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# Natural Vs Synthetic Anti-biofilm Drugs

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**Recognition of the fact that bacterial biofilm may play a role in the pathogenesis of disease has led to an increased focus on identifying diseases that may be biofilm-related. Biofilm infections are typically chronic in nature, as biofilm-residing bacteria can be resilient to both the immune system, antibiotics, and other treatments. Observations also indicate that biofilm does not exclusively occur extracellularly, but may also be formed inside living cells. Furthermore, the presence of biofilm may contribute to the development of cancer. Thus, there is a dire need to develop effective treatment strategies against these biofilms.**



Biofilms have been recognised to be involved in many clinical infections, and evidence is accumulating that biofilms contribute to the pathogenesis, especially in chronic infections. Consequently, biofilm-related diseases are typically persistent infections that develop slowly, are rarely resolved by the immune system, and respond inconsistently to antimicrobial treatments.

For instance, the primary infection in endocarditis is a biofilm composed of both bacterial and host components located on the cardiac valve. Studies also suggest an association between colonic biofilm formation, dysbiosis and colorectal carcinogenesis.

More recently, researchers have suggested that chronic wound infections are due to the biofilm mode of growth of the bacteria. This idea is supported by recent studies that have demonstrated that chronic wound infections in fact are biofilm infections and observations indicate the presence of biofilms also in acute infections.

As a matter of fact, cystic fibrosis (CF) was the first infection where biofilm was recognised as part of the aetiology, and is probably the most thoroughly studied biofilm infection to date. Likewise, there are numerous diseases that are associated with biofilm formation such as otitis media, inflammatory bowel disease, colorectal cancer, bacterial vaginosis, chronic endometritis, chronic rhinosinusitis, urinary tract infections, pharyngitis, laryngitis etc.

However, even when biofilm is present, there is still a question whether the biofilm is the cause of the disease or the bacteria are just taking advantage of a favourable environment for colonisation caused by the disease.

Nevertheless, it is clear that both diagnosis and treatment of a number of chronic diseases need to take into account the importance of biofilm. Diagnostic criteria for biofilm infections are needed, and have already been suggested for a few diseases like cystic fibrosis and chronic wounds. Development of effective treatment against such infections is imperative.

“Pathogenic microorganisms and their chronic pathogenicity are significant concerns in biomedical research. Biofilm-linked persistent infections are not easy to treat due to resident multidrug-resistant microbes. Low efficiency of various treatments and in vivo toxicity of available antibiotics drive the researchers toward the discovery of many effective natural anti-biofilm agents. Natural extracts and natural product-based anti-biofilm agents are more efficient than the chemically synthesised counterparts with lesser side effects”, said Dr Rojita Mishra, Department of Botany, Polasara Science College.

Searching for a solution

A group of researchers from Banaras Hindu University are currently working on a biofilm-based approach to cure chronic wounds via phage therapy. The study has found out that wounds that took months to years to heal could be cured in a matter of days to months.

The researchers have also revealed that infections caused by multidrug-resistant strains and subsequent biofilm formation are the primary cause of the persistence of the wounds because conventional antibiotic therapy does not work. Search for alternatives to antibiotics has thus become a compulsion.

According to Dr Gopal Nath, Professor, Department of Microbiology, Banaras Hindu University, "Chronic wounds are considered a global problem. The direct medical cost of skin infections in the United States is approximately $75 billion, whereas $25 billion of this amount is used for chronic wound treatment. Infection with antibiotic-resistant bacteria and biofilm formation are critical factors halting the standard healing progress. Clinical trials of phage therapy have been initiated by the Banaras Hindu University and have reported the efficacy of topical phage in healing chronic wounds in three prospective exploratory studies."

Scientists at Allahabad-based Motilal Nehru National Institute of Technology are currently working on a new-age, low-cost and effective alternative to treating bacterial infections using medicines that do not cause resistance which often results from long and repeated use of antibiotic medicines. This approach too involves the use of biofilms.

Another approach that is being explored to combat the growth of biofilms is nanotechnology. Recent studies have reported the use of silver nanoparticles synthesised by the reducing activity of phyto-constituents present in the Indian medicinal plants.

Sharing more details about this new approach, Dr Yugal Kishore Mohanta, Assistant Professor, University of Science and Technology Meghalaya said, "Biofilm-forming bacteria are resistant to conventional antimicrobials due to the inability of the antimicrobial to penetrate the biofilm, evolution complex drug resistance properties, and biofilm mediated inactivation or modification of antimicrobial enzymes. Fortunately, nanoparticle-based antimicrobials have been developed and marketed to eradicate both planktonic and biofilm-forming antibiotic-resistant bacteria. Continuous research is being conducted to develop eco-friendly nanotechnologies utilising natural phytochemicals to produce metal nanoparticle-based antimicrobials for the control of biofilm-forming pathogens."

Hospital acquired infection is also a key area which is being dominated by biofilm-forming bacteria. The presence of biofilms consisting of common opportunistic and drug-resistant pathogens has been reported on medical devices like catheters and prosthetics, leading to many complications.

"Deployment of bacteriophages is one of the promising approaches to invade biofilm that may expose bacteria to the conditions adverse for their growth. Bacterial biofilms are serious causes of device-related infections. Phages are ubiquitous viruses which infect bacteria and are being extensively explored as alternatives to antibiotics. Phages employ many strategies to better penetrate hard-to-reach bacterial cells in biofilms and have been found to be effective against many resistant nosocomial bacterial strains", said Dr Aditi Singh, Associate Professor, Amity University, Uttar Pradesh.

Chemical or natural way?

To find a significant and effective alternative against biofilm, focus on the discovery of different anti-biofilm molecules is something that is to be taken under serious consideration. Every anti-biofilm molecule has its specific mode of action but a single molecule may follow more than one mechanism. Information regarding mechanism of action provides better understanding about the nature of biofilms, which can be further used to develop new and successful drug molecules with the previously known target of action.

"The naturally derived antimicrobials have more biochemical and structural diversity compared with synthetic drugs, this could be very useful in developing various alternative therapies and in-silico pharmaceutical approaches. Additionally, the high complexity of natural products allows enhanced selective binding to the target. The disadvantage of using naturally derived anti-biofilm agents is their high cost, less sustainability; more time consumption and sometimes they show different results once extracted from their sources. In contrast, synthetic drugs are cost effective and consume less time but many of them show adverse side effects", said Dr Vishvanath Tiwari, Assistant Professor, Department of Biochemistry, Central University of Rajasthan.

Although researchers are exploring both chemical and natural ways to combat biofilm formations and related infections, we are yet to see definite solutions and applications in front of us. Maybe a combination therapy of natural agents with commercial antibiotics needs to be exploited in the future to advance anti-biofilm activity. The discovery of accurate markers that are sensitive and stable can resolve the problem and help in better quality control of natural anti-biofilm agents, or in combination with antibiotics.

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