3 Biotech (2024) 14:111
https://doi.org/10.1007/s13205-023-03904-5

REVIEW ARTICLE

A review on pharmacological studies of natural flavanone: pinobanksin

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Received: 27 September 2022 / Accepted: 18 December 2023 / Published online: 13 March 2024

Abstract

Herbal medicinal drugs, or phytotherapy, have historically played a pivotal role in treating human ailments. In the contemporary medical landscape, there is a burgeoning interest in natural products owing to their diverse and health-beneficial components. Among these, bioactive phytochemicals represent a dynamic area of global research. This study focuses on pinobanksin, a potential polyphenolic component identified through meticulous scientific research and purified using advanced chromatographic techniques from various sources, including plants, propolis, and honey. Pinobanksin has emerged as a compelling subject of investigation, exhibiting a spectrum of pharmacological effects. Scientific studies have unveiled its prowess as an anti-oxidant, anti-bacterial, anti-inflammatory, anti-parasitic, anti-mutagenic, anti-proliferative, and anti-angiogenic agent. This literature review systematically synthesizes the existing body of research on pinobanksin, providing a comprehensive overview of its diverse pharmacological activities. In light of its multifaceted pharmacological profile, pinobanksin stands out as a promising scaffold for future drug discovery endeavors. This review not only consolidates the current understanding of pinobanksin's bioactivities but also underscores its potential as a valuable candidate for advancing therapeutic interventions.

Keywords Flavonoid · Pinobanksin · Phytochemical · Pharmacological properties

Introduction

The main source for enhancing the identification of new drugs is bioactive natural products with a wide range of structural variations and various pharmacological actions (Atanasov et al. 2021). It is essential for herbal compounds to develop into clinically useful medication therapy to treat many chronic diseases, as plant-derived potential chemicals in the natural crude extracts are identified, purified, and pharmacologically examined (Tahir et al. 2022). Natural substances from plants, known as phytochemicals, have led scientists to discover complementary therapeutics that are safe and effective. Since ancient times, organic substances engaged in plant defense mechanisms, such as secondary metabolites, have been known to enhance human health (Bruce 2022). Drug incorporation depends on bioavailability, decreased toxicity, and preserved activity, which is challenging for some compounds to accomplish. Flavonoids, terpenoids, and tannins, which are secondary metabolites, have been shown to have improved bioavailability and to be efficacious even at low doses (Saggar et al. 2023). Plants create phenolic chemicals as a result of biological processes and in reaction to environmental stress. Flavonoids and non-flavonoids are the two main categories. Flavonoids are benzopyrans that are abundantly present in fruits, vegetables, grains, and various parts of plants (Sandhar et al. 2011). Flavonoids were studied for their biological, nutraceutical, and clinical effects (Maimoona et al. 2011). Complexities in investigating flavonoids include heterogeneity of molecular structures and a lack of information on bioavailability. Flavanones are an important group of flavonoids, glycosylated by a disaccharide at the seventh position of the A-ring, playing a significant role in drug development. Flavanones are flavans with a 3,4-dihydro-2-aryl-2H-benzopyran-4-one skeletal structure, and their bioactivity structural orientation is C6–C3–C6 rings. Generally, flavanones are well studied for their anti-oxidant,

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anti-diabetic, lipid-lowering, anti-atherogenic, and anti-inflammatory properties.

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Pinobanksin (3,5,7-trihydroxy-2-phenyl-chroman-4-one) is a phenyl allyl flavanone compound commonly found in the heartwood of the genus Pinus, fruits, propolis, honey, bee bread, bee pollen, and bee wax. Pinobanksin is characterized by the absence of a B-ring. The recent literature reveals the biological activities of pinobanksin, which has potent anti-oxidant activity, anti-inflammatory, anti-microbial properties, and so on. Pinobanksin has evolved as a promising pharmacological agent, and our aim is to review the pharmaceutical and therapeutic applications of pinobanksin with its mechanism of action. Further research into this compound could pave the way for considerable insight into its potential biomaterial for therapeutics (Fig. 1).

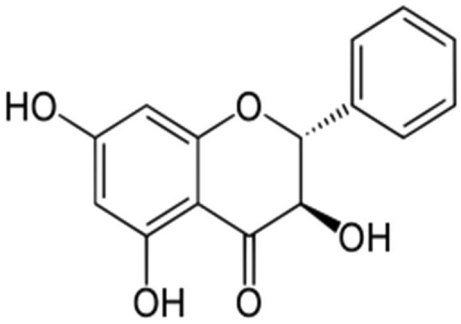


Fig. 1 Structure of pinobanksin. Molecular formula: $C_{15}H_{12}O_5$, Molecular weight: 272.25g/mol, Monoisotopic mass: 272.0684734957 Daltons, PubChem CID: 73202, IUPAC name: (2R,3R)-3,5,7-trihydroxy-2-phenyl-2,3-dihydro-4H-chromen-4-one, Various chemical names: 3,5,7-trihydroxy-2-phenyl-2,3-dihydro-4H-chromen-4-one, Systemic Name: 4H-1-Benzopyran-4-one, 2,3-dihydro-3,5,7-trihydroxy-2-, Nature of the compound: A trihydroxyflavonone(Li et al. 2023)

Sources of pinobanksin

Pinobanksin (PB) as a common polyphenol present in the genus *pinus* and its two subgenera, *Haploxylon* pine and *Diploxylon* pine. Erdtman is the first person to isolate pinobanksin from pine heartwood, *Pinus Banksiana* by precipitating it into an insoluble sodium salt which was then repeatedly purified by recrystallizing from toluene, formed as colorless needles. (Erdtman 1944) PB was reported to be present in all almost all species of genus *Pinus* such as *Pinus pinaster, Pinus radiata, Pinus banksiana, Pinus contorta, Pinus griffithii, Pinus resinosa, Pinus parviflora, Jackpine knot wood, and Pinus morrisonicola woods (Hata* 1955*,* Hillis and Inoue 1968*,* Willför et al. 2003, Sinclair and Dymond 1973, Lindberg et al. 2004, Neacsu et al. 2007, Loman 1970, Simard et al. 2008, Mahesh and Seshadri 1954, Fang et al. 1987, Pietarinen et al. 2006) PB can be referred to as dietary flavonoids as it is also present in various propolis and a variety of honey obtained from different parts of the world (Lu et al. 2013). Biosynthetically pinobanksin can be prepared by hydroxylation of another flavanone, pinocembrin (Conde et al. 2013).

This figure presents the chemical structures of ester derivatives derived from pinobanksin, including pinobanksin-3-O-acetate, pinobanksin-3-O-propanoate, pinobanksin-3-O-butyrate, pinobanksin-3-O-pentanoate, and pinobanksin-3-O-hexanoate (Fig. 2). The distinctive molecular configurations of these ester derivatives are essential components in understanding the chemical

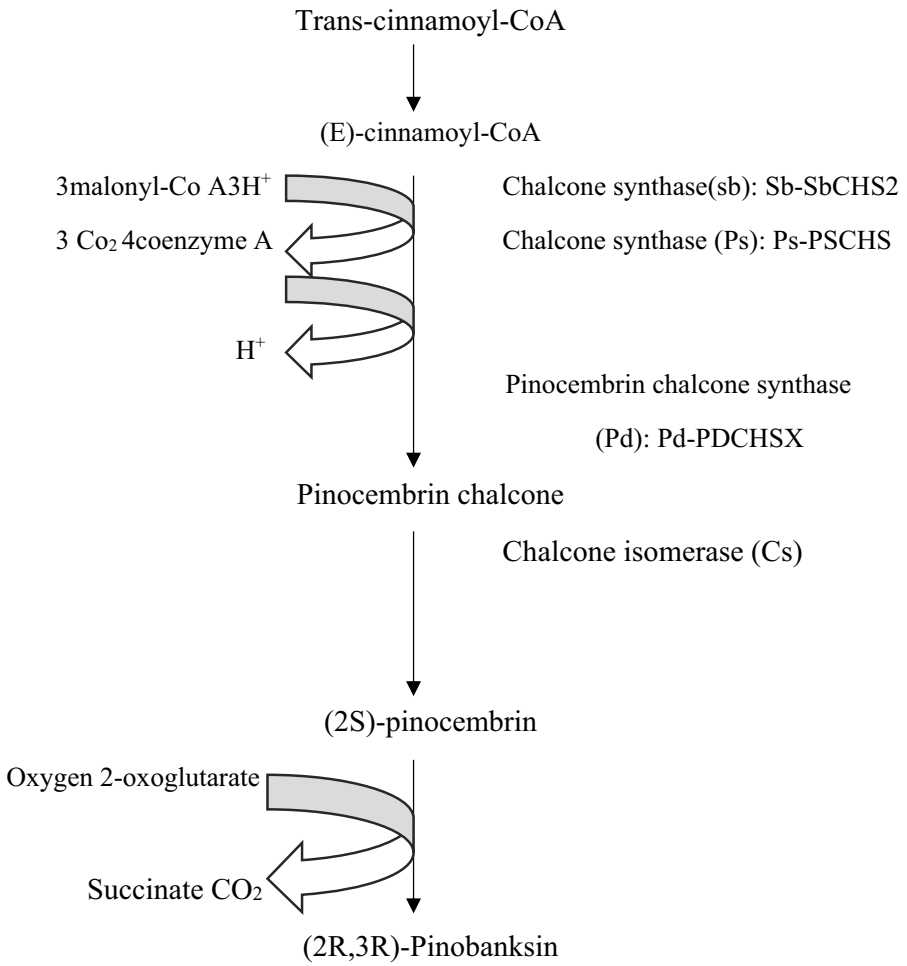


Fig. 2 Biosynthesis of pinobanksin (Metacyc pathway, Foerster H, TAIR) (Zheng et al. 2018)

composition and potential pharmacological activities of pinobanksin (Table 1).

The pharmaceutical properties of pinobanksin (PB)

Anti-oxidant activity

The most common phenolic chemicals with widespread anti-oxidant action are flavonoids. Tocopherol radicals were reduced by PB, reducing lipid peroxidation of lipoproteins (LPLs) (Ondrias et al. 1997). The ability of PB to attenuate ADP/Fe (II)-induced lipid peroxidation was demonstrated by inducing 10 mM CaCl2 with 1.5 mM inorganic phosphate or 30 mM mefenamic acid mitochondrial swelling. Pinobanksin-3-O-acetate and pinocembrin, on the other hand, were less efficient (Santos et al. 1998). Zheng et al. found that in a dose-dependent manner, PB exerted pro- and anti-oxidant effects in 150 µm H2O2-induced ROS generation in H9c2 cells. PB (60–80 µm) prevented lipid peroxidation by inhibiting alpha-tocopherol radicals, and bioavailability was identified to be 9.36 ± 0.28 mg/g DW (Zheng et al. 2018). An anti-oxidant study was conducted to compare the predominant flavonoid compound PB (34.9–1775.5 µg/g) found in 70% ethanolic extract and aqueous extracts of balsam poplar (*Populus balsamife* L.) buds to the standard p-coumaric acid (Stanciauskaite et al. 2021). Flavonoids including PB and pinobanksin-3-O-acetate found to be the anti-oxidant flavonoids in Chinese Beijing propolis determined by various methods such as DPPH, ABTS, FRAP, ORAC, and CAA (Sun et al. 2015). Six knot wood flavonoid isolations revealed the presence of PB and its ester derivative pinobanksin-3-O-acetate; furthermore, all flavonoids isolated from Jack pine and European aspen showed anti-oxidant potential in comparison with the Trolox standard.

XOD (Xanthine oxidase) inhibitor

Xanthine oxidase, an enzyme catalyzing the conversion of oxidation of Xanthine or hypoxanthine to uric acid, leads to hyperuricemia causing gout and kidney stones. In enzyme kinetic and molecular docking simulation studies conducted by Dang et al. PB (IC50 = 137.32 or 125.10 µM) exerted excellent inhibition of XOD (Xanthine oxidase (XOD, EC 1.17.3.2)), converting substrate to uric acid leading to the

Table 1 Structure of ester derivatives of pinobanksin (Wieczorek et al. 2022)

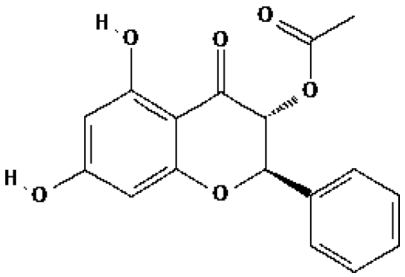
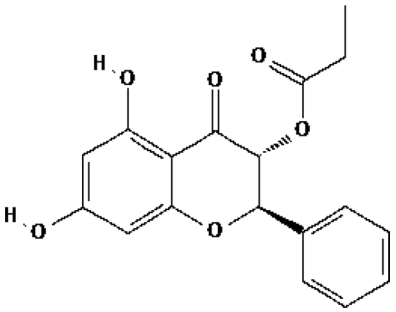
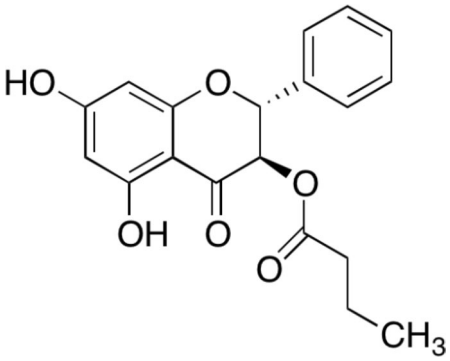
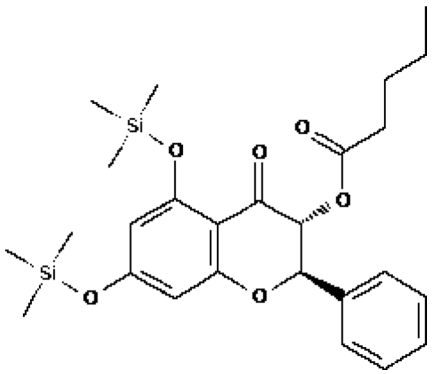
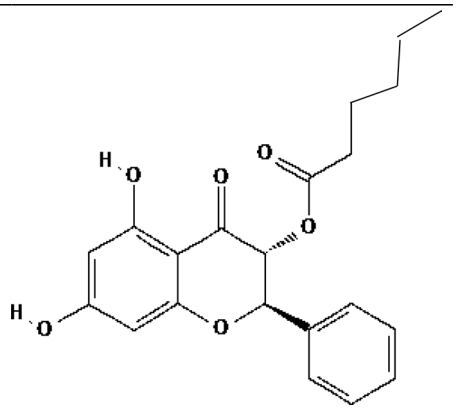
Pinobanksin-3-O-acetate	
Pinobanksin-3-O-propanoate	
Pinobanksin-3-O-butyrate	
Pinobanksin-3-O-pentanoate	

Table 1 (continued)

Pinobanksin-3-O-hexanoate	

generation of free radicals. PB prevented the binding of substrate (xanthine/hypoxanthine) to XOD by entering the hydrophobic cavity (molybdopterin domain) and formed H-bonds with Ser-876 of XOD, Asn-768, Glu-1261, and Phe-914 amino acid residues and formed aromatic (π–π) interactions, thereby changing the conformation of XOD (Dong et al. 2016).

Anti-microbial property

PB was earlier reported to have an effective anti-bacterial property (Sabire 2023). The anti-bacterial property of PB isolated from South African propolis was evaluated against gram-positive bacteria (*Enterococcus faecalis* ATCC 29212, *Staphylococcus aureus* ATC 126000) and gram-negative bacteria (*Escherichia coli* ATCC 8739, *Moraxella catarrhalis* ATCC 23246), and the activity was due to the presence of intense ion fragments corresponding to m/z ratio 271 and 325. The study conducted different concentrations of propolis against *Aspergillus parasiticus*, *Aspergillus niger*, *Altemaria alternata*, *Botrytis cinera*, *Fusarium oxysporum* f.sp. melonis, and *Penicillium digitatum*. The phenolic compounds responsible for the antimycotic property are caffeic acid, benzyl cumarete, PB, and pinocembrin. Kasote D et al. investigated anti-microbial and anti-quorum sensing of South African propolis extracts, which revealed anti-fungal and anti-bacterial properties of pinocembrin and PB, whereas anti-QS was detected only in Caffeic acid (Kasote et al. 2015). The anti-fungal activity of Chinese propolis extracts (200 mg/L), pinocembrin, PB, chrysin, and galangin were determined against *Penicillium italicum*, suggesting that it can be used as a bio-preservative to control citrus blue-mold post-harvest diseases (Yang et al. 2011). Molecular docking studies show that Egyptian propolis extracts encapsulation in the liposomal formulation can be a promising therapeutic treatment against COVID-19, which was compared to standard antivirals Avigan, hydroxychloroquine, and Remdesivir. Rutin and caffeic acid showed higher binding affinity, wherein the binding affinity of PB (Internal Coordinate Mechanics (ICM = − 54.08)) to 3-CL protease (Mpro) compared to Avigan, formed five hydrogen bonds with GLN110, THR111, and SER158, and PB (ICM = -77.4) to spike S1 glycoprotein compared to hydroxychloroquine and formed three hydrogen bonds with TRP436 and PHE342. In docking studies of bioactive components in Alpinia officinarum against ZIKV NS2B-NS3 protease, PB showed the highest docking score with Palmatine and Nelfnavir in comparison and was subjected to in silico studies showed desirable ADMET properties. PB was concluded to be a highly potential bioactive compound against Zika virus (ZIKV) infection (Gbore et al. 2023).

Anti-mutagenic effect

Anti-mutagenic agents from natural sources are referred to as organic antimutagens that combat the disorders caused by mutagens. Based on the research, PB exerted anti-mutagenic properties against ofloxacin-induced bleaching of Euglena. gracilus. PB (20 µmol/l) reduced the white colonies to under 66%, showing high anti-bleaching activity of ofloxacin (43µ mol/l) (Lívia et al. 1998).

Anti-inflammatory property

The anti-inflammatory property PB was assessed, showing it exhibited pro-inflammatory and anti-inflammatory responses in a dose-dependent manner, and PB (5–80 µm) exhibited an anti-inflammatory response in LPS (lipid polysaccharides) induced H9c2 cells (Xu et al. 2022). The main bioactive components found in Mayan propolis were Coumaric acid, pinocembrin, pinobanksin-3-O-acetate, pinobanksin-3-O-propionate, and PB derivatives. The compounds might be responsible for the anti-inflammatory properties of Mayan

propolis in in vivo and in vitro conditions (Xool-Tamayo et al. 2020).

Anti-proliferative activity

PB, a common flavonoid in Sonoran propolis (SP), was reported as an apoptotic inducer that activated caspase 3, 8, and 9 signaling pathways and induced the loss of mitochondrial membrane potential (ΔΨm). Anti-proliferative properties of SP extracts were studied in B-cell lymphoma (M12.C3.F6) cell lines. The MTT cell viability assay confirmed the anti-proliferative effect by significantly inhibiting cancer cell proliferation in a dose-dependent manner of PB (52.1 µM or 14.2 µg/mL) and its ester derivatives pinobanksin-3-O-propanoate (67.0 µm or 22.0 µg/mL), pinobanksin-3-O-butyrate (49.9 µM or 17.0 µg/mL), pinobanksin-3-O-pentanoate (51.3 µm or 18.3 µg/mL), pinobanksin-3-O-hexanoate (76.6 µM or 28.3 µg/mL). The esterified derivative pinobanksin-3-O-propanoate induced apoptotic activity is the highest compared to other isolated compounds (Alday et al. 2015). Pinocembrin and pinobanksin-3-O-acetate were the characteristic compounds in New Zealand propolis, responsible for the anti-proliferative activity reported by Catchpole et al. and PB, pinocembrin, and pinobanksin-3-O-acetate showed no effects on all experimented cell lines (Catchpole et al. 2015).

Apoptotic induction

The in vitro and in vivo anti-angiogenic activity of PB was initially investigated in human umbilical vein endothelial cells (HUVECs) and the chick embryo chorioallantoic membrane (CAM) assay. In HUVEC, PB (200 µm) hindered the proliferation and migration of endothelial cells, crucial processes in angiogenesis, inducing apoptosis without showing cytotoxicity. In vivo, PB (10–200 nmol/egg) suppressed the formation of new blood capillaries and neovascularization in the membrane of the developing chick embryo. In prostate cancer cells, the ethanolic extract of Polish propolis (PB, chrysin, methoxyflavonone, p-coumaric acid, ferulic acid, and caffeic acid) regulated Tumor Necrosis Factor-related apoptosis-inducing ligand (TRAIL)-mediated immunochemoprevention (Szliszka et al. 2013). PB exhibited anti-angiogenic activity in HUVECs and chick embryo CAM assay. In prostate cancer cells, PB and other propolis components regulated TRAIL-mediated immunochemoprevention (Szliszka et al. 2013).

Anti-leishmanicidal activity

PB is a common flavonoid found in ethanolic extracts and nanoparticles of Brazilian red propolis, demonstrating inhibitory effects on L. braziliensis (Do Nascimento et al. 2016). The anti-protozoal effects of European propolis-derived phytochemicals were investigated against veterinary trypanosome pathogens such as Trypanosoma brucei, Trypanosoma congolense, Leishmania mexicana, and the bee parasite Trypanosomatids Crithirdia fasciculata. Orthogonal partial least squares (OPLS) analysis revealed that the highest activity against T. brucei was associated with two butyrate and propionyl esters of PB, while against T. congolense and C. fasciculata, methyl esters of galangin and pinobanksin exhibited significant activity.

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Cytotoxic effects

In PANC-1 human pancreatic cancer cells, PB (17.9 µM) and pinobanksin-3-O-acetate (9.1 µM) in the methanolic extract of Mexican propolis exhibited in vivo cytotoxic effects, causing a 50% death of cells, particularly in NDM.

Other activities

Turkish propolis, containing flavonoids such as galangin, quercetin, kaempferol, apigenin, pinobanksin, pinocembrin, and pinostrobin, was observed to reduce alcohol-induced acute liver damage (Daleprane and Abdalla 2013). Investigation into propolis extracts, including PB, galangin, chrysin, and pinocembrin, revealed effects on ameliorating insulin resistance in type-2 diabetes. The study found that PB and chrysin were inactive, while pinocembrin and galangin demonstrated effectiveness in improving insulin resistance (Liu et al. 2018) . Brazilian red propolis was evaluated for its efficacy in combating dental caries-causing cariogenic bacteria such as Streptococcus mutants, Lactobacillus acidophilus, and Candida albicans. Ethyl acetate extracts of *Brazilian propolis*, containing flavonoids (liquiritigenin, PB, pinocembrin, and isoliquiritigenin) and isoflavonoids (daidzein, formononetin, and biochanin A) loaded in micellar nanoparticles, exhibited anti-bacterial properties (Celerino et al. 2018). PB, along with pinocembrin, chrysin, and galangin (an important flavonoid in propolis extracts), entrapped in

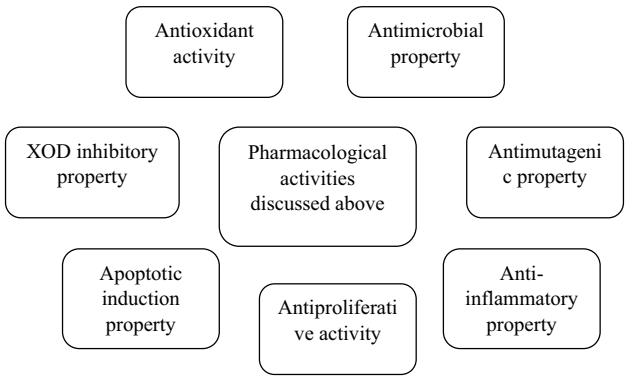

Fig. 3 Pharmacological activities of pinobanksin discussed in this review (Chen et al. 2023)

oromuco-adhesive films, efficiently reduced oral recurrent aphthous ulcers (Arafa et al. 2018). In one study, PB was identified as inefficient in activating free fatty acid receptor 4. Additionally, due to its robust anti-oxidant potential, PB has been recognized as a neuroprotective agent, effectively reducing intracellular and extracellular levels of AGEs (Boisard et al. 2014). Furthermore, its compound, Pinobanksin-3-cinnamate (2R, 3S), a newly discovered flavanone isolated from *Alpinia galanga* Willd. seeds, demonstrates noteworthy in vitro neuroprotective effects (Xin et al. 2014).

This schematic diagram illustrates the diverse pharmacological activities attributed to pinobanksin as discussed in the review (Fig. 3). These activities include anti-oxidant effects, anti-inflammatory properties, anti-microbial and anti-bacterial actions, anti-proliferative and apoptotic (Bang and Ahn 2021) induction, anti-angiogenic effects, anti-leishmanicidal activity, and cytotoxic effects. The comprehensive overview provides insights into the potential therapeutic applications of pinobanksin across various medical domains.

Conclusion

This comprehensive review positions pinobanksin (PB) as a compelling pharmaceutical candidate derived from natural sources. While acknowledging its potential, the existing body of research reveals a notable gap in our understanding due to the lack of in-depth and in vivo experiments, leaving the therapeutic relevance of pinobanksin not fully explored. To bridge this knowledge gap, further investigations, particularly in clinical settings, are imperative to unveil the complete pharmacological profile of pinobanksin. The review systematically synthesizes the existing research on the diverse bioactivities of pinobanksin, offering a solid foundation for inspiring and guiding future explorations in the field of natural products.

Author contributions BE: Conceptualization, Methodology, Investigation, Writing—Original draft preparation, Supervision, Review, and editing.

Funding This review article received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability Not applicable.

Declarations

Conflict of interest The authors declare that there are no conflicts of interest regarding the publication of this paper.

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