G60: Is there a role for the use of phytochemicals in management of patients with orthopedic implant associated infections?

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Response/Recommendation: While *in vitro*, *in silico*, and limited *in vivo* animal studies have demonstrated the antimicrobial activity of several phytochemicals and their efficacy against biofilm formation, there is currently a lack of clinical studies supporting the use of phytochemicals in the management of patients with orthopedic implant associated infections.

Level of Evidence: Limited
Delegate Vote:

Rationale

Owing to the increasing microbial resistance to conventional anti-infectives, there is a growing need for alternative antimicrobial strategies to effectively combat orthopedic implant associated infections. The rise of multidrug-resistant pathogens necessitates the exploration of novel therapeutic approaches that can circumvent the limitations of traditional evidence-based therapies. In this context, although known for centuries in traditional medicine, phytochemicals emerge as potentially valuable adjuncts or alternatives to conventional antimicrobial treatments. Phytochemicals are bioactive compounds derived from plants, showcasing a wide range of biological activities, including antibacterial, antifungal, and antiviral effects. Therefore, this assignment aimed to evaluate the evidence supporting the use of phytochemicals in management of patients with orthopedic implant associated infections.

The database search, which included PubMed, Scopus, and Web of Science, yielded a total of 612 results. After merging 19 duplicates, 593 records remained for screening based on titles and abstracts. Following the assessment of titles and abstracts for eligibility, 49 studies advanced to the full-text screening phase. However, the full-text review revealed substantial heterogeneity among the studies, rendering them ineligible for a pooled analysis. Furthermore, no clinical studies specifically addressing this topic were identified. As a result, the assignment necessitated a narrative approach.

Several phytochemicals have been experimentally demonstrated to possess efficacy against biofilm formation and exhibit antimicrobial activity *in vitro* or *in silico*. Examples of these agents include curcumin [1], Rosa canina L. extract [2], thymol [3], Moringa oleifera L. extract [4],

Trifolium repens L. extract [5], Cissus quadrangularis L. extract [6], spectrum of essential oils [7], Manuka honey components [8], green tea extract [9], oregano oil [10], isoliquiritigenin [11], Posidonia oceanica L. [12], resveratrol [13], or variety of other flavonoids, triterpenoids, carboxylic acids and their derivates [14]. Nevertheless, examination of the existing literature revealed a markedly limited number of animal and human studies available to investigate the *in vivo* behavior of the aforementioned agents, as their pharmacokinetics and pharmacodynamics may differ compared to experimental laboratory settings.

Additionally, despite the extensive documentation of the antibacterial and antifungal properties of these phytochemicals, there remains a critical gap in evidence regarding their applicability in the context of orthopedic implant infections. This deficiency underscores the need for further research to validate the effectiveness and safety of these agents in clinical settings. Furthermore, the spectrum of targeted bacteria and fungi is restricted to specific species, raising concerns about the generalizability to less common pathogens. Another critical area that warrants investigation is the potential synergistic effects of phytochemicals when used in conjunction with conventional therapies to enhance treatment efficacy. While there exist experimental reports suggesting that combination of phytochemicals with antibiotics can promote bacterial eradication [15], comprehensive clinical trials are necessary to establish the validity of these findings.

Although phytochemicals seem to be a promising preventive and treatment option, they are limited to the preclinical setting and thus lack supporting clinical data, making them only promising candidates for further research. Conclusively, given the absence of the sufficient data, applicability of phytochemicals in management of patients with orthopedic implant associated infections remains unclear.

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