Natural product based anti-adhesion therapy- innovative prevention against bacterial infections

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**Implications**

Antimicrobial resistance (AMR) resistance, similar to climate change, is a shared global problem (Gelband & Laxminarayan 2015). AMR threatens the effective prevention and treatment of an ever-increasing range of infections. There are plenty of resistant bacteria that cause common infections such as urinary tract infections and pneumonia. In addition to causing death, disability and suffering AMR has huge economic impacts. The alarming increase in drug-resistant bacteria means that there is a need for novel means of fighting against bacterial infections. One feasible approach is to use agents that interfere with the ability of the bacteria to adhere to the tissues of the host, the initial stages of the infectious process. Our research project deals with milk oligosaccharides, wild berry and herbal bioactive polyphenols in prevention of bacterial attachment to human nasopharynx. We have focused on major human respiratory pathogenic bacteria. By employing several in vitro techniques we have shown that wild berry molecular fractions inhibit the binding of the serious human pathogen *Neisseria meningitidis*, associated with fatal invasive infections, meningitidis and septicemia. Anti-infective properties of wild berry fractions against different Streptococci causing human respiratory infections, newborn meningitis, animal diseases and associated with dental caries have been detected as well. Inhibitory activity of the berry material has been extracted especially from wild *Vaccinium* berries (bilberries, cranberries, and lingonberries) and from crowberries. Bioactive wild berry polyphenols represent organic products from wild forests subjected under organic certification.

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 **BA I**

Figure 1- Inhibition (I) of bacterial adhesion (BA) to host cell surface. The possible attachment mechanisms of *Neisseria meningitidis* (BA): outer membrane proteins (A), pilin protein (B) or tip-located PilC protein (C) bind to the oligosaccharide structures of surface receptor of host cell. Bacterial adhesins bind to soluble receptor analogs when the binding of bacteria to host cell is inhibited (I). (I: according to Zopf & Roth, Lancet 1996; BA: according to Nassif 1999, modified by Anni Kleino)

**Background and objectives**

The prevention by anti-adhesion is directed to the initial attachment of the bacteria to human cells in the first step of microbial colonization and pathogenesis. Antiadhesive prevention can reduce the spread of the bacteria from person to person or from contaminated food. With anti-adhesion therapy bacterial infections could also be reduced by affecting on the amount of the healthy carriers. In anti-adhesion therapy components isolated from natural products such as berries, milk and herbs can be employed. Plants produce several bioactive compounds in response to environmental stress found in berries. Berry phenolic compounds can act against plant pathogens and may also cross-react with human pathogens. These substances can be curing or preventive. A well-known example is the use of cranberries to protect against *E.coli* urinary tract infections. The idea of present research was to investigate the ability of Northern wild berry bioactive components to prevent bacterial attachment to human respiratory mucosa and to prevent bacterial coaggregation associated with dental caries.

**Results and discussion**

We found anti-infective milk, wild berry and berry juice, and Chinese herbal molecular fractions and that inhibited the binding of pathogenic Neisseria bacteria causing serious human meningitis and septicemia (Hakkarainen et al. 1995, Toivanen et al. 2009, 2011, Huttunen et al. 2016). Anti-infective properties of berry fractions against different Streptococci causing human respiratory infections, newborn meningitis or animal diseases and against oral pathogens was detected as well (Huttunen et al. 2011, Toivanen et al. 2010, Riihinen et al. 2011). Inhibitory activity of the wild berry material has was revealed especially from *Vaccinium* berries and is associated with polyphenols, mainly with proanthocyanidins and/or anthocyanins. Today we aim to develop innovative anti-infective organic food products, which will be submitted to controlled clinical trials. We are also studying antimicrobial activity of wild natural products against food poisoning bacteria (Obey et al. 2016).The food products based on our research results are aimed to be consumed both in developed and developing countries against bacterial infections. Bioactive wild berry and other organic natural products provide a great future potential in controlling infectious diseases both in anti-adhesive and antimicrobial way. They can be utilized in their natural form or in functional food development to protect healthy consumers. The product development could also be directed especially to risk groups, to newborns, elderly people, military servants and immune compromised patients.

**How work was carried out?**

The studied berries and berry juices were fractionated into molecular weight factions using centrifugal devices and for solid phase subfactionation C-18 SPE cartridges were employed. Molecular characterization of the bioactive berry and berry juice fractions was carried out by using NMR and HPLC-mass-spectrometry technologies. Several in vitro anti-adhesion techniques was used including hemagglutination inhibition, microtiter cell binding and and dot binding assays, antiaggregation assay, cell culture studies and pilot clinical trials. Antimicrobial activity was tested in microtiter broth microdilution assay or by disc diffusion method. The studied bacteria were submitted to the experiments as vital whole bacterial cells or using their isolated adhesive pili structures.

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