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Phytochemical and Pharmacological Review of *Arcangelisia flava* (L.) Merr: Insights into Its Bioactive Compounds and Therapeutic Potential

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ABSTRACT

Arcangelisia flava (L.) Merr., commonly known as *kayu kuning*, is a medicinal plant traditionally used in Southeast Asian medicine. Various studies have identified bioactive compounds such as furanoditerpenes, alkaloids, flavonoids, tannins, and phenolic compounds that contribute to its pharmacological activities, including antimicrobial, antioxidant, and antidiabetic effects. Despite the growing body of research on its pharmacological potential, the mechanisms of action of these bioactive constituents remain inadequately understood, and clinical evidence supporting its use in modern therapy is still limited. This systematic review compiles data from diverse scientific sources, focusing on the phytochemical composition, extraction methods, pharmacological activities, and comparisons with conventional pharmaceutical agents. The analysis revealed that *A. flava* contains various bioactive constituents responsible for its therapeutic effects. Furanoditerpenes demonstrate antimicrobial and antifungal activity, while alkaloids and phenolic compounds exhibit significant antioxidant and antidiabetic properties. Extraction techniques varied across studies, affecting the efficiency of bioactive compound isolation. Comparisons with standard pharmaceuticals suggest that *A. flava* extracts exhibit comparable efficacy in several pharmacological domains. These findings indicate that *A. flava* holds considerable promise as a natural therapeutic agent. However, further investigations are needed to clarify its pharmacological mechanisms through pharmacokinetic and pharmacodynamic studies, as well as clinical trials to confirm its safety and effectiveness in human applications. The integration of modern technological approaches such as metabolomics and bioinformatics could facilitate the identification, standardization, and development of phytopharmaceutical products derived from *A. flava*, thereby advancing its potential use in evidence-based medicine.

Key words: *A. flava*; antimicrobial; antioxidant; antidiabetic; phytochemistry

INTRODUCTION

The utilization of medicinal plants in healthcare has significantly increased due to the growing demand for safer and more effective natural therapies. One plant that has attracted considerable attention in the fields of phytochemistry and pharmacology is *Arcangelisia flava* (L.) Merr., commonly known as *kayu kuning* (Suzuki *et al.*, 2011; Diliarosta *et al.*, 2021; Forestryana *et al.*, 2022). Traditionally used across Southeast Asia for treating various ailments such as infections, inflammation, and metabolic

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disorders (Tan *et al.*, 2019), *A. flava* has been scientifically recognized for its diverse bioactive compounds, including furanoditerpenes, alkaloids, flavonoids, tannins, and phenolic compounds (Kawakami *et al.*, 1987; Suzuki *et al.*, 2011). These compounds contribute to its pharmacological activities, such as antimicrobial, antioxidant, and antidiabetic effects, highlighting its potential as a natural source for modern therapeutic agents (Cheng *et al.*, 2021; Delica *et al.*, 2023; Delica *et al.*, 2024).

Despite numerous studies confirming the pharmacological potential of *A. flava*, several challenges remain in comprehensively understanding the mechanisms of its bioactive compounds. A major limitation is the lack of systematic studies correlating its phytochemical composition with biological activities. Additionally, variations in extraction and fractionation methods across studies complicate the standardization of *A. flava* extracts (Sriwilaijareon *et al.*, 2002). Furthermore, there is a scarcity of clinical studies supporting the efficacy and safety of *A. flava* in therapeutic applications, necessitating more comprehensive and standardized research efforts.

Current research gaps indicate that while the pharmacological activities of *A. flava* have been widely explored, most studies are limited to small-scale *in vitro* and *in vivo* experiments. Few investigations have delved into the molecular mechanisms of its bioactive compounds in complex biological systems. Moreover, comparative studies between *A. flava* extracts and standard pharmaceutical compounds are scarce, limiting the understanding of its clinical efficacy. Therefore, an integrative approach is needed to bridge phytochemical findings with therapeutic potential more holistically.

The urgency of this review lies in the need for scientific standardization and validation of *A. flava* to facilitate its development into safe and efficacious phytopharmaceutical products. Given the global trend toward herbal medicine, this research holds strategic value in supporting the exploration of medicinal plants as sustainable alternative therapies. This review also aims to provide a scientific foundation for the development of *A. flava*-based pharmaceuticals, both in standardized extract forms and as isolated bioactive compounds for modern formulations.

The objective of this review is to provide a systematic overview of the phytochemical composition, extraction methods, pharmacological activities, and therapeutic potential of *A. flava*. By analyzing existing research, this review seeks to present comprehensive information on the benefits of *A. flava* and guide future research directions. Additionally, this study aims to identify opportunities for developing *A. flava* as a high-efficacy phytopharmaceutical candidate suitable for further pharmaceutical industry applications.

The hypothesis proposed in this review is that *A. flava* contains bioactive compounds responsible for its pharmacological activities, particularly antimicrobial, antioxidant, and antidiabetic effects. Furthermore, the extraction and isolation methods employed are hypothesized to influence the bioactive compound content and pharmacological efficacy. This review aims to elucidate the relationships between the chemical constituents of *A. flava* and their biological activities, optimizing its use as a scientifically validated herbal therapy.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure the validity and accuracy of the study selection process (Page *et al.*, 2021). A comprehensive literature search was performed using major scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search strategy employed a combination of keywords such as *A. flava*, phytochemistry, and bioactive compounds.

The initial search yielded 85 relevant articles. A multi-step screening process was then applied to refine the selection. First, articles were screened based on their type, excluding non-research publications such as editorials and conference

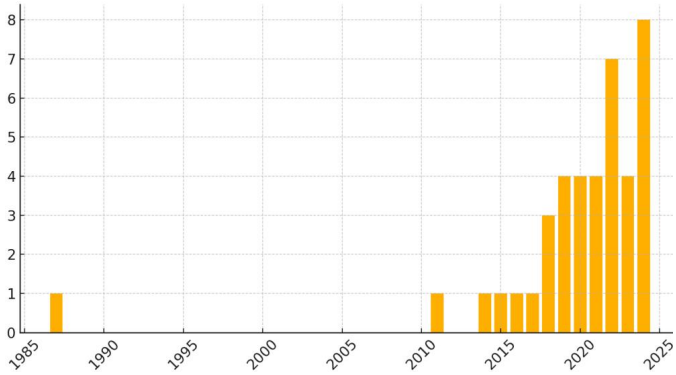

Figure 1. Distribution of research on *A. flava* by year.

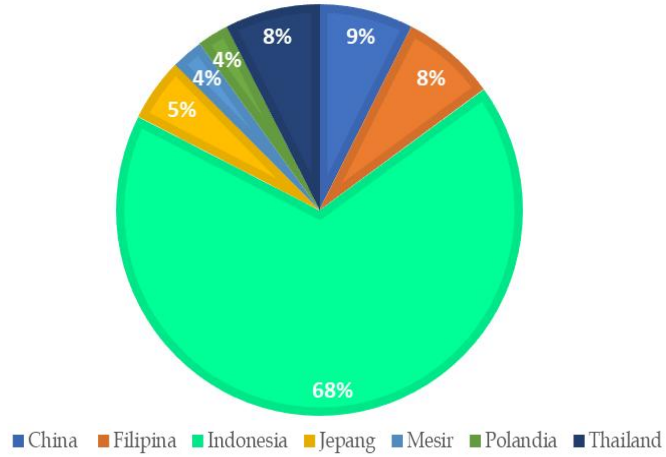

Figure 2. Percentage distribution of research on *A. flava* by country.

abstracts, which reduced the number to 63 articles. Next, articles were filtered by language, retaining only those published in English, resulting in 62 articles. The third step involved applying exclusion criteria, which led to the removal of 43 articles that did not directly address the phytochemistry or pharmacological activities of *A. flava*, were review articles without primary data, or focused solely on botanical aspects without analyzing active compounds. Finally, 40 articles that met the inclusion criteria were reviewed in full text to confirm their relevance and alignment with the review's objectives. All 40 articles were included in the final systematic analysis.

Data extraction focused on several key aspects, including the phytochemical composition of *A. flava*, methods of extraction and fractionation, pharmacological activities, and comparisons with standard pharmaceutical compounds. Variations in extraction solvents and methodologies were documented to evaluate their impact on the efficacy of bioactive compound isolation and pharmacological outcomes.

The entire study selection process is visualized in a PRISMA flow diagram, illustrating each stage of the screening and the final inclusion of articles. This diagram enhances the transparency of the review process and facilitates reproducibility for future research.

RESULTS AND DISCUSSION

Publication trends

The analysis of publication trends indicated that research on *A. flava* began in 1987 (Kawakami *et al.*, 1987) and has seen a resurgence since 2010 (Suzuki *et al.*, 2011). The increased number of studies in the last decade suggested a growing interest in exploring the plant's pharmacological, phytochemical, and therapeutic potential (Figure 1). The uneven distribution of publications over the years may be attributed to factors such as technological advancements in analytical methods, funding availability, institutional priorities, and fluctuating scientific interest in natural product research. However, the recent upward trend underscored the plant's rising significance in the field of medicinal plant research.

Geographical distribution of research

The geographical distribution of *A. flava* studies revealed that Indonesia leads with 27 publications, reflecting the plant's cultural and medicinal relevance within the region, particularly in traditional practices like *jamu*. This dominance highlights Indonesia's role as a primary hub for *A. flava* research (Liem *et al.*, 2018; Ramadani *et al.*, 2018). Other countries such as China, the Philippines, and Thailand each contributed three studies, indicating regional interest, albeit on a smaller scale (Jitjak, 2022; Delica *et al.*, 2023; Nhon Hoang *et al.*, 2023). Meanwhile, Japan, Egypt, and

Poland reported limited research (Figure 2), suggesting an untapped potential for global exploration (Nurbaity, 2011; Mokhtar *et al.,* 2022; Miłek *et al.,* 2024). The disparity in research distribution presented opportunities for international collaboration to further investigate *A. flava's* pharmacological properties and its potential in modern pharmaceutical applications.

Sample types and phytochemical composition

Studies on *A. flava* have utilized various sample types, ranging from crude plant extracts to isolated bioactive compounds from specific plant parts. Commonly studied samples included yellow wood extracts, aqueous root extracts, and isolated compounds such as furanoditerpenes and pachybasin (Figure 3) from endophytic fungi (Kawakami *et al.,* 1987; Suzuki *et al.,* 2011).

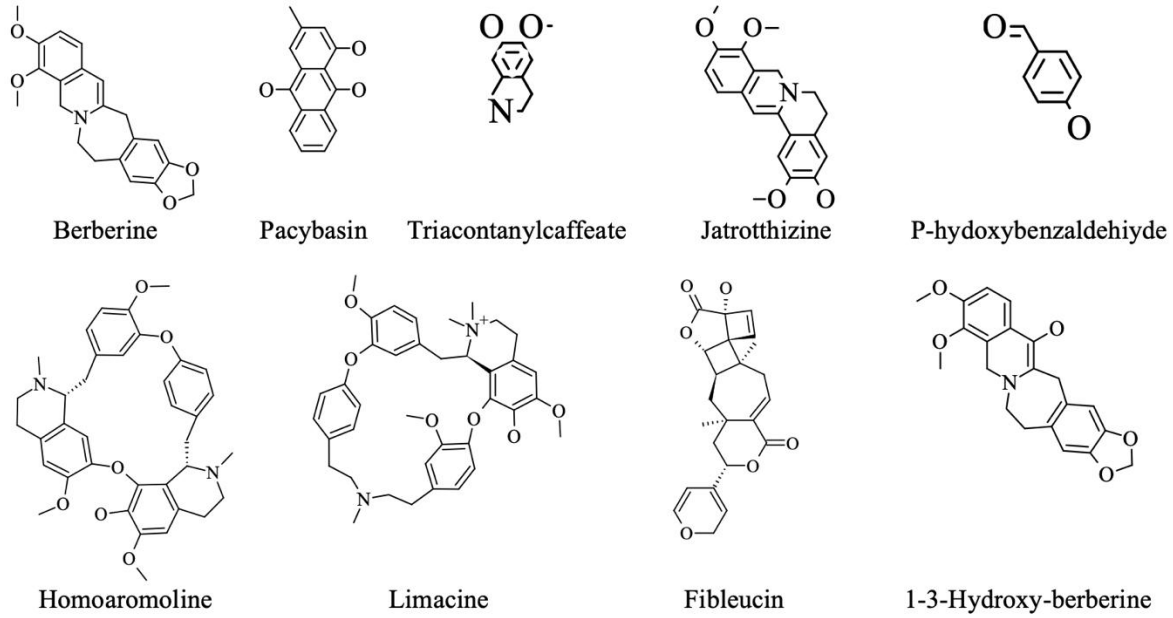

Figure 3. Two-dimensional structure some of *A. flava* derived compounds.

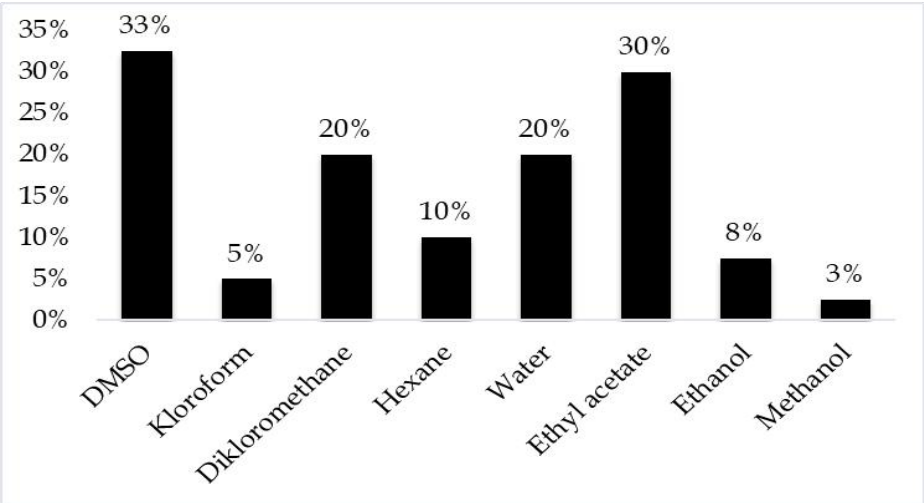

Figure 4. Percentage of solvent used in the extraction/ fraction on *A. flava*.

The diversity in sample selection reflected different research approaches aimed at identifying bioactive compounds and evaluating their pharmacological effects. Furanoditerpenes have been widely studied for their antimicrobial and antifungal activities, while yellow wood extracts were often investigated for their antioxidant and antidiabetic properties (Wahyudi *et al.*, 2016; Ratnadewi *et al.,* 2020). Recent trends show a shift towards isolating specific compounds for detailed characterization, highlighting the move from exploratory studies to targeted pharmacological research.

Tabel 1. Data of solvent, compounds, and phatmacology activities.

Solvent extraction/fractionation	Sample	Pharmacology activities	References
Dichloromethane	Secondary metabolites of *A. flava*	Palmatine and fibraurine show significant antifungal activity.	(Hendra *et al.*, 2024)
Distilled water	Aqueous extract of Thai traditional medicine including *A. flava*	No acute toxicity was found, but slight biochemical changes were observed.	(Katisart *et al.*, 2023)
DMSO, culture media	Berberine from *A. flava* against Plasmodium *falciparum* telomerase	Berberine from *A. flava* inhibits Plasmodium falciparum telomerase.	(Sriwilaijareon *et al.,* 2002)
Ethanol	Medicinal plant antiparasitic extract	*A. flava* extract is effective against *Plasmodium*.	(Ramadani *et al.,* 2018)
Ethanol	*A. flava* extract for hepatoprotection	*A. flava* extract protects the liver from acetaminophen-induced hepatotoxicity.	(Liem *et al.*, 2018)
Ethanol	Ethanol extract of *A. flava*	UV exposure affects the yield and composition of extracted metabolites.	(Mulyani *et al.*, 2019)
Ethanol	*A. flava* stem extract as an anti-inflammatory	*A. flava* extract shows strong anti-inflammatory effects.	(Pratama *et al.*, 2023)
Ethanol	70% ethanol extract of *A. flava* stems	*A. flava* extract inhibits IL-1β and NO.	(Pratama *et al.*, 2023)
Ethanol	70% ethanol extract of *A. flava* stems	*A. flava* extract effectively reduces NO and IL-1β, with potential as an osteoarthritis treatment.	(Pratama *et al.*, 2024)
Ethanol	Yellow root extract in film-forming hydrogel	Film-forming hydrogel with yellow root extract shows good characteristics.	(Annisa *et al.*, 2024)
Ethanol	Liana wood extract from Wallacea	Liana extract shows significant antioxidant activity.	(Hapid *et al.*, 2021)

Extraction methods and solvent efficiency

The extraction and fractionation methods employed in *A. flava* research significantly influence the yield and efficacy of bioactive compounds. Methanol (33%) and ethanol (30%) were the most effective solvents, indicating the efficiency of polar solvents in extracting bioactive compounds such as alkaloids and phenolics.

Tabel 1. Lanjutan……

Solvent Extraction/Fractionation	Sample	Pharmacology activities	References
Ethanol extract	Secondary metabolites of *A. flava* for antibacterial activity	Berberine shows strong binding to antibacterial targets.	(Pratama *et al.*, 2018)
Ethyl acetate	Dihydroberberine from Phellodendri Chinese Cortex	Dihydroberberine shows strong anti-inflammatory effects.	(Tan *et al.*, 2019)
Ethyl acetate extraction	Endophytic bacteria from *A. flava*	Endophytic bacteria produce antimicrobial compounds.	(Sipriyadi *et al.*, 2022)
Ethyl acetate, methanol	Phytoconstituents of *A. flava*	Berberine and related compounds are effective as enzyme inhibitors.	(Levita *et al.*, 2018)
Ethyl acetate, methanol, water	Gradient extract of *A. flava* stems	Methanol extract of *A. flava* shows significant antioxidant and antimicrobial activity.	(Delica *et al.*, 2024)
Hexane	Hexane extract of *A. flava* stems	Hexane extract is rich in hydrocarbons and esters.	(Delica *et al.*, 2023)
Hexane, ethyl acetate, methanol	Yellow Wood Extract (*A. flava*)	Yellow Wood extract has potential as a natural antioxidant and antidiabetic.	(Wahyudi *et al.*, 2016)
Hexane, ethyl acetate, methanol	Plant extracts from Meru Betiri National Park	Some plant extracts have higher potential compared to acarbose in inhibiting diabetes-related enzymes.	(Ratnadewi *et al.*, 2020)
Liquid broth for fermentation, organic solvent	Pachybasin from endophytic fungi of *A. flava*	Pachybasin shows antimicrobial activity against several bacteria and pathogenic fungi.	(Wulansari *et al.*, 2014)
Methanol	*A. flava* as ethnomedicine	*A. flava* can be an alternative natural antibiotic.	(Diliarosta *et al.*, 2021)
Methanol, chloroform	Furanoditerpenes from *A. flava*	The structure of new furanoditerpenes was determined by NMR.	(Kawakami *et al.*, 1987)
Methanol, chloroform	Furanoditerpenes from *A. flava*	Furanoditerpenes have potential as natural antifungals.	(Suzuki *et al.*, 2011)
Methanol, dichloromethane	Phytoconstituents of *A. flava*	Phytochemicals in *A. flava* match the iNOS pharmacophore model.	(Liem *et al.*, 2018)

Water and ethyl acetate demonstrated moderate efficiency (20%), while non-polar solvents like hexane (10%), dichloromethane (8%), and chloroform (5%) showed lower extraction efficiency (Figure 4). The choice of solvent not only affected the quantity of extracted compounds but also determineed the pharmacological activity. For instance, ethanol extracts showed higher alkaloid content, correlating with stronger antimicrobial and antimalarial activities, while chloroform extracts exhibited notable anticancer effects due to their ability to extract semi-polar compounds (Ramadani *et al.,* 2018).

Identified bioactive compounds and pharmacological activities

Phytochemical analysis of *A. flava* had identified a range of bioactive compounds, including furanoditerpenes, alkaloids, tannins, saponins, and phenolic derivatives like tryacontanyl caffeate. Furanoditerpenes and alkaloids, particularly protoberberine alkaloids such as berberine, palmatine, and jatrorrhizine (Keawpradub, Dej-adisai & Yuenyongsawad, 2005; Hendra *et al.,* 2024), were the most frequently isolated compounds due to their significant pharmacological properties. These alkaloids exhibit strong antibacterial activity against gram-positive bacteria, such as *Staphylococcus aureus*, through mechanisms like inhibition of DNA and protein synthesis. Additionally, flavonoids contributed to the plant's antioxidant properties, protecting cells from oxidative stress. The presence of pachybasin, isolated from endophytic fungi associated with *A. flava*, further underscores the plant's diverse pharmacological potential

Tabel 1. Lanjutan …..

Solvent Extraction/Fractionation	Samples	Pharmacology activities	References
Methanol, dichloromethane	Extract of Arcangelisia genus	Arcangelisia genus contains various alkaloids with broad pharmacological activities.	(Cheng *et al.,* 2021)
Methanol, dichloromethane	Extract of Annona glabra and Annona squamosa	Silver nanoparticles enhance antibacterial and anticancer effects.	(Mokhtar *et al.,* 2022)
Methanol, ethanol	Ornamental stem extract	Ornamental Barberry stem has potential as a natural berberine source.	(Miłek *et al.,* 2024)
Methanol, n-hexane, ethyl acetate, dichloromethane	Root extracts of *A. flava*	Dichloromethane extract is the most effective against Candida.	(Agustha *et al.,* 2024)
Methanol, water	Yellow root extract from West Sumatra	*A. flava* has potential as a natural antibacterial.	(Diliarosta *et al.,* 2021)
Water	Water extract of *A. flava* roots	*A. flava* extract is effective as a natural food additive for acidity stabilization and as an antimicrobial.	(Heryani & Nugroho, 2015)
Water, brackish water	Yellow root water and brackish water decoction	Brackish water decoction shows lower toxicity compared to regular water.	(Pramono *et al.,* 2020)
Water, ethanol	Medicinal plants in Kalimantan	Medicinal plants in Kalimantan have high pharmacological benefits.	(Novaryatiin & Indah, 2019)

(Cheng *et al.,* 2021; Purwaningsih *et al.,* 2023).

The pharmacological activities of *A. flava* were broad, encompassing antimicrobial, antifungal, antioxidant, antidiabetic, anti-inflammatory, and anticancer effects. Anti-inflammatory activity was the most prominent (15%), followed by antibacterial (13%), antimicrobial (13%), and anticancer/toxicity activities (13%). The plant's antimicrobial properties were largely attributed to furanoditerpenes and pachybasin, which inhibit the growth of pathogenic microorganisms (Suzuki *et al.,* 2011). Antioxidant activities, assessed through assays like DPPH and superoxide radical scavenging, were linked to phenolic compounds and flavonoids. *A. flava* also demonstrated antidiabetic potential by inhibiting enzymes such as α-glucosidase, thereby regulating blood glucose levels. Although antidiabetic activity represents a smaller proportion (5%) of research focus, it remains a crucial area for therapeutic development (Wulansari *et al.,* 2014).

The solvent extraction and fractionation methods employed in the studies of *A. flava* reveal significant pharmacological potentials, highlighting the effectiveness of various solvents in extracting bioactive compounds. Ethanol and its variants, particularly at 70%, demonstrated remarkable versatility, showing strong anti-inflammatory effects, hepatoprotective properties against acetaminophen-induced hepatotoxicity, and potent antioxidant activities. These ethanol extracts also proved effective in reducing osteoarthritis inflammation and enhancing hydrogel formulations, underscoring their broad therapeutic applications. Methanol and dichloromethane were particularly effective in isolating phytoconstituents and secondary metabolites. Methanol extracts aligned well with iNOS pharmacophore models, indicating their potential in anti-inflammatory therapies, while dichloromethane extracts exhibited significant antifungal and antibacterial properties, particularly against *Candida* (Tan *et al.,* 2019).

Hexane and ethyl acetate, often used in combination with methanol and water in multistep extractions, contributed to the antioxidant and antidiabetic properties of the extracts. Hexane extracts were rich in hydrocarbons and esters, enhancing their biological activities. Multistep extraction methods proved to increase the antioxidant and antimicrobial effectiveness of *A. flava* extracts, demonstrating the value of combining solvents to maximize bioactive compound yields (Table 1).

The pharmacological potential of these extracts was extensive. Antimicrobial activities were prominent, with berberine and related compounds from *A. flava* showing strong binding to antibacterial targets and inhibiting *Plasmodium falciparum* telomerase, indicating their potential in antimalarial therapies (Sriwilaijareon *et al.,* 2002). Additionally, the extracts' antioxidant properties played a crucial role in reducing oxidative stress, and their anti-inflammatory effects were particularly beneficial in managing conditions like osteoarthritis. Hepatoprotective effects were also significant, with *A. flava* extracts protecting the liver from drug-induced toxicity. Furthermore, plant extracts from Meru Betiri National Park exhibited superior potential compared to acarbose in inhibiting diabetes-related enzymes, highlighting their antidiabetic benefits (Ratnadewi *et al.,* 2020).

Ethnopharmacological insights from traditional used of *A. flava* in regions like Papua and Kalimantan were validated through scientific studies. Ethnobotanical plants demonstrated significant antimalarial, antibacterial, and pharmacological benefits, reinforcing the importance of integrating traditional knowledge with modern research. Safety profiles of these extracts were generally favorable. Aqueous extracts used in Thai traditional medicine showed no acute toxicity, and brackish water decoctions demonstrated lower toxicity and histological damage compared to regular water decoctions (Katisart *et al.,* 2023).

Over all, the diverse solvent extraction methods employed for *A. flava* have unveiled its vast pharmacological potentials. From antimicrobial and antioxidant properties to hepatoprotective and antidiabetic effects, these findings not only support traditional medicinal uses but also pave the way for developing novel

therapeutic agents (Figure 5). Future research should focus on isolating specific bioactive compounds, understanding their mechanisms of action, and conducting clinical trials to validate their efficacy and safety in humans.

Comparative analysis with standard pharmaceuticals

Comparative studies had demonstrated that *A. flava* extracts exhibited competitive efficacy when measured against standard pharmaceutical compounds. For instance, antioxidant activity has been compared to vitamin C, while antidiabetic effects have been evaluated against acarbose (Rajalakshmi *et al.*, 2021). In antimicrobial studies, *A. flava* extracts have shown comparable or superior effectiveness to conventional antibiotics in certain cases. These comparisons highlight the potential of *A. flava* as a viable natural alternative in modern pharmacotherapy, although further clinical validation is required to substantiate these findings.

Future perspectives

The findings from this review underscore *A. flava's* significant potential in pharmacological applications. However, future research should focus on elucidating the molecular mechanisms of its bioactive compounds through advanced pharmacokinetic and pharmacodynamic studies. The integration of modern technologies such as metabolomics and bioinformatics can further enhance the identification and standardization of bioactive compounds. Additionally, comprehensive toxicological assessments and clinical trials are essential to ensure the safety and efficacy of *A. flava* in therapeutic applications. International collaborations and interdisciplinary approaches will be critical in advancing *A. flava* from traditional use to standardized phytopharmaceutical development.

CONCLUSION

This systematic review highlighted *Arcangelisia flava* as a promising source of bioactive compounds with significant pharmacological potential. The plant contained diverse phytochemicals, including furanoditerpenes, alkaloids, flavonoids, tannins, and phenolic compounds, which contribute to its antimicrobial, antioxidant, antidiabetic, anti-inflammatory, and anticancer activities. Comparative studies with standard pharmaceuticals have demonstrated that *A. flava* extracts exhibit competitive efficacy, positioning the plant as a viable candidate for natural therapeutic applications.

Despite these promising findings, several research gaps remain. The current understanding of the molecular mechanisms underlying the pharmacological activities of *A. flava* was limited, and the variability in extraction methods hampers standardization efforts. Moreover, there was a lack of comprehensive toxicological data and clinical trials to validate the efficacy and safety of *A. flava* in human applications.

Future research should focus on exploring the pharmacokinetics and pharmacodynamics of *A. flava* bioactive compounds to elucidate their mechanisms of action. Standardized extraction methods and rigorous toxicological assessments are essential to ensure the reproducibility and safety of *A. flava*-based therapies. Additionally, clinical trials were necessary to confirm the therapeutic efficacy observed in *in vitro* and *in vivo* studies. The integration of advanced technologies, such as metabolomics and bioinformatics, can further enhance the identification and development of standardized phytopharmaceutical producted derived from *A. flava*. With these advancements, *A. flava* held great potential for contributing to the development of safe, effective, and scientifically validated herbal medicines.

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