Taming Staphylococcus aureus in the eczema skin microbiome

Atopic dermatitis, commonly known as eczema, is a skin condition that affects millions of people globally. The bacteria Staphylococcus aureus – a common and normally harmless member of the skin microbiome that can turn nasty in certain circumstances – has been linked to this condition. A team at the University of Michigan, USA, led by Dr Gabriel Núñez and Seitaro Nakagawa, in collaboration with Dr Greg Hillebrand of Amway Corporation, has conducted translational research into developing natural extracts of rosemary that could help disrupt the S. aureus virulence mechanisms involved in the itch, scaling, and redness of eczema and potentially other skin irritations.

The skin microbiome is a complex ecosystem of microbes that live on and within the skin. While most bacteria are harmless, some can become pathogenic under certain conditions. Staphylococcus aureus is a common skin bacterium that can cause infections and is often associated with eczema.

### The Skin Microbiome and Atopic Dermatitis

The skin’s primary role is to act as a physical and biochemical barrier to the outside world, protecting us from environmental stressors including invading pathogens. To that end, our skin plays host to a plethora of friendly microbes, including bacteria and yeast. This coexistence has no adverse effects and is often beneficial to us. However, these same friendly microbes can also turn on us. One particular species of bacteria that can be friend and foe alike, depending on the circumstances, is Staphylococcus aureus.

### From Harmless to Harmful?

A round bacterium that is found in clusters, S. aureus can exist as a harmless part of the skin microbiome for a significant percentage of the human population. In this form, it acts as a commensal, colonising the skin without any harm to the host. However, S. aureus can switch personalities like Dr Jekyll into Mr Hyde and become harmful, earning the title of an ‘opportunistic pathogen’. A well-known manifestation of this is methicillin-resistant Staphylococcus aureus (MRSA) infection, which was associated with 20,000 deaths in the US in 2017.

S. aureus is also thought to have a role in atopic dermatitis and other skin irritations. Previous data has suggested that 90% of atopic dermatitis patients have colonies of the bacteria present on the skin of their lesions, and biofilms of S. aureus have been directly associated with flare-ups of the condition.

### How Does S. Aureus Switch from Harmless to Harmful?

The transformation of S. aureus from a harmless commensal to virulent pathogen involves bacterial cell-to-cell communication called quorum sensing. Once the density of S. aureus reaches a certain level, or quorum, the entire colony will change its behaviour from that of a friendly commensal to that of a pathogen. The biochemical mechanisms involved in quorum sensing are well understood and so targeted inhibition of quorum sensing is proving to be an attractive approach for preventing S. aureus virulence.

In S. aureus, quorum sensing is regulated by a section of the bacterial genome known as agr, which stands for accessory gene regulator. Two transcriptional units, RNAII and RNAIII, are coded for by agr. After RNAII and RNAIII are produced, they go on to trigger the production of virulence factors. These include δ-toxin and PSMα, which cause mast cell degranulation and release of histamine and keratinocyte alarmins, which produce skin inflammation and itch. Thus, compounds that inhibit S. aureus agr activation might be useful in treating and mitigating skin irritation and the symptoms of eczema.

### How Rosemary Can Help Inhibit Quorum Sensing in S. Aureus?

Humans are not the only ones who can come under attack by unruly bacteria – plants also face the threat of bacterial infection by common virulence mechanisms and, therefore, are our allies. Importantly, on an evolutionary scale, plants have been in this war a lot longer than we have and have evolved sophisticated strategies and compounds to combat bacterial infection, which we can study to use for our own benefit. One such plant is rosemary.

Professor Gabriel Núñez, a molecular biologist and immunologist at the University of Michigan Medical School, screened over 4,000 compounds for agr-inhibiting activity. Of these, carnosic acid was found to be one of the most potent. Found in rosemary leaves at levels between 3% and 10%, carnosic acid is a diterpene that has been shown to have antioxidant and antimicrobial properties and is naturally present in several additives used in the food industry.

This discovery of carnosic acid as a potent agr inhibitor spurred Núñez and his colleague Dr Seitaro Nakagawa from the University of Michigan, and Dr Greg Hillebrand from Amway Corporation, to conduct further studies on this compound, as well as natural extracts of rosemary leaves containing carnosic acid. The findings from their research were published in the journal Antimicrobials in 2020.

The team tested these different compounds found in rosemary leaves at high concentration for their effectiveness at inhibiting agr-stimulated virulence in S. aureus, the first being carnosic acid. The second compound they tested was carnosol, another diterpene that is a derivative of carnosic acid. The third
The researchers then tested the effectiveness of rosemary extracts, carnosic acid, and carnosol in non-
laboratory strains of S. aureus isolated from patients with atopic dermatitis. They stimulated these 'real world' bacteria to activate quorum expression in the presence and absence of various concentrations of the test compounds. Three hours later, they collected the bacteria and isolated the mRNA. Quantitative real-time PCR (qPCR) was used to measure the expression of RNAII and psm genes. They found that all three test compounds inhibited these virulence genes. The researchers also measured the growth of the bacteria in the presence of each compound. The results showed that the extracts and compounds were specifically inhibiting quorum expression and quorum sensing and not acting through an antibiotic mechanism. In the future, compounds such as carnosic acid and carnosol (or rosemary extracts) could be incorporated into skincare formulations as active ingredients to specifically target flare-ups and occasional skin irritations where this bacterium has become established. Antihistamines can also be used to relieve itching, but have side effects including sleepiness and headaches. Injectable (e.g., dupilumab) can be very effective but also very expensive. Using natural plant-derived molecules with well-established safety profiles to inhibit quorum sensing in S. aureus holds great potential for treating and preventing eczema in a practical and cost-effective manner. In the future, compounds such as carnosic acid and carnosol could be incorporated into skincare formulations as active ingredients specifically target flare-ups and occasional skin irritations where this bacterium has not gone too far. In fact, the first vehicle-controlled randomised clinical trial of a topical rosemary formulation for the treatment of eczema lesions was completed by the Amway-University of Michigan team. The results look very promising and have been presented at a skin microbiome conference in Boston in November 2021, with a peer-reviewed paper describing the results of that study to be published soon. An example of the effectiveness of the new formulation containing rosemary extract in treating hand eczema is shown in Figure 2.