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Pharmacological potential of pomelo (*Citrus maxima*) peel: A bibliometric review of global research trends and future directions

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Abstract

Pomelo (*Citrus maxima*) is a widely cultivated tropical fruit with global production reaching approximately 8.55 million tons in 2023. This large-scale production generates a substantial amount of peel waste despite the fact that pomelo peel contains secondary metabolites with promising pharmacological potential. This study aimed to evaluate global research trends related to the pharmacological potential of pomelo peel using a bibliometric and review-based approach, as well as to identify future research directions. Data were collected from the Scopus database and filtered for English-language scientific articles, reviews, and conference proceedings. The analysis was performed using the Biblioshiny and VOSviewer software. In total, 251 relevant articles were identified between 2002 and 2025, with a significant increase in publications since 2020. Countries such as China, Vietnam, Nigeria, and Thailand have emerged as leading contributors, supported by institutions focused on natural product research. Research has evolved from compound characterization to pharmacological applications, including antioxidant, antidiabetic, antimicrobial, anticancer, anti-inflammatory, and other activities. Keyword analysis revealed a growing trend toward multidisciplinary approaches involving green synthesis, electroactive biosensors, and nanoencapsulation to enhance the stability and efficacy of bioactive compounds. Future studies should integrate nanotechnology and sustainable bioprocessing to advance the clinical validation and practical biomedical applications of pomelo peel.

Keywords: Biblioshiny, Bioactivities, Biopharmaceutical activities, Citrus, Pomelo peel

1. Introduction

Citrus maxima (Burm.) Merr., commonly known as "pomelo," is a widely cultivated fruit in tropical regions, especially in Southeast Asia [1]. Taxonomically, *C. maxima* is often considered synonymous with *Citrus grandis* Osbeck. In addition, this species has also been referred to in the literature using other scientific or common names such as "shaddock," "pummelo," and "limau bali." According to data from the Food and Agriculture Organization of the United Nations (FAO), the global production of pomelo in 2023 reached 8.55 million tons [2], generating a substantial amount of pomelo peel waste. While the fruit is widely consumed, much of its peel still goes to waste or is minimally utilized. However, pomelo peel contains a variety of bioactive compounds that have significant potential for pharmaceutical and health applications [3]. Some of the bioactive components found in pomelo peel include flavonoids, alkaloids, tannins, limonoids, essential oils, lycopene, and pectin [4]. Although the majority of pomelo peel waste is not utilized, these compounds show great promise as sources of raw materials for natural medicines. Therefore, it is crucial to explore the

Received 15 August 2025; accepted 6 January 2026.
Available online 22 July 2026

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https://doi.org/10.38212/2224-6614.3589
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月日知識庫

pharmacological potential of pomelo peel in order to maximize its utilization.

The bioactive compounds in pomelo peel, such as flavonoids, alkaloids, tannins, and essential oils, exhibit a range of beneficial pharmacological activities, including antioxidant, antidiabetic, anticancer, anti-inflammatory, antimicrobial, and hepatoprotective effects [3,5,6]. The most abundant phenolic components in pomelo peel are pectin and tannins, accounting for 23% [7]. Flavonoid compounds in pomelo peel, including naringin and hesperidin, have potent antioxidant, anti-apoptotic, antidiabetic, and anti-inflammatory effects [3]. Priscilla et al. (2014) also explained that naringin is a bioactive compound that can reduce the postprandial glycemic response by lowering plasma glucose levels, making it a promising candidate for diabetes treatment [8]. Essential oil from pomelo peel has been shown to suppress inflammatory mediators and pro-inflammatory cytokines in LPS-induced RAW 264.7 cells [9,10]. Additionally, compounds such as α-terpineol, 7-geranyloxycoumarin, marmin, and isomeranzin can inhibit edema induced by xylene and carrageenan and reduce the secretion of inflammatory factors [11].

With growing interest in the discovery and development of natural product-based medicines, pomelo peel has attracted increasing attention in recent years, both for its pharmacological activities and other potential applications. The number of studies on pomelo peel has increased significantly, particularly those focusing on its bioactive compounds and their roles in managing various health conditions. However, the majority of the existing research remains limited to laboratory experiments or in vitro/in vivo studies, with relatively few advances in clinical applications or ready-to-use pharmaceutical formulations. This lack of translational research highlights the need for a more in-depth exploration of the therapeutic potential of pomelo peel, especially in the development of effective and evidence-based therapies that include product development and application-oriented trials. Given the increasing public demand for safe and effective natural alternatives, pomelo peel holds considerable promise as a raw material for the formulation of modern herbal medicines [3,12].

The rapid growth of research in this field calls for comprehensive mapping to better understand global trends. Thus, bibliometric analysis plays a crucial role in identifying research developments related to pomelo peel and its pharmacological potential. It enables the mapping of publication trends, evaluation of collaborations among researchers and institutions, and identification of the most frequently studied topics over the past few decades. Such an analysis is essential to uncover existing research gaps and to guide the future development of this research area [13,14]. Despite the growing body of literature on pomelo peel, to date, no bibliometric study has systematically mapped global research trends on its pharmacological potential. Therefore, this study aimed to evaluate and map global research trends in the pharmacological potential of pomelo peel and its applications in the health sector using a bibliometric approach.

2. Materials and methods

2.1. Data collection

An in-depth literature search was conducted using the Scopus database, which is one of the most comprehensive and widely used global scientific databases. Our search of the references was based on PRISMA guidelines [15]. Keywords designed to identify articles related to the pharmacological potential of pomelo peel. The search string used was: (TITLE-ABS-KEY((“*Citrus maxima*” OR “*Citrus grandis*” OR “pomelo” OR “shaddock” OR “pummelo” OR “limau bali”) AND (“peel” OR “rind” OR “pericarp” OR “fruit skin”) AND (“medicin” OR “therapeutic” OR “pharmacolog” OR “traditional medicine” OR “biological effects” OR “bioactivities” OR “biochemical mechanism” OR “ethnomedicine” OR “ethnopharmacolog*” OR “pharmacological study” OR “antioxidant” OR “antimicrobial” OR “anticancer” OR “antidiabetic” OR “anti-inflammatory” OR “cardiovascular disease”)). The search was conducted on June 23, 2025. The retrieved documents were filtered based on publication type, focusing only on original research articles, conference proceedings, and review articles published in English. There were no restrictions on the time range for this search, allowing all relevant articles to be included regardless of their publication year. This step was performed to ensure the quality and relevance of the articles for the bibliometric analysis. The data were then downloaded in RIS, CSV, and BibTeX formats (Fig. 1).

2.2. Data analysis and visualization

Bibliometric analysis was performed using Biblioshiny from the R packages Bibliometrix (version 2024.12.1) and VOSviewer (version 1.6.20) to map research trends related to the pharmacological potential of pomelo peel [16,17]. Biblioshiny was used for an in-depth analysis of the data imported from

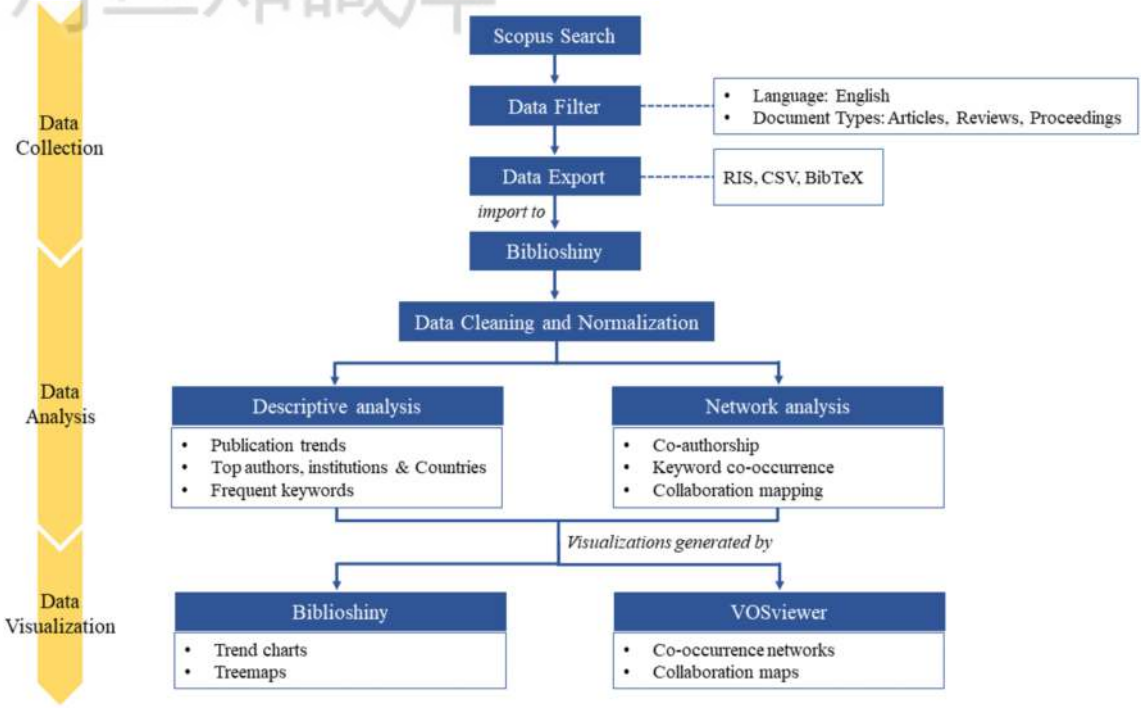


Fig. 1. Workflow of bibliometric analysis of pomelo peel pharmacological research.

the Scopus database in BibTeX format. Biblioshiny offers various capabilities, including statistical analysis, index computation, network analysis, and knowledge map creation. Using Biblioshiny, the data extracted from Scopus were analyzed to identify the annual publication trends, most productive authors, co-authorship patterns, affiliations, and frequently occurring keywords related to pomelo peel research [18]. VOSviewer version 1.6.20 was used to visualize author and affiliation collaboration networks and to create keyword co-occurrence mappings, which helped identify the relationships between research topics [19]. The combined use of VOSviewer and Biblioshiny provides a comprehensive approach for analyzing and visualizing the research landscape (Fig. 1). Biblioshiny delivers detailed metrics and thematic analyses, whereas VOSviewer offers intuitive visualizations, both of which are instrumental in uncovering research development trends, international collaborations, and identifying underexplored topics in the advancement of the pharmacological potential of pomelo peel.

3. Result

3.1. Performance analysis

The main data from the collection of articles related to pomelo peel and its pharmacological activity over the last 24 years (2002–2025) are presented in Table B1 (https://doi.org/10.38212/2224-6614.3589). The data were divided into three time periods to observe the evolution of research output trends, authorship, and citation impact. A total of 251 publications were generated based on the Scopus database. In the first period (2002–2009), five documents were produced, and this number increased nine-fold in the second period (2010–2017). The number of publications continued to increase in the third period (2018–2025), tripling compared with the previous period. In addition, the annual growth rate and number of authors continued to increase in each period, whereas the average document age decreased. This indicates a growing research interest in the pharmacological potential of pomelo peels. The number of contributing journals also increased, indicating broader interdisciplinary involvement in this topic. The increase in author keywords also reflects the diversification of the research topic coverage. The number of co-authors per document increased, whereas the number of international co-authorships decreased in the second period and then increased again in the third period. This indicates that global research networks have begun to strengthen over the past six years. The average number of citations per document decreased. This is likely because many publications are relatively new and do not have enough time to accumulate significant citations.

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3.2. Annual publication trends

The annual distribution of publications related to the pharmacological potential of pomelo peel demonstrated a clear and sustained upward trajectory over the past two decades, from 2002 to 2025 (Fig. 2). During the first period (2002–2009), the number of published articles ranged from zero to two per year. This number increased to 2–11 articles annually in the second period (2010–2017), with a relatively stable output. During the third period (2018–2025), the number of publications increased further, ranging from 13 to 36 articles per year. A notable surge occurred between 2020 and 2024, rising from 15 publications in 2020 to a peak of 36 publications in 2024. This trend reflects the increasing scholarly interest in the pharmacological potential of pomelo peels in recent years. By 2025, the total number of publications appears to decrease slightly to 23; however, this likely reflects incomplete indexing for the current year rather than a true decline in research activity. Overall, this pattern demonstrates a transition from sporadic early studies to a mature and rapidly expanding research field, underscoring the increasing recognition of pomelo peel as a promising source of bioactive compounds for pharmacological applications.

In terms of citation impact, early publications had a strong influence (Table B2) (https://doi.org/10.38212/2224-6614.3589). Articles from 2007 to 2009 recorded very high average total citations per article at 80 and 66, respectively, indicating substantial contributions in this field. From 2012 to 2015, the average number of citations remained moderate to high, at around 25–35 citations per article. Both productivity and citation performance have increased significantly between 2018 and 2020. Publications from 2018 to 2019 achieved the highest average citations per year, at 5.66 and 7.11, reflecting their rapid recognition in the scientific community. In contrast, although the number of articles continued to rise from 2021 to 2024, the average total citations per article gradually declined from 24.5 to 4.61, mainly because of the shorter citable period, which limited the accumulation of citations. Recent publications in 2025 recorded an average total number of citations per article of 0.52, which is reasonable considering their very recent publication. Overall, although the last five years have shown rapid growth in publication volume, earlier studies still have a relatively higher impact, highlighting their foundational role in the development of this research field.

3.3. The most productive authors, Co-authorship and collaboration patterns

A total of 251 articles published between 2002 and 2025 on the pharmacological potential of *C. maxima* peel involved contributions from 1156 authors. Table B3 (https://doi.org/10.38212/2224-6614.3589) lists the ten most prolific authors during this period. Author rankings are based on the number of publications (NA), followed by article fractional (AF)

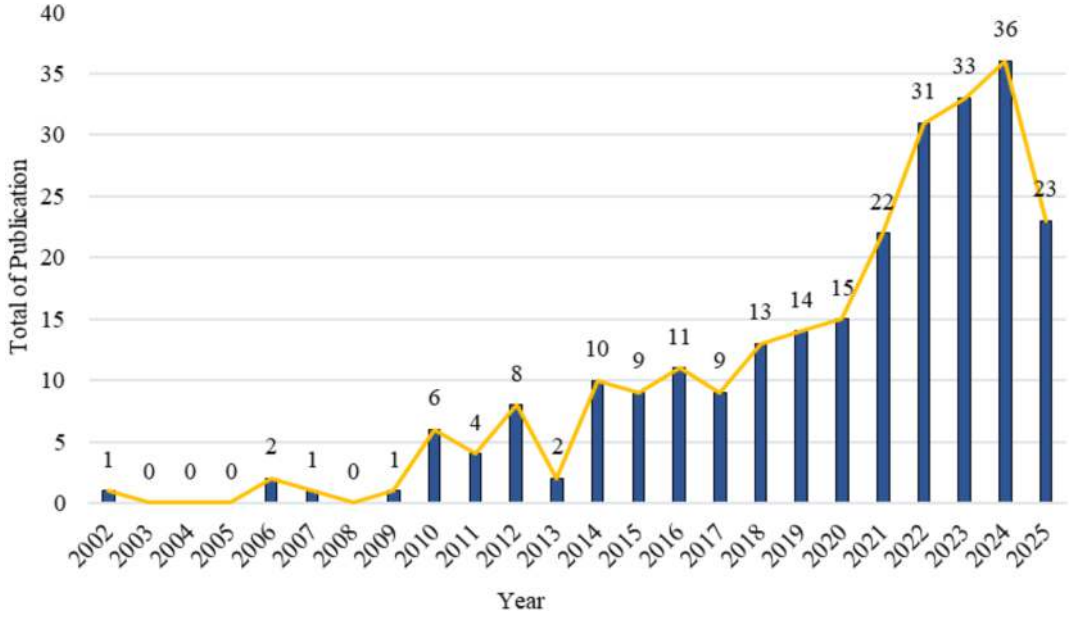


Fig. 2. Annual publication trends related to pomelo peel and its pharmacological activities (2002–2025).

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values. This ranking differs from the output generated by Biblioshiny, which ranks authors first by the NA and then alphabetically, making it less objective for authors with the same publication count. The AF value reflects the actual contribution of each author by considering the number of co-authors per publication. Additionally, the contribution ratio (AF/NA) was provided to illustrate the average depth of contribution for each author.

The top two authors, Ademosun OA. (Nigeria) and Oboh G. (Brazil), share the same NA (10 articles) and AF (3.31), making them the most prolific contributors, both in terms of quantity and actual involvement in co-authored publications. Notably, all ten articles by Ademosun and Oboh are collaborative works on the same publications, highlighting consistent research collaboration between the two authors despite their affiliations in different countries. These ten articles, published between 2012 and 2022, show sustained investigations into the pharmacological potential of pomelo peel, ranging from studies on phenolic compounds and antioxidant activity [20–22], targeted exploration of neuroprotective mechanisms and colon cancer [23,24], and in vivo testing of cognitive function, colon cancer, and functional food applications [25–29]. Liu Y. (Nigeria) and Zhang Y. (Brazil) followed these rankings. Meanwhile, several authors from China and the United States occupy subsequent positions, with NA values of 5–6 articles and AF scores between 0.66 and 0.99. Wang Y. had six articles with a relatively low contribution ratio (0.11), whereas Wang H., with five articles, had a higher contribution ratio (0.20), indicating that Wang H. tends to contribute more actively to each article.

Overall, the data indicate that research on *C. maxima* peel is highly collaborative across countries, with Nigeria, Brazil, China, and the United States being the dominant contributors. A visualization of the author collaboration is presented in Fig. 3. Xu Qiang appeared to be central to the collaboration network and was connected to numerous authors across multiple clusters. Fig. 3a illustrates the co-authorship network map, which consists of five clusters distinguished by color. The red and green clusters represent the groups with the densest interconnections, indicating a high intensity of collaboration within these groups. Xu Qiang appears as a central node bridging the clusters, while Ma Zhaocheng, Deng Xiuxin, and Huang Yue also play important roles as connectors between the author groups. The tight co-authorship relationships shown in this visualization demonstrate the strong collaborative nature of this research field. Fig. 3b presents the overlay visualization, highlighting the temporal dimension of collaboration during 2021–2024. The color of each node represents the publication time, with a gradient ranging from dark blue (earlier) to bright yellow (more recent). The blue-green and purple clusters dominated the activity in earlier periods (2021–2022), where Ma Zhaocheng, Huang Ding, and Deng Xiuxin were among the most active authors. By contrast, the yellow cluster on the right side shows the emergence of new groups of authors who have been more active in the last two years, such as Xu Yuanyuan, Guo Lingxia, Chen Peng, and Tang Qi. This pattern indicates a shift in collaborative focus toward a new generation of researchers. Xu Qiang remained the central connector between clusters, underscoring his primary role in the collaboration network across publication periods.

The top 20 relationships among authors (AU), author countries (AU_CO), and author affiliations (AU_UN) are presented in the Sankey diagram shown in Fig. A1 (https://doi.org/10.38212/2224-6614.3589). Xu Qiang, a highly collaborative author, is affiliated with Nguyen Tat Thanh University, China. The height of each box in the diagram indicates the number of publications associated with each entity. It is evident that the majority of authors are affiliated with institutions in China, including Liu Y, Li X, and Zhang Y, who are the three most prolific authors associated with Huazhong Agricultural University, Southwest University, Chongqing Normal University, and Jiangxi Agricultural University, respectively. Two other leading contributors, Ademosun O.A. and Oboh G., were affiliated with the Federal University of Technology, Nigeria. This pattern shows that most publications originated from a core group of authors affiliated with universities in Asia, particularly China, followed by contributions from Nigeria, Italy, Korea, the United States, Brazil, and Thailand. The strong link between authors, institutions, and countries highlights the importance of international collaborative networks in advancing research on the pharmacological potential of pomelo peel.

3.4. The most productive affiliates

The analysis of institutional affiliations demonstrates the diverse geographic distribution of research productivity on the pharmacological potential of pomelo peel. The details of the institutions with the highest number of publications are presented in Table B4 (https://doi.org/10.38212/2224-6614.3589). The largest number of research publications on the pharmacological activity of

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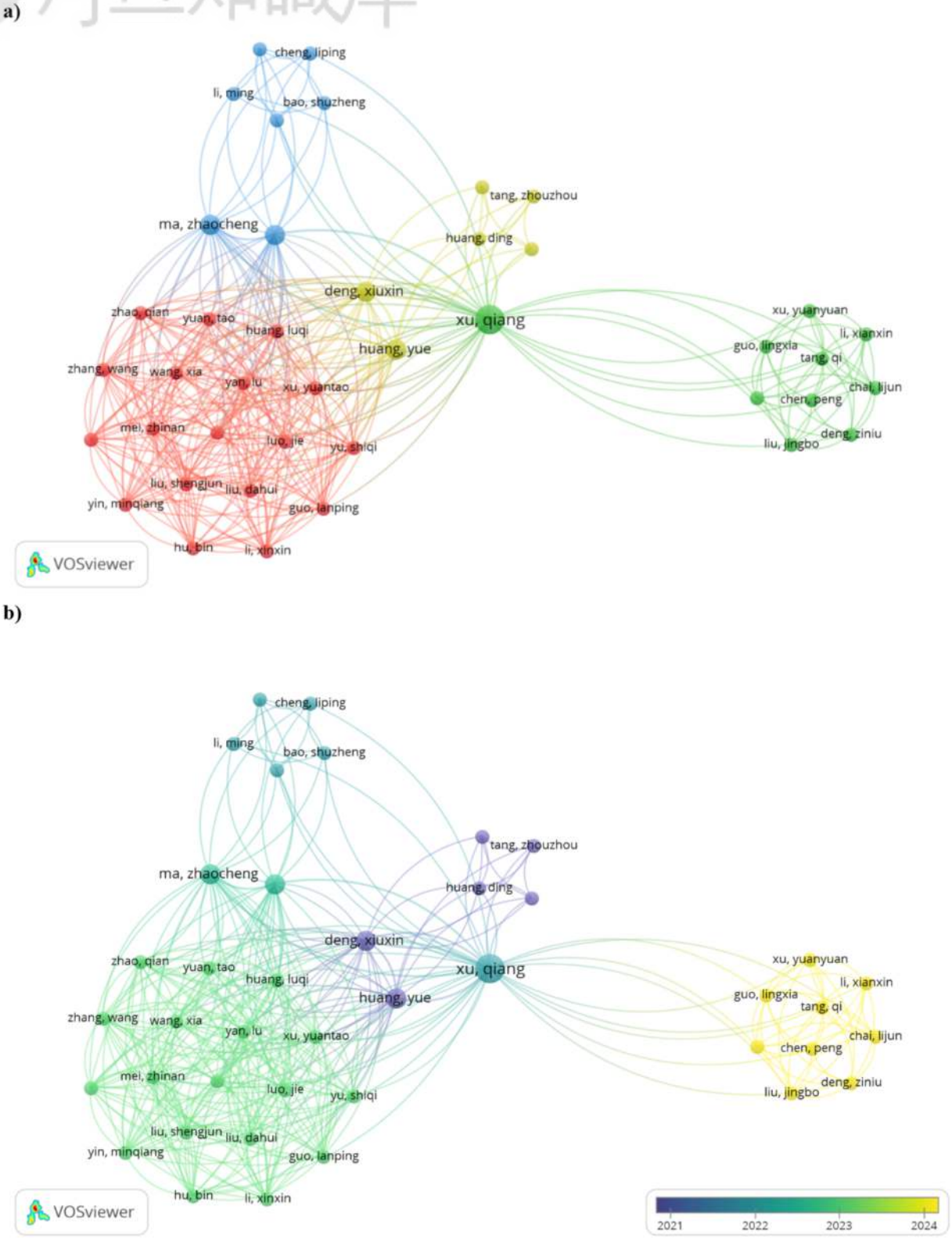


Fig. 3. Visualization of co-authorship in pharmacological research on pomelo peel: (a) network map and (b) overlay visualization by publication year.

月日知識庫

pomelo peel was produced by Huazhong Agricultural University (China), followed by Nguyen Tat Thanh University (Vietnam), and Southwest University (China). Asian institutions dominate this list, particularly those located in Vietnam, China, Taiwan, and Nigeria. This trend reflects widespread development and scientific interest in this topic across Southeast and East Asia.

Temporal trends in publication production by these institutions are shown in Fig. A2 (https://doi.org/10.38212/2224-6614.3589). Nguyen Tat Thanh University demonstrated the most rapid and sustained growth, initiating its publication activity in 2020 and increasing sharply to 42 articles by 2025. This trend indicates accelerated institutional engagement in scientific research and international collaboration over the last five years. Huazhong Agricultural University showed a similar upward trajectory, emerging in 2018 with five publications and steadily increasing to 44 articles by 2025, representing the highest cumulative output among all the institutions. This consistent growth highlights its pivotal role as a major research center in the agricultural and biotechnological sciences in China. In contrast, the Federal University of Technology has exhibited early involvement in the field, maintaining consistent productivity since 2012. Its output increased gradually, peaking at 22 publications in 2022, and subsequently stabilizing through 2025. This steady yet plateaued trend reflects a mature research environment with a sustained but limited expansion. Southwest University displayed moderate growth, remaining relatively inactive in the early years but accelerating after 2020, reaching 37 publications by 2023 and maintaining this level thereafter. The surge from 2020 to 2023 suggests a period of intensified institutional focus on scientific output. Fujian Agriculture and Forestry University was a late entrant, with publication activity appearing only after 2023, increasing rapidly to 21 articles by 2025. Although recent, this growth pattern reflects emerging research capacity and future potential for expansion. Overall, the publication landscape indicates a geographical shift in research leadership toward East and Southeast Asia, particularly driven by Vietnam and China. Institutions from these regions, such as Huazhong Agricultural University and Nguyen Tat Thanh University, have overtaken earlier contributors such as the Federal University of Technology. This dominance underscores Asia's growing influence in advancing agricultural, pharmacological, and natural product research, including studies on bioactive compounds derived from pomelo peel.

3.5. The most productive countries and collaboration patterns

The contribution of countries to research on the pharmacological activities of pomelo peel shows a pattern that is strongly dominated by Asian nations. Table B5 (https://doi.org/10.38212/2224-6614.3589) presents the ten most productive countries in publications related to the pharmacological activities of pomelo peel. China ranks first as the most productive country, with 94 articles that have generated 2486 citations and an average of 26.45 citations per article, demonstrating dominance in both quantity and scientific impact. India occupies the second position, with 32 publications and an average of 18.88 citations. Thailand and Nigeria followed, producing 13 and 11 articles, respectively, with Nigeria recording a high average citation count (28.55) comparable to China despite having fewer publications. Indonesia and Vietnam each contributed six articles; however, Vietnam stood out with the highest average citations (23.67), indicating the significant quality of its contributions, despite the smaller volume of documents. Other countries, such as Malaysia, Iraq, Korea, and Turkey, made smaller contributions, ranging from four to five articles. Korea achieved a relatively high average citation rate (21.50), whereas Malaysia and Turkey showed lower average citation figures.

A visualization of international collaboration among countries is shown in Fig. A3 (https://doi.org/10.38212/2224-6614.3589). As illustrated in Fig. A3a (https://doi.org/10.38212/2224-6614.3589), China occupies a central position and serves as the primary hub of global research cooperation on the pharmacological activities of pomelo peel. The network map shows that China maintains strong collaborative links with Vietnam, India, Thailand, Malaysia, Nigeria, and the United States, indicating its pivotal role in connecting Asian and non-Asian research communities. The large node size in China further signifies its dominant contribution in terms of publication output and research partnership intensity. By contrast, countries such as Vietnam and India appear as regional collaborators with moderate network centrality, often linked directly to China and to one another, reflecting the emergence of an interconnected Asian research cluster. Other countries, including Pakistan, Uzbekistan, and Mauritius, represent smaller peripheral clusters indirectly connected through China or regional intermediaries. Fig. A3b (https://doi.org/10.38212/2224-6614.3589) introduces the temporal dimension of the collaboration network. The color gradient

月日知識庫

reveals that most international collaborations involving China, Vietnam, and India intensified between 2018 and 2021, as indicated by the blue and turquoise nodes. More recent partnerships with France, Malaysia, and Mauritius have emerged after 2022, represented by green-to-yellow hues. This temporal progression suggests an ongoing expansion of China's international research collaborations beyond Asia, extending toward Europe, Africa, and the Indian Ocean. Overall, the visualization highlights China's dominance as the central driver of global research networks, in terms of both productivity and collaboration. Simultaneously, it reflects a broader diversification of international cooperation, where Asian institutions, particularly from Vietnam, India, and Thailand, are gaining strategic importance in cross-regional research partnerships.

3.6. The most productive and influential journals

Scientific journals play a crucial role in disseminating research findings and in advancing scientific knowledge. The analysis of journal productivity and impact in this study aimed to identify journals that contribute to the development of pharmacological research on pomelo peel and to assess the extent to which each journal disseminates and influences scientific progress in this field (Table B6) (https://doi.org/10.38212/2224-6614.3589). *Food Chemistry* and the *International Journal of Biological Macromolecules* were the most productive, each publishing seven articles. Other journals with notable output included *Molecules* (six publications), *International Food Research Journal* (four publications), and *Scientific Reports* (four publications). Although these journals play a prominent role in disseminating research on the pharmacological potential of pomelo peel, a discrepancy between productivity and influence was observed. For instance, although *Scientific Reports* published four articles, its total citation count remained relatively low (18 publications), indicating a limited per-article impact. Conversely, the *Journal of Agricultural and Food Chemistry* published only three relevant articles but garnered a total of 202 citations.

To evaluate the influence of journals in this study, local citation metrics such as total citations and the local h-index were used, as shown in Table B6 (https://doi.org/10.38212/2224-6614.3589). The local h-index represents the number of articles (h) that have each been cited at least h times, reflecting both productivity and consistency of impact in this research field. *Food Chemistry* ranked highest with a local h-index of 7 and 510 citations, indicating high publication volume and strong citation performance. *International Journal of Biological Macromolecules* and *Molecules* followed with a local h-index of 5, while journals such as *Plants* and *Evidence-Based Complementary and Alternative Medicine*, despite having fewer publications, showed comparable impact (h-index 2–3; >120 citations). This indicates that journals with lower publication volumes can serve as important channels for disseminating high-impact research.

To provide a broader understanding of journal influence beyond local citation metrics, the most recent Journal Impact Factors (JIF, 2024) from the Web of Science database were considered as additional references for evaluating journal reputation and global visibility [30]. The use of JIF values complements the local h-index by reflecting each journal's overall prominence and citation performance in the international scientific community. As shown in Table B6 (https://doi.org/10.38212/2224-6614.3589), Food Chemistry (IF = 9.8) and the International Journal of Biological Macromolecules (IF = 8.5) ranked highest, confirming their strong international standing in food and pharmaceutical research [30]. Other journals such as Molecules (IF = 4.6) and Scientific Reports (IF = 3.9) also demonstrated considerable influence owing to their multidisciplinary readership and wide accessibility [30]. In contrast, more specialized journals, including the International Food Research Journal (IF = 1.0) and the Journal of Chemistry (IF = 2.6), had relatively lower impact factors, indicating a narrower citation network. Although Evidence-Based Complementary and Alternative Medicine no longer possesses an official JCR impact factor due to its delisting from the Web of Science, it remains indexed in Scopus with a CiteScore of approximately 2.9 and an SJR of 0.51 [31,32]. Thus, the integration of both JIF and Scopus-based metrics provides a more comprehensive evaluation of journal influence, bridging local bibliometric performance with global visibility across disciplines related to the pharmacological potential of pomelo peel.

3.7. The most cited articles

The most-cited articles were analyzed to identify the most influential publications in shaping the direction, methodological approaches, and research focus on the pharmacological activities of pomelo peel. As summarized in Table B7 (https://doi.org/10.38212/2224-6614.3589), the top ten articles each received between 91 and 243 total citations, with annual *citation* averages ranging from 8 to 35 citations per year. The most cited article was authored

月日知識庫

by Wu et al. (2019) and published in *Food Hydrocolloids*, with 243 citations (an average of 34.7 citations per year) [33]. This study demonstrated that incorporating pomelo peel extract into pectin-based films significantly enhanced their antioxidant and antimicrobial activities. These findings highlight the potential of pomelo peel as a natural source of bioactive agents for use in food coatings and active-compound delivery systems. The second most-cited article by El Kantar et al. (2018), with 188 citations (23.5 citations per year), reviews the utilization of agricultural waste, including pomelo peel, as a source of bioactive compounds. This study emphasizes the high polyphenol content of pomelo peel and its potential antioxidant activity, which is applicable in the development of functional foods and health-related products [34]. The third highest-cited publication was a comprehensive review by Tocmo et al. (2020) in *Food Science and Food Safety*, with 152 citations (25.3 per year). This article discusses various bioactive compounds in pomelo, such as flavonoids and limonoids, and highlights their anticancer, anti-inflammatory, and hepatoprotective activities, underscoring the relevance of these compounds in the development of natural-product-based therapeutics [3].

Several recent studies (2018–2021) have also shown a significant impact, such as Huang et al. (2020) with 134 citations (22.3 per year), Wang et al. (2019) with 130 citations (18.57 per year), and Xiao et al. (2021) with 123 citations (24.6 per year) [35–37], indicating growing scientific interest in this research area. Although most of the highly cited articles were published in the past five to seven years, some influential studies remain prominent. For example, Xi et al. (2014) and Oboh & Ademosun (2012) received 119 and 118 total citations [22,38], respectively, demonstrating their long-term significance as foundational contributions to pomelo peel pharmacology.

3.8. Keywords dynamics, trend topics, and Co-occurrence mapping

The analysis of keywords in bibliometric research provides insights into the main research focus, emerging topics, and conceptual relationships in the pharmacological studies of pomelo peel. By examining the dynamics and co-occurrence patterns of keywords, it is possible to identify how key issues have evolved over time and to highlight potential directions for future investigation. As shown in Table B8 (https://doi.org/10.38212/2224-6614.3589), the most frequently used keyword is “antioxidant” (114 occurrences), underscoring the major emphasis on antioxidant mechanisms as a key pharmacological property of pomelo peel and its derived compounds. This is followed by “flavonoid” (81), reflecting the significance of flavonoid constituents as primary contributors to antioxidant and therapeutic effects. The presence of “nonhuman” (73), “controlled study” (67), and “animal” (58) suggests that a large portion of the research has been conducted through preclinical experimental models, indicating an early-stage focus on mechanistic and safety evaluations before clinical translation. The keywords “unclassified drug” (58) and “antioxidant activity” (56) further highlight the exploration of newly identified natural compounds whose pharmacological classifications are not yet fully established, reinforcing the experimental and discovery-driven nature of this research area. Meanwhile, terms like “chemistry” (45), “rat” (37), and “human” (35) reveal an integrative approach that combines chemical characterization with biological assessment in both animal and limited human studies. Overall, this pattern demonstrates that research on pomelo peel is primarily concentrated on antioxidant and flavonoid-based pharmacology, employing animal-controlled studies to elucidate the potential mechanisms of action. The inclusion of multidisciplinary terms, such as chemistry and pharmacological activity, reflects a growing convergence between phytochemical analysis, bioactivity testing, and therapeutic exploration, paving the way for future studies to advance from experimental models for clinical validation and application of pomelo peel–derived compounds.

The Trend Topics visualization (Fig. A4) (https://doi.org/10.38212/2224-6614.3589) illustrates the development of research themes related to the chemical, pharmacological, and technological studies of pomelo peel (*Citrus maxima*) and its bioactive compounds. Before 2013, research primarily focused on chemical analysis aspects such as “Fourier transform infrared spectroscopy,” “physical chemistry,” and “chemical composition.” This stage represents the initial effort of researchers to identify and characterize the main chemical components of pomelo peel as a foundation for subsequent studies. Between 2015 and 2018, research focus gradually shifted from pure chemical analysis toward biological and pharmacological evaluations, as indicated by the increasing frequency of terms such as “antioxidant,” “flavonoid,” “controlled study,” “animal,” and “nonhuman.” This transition signifies that researchers have begun to conduct experimental biological assays, using both in vitro and in vivo models, to explore the mechanisms of

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antioxidant and therapeutic effects of natural compounds present in pomelo peel. From 2019 to 2023, research intensity increased significantly, with dominant keywords including "antioxidant activity," "flavonoids," "enzyme inhibition," "drug determination," and "lipid peroxidation." lipid peroxidation. This trend highlights a stronger focus on bioactivity testing and pharmacological mechanism validation, where compounds, such as flavonoids, pectin, and neohesperidin, are increasingly associated with various biological effects, including antioxidant, anti-inflammatory, and antimicrobial activities. This period also reflects the emergence of a multidisciplinary research approach that integrates chemistry, molecular biology, and pharmacology within a unified research framework. After 2023, new research topics such as "green synthesis," electroactive sensors, "food packaging," and "dietary fiber" began to emerge. These topics indicate a growing shift toward applied and technology-oriented studies, including environmentally friendly synthesis methods, electrochemical biosensor development, and utilization of dietary fibers and natural active compounds in functional formulations. The main goal of these advancements is to enhance the stability, efficacy, and bioavailability of the bioactive compounds derived from pomelo peel. Furthermore, the recurring presence of analytical terms such as "thin layer chromatography" and "Fourier transform infrared spectroscopy" emphasizes that chemical analysis continues to serve as a methodological foundation supporting pharmacological and formulation studies.

Co-occurrence mapping (Fig. 4a), visualized using VOSviewer, revealed a dense network of interrelated keywords that represented the core structure of research on the pharmacological and chemical properties of pomelo peel. The network was divided into several clusters distinguished by color, signifying a distinct but interconnected thematic area within this field. The red cluster, dominated by keywords such as "antioxidant," "chemistry," "pectin," "Fourier transform infrared spectroscopy," "antimicrobial activity," and "essential oil," represents the chemical and analytical dimension of research. This cluster indicates that many studies have focused on the isolation, characterization, and functional evaluation of bioactive compounds, particularly focusing on their antioxidant and antimicrobial properties. The frequent co-occurrence of "physicochemical property" and "scanning electron microscopy" further supports the emphasis on material analysis and compound profiling. The green cluster, centered around "flavonoid," "phenol," "ascorbic acid," "enzyme inhibition," and "phytochemistry," reflects the bioactivity and mechanism-oriented studies. Research in this group has primarily explored flavonoid-rich compounds and their biochemical roles, including enzyme inhibition and oxidative stress modulation. The close association between "flavonoid" and "antioxidant" nodes suggests that these compounds are key contributors to the pharmacological efficacy of pomelo peel extracts. The blue cluster is largely associated with experimental and pharmacological models, encompassing terms such as "nonhuman," "animal experiment," "rat," "mouse," "in vivo study," and "anti-inflammatory activity." This cluster represents the preclinical stage of research, in which bioactive compounds are tested for their biological effects and safety profiles. The presence of related terms such as "tumor necrosis factor," "interleukin-1 beta," and "gene expression" indicates molecular-level investigations of anti-inflammatory and immunomodulatory mechanisms. The yellow cluster, featuring "drug effect," "essential oil," "oils volatile," and "antineoplastic agent," bridges the chemical and biological domains, pointing to emerging applications of pomelo peel compounds in drug discovery and formulation research. This cluster also demonstrates growing interest in volatile oils and natural antioxidants for pharmaceutical and nutraceutical development. Fig. 4b adds a temporal dimension, showing the evolution of research focus over time. Early studies (2017–2018, shown in darker blue) concentrated on in vivo pharmacological experiments and antioxidant assays, whereas recent publications (2020–2022, shown in green to yellow tones) have shifted toward applied and technology-integrated research, including pectin utilization, antibacterial formulations, and analytical optimization.

4. Discussion

4.1. Analysis of trends

The exploration of research trends related to the pharmacological activities of pomelo (*C. maxima*) peel over the past two decades (2002–2025) revealed a progressive, exploratory, and increasingly application-oriented development pattern. In the early stages, research was largely limited to the identification of chemical compounds and their basic biological activities [33,34]. However, as interest in natural products as therapeutic alternatives has grown, studies on pomelo peel have shown greater consistency in volume, methodological complexity, and scientific collaboration [3,35]. This progress is reflected in several key

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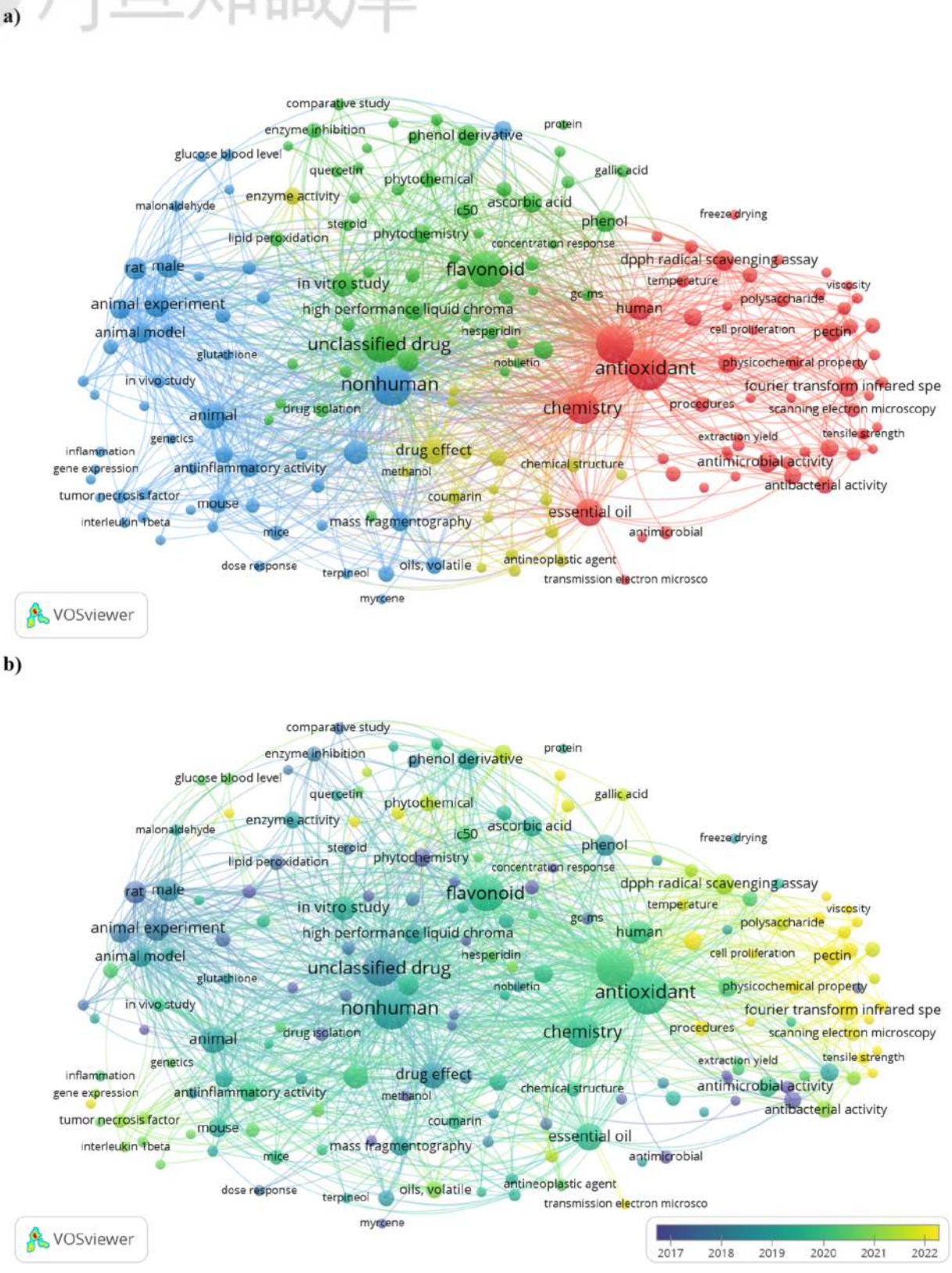


Fig. 4. Visualizations of the co-occurrence of keywords in pharmacological research on pomelo peel: (a) network map and (b) overlay visualization by publication year.

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publication indicators, from the increasing number of articles to the diversification of research topics. Although citation growth does not always align linearly with publication output, the diversity of content and multidisciplinary approaches suggests that this subject has evolved into a broader and increasingly mature research field.

The annual publication pattern on the pharmacological potential of pomelo peel has shown a marked increase in document output, particularly over the last five years. This surge reflects the global response to the rising demand for natural-product-based therapeutics, especially in the face of drug resistance, degenerative diseases, and a global push toward green innovation. The peak was observed during 2020–2024, reaching 36 publications in 2024, followed by a drop in 2025, likely owing to indexing delays [26,38–40]. Although publication output has increased, citations per document have declined, possibly because recent publications have not had enough time to accumulate citations [22,35]. This trend suggests that scientific visibility depends not only on volume but also on content quality, applicability, and dissemination. Therefore, enhancing problem-oriented research and producing well-structured manuscripts for international audiences is essential to ensure a long-term scientific impact.

Collaboration networks between authors and countries have gradually shifted from local partnerships to more global scientific alliances, although they are unevenly distributed. Authors such as Ademosun and Oboh have demonstrated consistent cross-country collaboration between Nigeria and Brazil [21,25]. Researchers from China and the United States have also actively contributed, although with more scattered participation. The emergence of collaborative clusters from multiple countries indicates that natural product research centers are no longer concentrated solely in developed nations but are also thriving in developing regions. Since 2018, co-authorship networks have become increasingly complex and interconnected, with figures such as Xu Qiang playing a key role in linking different author clusters [40,41]. However, international collaboration remains heavily centered in Asia and Africa, indicating significant potential for further global network expansion. Enhancing transnational cooperation through joint research projects, co-authored publications, and data sharing would greatly support the elevation of pomelo peel research at the global scientific stage.

The institutional affiliation analysis confirms that the key research centers in this field are primarily located in Asia and Africa, particularly in China, Vietnam, and Nigeria. Institutions such as Huazhong Agricultural University, Nguyen Tat Thanh University, and Southwest University represent the most active contributors, reflecting their strong institutional capacity and focus on natural product pharmacology. The Federal University of Technology (Nigeria) also demonstrates the growing participation of African institutions in this research domain. Several Chinese universities, including Fujian Agriculture and Forestry University, Jimei University, and Sun Yat-sen University, have further highlighted China's leading position as a global research hub. This pattern indicates a strategic research direction emphasizing the utilization of regionally abundant biological resources, such as pomelo, which thrives in tropical and subtropical climates. Moreover, institutions with strong foundations in applied sciences and natural product research tend to show higher productivity, suggesting that research success depends not only on the institutional scale, but also on strategic focus and scientific infrastructure.

China, India, and Thailand have emerged as leading contributors to pomelo peel research, with China ranking highest in both publication output and scientific influence. Nigeria and Indonesia, although producing fewer articles, showed a high citation impact, indicating the significant quality of their contributions. International collaboration maps demonstrate that China serves as a central hub of global partnerships in this field, maintaining strong ties with countries such as Nigeria, Thailand, the United States, and several European nations such as France and Mauritius [35,36]. Nonetheless, the uneven distribution of these partnerships and the tendency toward regional collaboration suggest that further efforts are needed to promote broader international engagement in the future.

From the perspective of scientific journals, a clear distinction exists between the most productive and influential journals. Food Chemistry and the International Journal of Biological Macromolecules rank high in terms of publication count, but journals such as the Journal of Agricultural and Food Chemistry though publishing fewer articles have significantly higher citation counts. This finding indicates that article quality and relevance outweigh publication quantity in determining influence. The local h-index further supports this, as journals with more focused scope and international reputations tend to enjoy greater visibility. Therefore, journal selection strategies play a critical role in maximizing both the dissemination and citation impact. Researchers are encouraged to

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consider not only journal prestige, but also the alignment between journal scope and article content to enhance scholarly reach.

The most cited articles were predominantly from 2018 onwards, highlighting the increased scholarly attention toward practical applications of pomelo peel research. These influential publications emphasize the importance of multidisciplinary approaches such as the use of pomelo peel in active food packaging, preservation technologies, and comprehensive reviews of bioactive compounds [3,33,34]. Articles with a broad scope and practical relevance tend to attract more citations across different scientific disciplines. Consequently, the development of review papers and interdisciplinary studies represents a strategic pathway for amplifying the scientific impact of future publications.

The results of keyword analysis and bibliometric visualization indicate that research on the pharmacological activities of *Citrus maxima* (pomelo) peel has undergone significant development over the past two decades. The dominance of terms such as “antioxidant” and “flavonoid” reflects the primary focus on the identification and characterization of bioactive compounds that act as natural antioxidants. This suggests that the scientific attention to pomelo peel stems from the potential of its polyphenolic and flavonoid compounds to scavenge free radicals and prevent oxidative stress factors known to play a key role in the onset of various degenerative diseases. The appearance of terms such as “nonhuman,” “controlled study,” and “animal experiment” indicates that research has moved beyond compound identification toward experimental validation and pharmacological evaluation. This shift demonstrates increasing methodological depth, as researchers have begun to assess the mechanisms of action, efficacy, and biological safety of compounds isolated from pomelo peel using preclinical testing models. Visualization of trend topics reveals that the direction of research has expanded toward applied and multidisciplinary approaches. Terms such as “green synthesis,” “electroactive sensor,” and “drug effect” drug effects illustrate the integration of pharmaceutical science, chemistry, and modern technology. This indicates that recent studies not only aim to understand the biological activities of natural compounds, but also seek to enhance their stability, efficacy, and sustainability through technological innovation.

Overall, the bibliometric findings confirm that pomelo peel research has evolved from basic phytochemical investigations to application-oriented and technology-driven studies. Pomelo peel is now regarded not merely as agricultural waste but as a strategic source of bioactive compounds with strong potential for development into health-promoting products, natural therapies, and sustainable pharmaceutical innovations. These findings also suggest that future research challenges lie not only in increasing publication output, but also in strengthening scientific collaboration, promoting interdisciplinary integration, and translating laboratory discoveries into practical applications that can have a meaningful impact on society and the health industry.

4.2. Pharmacological activities

The peel of pomelo contains a wide range of secondary metabolites such as flavonoids, phenolic acids, terpenoids, limonoids, and tannins. These compounds are known to possess various potential pharmacological activities, including antioxidant, antidiabetic, antimicrobial, anti-inflammatory, anticancer, and hepatoprotective effects. Evidence from experimental studies and recent bibliometric analyses indicate that pomelo peel could serve as a promising natural source of therapeutic agents, both for applications in functional foods and as an adjuvant therapy in the treatment of degenerative diseases (Table B9) (https://doi.org/10.38212/2224-6614.3589).

4.2.1. Antioxidant activity

Antioxidants are molecules capable of scavenging free radicals and reducing the oxidative damage caused by reactive oxygen species (ROS) in the body [42]. Free radicals can damage cellular structures, including DNA, proteins, and lipids, which are closely associated with the development of degenerative diseases, such as cancer, diabetes, and cardiovascular disorders. Therefore, antioxidants are essential for maintaining homeostasis and protecting the body from oxidative stress [43]. Common assays used to evaluate antioxidant capacity include DPPH (2,2-diphenyl-1-picrylhydrazyl), ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), FRAP (ferric reducing antioxidant power (FRAP), ORAC (oxygen radical absorbance capacity (ORAC), and CUPRAC (cupric reducing antioxidant capacity) [44]. These methods assess the ability of compounds to scavenge free radicals or reduce other pro-oxidant molecules, and the results are typically expressed as IC_{50} values or Trolox equivalents (TE).

Pomelo peel is an example of fruit waste that has demonstrated antioxidant potential owing to its content of bioactive compounds such as flavonoids,

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phenolics, and terpenoids. Several studies have shown that pomelo peel extracts have radical scavenging capacities [45–50]. Lü et al. (2016) investigated the antioxidant capacity of peel extracts from ten pomelo cultivars and reported significant variations in antioxidant activity among cultivars [47]. Sharma et al. (2022) supported these findings using in vitro and in silico approaches. In vitro assays demonstrated that *Citrus grandis* peel extract had free radical scavenging capacity with IC_{50} values of 119.42 μg/mL (DPPH) and 198.54 μg/mL (ABTS). In silico analysis using the PASS software predicted that flavonoids such as naringin, hesperidin, and rutin have high probability scores (Pa >0.7) as free radical scavengers, lipid peroxidase inhibitors, and antioxidants [51]. Another study by Al-Khalifa et al. (2023) showed that pomelo peel extract exhibited an IC_{50} value of 287.32 μg/mL in the DPPH assay, which was lower than that of sweet orange peel extract (IC_{50} 341.89 μg/mL), indicating stronger antioxidant activity in pomelo peel [52]. The antioxidant activity of pomelo peel is mainly attributed to flavonoids, such as naringenin and hesperidin, which have been shown to scavenge free radicals and reduce oxidative stress associated with degenerative diseases [48,52]. Extraction methods also influence the effectiveness of pomelo peel extracts in demonstrating their antioxidant activity. Several studies have indicated that extraction with 50–70% ethanol yields extracts with higher phenolic and flavonoid contents as well as stronger antioxidant activity. In a study by Inthachat et al., (2023), optimization of extraction conditions using response surface methodology showed that pomelo peel extracted with 50% ethanol at 30 °C for 4 h contained 15.79 mg GAE/g total phenolics and 4.50 mg QE/g total flavonoids. LC-ESI-MS/MS analysis identified hesperidin and naringenin in the extract, which contributed to its antioxidant properties [53].

The antioxidant compounds in pomelo peel act via multiple mechanisms. Fidrianny et al. (2016) demonstrated that pomelo peel extract inhibited lipid peroxidation, as measured by malondialdehyde (MDA) assays, and reduced protein aggregation [45]. Kuo et al. (2017) isolated coumarins and phenolic compounds from pomelo peel and demonstrated their ability to inhibit the formation of superoxide anions in human neutrophils, although their role in enhancing ROS-detoxifying enzymes has not been fully elucidated [54]. Further research by Tian et al. (2019) revealed that coumarins, such as columbianoside and meranzin hydrate I, isolated from pomelo peel increased SOD and GPx enzyme activity in normal liver (LO2) cells under oxidative stress, thereby lowering MDA levels [55]. Ha et al. (2022) also demonstrated that pomelo peel extract can reduce ROS production and decrease inflammatory cytokines such as IL-8 and TNF-α in A549 cells, supporting its dual antioxidant and anti-inflammatory roles [56]. Another study by Phetkul et al. (2024) showed that flavonoids from pomelo peel can induce the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) [57], which plays a role in upregulating antioxidant and detoxification gene expression.

The structure–function relationship of the antioxidant compounds in pomelo peel can be explained by the chemical characteristics of its flavonoids, coumarins, and essential oil constituents. Phenolic hydroxyl groups, particularly those at the ortho-dihydroxy (3′,4′-) position on the B-ring and the conjugated double bond system on the C-ring, play a crucial role in radical scavenging by donating hydrogen atoms or electrons to stabilize free radicals [51]. The structural variation between glycoside and aglycone forms, such as naringin and naringenin, also affects antioxidant performance: glycosides exhibit higher solubility and stability in polar solvents, whereas aglycones demonstrate stronger antioxidant effects through direct electron transfer [49,53]. Coumarins such as columbianoside and meranzin hydrate contain methoxy or prenyl substituents that enhance lipophilicity and cellular membrane permeability, thereby promoting antioxidant enzyme activity (SOD and GPx) and reducing lipid peroxidation (MDA) [54,55]. Meanwhile, essential oil components, such as limonene and α-terpineol, contribute indirectly by modulating redox-related signaling pathways, particularly through activation of the Nrf2 transcription factor, which regulates the expression of antioxidant and detoxification genes [11,58]. Overall, the antioxidant activity of pomelo peel results from the synergistic interaction between phenolic structures that act as electron donors, glycosidic modifications that improve bioavailability, and lipophilic terpenes that regulate cellular redox homeostasis (Fig. 5) [45,49,53,56].

In line with the molecular mechanisms mentioned above, recent studies have not only emphasized the role of bioactive compounds from pomelo peel but have also linked them with advanced extraction technologies and innovative approaches to enhance antioxidant effectiveness. Flavonoids such as naringin, hesperidin, naringenin, and rutin are recognized as the dominant constituents responsible for free radical scavenging, as demonstrated by DPPH, ABTS, and FRAP assays [59]. Other compounds, including coumarins (e.g.,

columbianoside and meranzin hydrate), have been shown to enhance antioxidant enzymes such as SOD and GPx, while lowering MDA levels, thereby exerting dual antioxidant and anti-inflammatory effects [10]. Essential oils, particularly limonene and α-terpineol, also contribute by modulating oxidative stress and inflammatory responses [11]. Furthermore, cultivar variability and peel tissue differentiation (flavedo vs. albedo) significantly influence phenolic and flavonoid content as well as antioxidant capacity [47]. Post-harvest processes, such as drying methods, have also been reported to affect the phenolic composition and antioxidant potential, highlighting the importance of technical parameters in standardizing extracts [46]. Collectively, pomelo peel can be regarded as a multi-component antioxidant system, whose activity is shaped by both biological and technological factors.

Advances in sustainable extraction technologies have enabled more efficient, environmentally friendly, and standardized recovery of pomelo peel bioactive compounds. Supercritical CO_2 (SC−CO_2) extraction has been reported to yield flavonoid-rich extracts with superior antioxidant activity compared to conventional solvent extraction owing to its ability to preserve thermolabile constituents and minimize solvent residues [49]. Response Surface Methodology (RSM) optimization applied to albedo fractions further enhanced phenolic and flavonoid content, as well as antioxidant capacity, through precise control of extraction parameters [53]. Pulsed electric field (PEF) treatment of citrus fruits has been shown to facilitate polyphenol release and improve the diffusion efficiency of bioactive compounds [34]. On the analytical front, recent developments in electrochemical platforms have enabled rapid, sensitive, and real-time assessment of antioxidant activity [44]. The integration of green extraction/synthesis with advanced analytical technologies supports the framework of a circular bioeconomy, transforming pomelo peel into a sustainable and value-added source of natural antioxidants [34,44,49,53].

The applications of pomelo peel antioxidants have now extended beyond traditional in vitro testing to include food systems, materials science, and biomedical fields. In the food industry, pomelo peel extracts have been shown to delay lipid

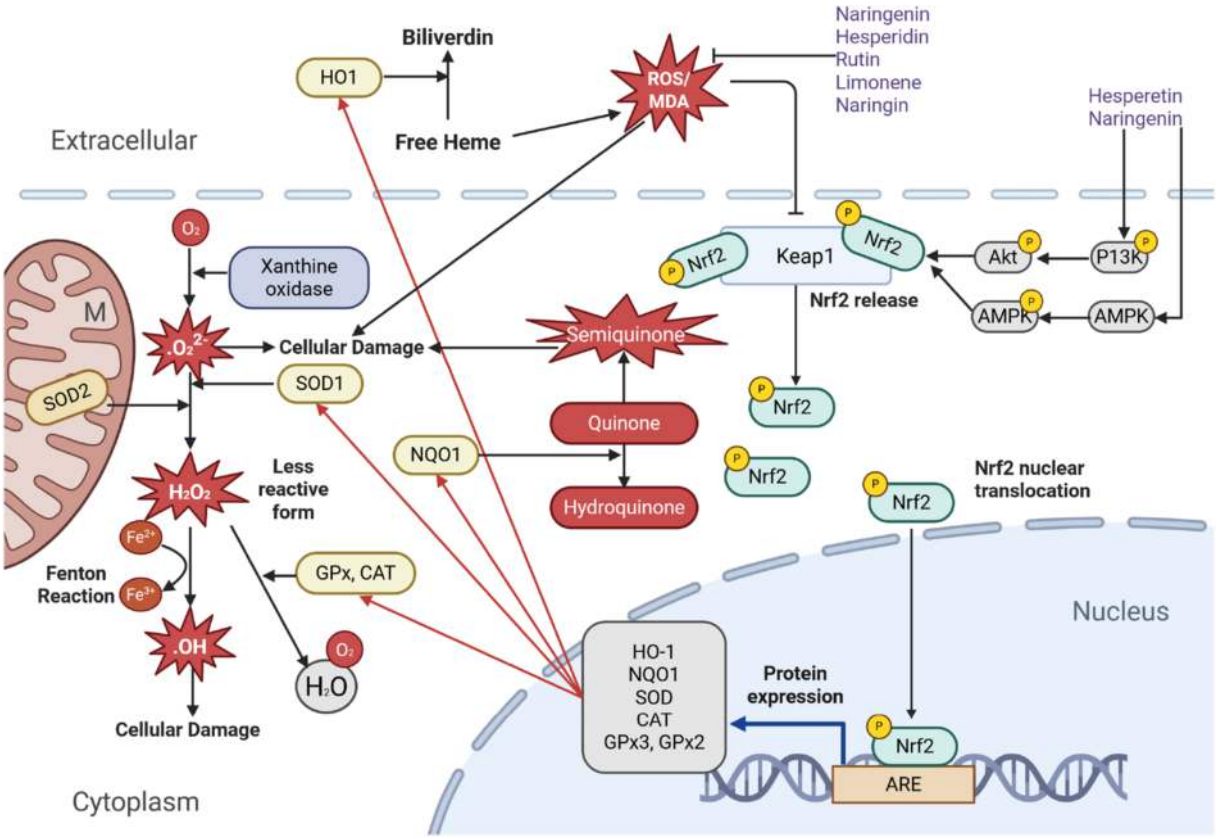


Fig. 5. Signaling pathways underlying the antioxidant activity of bioactive compounds in pomelo peel (Created in BioRender. Fernando, D. (2025) https://BioRender.com/beinorg).

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peroxidation and enhance the stability of edible oils, whereas peel-derived flours have been incorporated into edible films and active packaging [33,50]. In materials science, pomelo peel-derived carbon has been engineered into high-surface-area electrocatalytic materials for electrochemical sensors, enabling the sensitive detection of compounds such as kaempferol [60]. In biomedical applications, carbonized cellulose aerogels derived from pomelo peel have demonstrated rapid hemostatic effects on trauma-induced bleeding, indicating their potential use as functional biomaterials [61]. To address the issues of stability and bioavailability of flavonoids, formulation strategies such as naringin–metal complexation have been developed, offering oxidative protection and improved bioefficacy [62]. Thus, the integration of nanoencapsulation, smart packaging, electroactive sensors, and biomaterial positions in pomelo peel is a strategic candidate for innovation in green chemistry, pharmaceuticals, and advanced material engineering [33,50,60–62].

4.2.2. Antidiabetic activity

Diabetes is a chronic metabolic condition characterized by impaired regulation of blood glucose levels [63]. Dysregulation can be caused by various factors, including insulin deficiency, insulin resistance, pancreatic dysfunction, oxidative stress, and systemic inflammation. If not properly managed, diabetes may lead to serious complications such as neuropathy, kidney dysfunction, and cardiovascular disease [63–65]. Pomelo peel is a fruit waste that contains active compounds, such as flavonoids, phenolics, coumarins, and pectin, which exhibit notable antidiabetic activity. Numerous studies have demonstrated that pomelo peel extract inhibits carbohydrate-digesting enzymes, enhances glucose metabolism, improves lipid profiles, reduces oxidative stress, and supports tissue regeneration and gut microbiota balance [66–70].

Oboh and Ademosun (2011) investigated the effects of free and bound phenolic extracts from pomelo peel on the activities of α-amylase, α-glucosidase, and angiotensin I-converting enzyme (ACE). Both extracts significantly inhibited the activity of these enzymes in vitro, with bound phenolics showing greater α-amylase inhibition and free phenolics demonstrating stronger ACE inhibition. This study highlighted the dual role of pomelo peel in managing blood glucose and blood pressure, which are both relevant to diabetes-related complications [71]. Lim and Loh (2016) also reported that the phenolic extracts of pomelo peel exhibited dose-dependent inhibition of α-amylase and α-glucosidase, along with strong antioxidant activity, as demonstrated by DPPH and ABTS assays. This suggested a synergistic mechanism between enzyme inhibition and oxidative stress reduction. In vivo evidence supports these findings [72]. Ahmad et al. (2018) found that oral administration of pomelo peel extract in streptozotocin-induced diabetic rats accelerated wound healing by enhancing collagen synthesis and lowering blood glucose levels [68]. Ulla et al. (2019) showed that supplementation with pomelo peel powder for 21 days in alloxan-induced diabetic rats improved glucose tolerance, reduced liver enzyme levels, and decreased oxidative stress [73]. Ani and Ochu (2020) reported that oral administration of pomelo peel extract at doses of 200–600 mg/kg body weight for 14 days reduced blood glucose levels by 70.17%, increased HDL cholesterol, and decreased total cholesterol and triglycerides, with no significant hepatotoxicity [74]. Similarly, Mohammed et al. (2021) demonstrated improved glycemic control and lipid metabolism in diabetic rats following treatment with an ethanol extract of pomelo peel [70]. Najar et al. (2022) showed that pomelo peel extract not only reduced glucose and lipid levels, but also suppressed inflammation and oxidative stress in cardiac tissue [69], indicating its protective role against cardiovascular complications associated with diabetes.

Recent studies have explored novel modifications to enhance the antidiabetic potential of pomelo peels. Zang et al. (2023) modified pomelo peel pectin and found that it effectively reduced blood glucose levels, improved lipid metabolism, and enhanced gut microbiota composition by increasing beneficial microbes, such as Akkermansia and Lactobacillus. Zheng et al. (2024) applied fermentation using *Pomelo*, which increased the phenolic and flavonoid content in the extract. The fermented extract showed enhanced inhibition of α-amylase and α-glucosidase along with increased glucose uptake and glycogen synthesis in HepG2 liver cells [67]. Overall, the antidiabetic mechanisms of pomelo peel involve: (1) inhibition of carbohydrate-digesting enzymes to prevent postprandial glucose spikes, (2) improvement of insulin sensitivity, (3) reduction of oxidative stress and inflammation, (4) support for tissue regeneration and wound healing, and (5) modulation of the gut microbiota to regulate glucose metabolism. These effects are largely attributed to the presence of bioactive compounds such as naringin, hesperidin, pectin, and coumarins (Fig. 6) [11].

The structure–function relationship underlying the antidiabetic potential of pomelo peel is primarily associated with its major bioactive

constituents, particularly flavonoids, coumarins, and pectins. Flavonoids, such as naringin, hesperidin, and naringenin, contain multiple hydroxyl groups capable of forming hydrogen bonds and hydrophobic interactions with the catalytic sites of carbohydrate-hydrolyzing enzymes, such as α-glucosidase and α-amylase, resulting in effective postprandial glucose regulation [3,8,35,71,72]. The flavanone backbone (C6–C3–C6) and conjugated aromatic rings further enable π–π stacking interactions with the aromatic residues of these enzymes, thereby enhancing their inhibitory strength [75]. Coumarins also contribute to glucose homeostasis and blood pressure regulation by modulating angiotensin-converting enzyme (ACE) activity and carbohydrate-digesting enzymes through similar binding mechanisms [10,71]. In addition, pectin in pomelo albedo exerts its effect through structural and physicochemical mechanisms, including increasing intestinal viscosity, binding bile acids, and slowing glucose absorption, while promoting beneficial gut microbiota that enhance insulin sensitivity [9,76]. Fermentation of pomelo peel with Aspergillus oryzae has been shown to increase the release of aglycone flavonoids and phenolic compounds, thereby intensifying α-glucosidase and α-amylase inhibition and enhancing glucose uptake and glycogen synthesis in hepatic cells [67]. These structure-based interactions collectively explain the molecular basis of pomelo peel's antidiabetic properties, as confirmed by in vivo evidence showing improved glucose tolerance, lipid metabolism, and tissue regeneration in diabetic models [68–70,73,74].

In line with recent research trends, the antidiabetic activity of pomelo peel is attributed not only to its major bioactive compounds, such as naringin, hesperidin, and naringenin, but also to innovative technologies that enhance their stability, efficacy, and bioavailability. Approaches involving biopolymer modification have shown promising outcomes, with modified pectin from pomelo peel demonstrating significant effects in lowering blood glucose, improving lipid metabolism, and modulating gut microbiota by increasing the abundance of Akkermansia and Lactobacillus, both of which are

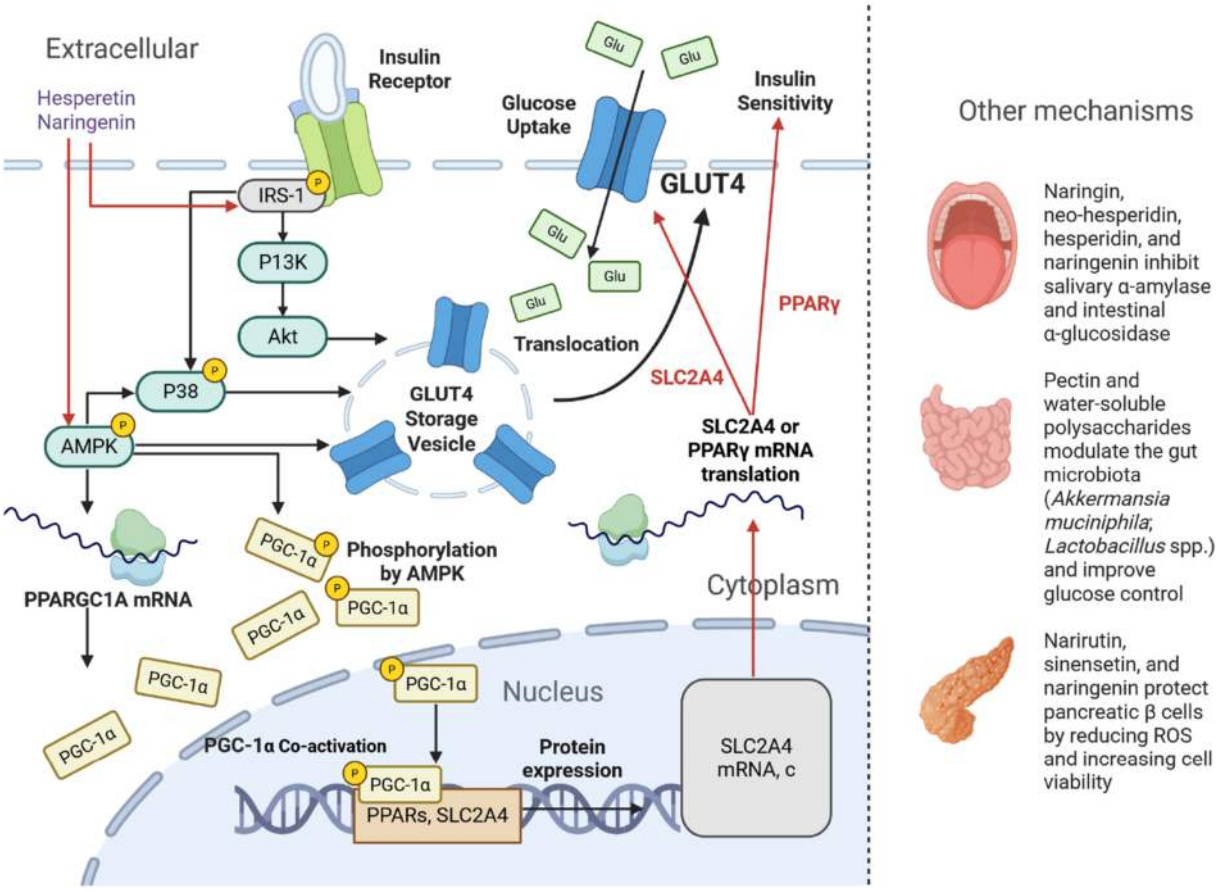


Fig. 6. Signaling pathways underlying the antidiabetic activity of bioactive compounds in pomelo peel (Created in BioRender. Fernando, D. (2025) https://BioRender.com/tni8z2v).

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crucial for improving insulin sensitivity [76]. Furthermore, fermentation with Aspergillus oryzae has been reported to elevate phenolic and flavonoid content, thereby strengthening the inhibitory effects against α-amylase and α-glucosidase while simultaneously enhancing glucose uptake and glycogen synthesis in HepG2 liver cells [67]. These findings indicate that the integration of fermentation biotechnology and polymer engineering represents an effective strategy to optimize the antidiabetic potential of pomelo peel and broaden its applications in the functional food and pharmaceutical sectors.

Moreover, the application of nanotechnology and electroactive sensing platforms provides a new direction for advancing the antidiabetic potential of pomelo peels. Through green synthesis approaches, pomelo peel extracts have been used to produce silver and copper nanoparticles with high biological activity [77–80]. Although much of the current research has focused on their antimicrobial properties, these nanoparticles hold significant promise as drug delivery systems capable of stabilizing flavonoids, such as naringin and hesperidin, while enhancing their bioavailability and enabling controlled release. Similarly, nanoencapsulation strategies are considered pivotal for protecting flavonoids from oxidative degradation and ensuring their targeted distribution to metabolic tissues. On the diagnostic side, pomelo peel-derived carbon has been explored for the fabrication of electroactive biosensors, enabling the rapid and sensitive detection of key diabetes-related enzymatic activities, which can support more precise and personalized therapeutic approaches.

4.2.3. Antimicrobial activity

Infectious diseases caused by microbial pathogens are among the causes of high morbidity and mortality worldwide [81]; therefore, it is necessary to develop more effective and safe antimicrobial agents. The peel of pomelo has been identified as a potential antimicrobial agent due to its content of bioactive compounds such as flavonoids (naringin, hesperidin), tannins, phenolics, saponins, and essential oils [59,82–84]. Aichayawanich & Ngaouwthong (2012) investigated the crude ethanol extract of pomelo peel against *Staphylococcus aureus* and observed an inhibition zone of 11.5 mm at a 20% concentration, indicating that flavonoids and alkaloids in the extract can disrupt bacterial membranes and metabolic processes [85]. A subsequent study by Sugumaran et al. (2017) optimized the antibacterial activity of flavonoid-rich pomelo peel extract against *S. aureus* using response surface methodology and identified optimal conditions at pH 4.8 and 200 mg/mL concentration [86]. Mastuki et al. (2024) tested flavedo extracts using ethyl acetate and dichloromethane solvents, revealing that ethyl acetate extracts were effective against gram-positive bacteria, such as *Staphylococcus aureus and Bacillus cereus* (inhibition zones of 14–14.7 mm), whereas dichloromethane extracts were more active against *Escherichia coli* [84]. Recently, Nguyen et al. (2024) isolated naringin from *C. maxima* var. Duong La Cam, containing 114 mg/gDW, and found it effective against *S. aureus* (MIC 5 mg/mL) and *E. coli* (Minimum Inhibition Concentration 2.5 mg/mL) primarily by disrupting the integrity of bacterial cell membranes [59].

Essential oils derived from pomelo peel have also demonstrated significant antimicrobial potential. Tao and Liu (2012) studied the essential oil from the Shatian variety of pomelo peel, which was dominated by limonene (89.96%), and reported notable activity against *S. aureus* (inhibition zone of 20.71 mm; MIC 4.69–37.5 μL/mL) [87]. Similarly, Lan-Phi & Vy (2015) reported that pomelo peel essential oil containing 90.1% limonene exhibited strong activity against *S. aureus* (13.6 mm inhibition zone) and moderate activity against *E. coli* and Candida albicans [82]. Karakaya et al. (2022) found that limonene (76.97%) from pomelo flavedo essential oil displayed antibacterial activity against *S. aureus* and B. cereus (MIC 2000–16000 μg/mL), although it was ineffective against gram-negative bacteria, such as *E. coli* and S. Enteritidis [88]. Mai et al. (2022) utilized supercritical CO_2 extraction to isolate limonene and naringin, which exhibited antimicrobial activity against Moraxella catarrhalis (MIC 0.25 mg/mL), Streptococcus pyogenes (1 mg/mL), and Trichophyton rubrum (MIC 6.25–25 mM), with mechanisms involving membrane disruption and enzymatic interference [89]. Anastasopoulou et al. (2024) further reported that essential oil from pomelo cultivated in Greece demonstrated higher antimicrobial activity against *S. aureus* and *E. coli* than conventional orange and tangelo peels, emphasizing that geographical origin can influence antimicrobial efficacy [83].

The development of nanoparticles based on pomelo peels is an emerging and innovative approach. Huo et al. (2018) synthesized silver nanoparticles (AgNPs) using pomelo peel extract, producing particles 4–11 nm in size that were effective against *E. coli*, *S. aureus*, Fusarium oxysporum, and Verticillium dahliae, primarily through ROS generation and membrane damage [77]. Similarly, Long Do et al. (2023) synthesized AgNPs from pomelo peel extract and demonstrated strong activity against MRSA, with an inhibition zone of 11.7 mm and MIC of 8.27 mg/mL, and

potent membranolytic effects [78]. Das et al. (2023) confirmed that AgNPs with an average size of 19.09 nm are effective against *S. aureus* and *Klebsiella pneumoniae* [80]. Additionally, Liu et al. (2023) and Nguyen et al. (2023) developed copper nanoparticles (CuNPs) from pomelo peel that exhibited very low IC_{50} values against Fusarium solani and Colletotrichum gloeosporioides (2.59–2.69 pM), suggesting a strong antifungal activity via cell wall penetration and oxidative stress induction [90].

Overall, these studies confirm that pomelo peel contains active compounds, such as limonene, naringin, flavonoids, and terpenoids, that exhibit broad-spectrum antimicrobial activity. Extraction methods and formulations such as essential oils, nanoparticles, and functional applications play critical roles in determining their efficacy. In summary, the antimicrobial mechanisms of pomelo peel include: (1) disruption of microbial cell membranes, leading to leakage of intracellular contents; (2) inhibition of protein and nucleic acid biosynthesis; (3) induction of reactive oxygen species (ROS), resulting in oxidative stress in microbial cells; (4) interference with vital bacterial and fungal enzymes; (5) penetration of metal nanoparticles into cells, damaging organelle structures; and (6) interactions with cell wall components, compromising microbial structural integrity (Fig. 7). These mechanisms provide synergistic antimicrobial effects and highlight the potential of pomelo peel as a natural antimicrobial agent.

The antimicrobial activity of pomelo peel is strongly governed by the structural characteristics of its major bioactive constituents, particularly their functional groups, lipophilicity, and aromatic substitution patterns. Monoterpenes, such as limonene, possess a nonpolar cyclic hydrocarbon backbone that facilitates penetration of microbial phospholipid bilayers, leading to altered membrane permeability, ion leakage, and eventual cell lysis [82,87,88]. Oxygenated terpenes, including linalool and nootkatone, contain hydroxyl or carbonyl groups that allow hydrogen bonding with membrane proteins, thereby disrupting transport and respiratory enzyme functions [83]. Flavonoids, such as naringin and hesperidin, exert antimicrobial effects related to hydroxyl and methoxy group positions on the B-ring and the C2=C3 double bond, which enhance interactions with microbial enzymes and promote membrane disruption [59]. Deglycosylation of naringin to naringenin increases lipophilicity, thereby improving diffusion across membranes and potentiating bactericidal effects against *Staphylococcus aureus* and *Escherichia coli* [59,88]. Furthermore, polymethoxyflavones (PMFs)

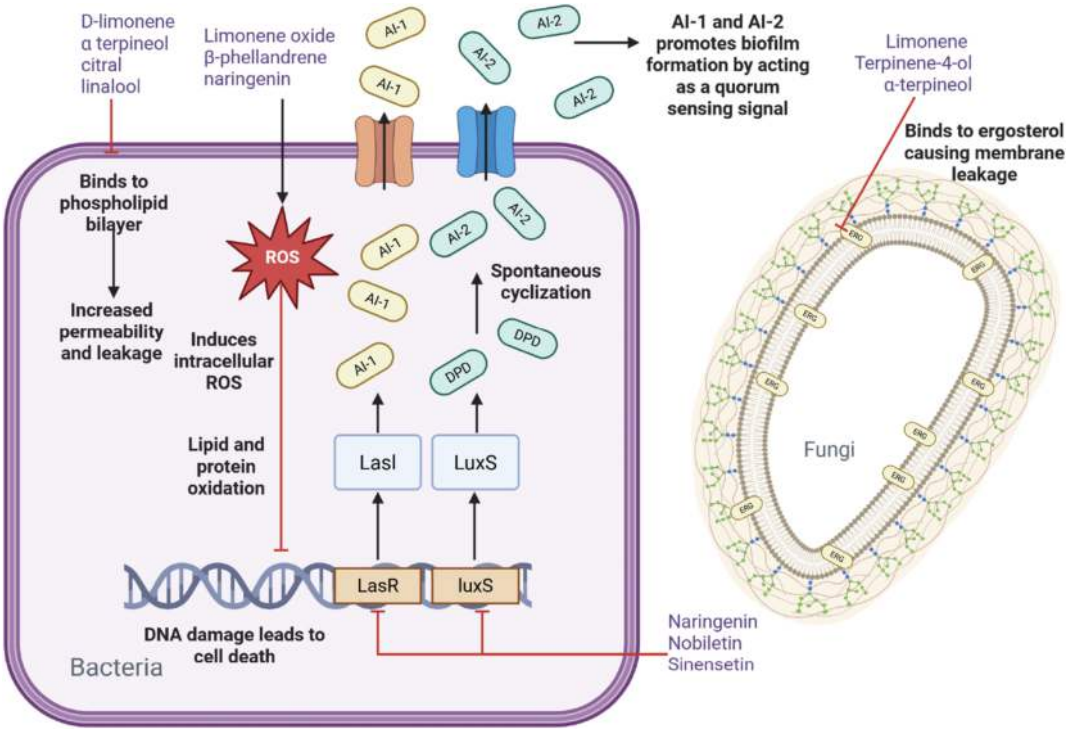


Fig. 7. Signaling pathways underlying the antimicrobial activity of bioactive compounds in pomelo peel (Created in BioRender. Fernando, D. (2025) https://BioRender.com/svseux0).

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exhibit high oxidative stability and inhibit protein biosynthesis via π−π stacking interactions with microbial nucleic acids, whereas tannins and phenolics chelate essential metal ions and precipitate microbial proteins [82,83,88]. Collectively, these structural determinants indicate that the antimicrobial potential of pomelo peel arises from synergistic mechanisms involving lipophilicity-driven membrane penetration, electrostatic interactions, and biosynthetic enzyme inhibition.

In line with recent research trends, the antimicrobial activity of pomelo peel is no longer solely attributed to classical bioactive compounds such as naringin, hesperidin, and limonene but also involves other volatile and novel molecules, including α-pinene, γ-terpinene, and polymethoxyflavones (PMFs), which have been reported to inhibit the growth of pathogenic bacteria and fungi [59,82,83,88]. Essential oils dominated by limonene have demonstrated notable inhibitory effects against *Staphylococcus aureus*, *Escherichia coli*, and Candida albicans by disrupting microbial membranes and interfering with protein biosynthesis [82,87,88]. However, the limitations in the stability and bioavailability of these volatile components have prompted the application of advanced extraction and formulation methods. For instance, supercritical CO_2 extraction has been employed to isolate limonene and naringin, which significantly enhance antimicrobial activity against Streptococcus pyogenes and Trichophyton rubrum, with proposed mechanisms including membrane damage and enzymatic inhibition [89]. These findings highlight that the effectiveness of pomelo peel bioactives is strongly dependent on the extraction techniques and delivery systems used, which opens new avenues for applications in food preservation, pharmaceuticals, and natural healthcare products.

The application of green synthetic approaches using pomelo peel extract has emerged as a promising strategy for broadening its antimicrobial potential through the biosynthesis of metal nanoparticles. Pomelo peel extracts have been used to reduce silver and copper ions into silver nanoparticles (AgNPs) and copper nanoparticles (CuNPs) of nanoscale size (4–20 nm), which demonstrated strong antimicrobial activities. Huo et al. (2018) reported that AgNPs synthesized from pomelo peel were effective against *E. coli*, *S. aureus*, Fusarium oxysporum, and Verticillium dahliae via reactive oxygen species (ROS) induction and membrane disruption [77]. Similarly, Long Do et al. (2023) demonstrated that AgNPs inhibited methicillin-resistant *Staphylococcus aureus* (MRSA) with an inhibition zone of 11.7 mm and MIC of 8.27 mg/mL, while Das et al. (2023) confirmed that AgNPs with an average size of 19.09 nm were highly active against *S. aureus* and *Klebsiella pneumoniae* [78,80]. Furthermore, Liu et al. (2023) and Nguyen et al. (2023) developed CuNPs that displayed potent antifungal effects against Fusarium solani and Colletotrichum gloeosporioides, with IC_{50} values as low as 2.59–2.69 pM [90]. Collectively, these results suggest that green synthesis not only produces environmentally friendly antimicrobial agents, but also provides a platform for intelligent drug delivery systems based on pomelo-derived bioactive compounds.

Beyond green synthesis, other modern technologies, such as nanoencapsulation and electroactive sensors, have been explored to enhance the antimicrobial efficiency of pomelo peel compounds. Chen (2018) showed that emulsification of pomelo peel essential oil with water-soluble chitosan produced a nanoemulsion with higher stability and solubility, leading to improved antibacterial activity against *S. aureus* and *E. coli* compared to unformulated essential oil [91]. Similarly, Ding et al. (2024) reported that the microencapsulation of flavonoids in melamine resin significantly improved stability, enabled controlled release, and enhanced antibacterial effects by more than 40% [92]. On the diagnostic side, Liu (2017, 2023) demonstrated that carbon-based nanomaterials derived from pomelo peel can be utilized in electroactive biosensors with high sensitivity, which holds the potential for real-time monitoring of antimicrobial activity. Furthermore, active packaging applications have been proposed, in which flavonoid-rich pomelo peel extracts were incorporated into paper-based materials, effectively suppressing foodborne pathogens, such as Bacillus cereus [92]. Thus, the integration of classical bioactive compounds (naringin, hesperidin, limonene, PMFs, and pectin) with innovative technologies (green synthesis nanoparticles, nanoencapsulation, microcapsules, active packaging, and electroactive biosensors) substantially expands the antimicrobial applications of pomelo peel, moving beyond traditional therapeutic uses toward innovative solutions in food safety, pharmaceuticals, and eco-friendly materials.

4.2.4. Anticancer activity

Cancer is characterized by uncontrolled cell proliferation, resistance to programmed cell death (apoptosis), and the ability to invade healthy tissues and form metastases [93]. This process is influenced by various factors, including oxidative stress, cell cycle dysregulation, genetic mutations, and the tumor microenvironment, which supports cancer

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cell survival and growth. Current cancer therapies employ multidimensional approaches such as chemotherapy, radiotherapy, immunotherapy, and molecular-targeted interventions. However, these treatments are often associated with significant side effects and emergence of drug resistance [93,94]. Therefore, exploration of natural compounds from plant sources, including pomelo peel, has become a central focus in the search for safer and more effective anticancer agents. Pomelo peel is an agricultural waste product known to contain bioactive compounds, such as naringin, limonene, tangeretin, nobiletin, phenolics, and polysaccharides, which have demonstrated antiproliferative, pro-apoptotic, and immunomodulatory activities [95–97]. Sajid et al. (2016) investigated the chemical composition and biological activity of essential oils derived from pomelo peels. The results revealed that limonene, a major constituent, significantly reduced the viability of DLA cancer cells (81.25% inhibition), possibly through apoptosis induction and antioxidant effects, along with antimicrobial activity, which supports its overall anticancer potential [98]. Similarly, Nair et al. (2018) confirmed that pomelo peel essential oil could inhibit DLA cancer cell growth both in vitro and in vivo through mechanisms involving cell cycle arrest and apoptosis induction mediated by flavonoids and phenolics such as limonene [39].

In 2018, Yu et al. identified that polysaccharides extracted from pomelo peel were capable of suppressing S180 tumor growth in mice, enhancing lymphocyte proliferation and natural killer (NK) cell activity, as well as modulating cytokine expression, such as IL-2 and TNF-α [99]. The immunomodulatory and pro-apoptotic activities of this extract indicate its potential as an antitumor agent that boosts the immune system. Eom et al. (2022) demonstrated that the dichloromethane fraction of pomelo peel induces apoptosis in colorectal cancer cells (HCT-116 and HT-29) through increased ROS generation, regulation of the Bcl-2/Bax protein ratio, cytochrome c release, and caspase activation. This fraction significantly reduced cell viability and induced DNA fragmentation, suggesting its role as a mitochondrial pathway-mediated inducer of apoptosis [100]. These findings are supported by Liu et al. (2025), who developed carbon materials from pomelo peel for use in electrochemical sensors to detect kaempferol, a well-known anticancer compound [60]. Monteiro et al. (2023) studied the effects of an ethanol–water extract of pomelo peel on triple-negative breast cancer cells (MDA-MB-231) and reported that the extract, rich in naringin, inhibited cell proliferation, migration, and colony formation [97]. Similarly, Yakõncõ et al. (2025) evaluated the cytotoxic effect of pomelo peel on MCF-7 breast cancer cells and found that polymethoxyflavones (PMFs), such as nobiletin and tangeretin, exhibited high cytotoxic activity, with IC_{50} values ranging between 10 and 25 μg/mL. These compounds are known to inhibit cell proliferation, induce apoptosis, and exert anti-inflammatory and antioxidant effects [96]. Mohammed et al. (2024) investigated the cytotoxic activity of pomelo peel extract against brain cancer (A172) and pancreatic cancer (Capan-2) cells and found significant cytotoxic effects, including cytochrome c release, despite the relatively high IC_{50} values [95]. Phytochemicals such as flavonoids, terpenoids, and alkaloids may act synergistically to induce cell death via membrane disruption and apoptosis pathways.

A novel approach was introduced by Yang et al. (2024), who developed a hydrogel sponge based on delignified pomelo peel modified with gallic acid and copper metal–organic frameworks (MOFs) [101]. This combination exhibited strong antimicrobial properties and accelerated healing of biofilm-infected wounds. Although the primary focus was on wound healing, the antioxidant and antibacterial properties also support its potential application in managing wounds in patients with cancer or in drug delivery systems. Atta et al. (2019) adopted a different strategy by synthesizing naringin–metal complexes from pomelo peel. These complexes exhibited greater cytotoxic activity than pure naringin and outperformed adriamycin, particularly in MCF-7 and A549 cancer cell lines [62]. This enhanced anticancer effect is likely due to interactions between the metal complexes and cancer-related DNA/proteins. In a recent study, Phetkul et al. (2025) found that ethanol extracts of pomelo peel and leaves contained bioactive compounds, such as flavonoids, coumarins, and terpenoids, showing modest but consistent antioxidant and anticancer activities. Although the anticancer potency remains lower than that of conventional drugs, these results reinforce the phytochemical profile of pomelo as a natural source of therapeutic agents [57].

The structure–activity relationship (SAR) of the major compounds found in pomelo peel revealed that their chemical structures and functional group substitutions play crucial roles in determining their anticancer potency. Polymethoxyflavones such as nobiletin and tangeretin possess multiple methoxy groups that increase lipophilicity, thereby facilitating membrane permeability and strengthening interactions with apoptosis-related proteins. Their

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planar aromatic structures and methoxy substitutions have been shown to inhibit PI3K/Akt and NF-κB signaling pathways, which are responsible for promoting cancer cell proliferation and survival [1,40]. Flavanone naringin, a glycosylated form, exhibits enhanced cytotoxicity upon conversion to its aglycone, naringenin, through deglycosylation due to reduced polarity and improved affinity for pro-apoptotic intracellular targets. Moreover, the formation of naringin–metal complexes has been reported to increase stability and cellular permeability while intensifying oxidative stress-induced apoptosis [62].

Additionally, the monoterpene limonene, characterized by a hydrophobic cyclic structure, primarily disrupts the integrity of cancer cell membranes, elevates reactive oxygen species (ROS) levels, and triggers apoptosis via the mitochondrial pathway [39,98]. Nonpolar fractions such as dichloromethane extract, which is rich in aromatic compounds, exert similar effects through ROS generation, alteration of the Bcl-2/Bax ratio, cytochrome c release, and caspase activation, hallmarks of mitochondria-mediated apoptosis [100]. Meanwhile, polysaccharides containing β-glucan and pectin structures exhibit immunomodulatory effects by stimulating lymphocyte and natural killer (NK) cell activity as well as by enhancing the expression of cytokines such as IL-2 and TNF-α, indirectly contributing to tumor suppression [99]. Overall, structural characteristics such as increased methoxylation, deglycosylation, and enhanced lipophilicity are consistently associated with greater membrane permeability, balanced oxidative stress modulation, and inhibition of pro-survival signaling pathways, leading to apoptosis induction [1,39,40,62].

In line with current research trends, recent studies have extended the anticancer exploration of pomelo peel beyond the conventional evaluation of its bioactive components toward the integration of advanced technologies to enhance its efficacy, stability, and bioavailability. One prominent approach is green synthesis, which employs pomelo peel extracts as reducing and stabilizing agents for eco-friendly production of metallic nanoparticles. This method enables the formation of silver nanoparticles (AgNPs) and copper nanoparticles (CuNPs), which exhibit remarkable cytotoxic effects against various cancer cell lines through mechanisms involving reactive oxygen species (ROS) overproduction, mitochondrial membrane disruption, and DNA fragmentation, ultimately triggering apoptosis via the mitochondrial pathway. Several studies have demonstrated that *C. maxima* based nanostructures not only enhance anticancer potency but also minimize nonspecific toxicity compared to conventionally synthesized materials [77–80,95]. Additionally, the development of electroactive biosensors derived from pomelo peel carbon matrices, as reported by Liu et al. (2025), represents a novel diagnostic tool capable of sensitively detecting flavonoid anticancer agents, such as kaempferol. This innovation broadens the biomedical applications of pomelo peel by transforming it into a high-value bioelectrochemical material suitable for cancer diagnosis and therapeutic monitoring [60].

Furthermore, recent advancements have focused on nanoencapsulation and biopolymeric drug delivery systems utilizing pomelo peel-derived materials to improve the controlled release and cellular uptake of bioactive compounds, such as naringin, nobiletin, and tangeretin. As demonstrated by Atta et al. (2019), the synthesis of naringin–metal complexes markedly enhanced the cytotoxic efficacy against breast (MCF-7) and lung (A549) cancer cells, while improving stability and membrane permeability [62]. These findings highlight the benefits of molecular complexation and nanoscale encapsulation in protecting bioactive compounds from degradation within biological environments and achieving targeted tissue delivery. In addition, a hydrogel sponge developed from delignified pomelo peel and functionalized with gallic acid and metal–organic frameworks (MOFs) has shown potential in wound healing and topical drug delivery, particularly for cancer patients with biofilm-related complications [101]. The integration of antioxidant, antimicrobial, and cytotoxic properties into such multifunctional materials highlights their applicability in next-generation biomedical and oncological therapies.

From a pharmacochemical perspective, the integration of green nanotechnology, electroactive sensing, and targeted nanoformulation approaches has transformed pomelo peel bioactive compounds from natural chemopreventive agents to key components for precision cancer therapy and molecular diagnostics. The synergistic interactions between naringin, limonene, tangeretin, nobiletin, and polysaccharides contribute to the inhibition of cancer cell proliferation, induction of apoptosis, and modulation of the oxidative and inflammatory pathways. Collectively, these findings demonstrate that the anticancer mechanisms of pomelo peel include (1) induction of apoptosis via the mitochondrial pathway, (2) inhibition of cancer cell proliferation and migration, (3) regulation of the cell cycle and caspase activation, (4) reduction of

oxidative stress and inflammation, (5) modulation of immune responses, and (6) potential applications in drug delivery or diagnostic sensors (Fig. 8). This multidisciplinary integration underscores the significance of pomelo not only as a rich source of bioactive anticancer compounds but also as a bio-inspired platform for sustainable pharmaceutical and biomedical innovations [60,62,77,95,101].

4.2.5. Anti-inflammatory activity

Inflammation is a biological response triggered by pathogenic stimuli, irritation, or tissue injury, which when persistent, may lead to various degenerative diseases [102,103]. Pomelo peel has been extensively investigated as an anti-inflammatory agent owing to its bioactive compound content, including flavonoids, coumarins, and essential oils. Several studies have demonstrated the significant anti-inflammatory activity of pomelo peel through various molecular mechanisms both in vitro and in vivo [104–109]. Sood et al. (2010) reported that 7,8-dimethoxycoumarin (DMC), isolated from pomelo peel, exhibited anti-inflammatory and anti-secretory effects in rats with pyloric ligation-induced gastritis. DMC reduced gastric acid volume and ulcer index as well as decreased TBARS levels and myeloperoxidase activity, primarily through the inhibition of prostaglandins and oxidative stress [108]. Furthermore, Kuo et al. (2017) identified active compounds such as isomeranzin and epoxybergamottin from *Citrus grandis* (a synonym of *C. maxima*), which significantly inhibited superoxide anion production and neutrophil elastase activity, indicating their potential as anti-inflammatory and neuroprotective agents [54].

Wang et al. (2021) investigated the effects of naringin on lipopolysaccharide (LPS)-induced PC12 neuronal cells and demonstrated that naringin suppressed apoptosis and reactive oxygen species (ROS) production while downregulating IL-1β and TNF-α expression through inhibition of the TLR4 and NF-κB signaling pathways, indicating its neuroprotective role in inflammation [105]. Additional support for the anti-inflammatory potential of pomelo peel was provided by Malleshappa et al. (2018), who showed that ethanol extracts of pomelo peel inhibited carrageenan-induced paw edema and stabilized red blood cell membranes, which

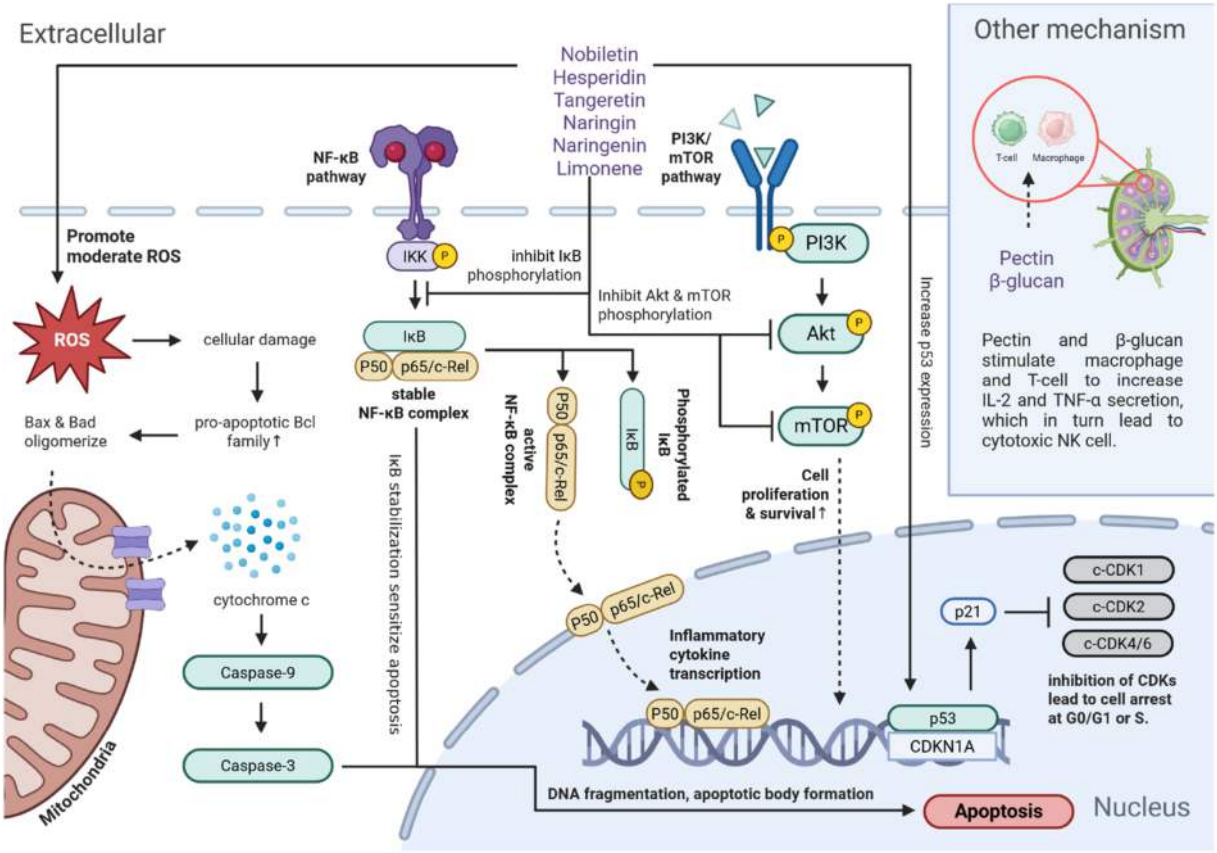


Fig. 8. Signaling pathways underlying the anticancer activity of bioactive compounds in pomelo peel (Created in BioRender. Fernando, D. (2025) https://BioRender.com/xpjielx).

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was attributed to the presence of flavonoids and terpenoids [107]. In silico studies by Nandeesh et al. (2018) further supported these findings, showing that hesperidin and naringin from pomelo peel exhibited high binding affinities toward key inflammatory targets (IL-6 and NF-κB) in molecular docking simulations [110]. Zhao et al. (2023) explored the anti-inflammatory properties of coumarins derived from pomelo peel, specifically auraptene and marmin, which significantly reduced tissue swelling and cytokine production by inhibiting the NF-κB and MAPK signaling pathways [106].

Ishida et al. (2019) studied aqueous extracts from the peel of Kawachi-bankan (a variety of pomelo) and observed a significant reduction in TNF-α and IL-6 levels, along with inhibition of p38 MAPK phosphorylation and NF-κB activation both in vitro and in vivo [109]. Wang et al. (2021) investigated the effects of pomelo peel essential oil on cerebral ischemia-reperfusion injury in rats with cardiac arrest. The oil attenuated necroptosis by downregulating TNF-α, RIPK1, and p-MLKL expression and modulating the NF-κB and MAPK inflammatory signaling pathways [105]. Yang et al. (2025) examined the essential oil of pomelo peel, which contained α-terpineol and D-limonene. These components significantly reduced TNF-α, IL-6, and IL-8 levels in LPS-stimulated RAW264.7 macrophages by inhibiting NF-κB and p38 MAPK pathways [58]. Zheng et al. (2024) analyzed flavonoids in citrus peel using UPLC-Q-TOF-MS/MS and revealed that naringin and hesperidin from *C. maxima* activated the Nrf2 pathway and suppressed NF-κB signaling in LPS-exposed A549 cells, leading to reduced ROS and proinflammatory cytokine production [104]. Overall, the anti-inflammatory activity of pomelo peel is mediated through multiple mechanisms: (1) inhibition of the NF-κB and MAPK signaling pathways, (2) suppression of proinflammatory cytokine production (TNF-α, IL-6, IL-1β), (3) reduction of oxidative stress via Nrf2 activation, (4) inhibition of necroptosis and inflammatory cell apoptosis, and (5) enhancement of adaptive immune responses (Fig. 9). These findings highlight pomelo peel as a promising natural therapeutic source for the management of inflammatory and neurodegenerative conditions.

The structure–activity relationship (SAR) of anti-inflammatory compounds from pomelo peel indicates that the phenolic substitution pattern and degree of lipophilicity determine their ability to modulate the NF-κB/MAPK pathways and activate the Nrf2 axis. Glycosylated flavonoids, such as naringin and hesperidin, are more stable in aqueous environments, while their aglycone forms (e.g., naringenin), which exhibit higher lipophilicity, suppress IL-1β, IL-6, and TNF-α expression by inhibiting the TLR4–MyD88–TRAF6 cascade and inducing Nrf2-dependent HO-1 and SOD enzymes [104,105]. Polymethoxyflavones (tangeretin and nobiletin) possessing multiple methoxy groups enhance membrane affinity and strengthen the inhibition of MAPK phosphorylation and NF-κB translocation while simultaneously contributing to antioxidant effects characteristic of citrus essential oils [58]. Among coumarins, the 7,8-dimethoxy motif and/or terpenoid or prenyl side chains (as in auraptene and marmin) improve hydrophobic interactions with inflammatory targets, correlating with decreased neutrophil elastase activity, reduced ROS formation, and improved gastric pathological parameters in vivo [10,108]. Furocoumarin and epoxy-coumarin derivatives (isomeranzin and epoxybergamottin) containing rigid oxygenated heteroatoms exhibit potent inhibition of superoxide anion generation and elastase activity, underscoring the critical role of oxygenated moieties in modulating neutrophil activation [54]. Major monoterpenes such as D-limonene and α-terpineol, owing to their high lipophilicity, stabilization of cellular membranes, and suppression of TNF-α–RIPK1–p-MLKL and NF-κB/p38 cascades, result in the attenuation of pro-inflammatory cytokine production in both cellular and ischemia-reperfusion models [58,105].

Recent advancements in pharmaceutical technology have emphasized nanoencapsulation as an innovative approach to enhance the stability and bioefficacy of bioactive compounds derived from pomelo peels with potent anti-inflammatory properties. Major constituents, such as naringin, hesperidin, auraptene, marmin, and 7,8-dimethoxycoumarin (DMC) are prone to oxidative degradation and exhibit low oral bioavailability under physiological conditions [92]. The incorporation of these compounds into biopolymeric nanocarriers based on pectin, chitosan, or citrus-derived polysaccharides has demonstrated significant improvements in both stability and controlled release at target inflammatory sites. Nanoencapsulation acts as a molecular shield, enabling sustained delivery and enhanced absorption within the inflamed tissues. Recent studies reported that nanoemulsion systems containing pomelo peel essential oils markedly improved the stability of D-limonene and α-terpineol, while showing superior inhibition of NF-κB, MAPK, and TNF-α signaling compared to conventional extracts [91,92,103,104]. Mechanistically, this enhanced anti-inflammatory activity is

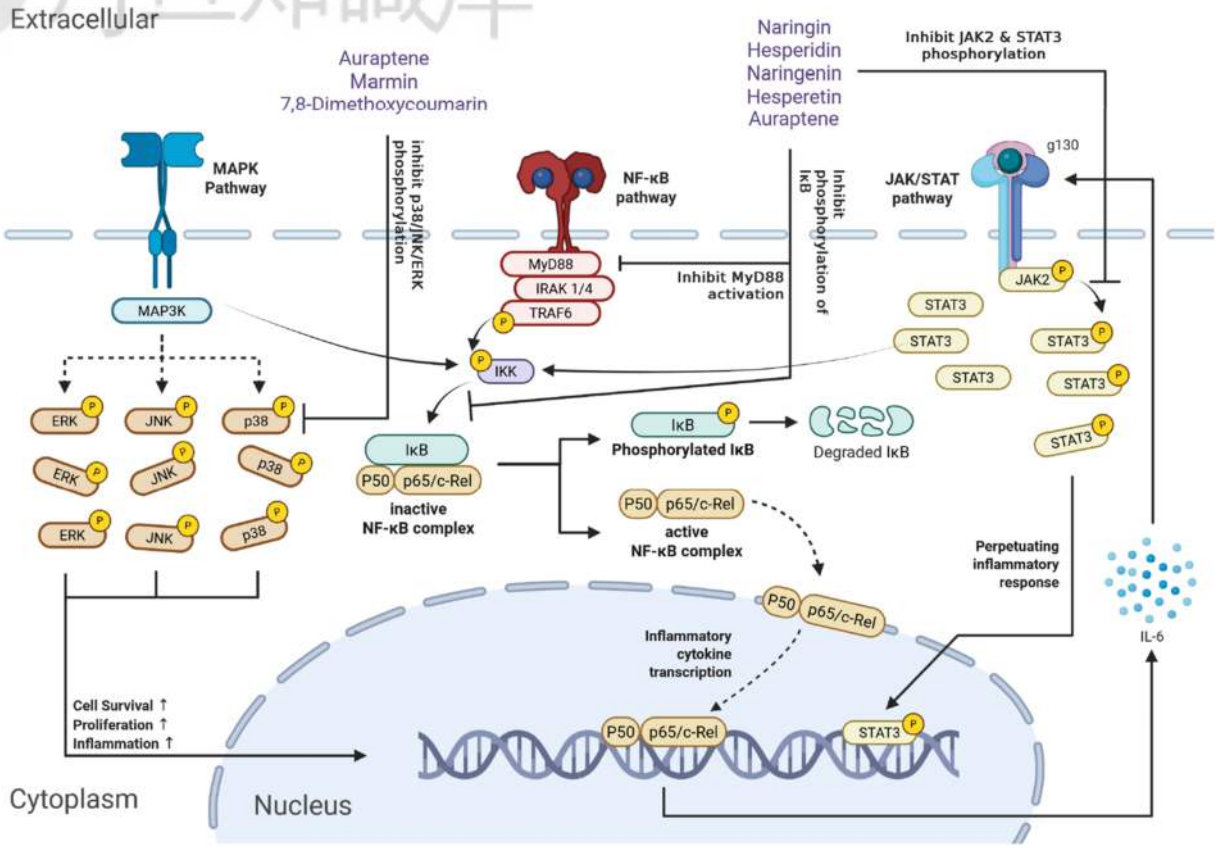


Fig. 9. Signaling pathways underlying the anti-inflammatory activity of bioactive compounds in pomelo peel (Created in BioRender. Fernando, D. (2025) https://BioRender.com/axe5ioi).

associated with the activation of the Nrf2/Keap1 antioxidant pathway, upregulation of endogenous antioxidant enzymes, and suppression of proinflammatory cascades. Thus, nanoencapsulation not only enhances bioavailability but also optimizes the systemic and local anti-inflammatory responses of pomelo-derived compounds.

Another emerging technological approach involves green synthesis of bioactive metal nanoparticles using pomelo peel extracts. This eco-friendly process employs natural flavonoids and phenolics as reducing and stabilizing agents to synthesize silver (AgNPs) and copper (CuNPs) nanoparticles without hazardous chemicals. Studies by Huo et al. [77] and Do et al. [78] demonstrated that these biosynthesized nanoparticles exhibit multifunctional biological effects, including significant anti-inflammatory activity through suppression of oxidative stress, inhibition of iNOS and COX-2 gene expression, and modulation of the MAPK/NF-κB pathways. Their high redox potential enables regulation of the intracellular oxidant–antioxidant balance, thereby reducing the excessive release of inflammatory mediators. Furthermore, advanced extraction techniques such as supercritical CO_2 extraction and pulsed electric field (PEF) processing have been shown to improve the yield and integrity of phenolic and flavonoid compounds without causing thermal degradation [34,49]. Extracts obtained via these methods contain higher levels of hesperidin, naringin, and limonene, which correlate positively with NF-κB inhibition and activation of cytoprotective enzymes, including HO-1 and SOD. Collectively, the green synthesis and modern extraction technologies reinforce the therapeutic potential of pomelo peel as a sustainable and biocompatible source of natural anti-inflammatory agents.

Beyond these applications, novel research has explored biomimetic and smart delivery systems that utilize pomelo peel-derived biomaterials to modulate chronic inflammatory responses. One innovative development is the creation of carbonized cellulose aerogels derived from pomelo peel biomass, which accelerates the healing of inflamed or infected wounds by reducing the accumulation of reactive oxygen species (ROS) and maintaining local redox balance [61]. The high porosity and low

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thermal conductivity of these aerogels allow them to stabilize the microenvironment while minimizing immune overactivation. In pharmaceutical applications, the integration of flavonoids, coumarins, and essential oils into biocompatible semiconducting matrices offers synergistic benefits between the antioxidant and anti-inflammatory mechanisms.

4.2.6. Other bioactivities

In addition to the various pharmacological activities previously described, pomelo peel also exhibits other notable bioactivities, including its role in lipid regulation, obesity prevention, and modulation of the gut microbiota. Yu et al. (2022), Zhang et al. (2024), and Ni et al. (2023) reported that extracts and dietary fibers derived from pomelo peel significantly reduced total cholesterol, triglycerides, and LDL levels while increasing HDL levels. These effects are accompanied by an increase in short-chain fatty acid-producing beneficial bacteria, a decrease in the Firmicutes/Bacteroidetes ratio, and improved intestinal epithelial integrity, thereby contributing to metabolic health and the prevention of obesity [9,111,112]. Similar findings were reported by Mohammed et al. (2021) and Ani and Ochu (2020), who found that pomelo peel extract also improved lipid and glucose metabolism and enhanced liver function in high-fat diet models [70,74].

The lipid-regulating and anti-obesity properties of pomelo peel are closely related to the structural characteristics of its major bioactive compounds, particularly the flavonoids and pectic polysaccharides. Flavonoids, such as naringin and hesperidin, possess a flavanone backbone with multiple hydroxyl and glycosidic substituents that enhance polarity and facilitate interaction with lipid metabolism enzymes, including HMG-CoA reductase and pancreatic lipase [35,111]. The presence of C-7 glycosylation and hydroxyl groups at C-5 and C-4′ enables these compounds to form hydrogen bonds with catalytic residues, thereby competitively inhibiting cholesterol biosynthesis and lipid absorption [9,111]. Pectin from pomelo peel, characterized by α-(1→4)-linked galacturonic acid residues and a high degree of methyl esterification, exhibits strong anionic properties that allow bile acid sequestration and delayed lipid diffusion in the intestine [9]. The synergistic action between the amphiphilic flavonoid structure and negatively charged polysaccharides promotes lipid excretion, reduces adipogenesis, and modulates the gut microbiota composition [111,112]. Thus, the molecular architecture of these compounds underlies the dual hypolipidemic and prebiotic effects of pomelo peel, contributing to its efficacy in obesity prevention and metabolic regulation (Fig. 10).

Pomelo peel has also demonstrated hepatoprotective effects in various liver injury models, as evidenced in studies by Chowdhury et al. (2015), Tian et al. (2019), Hafez and Hamed (2021), Hu et al. (2022), and Dutta et al. (2025). Bioactive compounds, such as coumarins and flavonoids, have been shown to reduce liver enzymes (ALT, AST, and ALP) and oxidative stress markers (MDA and NO), while enhancing the activity of antioxidant enzymes, such as SOD and GSH-Px. In addition to reducing inflammation and lipid peroxidation, pomelo peel extracts also decreased liver fibrosis and improved liver tissue architecture, as confirmed by histopathological evaluation. Its hepatoprotective activity has been demonstrated under conditions of liver toxicity induced by CCl_4, alcohol, aflatoxin B1, and Cryptosporidium infections (Fig. 11) [48,55,113–115].

The hepatoprotective effects of pomelo peel are strongly linked to the structural configuration of its dominant phytochemicals, particularly, flavonoids, coumarins, and limonoids. Flavonoids, such as naringin and hesperidin, contain conjugated aromatic rings with hydroxyl groups at positions C-5, C-7, and C-4′, which enable strong electron-donating capacity and radical scavenging activity, thereby protecting hepatocytes from oxidative stress-induced apoptosis [55,111]. Their glycosidic linkages enhance solubility and facilitate interaction with hepatic enzymes, such as glutathione reductase and catalase, promoting redox homeostasis and membrane stabilization [48]. Coumarins, such as auraptene and marmin, characterized by a benzopyrone nucleus and a prenyl side chain, exhibit lipophilicity that allows their accumulation in liver tissues, where they inhibit cytochrome P450-mediated lipid peroxidation and suppress TGF-β/Smad signaling involved in fibrosis [55,114]. Additionally, the furan and lactone moieties present in limonoids confer electrophilic reactivity that supports phase II detoxification via the activation of the Nrf2/ARE pathway [115]. These structural attributes collectively underpin the hepatoprotective mechanisms of pomelo-derived compounds, linking their electron-rich aromatic scaffolds and substituent diversity to their antioxidant, anti-fibrotic, and cytoprotective activities in liver tissue.

Another pharmacological activity of pomelo peel is its neuroprotective potential (Fig. 12). Naringin isolated from the peel has been reported by Wang et al. (2013) to enhance CaMKII activity and improve long-term memory in a rat model of

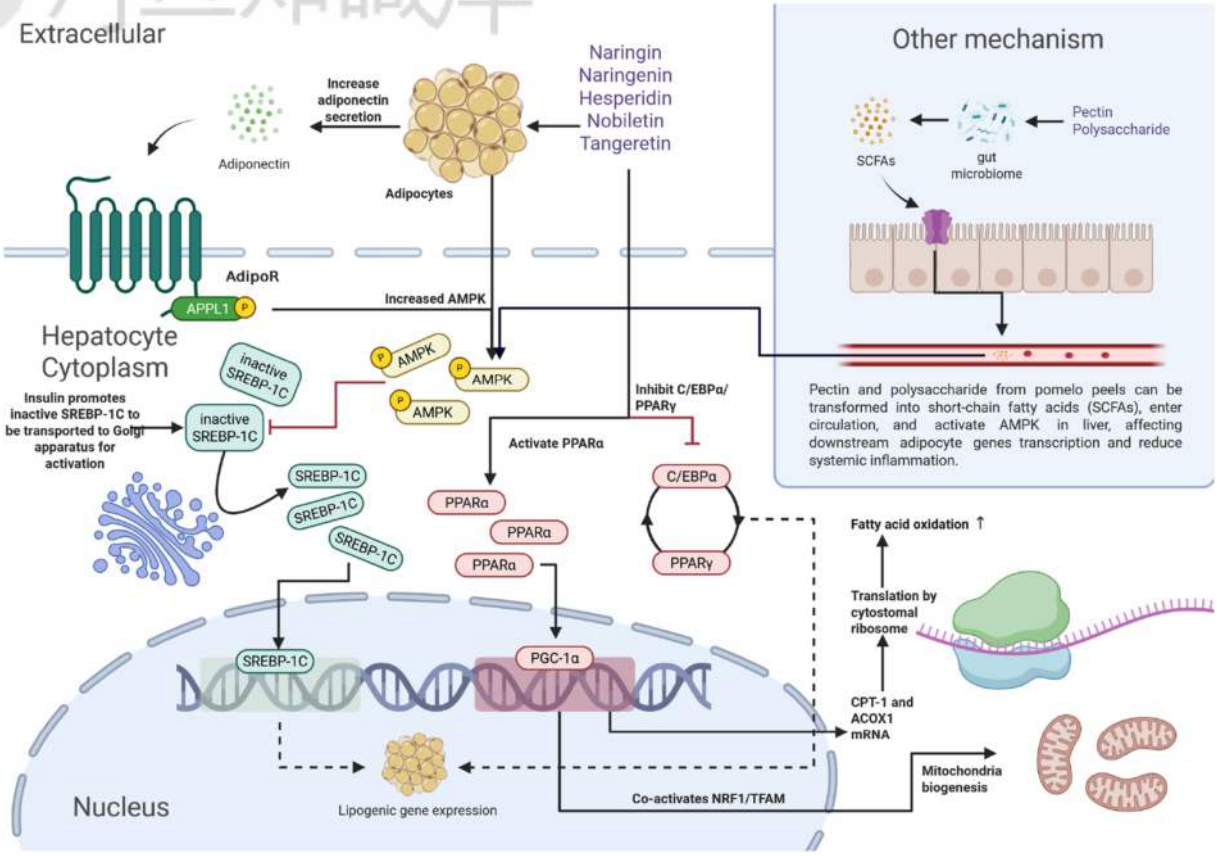


Fig. 10. Signaling pathways underlying the lipid-regulating and anti-obesity activities of bioactive compounds in pomelo peel (Created in BioRender. Fernando, D. (2025) https://BioRender.com/gwyp1vt).

Alzheimer's disease by promoting synaptic plasticity [116]. Additional research by Ademosun et al. (2022) demonstrated that the incorporation of pomelo peel extract into ice cream products improved blood lipid profiles, enhanced antioxidant activity, and supported liver function, suggesting its potential use in functional foods [29]. Furthermore, Xu et al. (2025) reported that fermented protein derived from a combination of pomelo peel and soybeans improved the immune response and gut health of bass fish, highlighting its applicability in animal nutrition [41].

The neuroprotective potential of pomelo peel is closely associated with the structural characteristics of its flavonoid constituents, particularly, naringin, naringenin, and hesperidin. These compounds share a common flavanone backbone with hydroxyl substitutions at C-5 and C-7 on the A-ring and at C-4′ on the B-ring, which are crucial for their antioxidant and anti-apoptotic effects in neuronal tissues [116]. The presence of the C2–C3 single bond in the flavanone structure facilitates free-radical neutralization while maintaining molecular stability under oxidative conditions, thereby preventing neuronal lipid peroxidation and mitochondrial dysfunction [51]. Additionally, the glycosidic linkage in naringin enhances its bioavailability and ability to cross the blood–brain barrier, allowing modulation of neuroinflammatory signaling pathways, such as NF-κB and MAPK [54,115]. Naringin and hesperidin also exhibit a high affinity for CaMKII and CREB-related receptor sites, which are essential for synaptic plasticity and memory consolidation in neurodegenerative models [116]. The conjugated aromatic systems and electron-donating hydroxyl groups of these flavonoids directly contribute to their neuroprotective and neuromodulatory efficacy by reinforcing antioxidant defense, enhancing neuronal survival, and regulating neurotransmitter balance.

Beyond its previously described properties, pomelo peel also exhibits other bioactivities that have attracted increasing scientific attention in recent years. An emerging area of interest is its neuropsychopharmacological potential. Dutta et al. (2025) demonstrated that the essential oil of pomelo peel formulated as an inclusion complex exerted significant anxiolytic and antidepressant effects

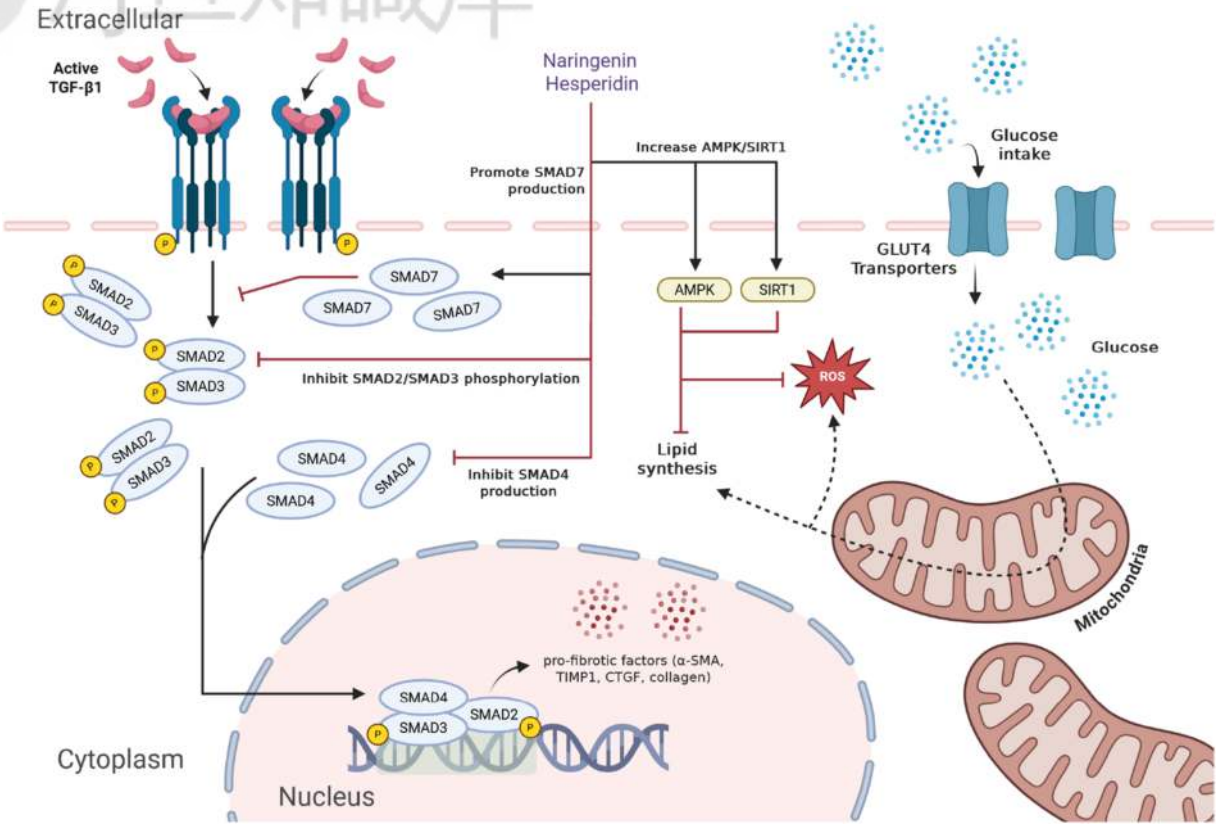


Fig. 11. Signaling pathways underlying the hepatoprotective activity of bioactive compounds in pomelo peel (Created in BioRender. Fernando, D. (2025) https://BioRender.com/whndagt).

through the modulation of GABAergic and serotonergic pathways [115]. The inclusion complex enhanced the stability and bioavailability of volatile components such as limonene, linalool, and citral, which have known affinities for $GABA_A$ receptors. This mechanism contributes to the reduction of neuronal hyperactivity and the promotion of relaxation. These findings suggest that pharmaceutical complexation is an effective strategy to optimize the biological activity of volatile natural compounds derived from pomelo peel. Furthermore, this approach highlights the potential of pomelo-derived volatiles as natural neuromodulatory agents for managing anxiety and mild depressive disorders.

The neuromodulatory and anxiolytic activities of pomelo essential oil are largely influenced by the structural configuration of its major monoterpenes, including limonene, linalool, and citral. Limonene, characterized by a monocyclic structure with conjugated double bonds, facilitates interaction with lipid membranes, enhancing neuronal membrane fluidity and modulating ion channel permeability linked to $GABA_A$ receptor regulation [115]. Linalool, containing both hydroxyl and double-bond functional groups, contributes to GABAergic modulation through hydrogen bonding and π−π interactions with the receptor's benzodiazepine-binding site, leading to sedative and anxiolytic outcomes. Citral, an α,β-unsaturated aldehyde, acts as a mild agonist on $5\text{-}HT_1A$ receptors due to its electrophilic carbonyl group, which enables covalent or reversible interaction with receptor nucleophilic residues, thereby modulating serotonergic transmission. The combined presence of these volatiles within the essential oil produces synergistic effects, where lipophilicity enhances blood–brain barrier permeability and receptor accessibility, amplifying overall neuropsychopharmacological potency. Structurally, the high degree of unsaturation and the presence of reactive oxygenated moieties underpin their antioxidant and neurosedative profiles, validating the link between molecular configuration and biological efficacy in central nervous system modulation.

In the field of environmental and material sciences, remarkable advancements have been made in the use of pomelo peel as a biosorbent and multifunctional bio-based material. Liu et al. (2023) reported that biochar derived from pomelo peel pyrolysis exhibited a high adsorption capacity toward toxic compounds such as tetrakis

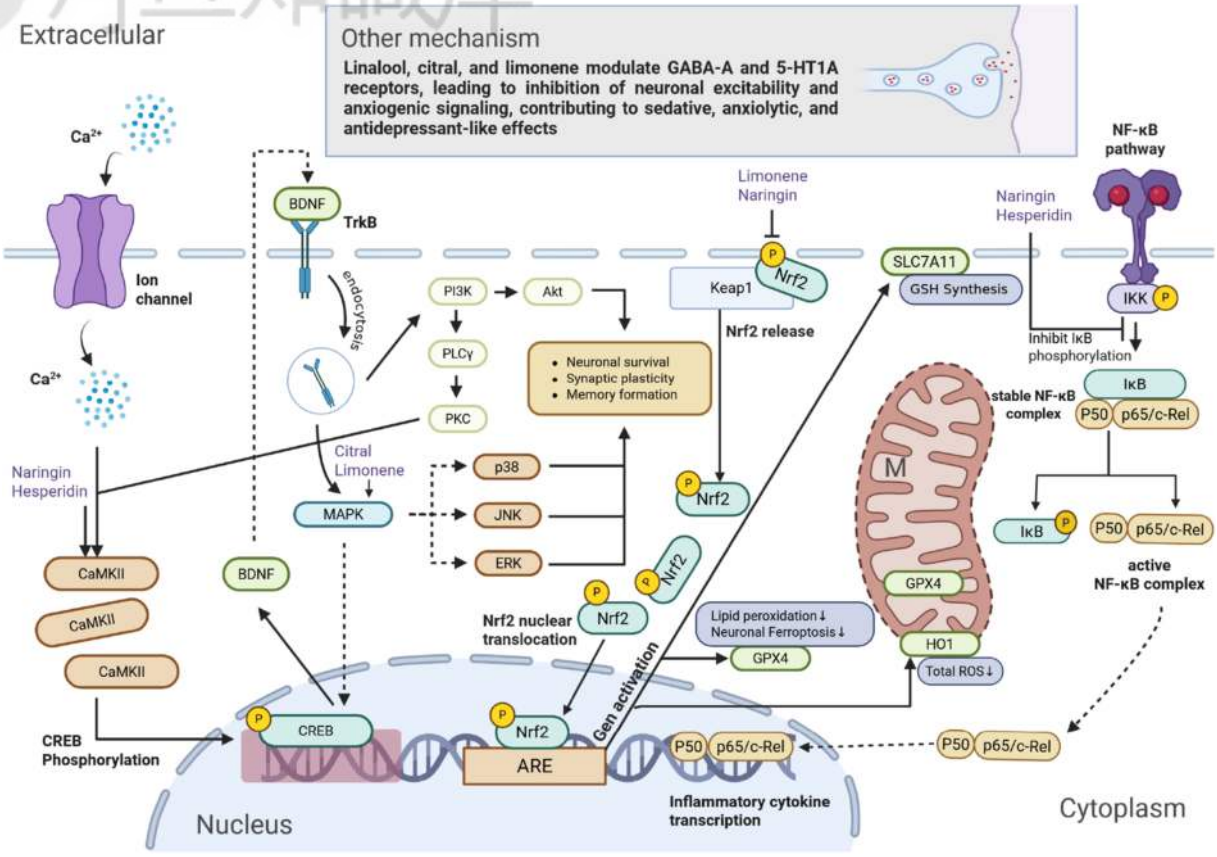


Fig. 12. Signaling pathways underlying the neuroprotective and neuromodulatory activity of bioactive compounds in pomelo peel (Created in BioRender. Fernando, D. (2025) https://BioRender.com/6egn76c).

(hydroxymethyl)phosphonium chloride, while simultaneously displaying antimicrobial properties against pathogenic bacteria [90]. This dual activity is attributed to the presence of active carbon sites and phenolic functional groups that are capable of binding and neutralizing reactive molecules. Such biomaterials exemplify the concept of green valorization, which aims to transform agricultural waste into high-value environmentally friendly products. Furthermore, pomelo peel-derived biochar shows potential as an adsorbent for water purification and a precursor for antimicrobial biocomposites. These developments not only enhance the economic value of pomelo peel but also contribute to sustainable biotechnology and circular bioeconomy initiatives.

The integration of nanotechnology and green synthesis has emerged as a key innovation in the exploration of pomelo peel bioactivity. Studies by Huo et al. (2018) and Das et al. (2023) demonstrated that pomelo peel extracts can serve as natural reducing and stabilizing agents in the green synthesis of silver nanoparticles (AgNPs) with uniform size distribution and high stability [77,80]. The resulting nanoparticles displayed potent antioxidant and antimicrobial activities without the use of toxic chemical reagents. These effects are largely driven by bioactive constituents such as flavonoids, polyphenols, and ascorbic acid, which function as both reducing agents and capping molecules during nanoparticle formation. This eco-friendly nanotechnological approach broadens the applications of pomelo peel to fields such as nanomedicine, photocatalysis, and antimicrobial packaging materials. Consequently, pomelo peel has emerged as a competitive natural source for sustainable biomaterial innovation aligned with green chemistry principles.

Recent advances have highlighted the potential of pomelo peel for the development of electroactive biomaterials and biosensing systems. These technologies aim to develop natural-based electrochemical sensors with high selectivity and sensitivity for the detection of bioactive compounds. Carbonized pomelo peel biomass can be engineered into electroactive materials through controlled pyrolysis, producing a high surface area and electrical conductivity [60]. These materials have been utilized in conductive polymer-based

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biosensing platforms for the detection of phenolics and flavonoids in biological matrices. This innovation represents a major step toward eco-friendly bioelectronics and biosensing technologies by converting agricultural residues into high-performance analytical materials. Moreover, these systems have promising applications in pharmaceutical quality control, food safety monitoring, and diagnostic assays.

Equally important are advancements in drug delivery and regenerative biomaterials derived from pomelo peels. Yang et al. (2024) developed a bioactive sponge based on pomelo peel modified with gallic acid and copper-containing metal–organic frameworks (MOFs), which demonstrated excellent efficacy in healing biofilm-infected wounds by promoting angiogenesis, granulation tissue formation, and reducing scar formation [101]. Similarly, Wan et al. (2024) fabricated a carbonized cellulose aerogel from pomelo peel that exhibited rapid hemostatic action and superior blood absorption compared with commercial materials [61].

The remarkable hemostatic and wound-healing properties of pomelo-derived biomaterials are closely associated with the structural features of their primary bioactive constituents, including flavonoids, phenolic acids, polysaccharides, and metal–organic complexes (Fig. 13). The phenolic hydroxyl groups of flavonoids, such as naringin and hesperidin, enable strong hydrogen bonding and radical-scavenging interactions, which accelerate tissue regeneration by reducing oxidative damage at wound sites [61,101]. The π-conjugated ring systems within these flavonoids facilitate electron delocalization, enhancing their redox stability and supporting angiogenesis by modulating the vascular endothelial growth factor (VEGF) pathways. Polysaccharides derived from pomelo peel possess repeating hydroxyl and carboxyl groups that contribute to high water retention, film-forming ability, and electrostatic interactions with cellular membranes, thereby creating a moist microenvironment that is favorable for fibroblast proliferation and collagen synthesis. Furthermore, the coordination of gallic acid with copper ions in metal–organic frameworks (MOFs) enhances catalytic redox reactions and stimulates hemostasis through platelet activation and coagulation cascade initiation. Structurally, the synergy between aromatic polyphenols and transition metal centers in

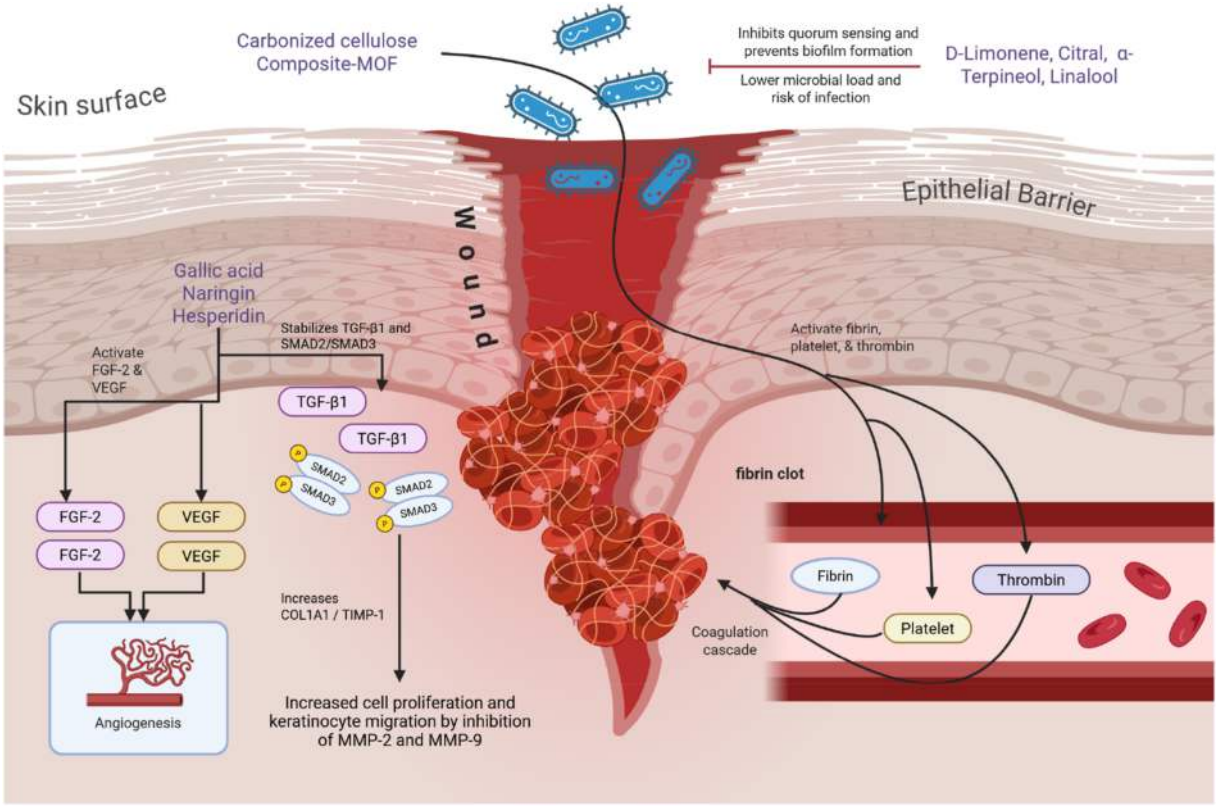


Fig. 13. Signaling pathways underlying the hemostatic and wound-healing activity of bioactive compounds in pomelo peel (Created in BioRender. Fernando, D. (2025) https://BioRender.com/x4vxswo).

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these hybrid matrices underpins their multifunctional bioactivity by combining antioxidant, antimicrobial, and pro-hemostatic effects essential for rapid wound closure and tissue remodeling.

Overall, recent research has revealed that the exploration of pomelo peel bioactivity has evolved from traditional phytochemical studies to multidisciplinary innovation, integrating biotechnology, nanomaterials, and sustainable biomass engineering. These efforts have led to the development of bioactive films, microcapsules, aerogels, biosorbents, and nano-based delivery systems with diverse biological and industrial applications. Core bioactive constituents, such as flavonoids, coumarins, limonoids, and polyphenols play critical roles in conferring both therapeutic effects and functional material properties.

4.3. Future trends of pomelo peel research in pharmacological applications

Research on the pharmacological activities of pomelo peel has made substantial progress over the past several years. Bibliometric data indicate that the primary research focus lies in the exploration of the antioxidant activity and bioactive potential of pomelo peels. In terms of publication volume, topics related to antioxidant capacity have increased sharply, particularly between 2016 and 2023. This trend highlights the growing awareness among researchers regarding the potential of pomelo peel as a natural antioxidant agent to counteract degenerative diseases caused by oxidative stress, such as cancer, diabetes, and cardiovascular disorders. The increased interest in essential oils derived from pomelo peel, especially from 2022 to 2023, further indicates a shift toward the investigation of aromatic and volatile compounds for therapeutic applications, including anti-inflammatory and antimicrobial treatments.

Over time, research on pomelo peel has expanded beyond producing countries and now demonstrates growing international collaboration. Bibliometric analysis shows that China leads global research output with significant contributions, followed by countries such as the United States, Thailand, and France. This reflects the intensification of international collaboration, which accelerates scientific advancement through complementary contributions across institutions. Expanding research networks in the Asia–Pacific region, including India, Malaysia, and Indonesia, also suggests that these countries are beginning to leverage their rich natural resources to support both traditional medicine and modern pharmacological integration. In addition, current trends indicate a shift toward broader pharmacological applications. The anti-inflammatory and antimicrobial properties of pomelo peel have been increasingly studied, thereby opening new avenues for treating infections and inflammatory conditions. With the increasing understanding of the role of gut microbiota in overall health, future research is expected to explore the role of pomelo peel in modulating gut microbiota, particularly in synergy with bioactive compounds such as naringin and pectin, which may contribute to metabolic and neurological health. Advancements in research methodologies have contributed to the deepening of knowledge in this field. Numerous studies have employed advanced technologies, such as HPLC-Q-TOF-MS, to isolate and identify the active compounds in pomelo peel. These methods allow for more comprehensive chemical profiling and help elucidate the pharmacological roles of specific compounds. More efficient extraction techniques and the use of nanoencapsulation to enhance the bioavailability of bioactive components are expected to become central to future research. These innovations are expected to accelerate the development of pomelo-based therapeutics.

Globally, research trends suggest that pomelos remain a key subject in the search for natural solutions to various health challenges. China is expected to maintain its leading role, particularly in advancing research focused on the circular economy and waste valorisation. Southeast Asian countries, as primary producers of pomelo, are also likely to deepen their exploration of their pharmacological potential within traditional medicine frameworks, while integrating modern pharmacological approaches to fully harness its therapeutic value. Research on pomelo peels is expected to evolve in several important directions. First, greater emphasis should be placed on novel pharmacological applications, especially in the areas of anti-inflammatory, antimicrobial, and gut microbiota-modulating therapies. Second, studies will become increasingly interdisciplinary, combining modern technologies, such as nanoencapsulation and advanced chemical analysis, to maximize the efficiency and bioavailability of bioactive compounds. Third, international collaboration will continue to strengthen, with China at the forefront and other Asia–Pacific countries emerging as significant contributors to the development of pomelo-based health innovation. These trends collectively suggest that pomelo peel will play a vital role in the future

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of pharmacological development, not only in conventional therapeutics but also in advancing natural, sustainable solutions for global healthcare.

Future research directions are projected toward the integration of nanotechnology, electrochemistry, and computational biology to maximize the pharmacological applications of pomelo peel. Green synthesis of nanoparticles using pomelo peel extracts has emerged as an eco-friendly and sustainable approach that aligns with global environmental objectives. Phytochemicals, such as flavonoids, terpenoids, and phenolic acids, present in pomelo peel act as both reducing and stabilizing agents during nanoparticle formation, eliminating the need for toxic chemicals. Silver, copper, and zinc oxide nanoparticles synthesized from pomelo peel have demonstrated strong antimicrobial, antioxidant, and anticancer properties, revealing their potential for targeted drug delivery, wound healing, and antimicrobial coatings [77–80]. Future research should focus on optimizing synthesis parameters, such as pH, temperature, and reactant concentration, to tailor nanoparticle morphology and functionality for specific biomedical applications. These advancements may also lead to the development of hybrid nanocomposites that combine metallic nanoparticles with biodegradable polymers, enhancing both efficacy and safety. Collectively, this research supports the transformation of pomelo peel into a renewable and multifunctional nanotherapeutic platform.

The advancement of nanoencapsulation technologies employing biopolymers such as pectin, cellulose, and lignin derived from pomelo peel is equally significant. These natural materials provide high biocompatibility, biodegradability, and structural stability, making them excellent carriers for controlled and sustained drug-release systems. Nanoencapsulation enhances the solubility, stability, and targeted delivery of hydrophobic bioactive compounds, such as naringin, tangeretin, and nobiletin, thereby improving their therapeutic potential [57,60]. Future innovations are expected to combine these systems with lipid-based nanocarriers or metal–organic frameworks (MOFs) to further increase bioavailability and selective tissue penetration. In parallel, computational pharmacokinetic modeling and artificial intelligence (AI) tools were employed to simulate the absorption, distribution, metabolism, and excretion (ADME) properties of encapsulated compounds. Such predictive modeling can streamline the formulation design and reduce reliance on extensive in vivo testing. This interdisciplinary integration will lay the foundation for precision phytopharmacology, enabling the customization of natural compound therapies based on disease-specific molecular targets.

Another promising direction involves the application of electroactive sensors fabricated from porous carbon materials derived from pomelo-peel biomass. These materials exhibit high surface areas, tunable porosities, and excellent electrical conductivities, allowing efficient electron transfer and signal amplification in electrochemical detection. Their abundant oxygenated functional groups enhance the adsorption of analytes, making them suitable for sensitive detection of pharmacologically relevant molecules such as kaempferol, dopamine, and glucose [60]. Future advancements are anticipated to integrate these carbon-based sensors into wearable or implantable biosensing devices for real-time monitoring of biomarkers related to oxidative stress and inflammation. Moreover, coupling biosensors with microfluidic systems can enable the rapid, high-throughput screening of natural compounds for pharmacological assays. This approach bridges analytical chemistry, materials science, and pharmacology, providing a platform for developing point-of-care diagnostic tools and precise drug evaluation systems.

Furthermore, future studies are expected to deepen our molecular-level understanding of the pharmacological mechanisms of pomelo peel through network pharmacology, metabolomics, and in silico approaches. By employing molecular docking, quantum chemical modeling, and molecular dynamics simulations, researchers can systematically investigate multi-target interactions among flavonoids, coumarins, and key signaling pathways, such as NF-κB, MAPK, and Nrf2 [10,54,104]. The integration of multi-omics datasets (including transcriptomics, proteomics, and metabolomics) with AI-assisted modeling is expected to uncover synergistic effects among bioactive components. This comprehensive system-based approach will facilitate the discovery of novel bioactive molecules and clarify their complex mechanisms of action at the cellular and molecular levels. Such computationally guided research will be essential for developing evidence-based herbal pharmacotherapy and transforming traditional herbal medicine into a scientifically standardized therapeutic practice.

Moreover, the convergence of biorefinery technology, microbial fermentation, and sustainable chemistry will shape the future utilization of pomelo peel in a circular bioeconomy framework. Pomelo peel residues can be simultaneously valorized for biopolymer production, bioactive compound extraction, and nanomaterial synthesis, thereby

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minimizing waste and maximizing the resource efficiency [3,36]. Future research will likely emphasize the standardization of extraction protocols, optimization of fermentation processes, and industrial-scale bioprocessing to enable consistent quality and scalability. The implementation of a life-cycle assessment (LCA) will ensure environmental sustainability and carbon neutrality in pomelo-based product development. Moreover, coupling advanced analytical tools, such as LC-HRMS, UPLC-Q-TOF-MS/MS, and spectroscopic imaging, will facilitate accurate chemical fingerprinting, compound authentication, and batch-to-batch reproducibility across laboratories [75,104]. Together, these advancements mark a paradigm shift in natural product pharmacology, where pomelo peel serves as a model bioresource linking traditional ethnomedicine with cutting-edge technological innovations, paving the way for sustainable global health solutions.

5. Conclusion

A bibliometric study revealed significant progress in the research on the pharmacological activities of pomelo peel (*C. maxima*) from 2002 to 2025. Over the past two decades, research focus has shifted from the identification of bioactive compounds to a more in-depth exploration of their therapeutic potential. The most extensively studied pharmacological activities include antioxidant, antidiabetic, antimicrobial, anticancer, anti-inflammatory, hepatoprotective, neuroprotective, and immunomodulatory effects as well as roles in lipid regulation, wound healing, antibiofilm activity, gut microbiota modulation, biosorbents, and environmental applications. The sharp increase in publication volume, particularly since 2020, along with expanded international collaboration reflects the growing global relevance of this topic. Countries such as China, Vietnam, Nigeria, and Thailand have emerged as major research hubs supported by productive institutions with a strong focus on natural products and public health. Keyword and topic trend analyses indicated a shift from laboratory-based studies to more applied and multidisciplinary approaches. Pomelo peel exhibits diverse pharmacological activities, including antioxidant, antidiabetic, anti-inflammatory, antimicrobial, hepatoprotective, neuroprotective, and anticancer effects, primarily attributed to its flavonoids (naringin, hesperidin, tangeretin, and nobiletin), coumarins, polysaccharides, and essential oils (limonene, linalool, and citral). Recent studies have indicated a shift toward multidisciplinary approaches through the application of green synthesis, nanoencapsulation, and electroactive biosensors to enhance the stability and bioavailability of bioactive compounds. Green synthesis enables eco-friendly production of nanoparticles with strong antimicrobial, antioxidant, and anticancer activities, while biopolymer-based nanoencapsulation allows targeted and controlled release of compounds such as naringin and tangeretin. In addition, electroactive carbon materials derived from pomelo peel have been developed for precision pharmacological biosensors. The integration of nanotechnology, computational biology, and sustainable bioprocessing within a circular bioeconomy framework has positioned *C. maxima* as a strategic bioresource for natural therapies, intelligent diagnostics, and sustainable biomedical innovation.

Author contributions

Indah Zunita Sari contributed to the conception and design of the study as well as the initial data collection. Indah Zunita Sari conducted the data analysis using Biblioshiny, interpretation of results, and drafting of the initial manuscript, including sections on pharmacological activities (antioxidant, antidiabetic, antimicrobial, anticancer, anti-inflammatory, and other bioactivities) and future research trends. Alma Nur Azizah was also involved in data analysis using Biblioshiny, contributed to the sections on the most influential journals and articles, keyword dynamics, bibliometric discussion, and assisted with data visualization. Fitriana Nur Hanifah was responsible for data analysis using VOSviewer, particularly the mapping of authors, affiliations, countries, and collaboration patterns, and contributed to the writing of the methodology and results sections. David Fernando contributed to the manuscript revision and data visualization, particularly in developing schematic representations and illustrating molecular mechanisms and signaling pathways of pomelo peel bioactivities. Agung Endro Nugroho provided critical revision of the manuscript, particularly the pharmacological activity section, ensuring scientific accuracy and relevance to pharmaceutical and clinical perspectives. Abdul Rohman supervised the development of the conceptual framework, thoroughly reviewed the manuscript for intellectual content, and approved its final version for publication. All authors have read and approved the final version of the manuscript and agreed to be accountable for all

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aspects of the work, ensuring that any issues related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest

The authors declare no conflicts of interest regarding this investigation.

Acknowledgments

The authors gratefully acknowledge the funding support provided through the Bantuan Insentif Mahasiswa (BIMA) Program for Master's Thesis Research under Contract Number 2635/UN1/DITLIT/Dit-Lit/PT.01.03/2025 from the Ministry of Higher Education, Science, and Technology, Indonesia.

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