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EDITORIAL

A multifaceted bioactive resource of stingless bees: Unlocking the therapeutic anti-antimicrobial-resistance (anti-AMR) potential of pot-pollen

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ABSTRACT

Pot-pollen, a probiotic processed by stingless bees, has gained attention for its nutraceutical properties and pleasant sour taste. The aim of this editorial is to illustrate the state-of-the-art of pot-pollen research with a bibliometric overview using the Scopus database to value the experimental bioactivity (antimicrobial, antioxidant, anti-inflammatory, and anticancer) of pot-pollen, and the standards for quality control and safety of pot-pollen legislation, considered mandatory for clinical applications of this highly variable natural product. The bibliometric analysis since 2014 revealed a growing interest in pot-pollen research, with a focus on the following academic disciplines: Agricultural and Biological Sciences, Engineering, Biochemistry, Genetics and Molecular Biology, and Environmental Science. Nevertheless, the lack of medicine in subject areas and clinical research in medical journals, indicates a necessity for further studies on the potential applications of pot-pollen in human health. In conclusion, pot-pollen emerges as a bioactive material with health benefits, and a novel synergism with antibiotics reveals its therapeutic anti-antimicrobial-resistance (anti-AMR) potential, deserving further research to fully elucidate its potential in modern medicine.

Keywords: antimicrobial resistance; bibliometrics; bioactivity; pot-pollen; synergism with antibiotics.

Introduction

Stingless bees are pantropical Hymenopterans of the Family Apidae and the Tribe Meliponini with a biodiversity of 605 species.[1] The oldest fossil of a bee is an extinct stingless bee in New Jersey amber dating back to the late Cretaceous.[2] Pot-honey, pot-pollen, cerumen and propolis produced in their nests have traditional medicinal uses with prospective scientific demonstrations.[3-5] Stingless bee keeping is also known as meliponiculture.

The fermented nature of pot-pollen makes it a probiotic food of ancestral value for native people. This natural product, is a dietary resource of tropical meliponiculture. The sensory qualities of biofermented pollen in cerumen pots of stingless bee nests are appreciated by native cultures. The sour taste conferred by aliphatic organic acids (AOA) reminds a lemonade or tamarind juice (P Vit, personal observations). A Huottuja stingless bee keeper prepared the cold drink to celebrate the declaration of Atures Municipality Stingless Bee Sanctuary, Amazonas state of Venezuela.[6] It was based on the Ajavitto *Tetragona clavipes* (Fabricius, 1804) pot-pollen diluted with water and sweetened with pot-honey from her Alto Carinagua meliponary.[7] In Brazil, the pot-pollen cost varies from 32 to 257 US$/kg according to the meliponine species.[8] This is a valued material with economic benefits for stingless bee keepers.

Compared to pot-honey and stingless bee propolis, pot-pollen is an emerging medicinal material that deserves further attention for applications in human health. Therefore, recent contributions show a path for needed clinical scientific developments after a bibliometric classic analysis visualizing the state-of-the-art of scientific literature about pot-pollen in just a decade of studies. This brief dissertation aims to highlight the innovative nature of pot-pollen as a reservoir of biomolecules with broad health applications. It advocates for strengthened research efforts and the establishment of quality control and safety standards, which are essential for integrating pot-pollen into modern healthcare solutions. Addressing these gaps could unlock new therapeutic avenues, contributing to innovative solutions challenging public health problems, including antimicrobial resistance.

Methodology

To obtain the bibliometric data, we utilized the Scopus database,[9] renowned for being one of the most comprehensive scientific sources available. On September 2, 2024, a bibliometric search was conducted using the field TITLE-ABS-KEY, which includes the titles, abstracts, and keywords of publications. Initially, an attempt was made with the query string (antibiotic AND pollen AND synergism), but no documents were retrieved. A subsequent search for (pot-pollen) was effective, and to refine the results, documents containing references about fossils were excluded using the query string (pot-pollen AND NOT fossil). The data were then organized based on the Scopus ranking, which arranges results in a descending order according to the number of documents, and in alphabetical order within each descriptor. We summarized the findings for the top five contributors in terms of authorship, affiliations, countries, publication sources, sponsors, and subject areas. To provide further insights, the Scopus Analyze Search Results tool was used to communicate the percentage distributions of document types and subject areas. We screened the papers and manually noted the primary subjects included in each abstract in order to determine the thematic focus. We categorized research themes into groups such as chemical or nutritional composition, and palynological characterization of pot-pollen, acknowledging that some studies involve several subjects. The goals of the palynological studies were further separated into categories such as food characterization, pollination dynamics, bee foraging behavior, and forestry. This thorough review helped to clarify the state of the pot-pollen research field at the moment.

Bibliometric overview on pot-pollen

The bibliometric overview reveals a significant opportunity for research into the medical applications of pot-pollen. The preferred document types in the 42 retrieved publications of the Scopus database are original articles (45.2%), book chapters (35.7%), and conference papers (11.9%), on subject areas where medicine is not yet visualized, indicating an urgent need for further medical research into pot-pollen as an innovative stingless bee material for human health and potential clinical applications. Most scientific research has been accomplished in Agricultural and Biological Sciences (33.0%), Engineering (19.4%), Biochemistry, Genetics and Molecular Biology (18.4%), and Environmental Science (16.5%). Main topics of the dataset were on artificial dietary substitutes (1), bioactivity (6), chemical or nutritional composition (10), diversity of stingless bees (1), fluidized bed drying (5), marketing (1), melittology (1), metabolomics (1), microbiology (3), pests (1), productivity (3), safety (1), standards or legislation (2), palynology for food characterization (5), bee foraging (9), pollination (1), and forestry (2).

The most productive authors have published 3 to 6 documents on this recent field of research, focused on bioactivity and chemical composition P Vit (6) and E Pérez-Pérez (4) at Universidad de Los Andes, Mérida, Venezuela; palynology OM Barth (4) from Instituto Oswaldo Cruz, Fiocruz, Rio de Janeiro, Brazil; and optimized drying methods of pot-pollen LA Halim (4) and ASM Yudin (3) at Universiti Malaysia Pahang, Pekan, Malysia.

Universidad de Los Andes, Mérida, Venezuela and the University of Sydney, Australia were the two leading institutions with seven publications on pot-pollen, followed by Universidade de São Paulo, Brazil (5), Instituto Oswaldo Cruz, Brazil (4), and Universiti Malaysia Pahang, Malaysia (4). The top-five countries on pot-pollen publications were Brazil (15), Australia (13), Venezuela (12), Malaysia (5), and Indonesia (4). Major fundings sponsored 20 projects from the Brazilian Conselho Nacional de Desenvolvimento Científico e Tecnológico (5), and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (5), Universiti Malaysia Pahang (4), Bundesministerium für Wissenschaft, Forschung und Wirtschaft, Austria (3), and the Ministry of Higher Education, Malaysia (3).

In Table 1, the sources selected by authors to disseminate their findings show the notable absence of clinical journals, a limitation that is expected to be addressed in

the near future. The source hosting most publications was a book, followed by two conference series, and two journals; one of them on apicultural research and the other on rural development. Their h-index varied between 35 and 91.

Table 1. Top-five sources hosting research of pot-pollen since 2014

Ranking	NP[1]	Pot-pollen research Sources (h index, Quartile, impact score, publisher, country)[2]
1	16	Pot Pollen In Stingless Bee Melittology Springer, Switzerland
2	3	Iop Conference Series Materials Science And Engineering (h 54, Q-, 0.50) IOP Publishing Ltd., United Kingdom
3	2	Journal Of Apicultural Research (h 66, Q2, 2.08) Taylor and Francis Ltd., United Kingdom
4	2	Journal Of Physics Conference Series (h 91, Q-, 0.48) IOP Publishing Ltd., United Kingdom
5	2	Livestock Research For Rural Development (h 35, Q3, 0.56) Centro para la Investigacion en Sistemas Sostenibles de Produccion Agropecuaria, Colombia

[1]Number of publications
[2] https://www.resurchify.com

Experimental bioactivity of pot-pollen organic extracts

Organic extracts of pot-pollen have demonstrated antimicrobial and antioxidant properties.[10-14] Their anti-inflammatory, anticancer and anti-drug-resistant bacterial actions have been studied in stingless bee species of a few countries. For example: 1. A synergistic antiproliferative effect was observed between Malaysian Kelulut *Lepidotrigona terminata* (Smith, 1878) pollen extracts and the anticancer drug cisplatin on breast cancer, compared to cisplatin alone, based on the MTT assay; reducing about 50% the therapeutic cisplatin dose.[15] 2. Oral administration of hydroethanolic extract of Tubí *Scaptotrigona* aff. *postica* (Latreille, 1807) pot-pollen from Brazil, needed 5 h to reduce 100% carrageenan-induced and dextran-induced paw edema in mice.[16] 3. Dietary supplementation with *Melipona seminigra* Friese, 1903 Brazilian pot-pollen controlled markers of metabolic syndrome in mice.[17] 4. The ethanolic extract of Angelita *Tetragonisca angustula* pot-pollen added to the antibiotics amikacin and meropenem, was inhibitory and bactericidal against six Gram negative extensively drug-resistant (XDR) bacteria of clinical origin: *Acinetobacter baumannii*, *Enterobacter ludwigii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Pseudomonas alcaligenes*.[18] This synergism is a promising approach of bioactive fermented pollen in stingless bee nests to enhance the action of commercial antibiotics against drug-resistant bacteria.

A recent finding on pot-pollen to combat antimicrobial resistance demands a clinical focus

The World Health Organization (WHO) has identified antimicrobial resistance (AMR) as a significant public health concern (WHO, 2022).[19] *T. angustula* pot-pollen ethanolic extract reduced the minimum inhibitory and bactericidal concentrations of amikacin and meropenem against six XDR Gram-negative bacteria.[18] This was the first demonstration of anti-AMR synergism of pot-pollen with aminoglycoside and carbapenem antibiotic classes, and also the first report of pot-pollen in a clinical journal. The synergistic efficacy of pot-pollen tested for one of the 605 stingless bee species interacting with a semi-synthetic and a synthetic antibiotic could be compared in other pantropical habitats of different countries, testing more stingless bee species, diverse botanical origin, bacterial priority pathogens, and antibiotics. A book proposal for a preliminary screening by the experts can do that, contributing to a suite of combinations for discoveries on the therapeutic potential of pot-pollen. Clinical applications to combat antimicrobial resistance could be envisaged escalating from innocuity and immune boosting interventions in healthy communities where it is produced, consuming a pot-pollen dose at fasting. A further approach would be based on pot-pollen extracts and pharmacological procedures to optimize its clinical action. The spectrum of antibiotic-resistant bacteria under investigation could be expanded to include the twelve multidrug-resistant (MDR), XDR, and pan-drug resistant (PDR) bacteria identified by the WHO (2024)[20] as a priority due to their substantial impact on public health.[20] The identification of microbiota associated with pot-pollen substrate of the nest would eventually define microbial transformations[21] explaining the concept of 'active pot-pollen'.[18]

A quality control proposal of pot-pollen standards is mandatory

The recommended stingless bee honey standards by Vit et al. (2004)[22] were neglected because the international CODEX-STAN defines honey as only produced by *Apis mellifera*.[23] Therefore, a state norm was created for *Melipona* honey in Bahia, Brazil (ADAB, 2014),[24] the first national norm proposed Kelulut stingless bee honey standards in Malaysia (2017),[25] and the second national norm suggested Yateí *Tetragonisca fiebrigi* standards in Argentina (2019).[26] Preliminary pot-pollen standards suggested to protect consumers, pharmaceutical developments, and clinical applications, considered data on contents of ash <5%, carbohydrates 15–55%, lipids >1.5%, moisture <30%, and proteins >15% derived from seven species of stingless bees from Brazil, Mexico, Thailand and Venezuela[27]

The ISO 24382 bee pollen specifications were prepared in 2023.[28] Chemical, safety and health requirements were considered for dried, frozen and lyophilized *Apis mellifera* corbicular pollen. Besides the quality requirements, analytical methods, packaging, labelling, marking, storage and transportation of bee pollen were specified, including pollen collected by other bee species and harvested at the entrance of the hive. There are no established specifications on the chemical composition and safety of bee bread, the processed bee pollen inside the *Apis mellifera* nest. The reputed nutritional value of bee bread was explained by its increased protein digestibility if compared with bee pollen.[29]

Pot-pollen is processed by associated microbiota fermenting stingless bee pollen in the nest. These associations are important to understand the microbial origin of active principles and metabolomics[30]. Pot-pollen safety[31] complements previous literature on bioactivity, chemical or nutritional composition and botanical origin[32,33] for further drafting pot-pollen regulations including limits on heavy metals and microbiological quality. Harmonization studies are useful to validate quality standards of pot-pollen after critical assessment of the variability caused by diverse stingless bee species, botanical origins, and habitats.

Conclusions

Pot-pollen represents a novel bioactive resource with significant implications for the future of medicine. Its multifaceted properties, including antimicrobial, anti-inflammatory, and antineoplastic activities, position it as an important candidate for addressing some of the most pressing health challenges of our time, particularly antimicrobial resistance.

The combined effects of pot-pollen with conventional antibiotics improve treatment effectiveness against drug-resistant pathogens, which are a growing global health concern. Additionally, pot pollen may have a role in managing metabolic syndromes and enhancing immune responses, highlighting its versatility as a nutraceutical.

As our knowledge of pot-pollen bioactivity increases, it is important to prioritize clinical research to fully exploit its potential. Integrating pot-pollen into modern medical practices is a promising avenue for developing innovative treatments that combine scientific advances with useful properties of natural goods. This exploration not only expands our therapeutic tools, but also highlights the crucial role of biodiversity in the search for sustainable health solutions. Finally, we consider the innovative nature of pot-pollen as a reservoir of biomolecules with multiple health benefits. Encouraging its research and potential applications in future medical treatments is of paramount importance, particularly in areas where therapeutic options are scarce.

Conflict of interests: No conflict of interests is declared.

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