTESTINAL DISORDER

Usage of receptor analogous as adhesins against pathogens adherence through carbohydrate specific lectins have been reported. The receptors analogous such as saccharides are structurally similar to those of glycolipid and glycoprotein, are required for the adhesion. Therefore, saccharides could inhibit the adhesion on epithelial cells of intestine through competitive inhibition [23]. Further, primates infected with *Helicobacter pylori* have been treated with sialyl-3 lactose a specific inhibitor of adhesion of *H. pylori* to human gastric tissue culture cells and animals were evaluated. Report suggested that two animals out of six cured of the infection, and one animal cleared the infection transiently [35].

In-vitro adhesion studies on the effect of the high molecular weight non-dialyzable material (NDM) from cranberries using three strains of *H. pylori* with specificity for human gastric mucosal cells were analyzed [4]. NDM was found to inhibit sialic acid specific adhesion to human gastric mucus in a dose dependent and strain dependent manner. Significant adhesion inhibition was apparent when *H. pylori* strain were incubated with NDM but not when mucus cell alone was preincubated, or NDM was added after the bacteria had adhered to the mucus. Therefore non-dialyzable material could have *in vivo* protective effects against the development of *H. pylori* induced stomach ulcer [5].

Some of the most anti-adhesive agents identified thus so far are food ingredient. Human milk known to have anti-adhesion property, as it contained oligosaccharides and related compounds to which many bacteria can bind. Investigators began to explore the therapeutic effects of milk oligosaccharides and glycoproteins that act as inhibitors of bacterial adhesion. In one such study, it was found that fucosylated oligosaccharides in milk blocked the

infection in mice caused by *Campylobacter jejuni* and found to be associated with protection of breast fed infants against diarrhea [22].

USAGE OF ANTI-ADHESINS IN NEUROLOGICAL DISORDERS

Hyaluronic acid (HA) is glucosaminoglycan, a highly viscous biopolymer, which play an important role in many tissue repair processes. It has anti-adhesion effects by which fetal wounds heal without causing any defect, this may be due to high concentration of hyaluronic acid in the wound, and it is reduced in case of adults as it is readily degraded. The efficacy of HA in reducing adhesion in different types of injury to rat sciatic nerve have been demonstrated [31]. Further, it was reported that, HA have an anti-adhesion effect by separating injured nerve from adjacent tissue. In an another report cranberry juice supplements have been shown to improve the patient with spinal cord injury or neurological disorder [36].

USAGE OF ANTI-ADHESINS IN RESPIRATORY INFECTIONS

Pseudomonas aeruginosa, an important opportunistic pathogen associated with chronic airway infections. *P. aeruginosa* strains produces high levels of virulent factors exhibited an increased virulence potential with LecA and LecB lectin production. Therefore the virulence site could be successfully treated by application of a solution containing LecA and LecB specific sugars. The sugar solutions presumably prevented lectin-mediated bacterial adhesion to the corresponding human blood cells [11].

In addition, *Pseudomonas aeruginosa* causes respiratory tract infections in patients suffering from cystic fibrosis. Two lectins LecA and LecB, which exert different cytotoxic effects on respiratory epithelial cells and presumably facilitate bacterial adhesion to the airway mucosa. Here, outer membrane of the bacteria contains LecB, binds specifically to L-fucose form biofilm on the lung surfaces, suggesting an important role for LecB in this process. It is further demonstrated that, LecB protein carrying the mutation D104A, which results in a defective sugar-binding site, suggesting that LecB binds to specific carbohydrate ligands located at the bacterial cell surface [42].

Yersinia pestis, an aetiological agent of plague a pandemic disease that swept across Asia and Europe, between 14^{th} to 17^{th} centuries, caused millions of death. The transfer of infection from rat to man through the bite of infected rat flea (*Xenopsiella cheopsis*). The bacteria transmit to the local lymph nodes where they multiply. Multiplication of bacteria in the bloodstream results in septicaemia, allowing plague bacilli to cause secondary pneumonia [26].

The use of short-chain oligosaccharides to inhibit attachment of *Y. pestis* has been proposed as a potential therapeutic strategy [10, 34, 23]. Oligosaccharides have the ability to inhibit *Y. pestis* attachment to other human respiratory cell lines and murine monocyte cell line. It has been postulated that polymeric saccharides act by coating the bacterial cells, blocking interaction of the adhesins with their receptors. However, the differences in the oligosaccharide inhibitory profiles probably select differential expression of oligosaccharide receptors on the eukaryotic cell surfaces, and perhaps modulation of adhesion expression on the bacterial surface in response to receptors expressed on a particular cell type or tissue, would indicate oligosaccharides as therapeutic use for *Y. pestis* attachment during pneumonia [41].

It has also been reported that, 3'-sialyllacto-N-neotetraose from milk could be used as subject of a clinical trial for prophylaxis of acute otitis media to investigate its effect on nasopharyngeal carriage of bacteria (*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*). The compound was given intranasally to children and was observed that it did not have a beneficial effect. These bacterial species are known to produce multiple adhesins, only some of which are specific for sialyl-3P-lactose. In the clinical trial, there was no effect of the administered sugar as compared to the placebo group in preventing otitis media or colonization of the upper respiratory tract by the bacteria. It is possible, therefore, that, as suggested above, targeting only one out of several adhesins that the pathogens are capable of expressing may frequently be insufficient to prevent colonization and symptomatic infection [43].

USAGE OF ANTIADHESINS IN PREVENTION OF BIOFILM FORMATION

Bacterial adhesion and subsequent colonization of surfaces are the first steps toward forming biofilms, and they are responsible for many diseases. Eradication of biofilm is problematic since biofilms are resistant to innate host defenses [13]. Although mechanical removal and antibiotic treatment are the available measures to control biofilm formation, there was threatening call with the development of antibiotic resistance therefore a more promising strategy is the use of anti-adhesion therapy to prevent biofilm formation [38].

It has been estimated that 65% of infectious diseases are associated with the presence of bacterial biofilms. Further the prevalence of *S. aureus* as a human pathogen has been attributed both to its ability to form specific bonds with a wide variety of extracellular proteins and form biofilm. To study the potential role of early detachment events in initiating

secondary infections, the phenotypic attributes of *S. aureus* planktonic cells eroding from biofilms with respect to expression of the collagen adhesion, the collagen-binding abilities of *S. aureus* was correlated to the development of osteomyelitis and septic arthritis. The impact of collagen receptor expression on *S. aureus* adhesion to immobilized collagen *in-vitro* under physiologically relevant shear forces and therefore, this could lead to new therapeutic strategies to target secondary infections [19].

Helicobacter pylori causes peptic ulcer and gastric cancer. Biofilm facilitates *H. pylori* to survive in adverse environments. The effect of curcumin on *H. pylori* biofilm formation both qualitatively by pellicle assay and quantitatively by crystal violet staining was reported. Biofilm formation by *H. pylori* was tested at different concentrations of curcumin. It was observed that inhibition of biofilm formation at MIC of 16 μg/mL. Further the anti-adhesive activity of curcumin was assessed against *H. pylori* on human epithelial type 2-HEP-2 cells. Curcumin observed to be effective in inhibition of biofilm formation and has potential complementary medicine for curing of *H. pylori* biofilm related infections [25].

NEW TARGETS FOR ANTI-ADHESION THERAPY OF HUMAN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a debilitating inflammatory disease of the central nervous system (CNS). There has been a lot of interest in the use of anti-adhesion molecule therapy to prevent the recruitment of inflammatory cells to the CNS, thereby reducing the disease. Based on observations that blockade of α_4 integrin was beneficial in animal models of MS, interest has focused exclusively on this molecule in the treatment of human patients, and clinical trials are now under way (Miller et al., 2003). Promising initial results have provided an impetus for exploring other anti-adhesion pathways [16].

The P-selectin–PSGL-1 pathway is extremely effective in the infiltration of various leukocytes to the vessel wall, particularly at the high shear rates found in the CNS. A critical role for P-selectin or its ligand, PSGL-1, in the recruitment of leukocytes to the CNS in a number of models of inflammation, including a model of MS has been reported [27]. It has been reported that CD8+ cells from MS patients were more prone to adhesion than CD4+ cells through predominantly a P-selectin–PSGL-1, pathway. Anti-adhesin molecule blocking the P-selectin–PSGL-1 pathway could reduce the infiltration of leukocytes, and development MS [17].

ANTI-L-SELECTIN ANTIBODY THERAPY

Anti-adhesion molecule therapy prevents leukocytes from extravasating during exaggerated inflammation, blocking diapedesis which may be detrimental. Therefore, the potential risks of anti-L-selectin antibody therapy have been evaluated in a primate model of sepsis. Sixteen baboons were anesthetized and randomized into two groups. The experimental group received 2 mg/kg of the anti-L-selectin antibody HuDREG-55 and the control group received Ringer's solution prior to the onset of a 2h infusion of *Escherichia coli*. Mice treated with anti-L-selectin antibody eliminated viruses and parasites effectively. Anti-L-selectin antibody administration was associated with improved bacterial clearance. Further there was significant reduction of the CFU count [30]. Thus anti-L-selectin antibody therapy would theoretically decrease leukocyte recruitment to sites of infections as well as non-infectious inflammation. In infectious inflammation, decreased PMN recruitment to tissue could create the risk of impaired defense in patients with bacterial or viral infections. Administration of antibodies has been shown to increase morbidity and mortality in the baboon model of sepsis [45].

CONCLUSION

Anti-adhesive therapy is a new potential alternative approach to prevent adhesion of the antigen has been proposed as a way to combat microbial infections, since bacteria have become increasingly resistant to antibiotics. The prevalence of emerging and reemerging bacteria which are multidrug resistant would be treated with anti- adhesive agents would greatly reduce the incidence of most dreadful diseases.

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