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Review Article

Anti-inflammation and antioxidant potentials of *Avicennia* plants: A systematic review

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Abstract

Objective: *Avicennia* is a genus of coastal plants used in Indonesian folk medicine to treat diseases. This systematic review aimed to summarize and evaluate recent findings on the anti-inflammatory and antioxidant properties of *Avicennia* species, and explore their possible mechanisms in combating inflammation and oxidative stress.

Materials and Methods: Following PRISMA 2020 guidelines, literature search was conducted using databases (Science Direct, Google Scholar, Scopus, PubMed, PubPharm, and LILACs). Keywords such as "*Avicennia*," "anti-inflammatory," and "antioxidant" were used. Risk of bias was assessed using OHAT and SYRCLE's RoB tool.

Results: From 587 articles, 16 were selected for analysis (13 *in vivo* studies and 3 *in vitro* studies). The anti-inflammatory properties of *Avicennia* species have been associated with regulating cytokines levels, reducing nitric oxide production, and promoting lymphocyte proliferation. The *PI3K/Akt* and *mTOR* pathways emerged as central mechanisms. The antioxidant effects were observed through reduced lipid peroxidation, lower reactive oxygen species, and regulation of enzymatic antioxidants. Study quality varied in design, methods, and depth of mechanistic insights.

Conclusion: This review supports the traditional use of *Avicennia* for treating inflammation and oxidative stress. However, further research, especially on mechanisms of action and pharmacokinetics, is needed before clinical trials can be pursued for its therapeutic development.

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Introduction

Avicennia, or mangrove or "*api-api*", is a genus commonly found in mangrove forests located at the outermost areas or near the sea. These plants live in shallow muddy soils with sandy substrates that contain low organic matter and high salinity levels (Srikanth et al. 2016). Mangrove forests are primarily located in warmer parts of the world such as the equatorial region including Indonesia, Malaysia, Thailand, and India (Saenger et al. 2019). The total area of mangrove forests worldwide is approximately 137.600 square kilometers. In Indonesia, mangrove forests can be found on the western coastline of Sumatra, parts of the northern coastline of Java, Sulawesi, and Kalimantan, as well as the southern coastline of Papua. Referring to data from the Central Bureau of Statistics, Indonesia has the greatest amount of coastline, with approximately 95,000 kilometers, making its total area of mangrove forests about three million hectares (Statistik 2021). Mangroves are beneficial for preventing coastal erosion, serving as habitats for fisheries, mitigating climate change, and acting as a source of medicinal plants (Desiani et al. 2022; Fahrurrozi et al. 2024; Madusari et al. 2024). One of the various types of mangroves in mangrove forests is the genus *Avicennia*. In traditional medicine, the first study focused on the traditional use of *Avicennia*, particularly for treating malaria, hemorrhoids, rheumatism, sore throat, hepatitis, asthma, diarrhea, and other inflammatory conditions (Thirunavukkarasu et al. 2011). Empirically, communities living in coastal areas of Indonesia often use mangrove plants as medicinal plants to treat various illnesses.

Medicinal plants have traditionally been used as natural remedies for treating a wide range of diseases (Soudkhah et al. 2025; Nova et al. 2020; Vakkalagadda and Lankalapalli 2020). For an herb to be developed into herbal medicine or dietary supplement, its effects must be scientifically proven, and its mechanism of action should also be clearly explained (Kosoe et al. 2024; Wang et al. 2024). The therapeutic potential of *Avicennia* as a phytomedicine with anti-inflammatory and antioxidant potentials is well-established. Research has explored the effects of *Avicennia* plant extracts on conditions such as edema, arthritis, ulcerative colitis, and liver damage, using both *in vitro* and *in vivo* methods (Sumithra et al. 2011; Vellimalai et al. 2019; Victoria et al. 2012). This review aims to compile and analyze the scientific data of the anti-inflammatory and antioxidant potentials of *Avicennia* species, utilizing findings from experimental studies to support future researches.

Materials and Methods

This systematic review was conducted in accordance with the guidelines of the preferred reporting items for systematic review and meta-analysis (PRISMA) (Moher et al. 2010). The quality of the selected studies is summarized in Table 1. The risk of bias was assessed according to the guidelines of the systematic review centre for laboratory animal experimentation (SYRCLE) and the office of health assessment and translation (OHAT) (Chen et al. 2014).

Table 1. Evaluation of the quality of studies on the anti-inflammatory and antioxidant potentials of *Avicennia* plants.

First author	Species	Country of origin/ plants collection location/ or period of the year	Authenticated species	Voucher specimen deposited ?	Quality control reported?	Chemical analysis reported?
Sumithra (2011)	*Avicennia officinalis*	Machilipatnam port area of Krishna District of Andhra pradesh, India	Yes	No	No	No
Sura (2011)	*Avicennia officinalis*	Tamilnadu, India	Yes	No	No	No
Rise (2012)	*Avicennia marina*	Pichavaram mangrove forest, India	Yes	Yes	No	No
Fang (2013)	*Avicennia marina*	Techeng Island, Xiashan district, Zhanjiang, China. Period: September 2004	Yes	Yes	No	Yes - C NMR, FT-IR, HPSEC
Gandomani (2015)	*Avicennia marina*	Nayband port, Boushehr province, Iran. Period: April 2011	Yes	Yes	No	No
Kumar (2016)	*Avicennia marina*	Muthupet, Thiruvarur district, Tamil Nadu, India	Yes	Yes	No	No
Barbosa (2019)	*Avicennia schaueriana*	The northern coast of the state of Pernambuco, Brazil. Period: November 2014	Yes	Yes	No	UPLC-DAD-QTOF-MS/MS
Okla (2019)	*Avicennia marina*	Jazan district, Kingdom of Saudi Arabia	No	No	No	No
Vellimalai (2019)	*Avicennia marina*	Muthupet, Thiruvarur district, Tamilnadu, India	Yes	Yes	No	No
Al-Jaghthmi (2020)	*Avicennia marina*	Farasan Island, Jizan and Shuaiba area, Kingdom Saudi Arabia. Period: January 2018	Yes	No	No	No
Qurrohman (2020)	*Avicennia marina*	Lubuk Kertang, District West Brandan, Langkat, Indonesia	Yes	No	No	No
Sadoughi (2020)	*Avicennia marina*	The northern coast of Qeshm Island, Iran. Period: May 2017 (spring season)	Yes	Yes	No	No
Yi (2020)	*Avicennia marina*	Beihai City, China	Yes	Yes	No	Yes – HPLC
Yassien (2021)	*Avicennia marina*	Safaga city on the western side of the Red Sea coast, Egypt	No	No	No	No
Mitra (2022)	*Avicennia alba*	Sylhet, Bangladesh	Yes	No	No	No

NMR: Nuclear Magnetic Resonance; FTIR: Fourier Transform- Infrared Spectroscopy; HPSEC: High Performance Size Exclusion Chromatography; UPLC-DAD-QTOF-MS: Ultra-Performance Liquid Chromatography coupled with Diode-Array Detection and Quadrupole Time-Off light Mass Spectrometry; HPLC: High Performance Liquid Chromatography.

Search strategy

A search strategy was first performed in October 2024 in the following databases: Google Scholar, ScienceDirect, LILACS, Scopus, PubMed, and PubPharm. The manual review of the included articles aimed to identify any potential articles that might have been missed during the electronic search. The authors used the following combination of keywords in PubMed: *avicennia*[Title/Abstract] AND (oxidative[Title/Abstract] OR oxidant[Title/Abstract] OR antioxidant[Title/Abstract] OR inflammation[Title/Abstract] OR inflammatory[Title/Abstract] OR inflame[Title/Abstract]) NOT (review[Title/Abstract] OR systematic[Title/Abstract]). The reference lists of all the included articles were reviewed to identify additional relevant sources. Studies were selected based on their availability in English or *Bahasa Indonesia*, considering language barriers, the high cost of translation, and time efficiency. This study was not restricted by publication time. References were managed using Microsoft Excel™ and duplicate entries were removed using Zotero™.

Study selection and data collection process

Three independent authors screened the titles and abstracts, categorizing them as "yes," "no", or "maybe". Titles and abstracts were initially reviewed, followed by a full-text assessment, with both stages screened according to the eligibility criteria. The selection of studies and data collection were conducted independently by three authors (FK, MS, and AS). Any discrepancies were resolved through discussions with three additional authors (JF, MS, and BD).

Authors collected the data using a personalized data extraction sheet in Microsoft Excel™, including the following details: first author, year of publication, journal title, country of origin/collection location/season, plant part, type of extract, extract dose and method of administration, inflammation model or assay type, *in vivo* or *in vitro* model, number of animals per group and cell type, control used, evaluated parameters, and results. For both *in vivo* and *in vitro* models, the evaluated variables included the plant collection location, the specific plant part used, the type of extract, and the measured levels of inflammatory and antioxidant parameters. Data on the mean, percentage, and standard deviation were also recorded.

Eligibility criteria

The PICOS criteria were defined as follows: 1. Population: Animals (rats or mice), *in vitro* tests, or cells; 2. Intervention: Administration of extracts of different plant parts in *in vivo* and/or *in vitro* designs. *Avicennia* plants can be utilized in various forms including crude extracts, partitions, fractions, or isolated specific compounds; 3. Control: Negative controls (phosphate buffer saline or saline), positive controls (standard drug); 4. Outcome: anti-inflammatory activity, antioxidant activity; 5. Study design: experimental study.

This review included studies that were either *in vitro* or *in vivo* experiments and specifically investigated the anti-inflammatory or antioxidant potentials of *Avicennia*, with publications available in English or *Bahasa Indonesia*. For studies examining additional effects beyond anti-inflammatory and antioxidant activities, only relevant data were extracted—specifically, those presenting the data in graphs, tables, or text. Regarding the animal population criteria, studies involving male or female mice and rats were included. Additionally, *in vivo* studies utilizing inflammation models (such as paw edema model, colitis model, arthritis model, and etc.) were also considered. The criteria for exclusion during the title-abstract screening were as follows:

1. Studies performed *ex vivo* or *in silico* models
2. Treatment involving any plant other than the *Avicennia* species
3. Treatment involving nanoparticles
4. Book chapters, encyclopedias, conference abstracts, or short communications
5. *In vivo* studies that did not adhere to Ethics Committee standards
6. Phytochemical analyses, anatomical and morphological studies, or cytogenetic research
7. Cell viability outcomes, histological data, or toxicity test only
8. Studies without a control group

Risk of bias in individual studies

The completeness of reporting on the materials used in each selected study was evaluated based on details about the *Avicennia* species material, voucher specimens, quality control of the extract, and chemical analysis. The present review evaluated the risk of bias in the selected studies using the systematic review centre for laboratory animal experimentation (SYRCLE) tool which consists of 10 items covering six types of bias to assess methodological quality. These entries included selection bias (allocation concealment, baseline characteristics, and sequence generation), performance bias (random and blinding housing), detection bias (random and blinding outcome assessment), attrition bias (incomplete

outcome data), reporting bias (selective outcome reporting), and other possible biases (Athalye-Jape 2021; Chen et al. 2014; Ritskes-Hoitinga and Pound 2022). Bias data were compiled in Excel worksheet, with judgments categorized as follows: 'yes' for low risk of bias, 'no' for high risk of bias, and 'unclear' for insufficiently reported information.

As far as we are aware, there is no validated checklist currently available for assessing the risk of bias for *in vitro* studies (Almeida et al. 2021; Duchman et al. 2019). We utilized several checklists from the key data extraction elements in the office of health assessment and translation (OHAT) guideline for systematic reviews and evidence integration to evaluate potential bias for *in vitro* studies (Tran et al. 2021).

Results

Study Selection

A total of 587 articles were collected from the database search. After removing duplicates, 252 studies remained. Following title and abstract screening, 173 articles were excluded for various reasons, including four that were published in languages other than English and *Bahasa Indonesia*, 159 articles were unrelated to the anti-inflammatory or antioxidant potentials of *Avicennia*, six articles were excluded because they were non-experimental publications, and four articles used nanoparticles as the intervention. Full-text screening of the remaining 79 articles resulted in the exclusion of 63 studies based on the following criteria: 60 articles employed study models that were not deemed valid for demonstrating pharmacological effects, and three articles did not investigate *Avicennia* as the primary intervention. After reaching a consensus, the reviewers determined that sixteen studies met the eligibility criteria; thirteen of these are *in vivo* studies, while three are *in vitro* studies. Figure 1 presents a flowchart detailing the study selection and search process.

Quality Assessment

The quality and potential risk of bias of the included studies were evaluated. Table 1 presents the quality evaluation of studies examining the anti-inflammatory and antioxidant properties of *Avicennia* species. No naming inconsistencies were found, as all articles included full botanical taxonomic names. It is essential to verify each plant taxonomically and clearly state its full name, as incomplete species names can cause confusion among readers. Errors in plant nomenclature can create difficulties for other researchers, databases, and search engines (Dauncey et al. 2016; Rivera et al. 2014). Eight studies offered complete information on the botanical material and verified the *Avicennia* species by storing voucher specimens (Fang and Chen 2013; Gandomani and Malati 2014; Pereira et al. 2019; Kumar et al. 2016; Vellimalai et al. 2019; Victoria et al. 2012). Six studies reported the source of the *Avicennia* species but did not include voucher specimen documentation (Al-Jaghthmi et al. 2020; Mitra et al. 2022; Qurrohman et al. 2020; Rege et al. 2012; Sumithra et al. 2011; Sura et al. 2011). Two studies lacked adequate material information, as the source of the *Avicennia* species was not provided, and voucher specimens were absent (Okla et al. 2019; Yassien et al. 2021).

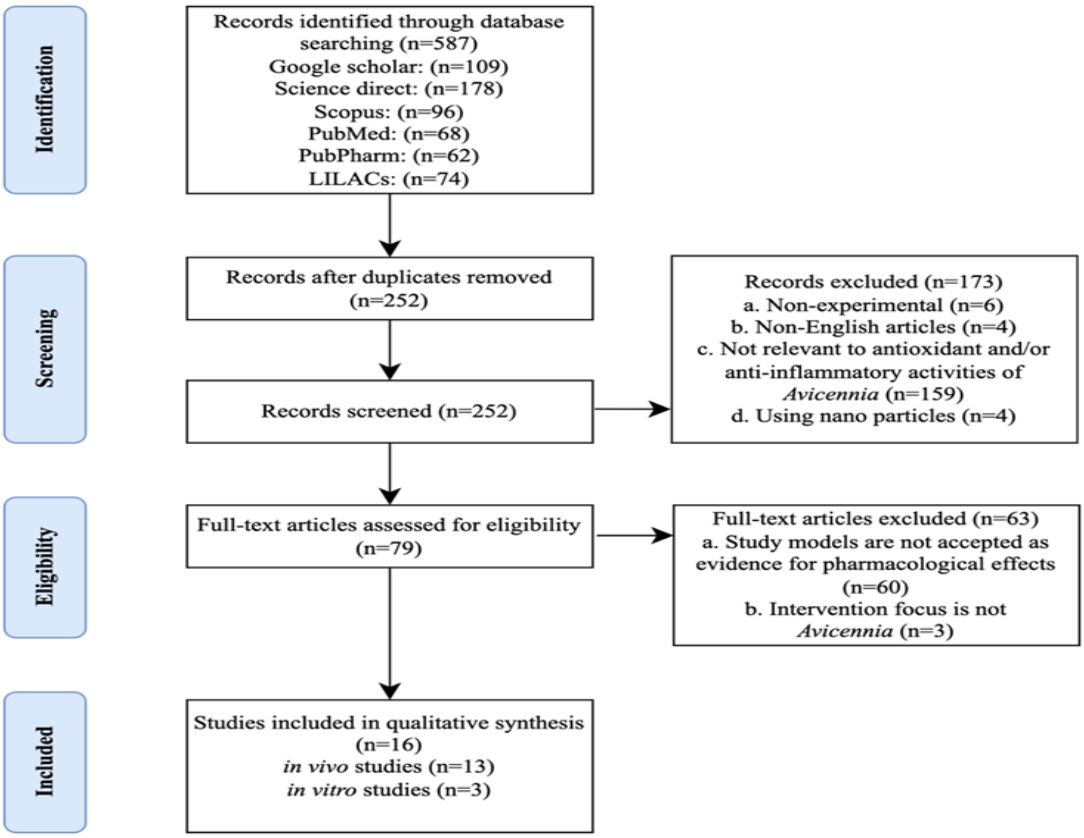

Figure 1 The flowchart depicts the articles selection process for this systematic review, in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Risk of bias within each study

Table 2 presents the risk of bias assessment for *in vivo* studies using SYRCLE's RoB tool. The analysis revealed that eight articles had an unclear potential for selection bias, as they only mentioned group division without specifying whether randomization was applied (Al-Jaghthmi et al. 2020; Mitra et al. 2022; Okla et al. 2019; Pereira et al. 2019; Sumithra et al. 2011; Sura et al. 2011; Kumar et al. 2016; Victoria et al. 2012). The other four articles mentioned that all animals were randomized but did not provide details about the randomization method used (Gandomani and Malati 2014; Sadoughi and Hosseini 2020; Yassien et al. 2021; Yi et al. 2020), and one article explained that the animals were randomized using the simple random sampling method (Vellimalai et al. 2019). The five articles were therefore evaluated as having a low risk of bias (Gandomani and Malati 2014; Sadoughi and Hosseini 2020; Yassien et al. 2021; Yi et al. 2020; Vellimalai et al. 2019). (1). Furthermore, all *in vivo* studies were deemed to have a low risk of bias regarding baseline characteristics, as the animals were either induced with an inflammatory condition or subjected to wounding prior to treatment (2). However, allocation concealment was deemed unclear in all *in vivo* studies because of a lack of sufficient information regarding the concealment procedure (3). Regarding performance bias, all studies were rated as having a low risk of bias since this type of bias is associated with random housing. The animals were kept under baseline conditions, including controlled temperature, and had access to water and food before the experiment conducted (4). However, regarding blinding (5), it was uncertain if the researchers managing the animals knew which groups were the control and which were the treatment groups. Both random outcome evaluation (6) and blinding (7)

were deemed uncertain in twelve articles, as the primary studies did not specify whether outcome analysis was conducted randomly or whether those analyzing the outcomes were blinded. One article stated that the outcome analysis was performed randomly (Sadoughi and Hosseini 2020). In assessing the risk of attrition bias (8), it was noted that none of the articles reported any animal loss during the experiment. No studies described outcomes related to the risk of reporting bias (9). Concerning other sources of bias (10), twelve articles were deemed to have a low risk of bias. One article was classified as unclear due to the absence of a normal control group of animals (Sura et al. 2011). In addition, three *in vivo* articles did not provide evidence of ethics committee approval (Gandomani and Malati 2014; Okla et al. 2019; Sumithra et al. 2011). The results of the risk of bias assessment for *in vitro* studies based on the OHAT guidelines (Table 3), indicate that the information bias of both articles was considered to probably have a low risk of bias (Qurrohman et al. 2020; Rege et al. 2012). This was due to the lack of information regarding the source of lymphocytes used in the studies, which is animal species as the source of lymphocytes not being clearly specified (Fang and Chen 2013). Two studies did not mention the statistical analysis methods used and the replication procedures used during the experiments (Qurrohman et al. 2020; Rege et al. 2012).

Table 2. Risk of bias in the thirteen in vivo studies included in the systematic review, assessed using SYRCLE's RoB tool.

Study	**Model**	**Selection Bias**			**Performance Bias**		**Detection Bias**		**Attrition Bias**	**Reporting Bias**	**Other**
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Sumithra (2011)	Paw edema	?	Y	?	Y	?	?	?	?	Y	Y
Sura (2011)	Gastric ulcer	?	Y	?	Y	?	?	?	?	Y	?
Rise (2012)	Ulcerative colitis	?	Y	?	Y	?	?	?	?	Y	Y
Gandomani (2015)	Arthritis	Y	Y	?	Y	?	?	?	?	Y	Y
Kumar (2016)	Liver damage	?	Y	?	Y	?	?	?	?	Y	Y
Barbosa (2019)	Gastric ulcer	?	Y	?	Y	?	?	?	?	Y	Y
Okla (2019)	Type 1 diabetes	?	Y	?	Y	?	?	?	?	Y	Y
Vellimalai (2019)	Liver damage	Y	Y	?	Y	?	?	?	?	Y	Y
Al-Jaghthmi (2020)	Type 2 diabetes	?	Y	?	Y	?	?	?	?	Y	Y
Sadoughi (2020)	Type 1 diabetes	Y	Y	?	Y	?	Y	Y	?	Y	Y
Yi (2020)	Vascular dementia	Y	Y	?	Y	?	?	?	?	Y	Y
Yassien (2021)	Hyperlipidemia	Y	Y	?	Y	?	?	?	?	Y	Y
Mitra (2022)	Paw edema	?	Y	?	Y	?	?	?	?	Y	Y

Y: Yes; N: No; ?: Unclear

Table 3. Risk of bias for *in vitro* studies based on OHAT guideline

Bias categories	**Questions**	**Fang and Chen (2013)**	**Rege et al. (2013)**	**Qurrohman et al. (2020)**
Selection bias	Was the dosage or exposure level properly randomized?	1	1	1
	Was the assignment to study groups effectively hidden from those involved?	1	1	1
Confounding bias	Did the study design or analysis consider key confounding and modifying variables?	1	1	1
	Did the researchers account for or control other exposures likely to introduce bias into the results?	1	1	1
Performance bias	Were the experimental conditions the same for all study groups?	1	1	1
	Did the researchers follow the study protocol as planned?	2	2	2
Detection bias	Were the individuals assessing outcomes unaware of the study group assignments or exposure levels?	1	1	1
	Were confounding variables measured consistently across all groups using valid and reliable methods?	3	3	3
	Is the exposure characterization trustworthy and reliable?	1	2	1
	Is the outcome assessment reliable and credible?	1	2	1
Selective reporting bias	Were all the measured outcomes fully reported? (Including authors' disclosure of conflicts of interest).	1	1	1
Information bias	Purity of chemical, number of replicates per group, report on data from positive controls, diagnostic or method to measure endpoint, statistical method	2	4	2

1: Definitely low risk of bias; 2: Probably low risk of bias; 3: Probably high risk of bias or Not Reported; 4: Definitely high risk of bias

Study characteristics

Species of *Avicennia* and part of the plant used

Four species of genus *Avicennia* were identified; *A. officinalis*, *A. marina*, *A. schaueriana*, and *A. alba*. *Avicennia marina* is the most widely studied species. The leaves are the most commonly used part of the plant in all the selected studies (Table 4). Therefore, leaves are also the part of *Avicennia* which most commonly consumed by the society.

Table 4. Articles on the anti-inflammatory and antioxidant potentials of the *Avicennia* genus.

First author	Species	Plant part	Solvent	Type of inflammation model/type of assay	Extract dose/ concentration	Control used	Results
Sumithra	*Avicennia officinalis*	Leaves	Methanol	Carrageenan, formalin, and adjuvant-induced paw edema	200, 400 mg/kg p.o	NC: 0.25% CMC. PC: Indomethacin 10 mg/kg	↓Paw edema
Sura	*Avicennia officinalis*	Leaves	Ethanol	Aspirin +pyloric ligation and indomethacin-induced ulceration on albino Wistar rats	250, 500 mg/kg p.o	NC: Normal saline. PC: Omeprazole 30mg/kg	↓Ulcer index
Rege	*Avicennia officinalis*	Leaves	Distilled water	$Fe2^{+}$-Ascorbic acid-induced lipid peroxidation on rat liver mitochondria *in vitro*	20, 200, 400 µg/ml	Butylated Hydroxyl Toluene	↓Lipid peroxidation inhibitory activity
Victoria	*Avicennia marina*	Whole plant	Methanol	Acetic acid induced ulcerative colitis on male BALB/c mice	10 mg/kg i.p	Sulfasalazine 100 mg/kg	↑SOD, ↑GPx, ↑GSH, ↓NO, ↓LPO, ↓wet colonic weights, ↓macroscopic inflammation score
Fang	*Avicennia marina*	Stem	Ethanol and distilled water	Concanavalin A and Lipopolysaccharide induced lymphocytes *in vitro*	50, 100, 200 µg/ml	*Not defined*	↑LPS-induced B lymphocyte proliferation
Gandomani	*Avicennia marina*	Leaves	Ethanol : Water (7:3)	Complete Freund's Adjuvant- induced arthritis on male Wistar rats	200, 400 mg/kg p.o	Ibuprofen 53 mg/kg	↓TNF-α, ↓IL-1β, ↓IL-6, and ↓Ankle diameter
Kumar	*Avicennia alba*	Leaves	Ethanol	Ethanol induced liver damage on male albino Wistar rats	100 mg/kg p.o	Silymarin 100 mg/kg	↑CAT, ↑SOD, ↑GPx, ↑GSH, ↓TBARS level
Pereira	*Avicennia schaueriana*	Leaves	Hexane, ethyl acetate, and ethanol	Ethanol induced- gastric ulcer on male Wistar male rats	50, 100, 200 mg/kg p.o	Pantoprazole 30 mg/kg	↓Ulcer index, ↓MPO, ↓NO
Okla	*Avicennia marina*	Leaves	Ethanol	Diabetic model on Swiss Webster mice	2mg/g p.o	NC: Phosphate buffered saline	↓NO, ↓H2O2, ↓MDA, ↑GSH, ↑CAT
Vellimalai	*Avicennia marina*	Leaves	Ethanol	Alcohol-induced liver toxicity on male albino Wistar rats	100 mg/kg p.o	NC: Normal saline. PC: Silymarin	↑CAT, ↑SOD, ↑GPx, ↑GSH, ↓LPO, ↓TBARS level
Al-Jaghthmi	*Avicennia marina*	Leaves	Distilled water	Diabetic model of male Wistar albino rats	400 mg/kg p.o	*Not defined*	↓MDA, ↑GSH, ↑CAT , ↑SOD
Qurrohman	*Avicennia marina*	Leaves	Chloroform: methanol (2:1, v/v)	WiDr colon cancer cells *in vitro*	60µg/ml	5-Fu	↓*P13k*, ↓*Akt1*, ↓*mTOR* ↑*p53*
Sadoughi	*Avicennia marina*	Leaves	Ethyl alcohol and distilled water (1:1, v/v)	Alloxan monohydrate-induced type 1 diabetic on male Wistar rats	50, 100, and 200 mg/kg p.o	*Not defined*	↓TNF-α, ↓IL-1β, ↓IL-6, ↑SOD, ↑CAT, ↑GPx
Yi	*Avicennia marina*	Fruit	Ethanol	Vascular dementia model on Sprague–Dawley rats	125, 500 mg/kg p.o	Oxiracetam 250 mg/kg/day	↓MDA, ↓NO, ↑GPx, ↑SOD
Yassien	*Avicennia marina*	Whole plant	Ethanol	Dexamethasone-induced hyperlipidemia on male albino rats	200, 400 mg/kg p.o	Atorvastatin 40 mg/kg	↓MDA, ↓NO
Mitra	*Avicennia alba*	Leaves	Methanol	Carrageenan induced paw edema on Swiss albino mice	200, 400, 500 mg/kg p.o	Indomethacin 10 mg/kg	↓Paw edema

CMC: Sodium carboxymethylcellulose; SOD: Superoxide dismutase; GPx; Glutathione peroxidase; GSH: Glutathione; NO: Nitric oxide; LPO: Lipid peroxidation; TBARS: Thiobarbituric acid reactive substances; LPS: Lipopolysaccharide; TNF: Tumor necrosis factor; IL: Interleukin; ELISA: Enzyme-linked Immunosorbent Assay; MPO: Myeloperoxidase; MDA: Malondialdehyde; CAT: Catalase; RT-PCR: Reverse Transcription Polymerase Chain Reaction; mTOR: mammalian Target of Rapamycin; NC: Negative control; PC: Positive control; p.o: per oral; i.p: intraperitoneal.

Extraction method and solvents used

Three extraction methods were identified: maceration, percolation, and centrifugal extraction. Four selected studies were found to use the percolation method (Fang and Chen 2013; Kumar et al. 2016; Sura et al. 2011; Vellimalai et al. 2019), one of which extracted *A. alba* leaves using percolation for 24 hr with ethanol as the solvent (Vellimalai et al. 2019). Three studies used centrifugation method (Victoria et al. 2012; Al-Jaghthmi et al. 2020; Yassien et al. 2021). Nine studies reported the use of the maceration method (Gandomani and Malati 2014; Sadoughi and Hosseini 2020; Sumithra et al. 2011; Rege et al. 2012; Okla et al. 2019; Pereira et al. 2019; Yassien et al. 2021; Yi et al. 2020; Qurrohman et al. 2020). Cold extraction (maceration) was the most commonly used method, while ethanol and methanol were the most commonly used solvents in selected studies.

Anti-inflammatory potentials of *Avicennia* plants

Avicennia modulates inflammatory cytokines production

Two studies evaluated the effect of *Avicennia* plants on cytokines production (Gandomani and Malati 2014; Sadoughi and Hosseini 2020). The cytokine outcome measurement technique used in the studies is enzyme-linked immunosorbent assay (ELISA). *Avicennia marina* inhibited the level of interleukin 6, interleukin 1β, and tumor necrosis factor-α dose-dependently in complete Freund's Adjuvant-induced rats. The group treated with the hydroalcoholic extract of *A. marina* demonstrated a notable decrease in cytokine production compared to the negative control group. This outcome was similar to the effect of the non-steroidal anti-inflammatory drug, ibuprofen, at a dosage of 53 mg/kg BW (Gandomani and Malati 2014). *Avicennia marina* also possessed anti-inflammatory effect by suppressing the same cytokines in alloxan monohydrate-induced type 1 diabetic Wistar rats in a dose-dependent manner (Sadoughi and Hosseini 2020).

Avicennia inhibits nitric oxide (NO) production

Five studies evaluated the effect of *A. marina* and *A. schaueriana* on the production of NO in *in vivo* model (Okla et al. 2019; Pereira et al. 2019; Victoria et al. 2012; Yassien et al. 2021; Yi et al. 2020). The extract of *A. marina* showed a suppressive effect on NO production in rats with hyperlipidemia induced by dexamethasone. The group treated with *A. marina* extract exhibited a significant decrease in NO production in a dose-dependent manner, compared to both the negative control group and the group receiving atorvastatin at a dose of 40 mg/kg BW (Yassien et al. 2021). The whole part of *A. marina*, administered at 10 mg/kg BW, decreased NO production in BALB/c mice with acetic acid-induced ulcerative colitis. Moreover, NO production in the *A. marina* group was lower than that in the group treated with sulfasalazine at 100 mg/kgBW (Victoria et al. 2012).

Avicennia induces lymphocytes proliferation

One study was found to prove the ability of *A. marina* in inducing lymphocyte proliferation. The acidic pectic polysaccharide in *A. marina*, HAM-3-IIb-II, was shown to significantly affect lipopolysaccharide-induced B lymphocyte proliferation at concentrations of 50, 100, or 200 µg/ml. However, HAM-3-IIb-II had minimal impact on concanavalin A mitogen-induced T lymphocyte proliferation at different concentrations when compared to the control group (Fang and Chen 2013). Lipopolysaccharide derived from the bacterial cell wall has been shown to impair the function of body organs and trigger oxidative stress by generating free radicals (Arab et al. 2023; Beheshtimanesh and Rajaei 2023).

Avicennia reduces inflammation in animal studies

Paw edema model is one of the most widely used *in vivo* models to study acute inflammation. Paw edema was measured using plethysmometer or caliper. *Avicennia officinalis* and *A. alba* exhibited anti-inflammatory potentials by significantly decreasing paw edema in both formalin and carrageenan-induced inflammation models (Mitra et al. 2022; Sumithra et al. 2011). *Avicennia marina* extract at 200 and 400 mg/kg BW dosage reduced the ankle diameter of complete Freund's adjuvant-induced arthritis on rats. The dosage of 400 mg/kg BW administered orally significantly restored the changes observed in arthritic rats to near-normal conditions (Gandomani and Malati 2014). Additionally, the administration of *A. schaueriana* and *A. officinalis* leaves extract to ethanol-induced ulcer rats model showed a reduction in the ulcer lesion index. Extract treatment at dosages of 250 and 500 mg/kg BW resulted in 18.7% and 34.4% inhibition of the ulcer index, respectively, in gastric ulcers induced by aspirin and pyloric ligation, measured by magnifying glass (Pereira et al. 2019; Sura et al. 2011).

Anti-inflammatory signaling pathway of *Avicennia*

One study evaluated the potential of *Avicennia* plant on inflammatory-related pathways. *Avicennia marina* was found to downregulate *PI3k*, *Akt1*, *Egfr*, and *mTOR* gene expressions, while upregulated *p53* gene expression in WiDr cells (human colon cancer cell line), measured by reverse transcription - Polymerase Chain Reaction (RT-PCR). Polyisoprenoid isolated from *A. marina* suppressed the expression of *PI3k*, *Akt1*, *Egfr*, and *mTOR* with the lowest *PI3k* gene expression ratio value to the internal standard (β-actin). Additionally, *A. marina* suppressed the cell cycle cancer phase G0-G1 phase and phase S. Polyisoprenoid and 5-Fu (positive control) enhanced the early phase of apoptosis in WiDr cell (Qurrohman et al. 2020).

Antioxidant potentials of *Avicennia* plants

Avicennia modulates enzymatic antioxidant production or activities

One study explained that the reduction of hydrogen peroxide (H_2O_2) production occurred after the administration of 2 mg/BW of *A. marina* to diabetic Webster mice. The alcoholic extract leaf extract of *A. marina* showed positive effects on the hepatic tissue pathology of diabetic mice. This was shown by the increase of antioxidants such as catalase (CAT) and glutathione (GSH) (Okla et al. 2019). Three *in vivo* studies also showed that CAT activity was affected by the administration of *A. marina* and *A. alba* (Al-Jaghthmi et al. 2020; Okla et al. 2019; Kumar et al. 2016). Four studies evaluated GSH levels in *in vivo* designs (Al-Jaghthmi et al. 2020; Okla et al. 2019; Kumar at al. 2016; Yassien et al. 2021). The activity of glutathione peroxide (GPx) was also induced by *A. marina* and *A. alba*. The administration of *A. marina* at dosages of 200 mg/kg BW and 400 mg/kg BW in diabetic mice resulted in greater induction of GPx activity compared to the control group treated with phosphate-buffered saline (Al-Jaghthmi et al. 2020; Okla et al. 2019). Furthermore, treatment with *A. marina* extract at dosages of 50, 100, and 200 mg/kg BW in type-1 diabetic rats led to a dose-dependent elevation in GPx levels (Sadoughi and Hosseini 2020). The GPx activity was also observed to increase in rats with ethanol-induced liver damage following the administration of 500 mg/kg BW *A. alba* extract (Kumar et al. 2016).

Avicennia inhibits lipid peroxidation

Avicennia officinalis and *A. marina* possess the ability to inhibit lipid peroxidation in *in vitro* and *in vivo* studies (Rege et al. 2012; Vellimalai et al. 2019; Victoria et al. 2012). The administration of aqueous extract of *A. officinalis* at 20, 200,

and 400 µg/mL concentration to Fe2+ and ascorbic acid-induced lipid peroxidation on rat liver mitochondria showed the lowering of lipid peroxidation (Rege et al. 2012). Lipid peroxidation was also reduced in rats with alcohol-induced liver damage after treatment with 100 mg/kg BW of *A. marina* ethanolic extract (Vellimalai et al. 2019). *Avicennia marina* inhibited lipid peroxidation by reducing malondialdehyde (MDA) levels in a diabetic rat model (Al-Jaghthmi et al. 2020; Okla et al. 2019), dementia rat model (Yi et al. 2020), and hyperlipidemia rats (Yassien et al. 2021). The phenylethanoid glycoside Marinoid J, isolated from *A. marina* fruit, significantly improved cognitive impairments in rats with vascular dementia. It protected hippocampal neurons by modulating proteins involved in oxidative stress, as evidenced by a 27.53% decrease in MDA levels within hippocampal tissue. This result was comparable to the group receiving oxiracetam as control (Yi et al. 2020). Furthermore, the MDA level in hyperlipidemia rats' liver was found to be low in treatment group receiving *A. marina* leaves extract. The MDA level was significantly different compared to the group that did not receive either the extract or the standard drug (Yassien et al. 2021). The ethyl acetate extract of *A. schaueriana* leaves, administered at dosages of 50, 100, and 200 mg/kg BW, demonstrated the ability to reduce myeloperoxidase levels in rat model of ethanol-induced gastric ulcers (Pereira et al. 2019). Methods used to measure the antioxidant parameter outcomes are enzymatic antioxidant assay and ELISA.

Discussion

Empirically for many years, *Avicennia* plants have been used as medicinal plants. Several active compounds found in *Avicennia* species have been widely shown to have therapeutic benefits including anti-inflammatory and antioxidant potentials (ElDohaji et al. 2020; Ibrahim et al. 2022; Mangrio et al. 2016). This systematic review evaluates the existing literature on the potentials of *Avicennia* plants in *in vitro* and *in vivo* studies, specifically focusing on their anti-inflammatory and antioxidant properties from biomolecular point of view. No clinical studies on humans were found, although it is empirically often used by coastal communities to treat various diseases. *In vitro* studies have highlighted the positive effects of *Avicennia* in improving oxidative status and inflammation in various diseases. Furthermore, nearly all animal studies have demonstrated that *Avicennia* and its active components have beneficial effects on inflammatory, oxidative, clinical, and immunological parameters. None of the studies included in the selection reported quality control data, as none of the *Avicennia* preparations were found to comply with the pharmacopeia monograph. Quality control in herbal medicines is essential to ensure their safety. Herbal medicines are commonly used, and there is a common belief among the public that natural products are free from contaminants, safe, and non-toxic. This misconception can lead to improper use, which may result in poisoning and serious health issues (Mukherjee 2019; Teschke and Eickhoff 2015).

Evaluating the quality of medicinal plants can be achieved by identifying chemical markers within a sample. Qualitative chemical evaluation involves identifying and characterizing the secondary metabolites of medicinal plants using various analytical methods. Phytochemical screening methods involve botanical identification, extraction using suitable solvents, purification, and characterization of active compounds with pharmaceutical relevance (Ingle et al. 2017). Chromatographic techniques such as thin-layer chromatography (TLC)/high-performance TLC (HP-TLC) and high-performance liquid chromatography (HPLC) are widely utilized for identifying and evaluating the quality of secondary

metabolites in medicinal plants. High-performance size-exclusion chromatography (HP-SEC), also known as gel permeation chromatography (GPC) is another example of chromatographic technique that is widely used for determining the molar mass and size distribution of biopolymers in aqueous or organic solvents. These methods provide both quantitative profiles and characteristic qualitative data of the metabolites. Spectroscopic techniques, such as IR, UV, and nuclear magnetic resonance (NMR) enable the quantification of multiple compounds with similar UV absorbance. These methods offer more comprehensive analysis of traditional medicines compared to the quantification of a single compound (Upton et al. 2020). Another method that is also a top-tier technique used in research, pharmaceuticals, and quality control for herbal medicines is quadrupole time-of-flight mass spectrometry (Q-TOF MS). The "quadrupole" part is a mass filter that selects ions based on their mass-to-charge ratio, and "time-of-flight" (TOF) measures the time ions take to reach the detector. This combination allows for high-resolution mass spectrometry that provides detailed molecular identification, structural information, and quantitative analysis of compounds (Allen and McWhinney 2019). Three studies reported the chemical analysis of *Avicennia* species using methods, such as HPLC, HPSEC, C NMR, FT-IR spectroscopy, and UPLC-DAD-QTOF-MS/MS (Fang and Chen 2013; Pereira et al. 2019; Yi et al. 2020).

In the present review, it was found that leaf of mangroves is the most commonly used part. The leaves are also the most frequently consumed part of *Avicennia* by society (Kusmana 2018; Kusmana and Sukristijiono 2016). Empirically, *Avicennia* leaves are safe for consumption. This is supported by toxicological assessments conducted on *Avicennia* plants. The LD50 analysis of *A. marina* leaf extract indicated a lethal dose of 2500 mg/kg BW. No behavioral changes or mortality were observed at doses of 500 and 1000 mg/kg BW. Furthermore, there were no significant differences in biochemical parameters (including SGOT, SGPT, ALP, sugar, and urea) between the control group and the extract group (Beula et al. 2012). *Avicennia* also demonstrated no toxic effects on the normal HEK-293 T cell line (Sukhramani and Patel 2013). The ethanolic leaf extract of *A. officinalis* showed no toxicity in Wistar albino rats when administered at dosages of 250 and 500 mg/kg BW (Sura et al. 2011).

The process of isolating compounds from natural sources targets the isolation of secondary metabolites because these compounds are believed and have been proven to provide health benefits. The goal of extracting natural products is to isolate the chemical compounds contained within the natural source (Wahyuningsih and Rakhwamati 2024). Maceration is the most commonly used method for isolating secondary metabolites in the *Avicennia* plants found in this study. Maceration is a method of separating compounds by soaking them in a solvent at a specific temperature (Karina et al. 2016). Soaking plant samples in a specific organic solvent causes the breakdown of cell walls and membranes due to the pressure difference between the inside and outside of the cell, allowing secondary metabolites within the cytoplasm to dissolve into the solvent (Patil 2020). One of the advantages of maceration is that natural materials do not undergo heating process, preventing degradation or damage of secondary metabolites (Azwanida 2015; Susanty 2016).

Several possible mechanisms may explain the beneficial effects of *Avicennia* plants in alleviating inflammatory diseases. *Avicennia* suppressed the production of pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α (Gandomani and Malati 2014; Sadoughi and Hosseini 2020). The increased generation and activity of pro-inflammatory cytokines promote immune activation and inflammation (Muzamil et al. 2021). The activation of the immune

system, inflammation, and oxidative stress are key factors in the onset and progression of various diseases (Abbas et al. 2015). *Avicennia* is shown to maintain its anti-inflammatory effects by interrupting pro-inflammatory pathways such as *Akt-1/mTOR* (mammalian Target of Rapamycin) pathway (Figure 2). This pathway is an important signaling cascade that regulates cell survival, growth, metabolism, and inflammation. The activation of *Akt1/mTOR* pathway includes three steps: the activation of Phosphoinositide 3-Kinases (*PI3Ks*), the activation of *Akt*, and the activation of *mTOR*. These steps lead to protein synthesis, cell metabolism, and immune function (Hawkins and Stephens 2015; Tilley et al. 2022). Considering that the *PI3K/Akt* and *mTOR* pathways are also correlated with the activation of other signaling pathways such Mitogen-Activated Protein Kinase (MAPK) and Nuclear Factor Kappa B (NF-κB) pathways (Acosta-Martinez and Cabail 2022; Torrealba et al. 2020), it is possible that *Avicennia* species may also influence these pathways.

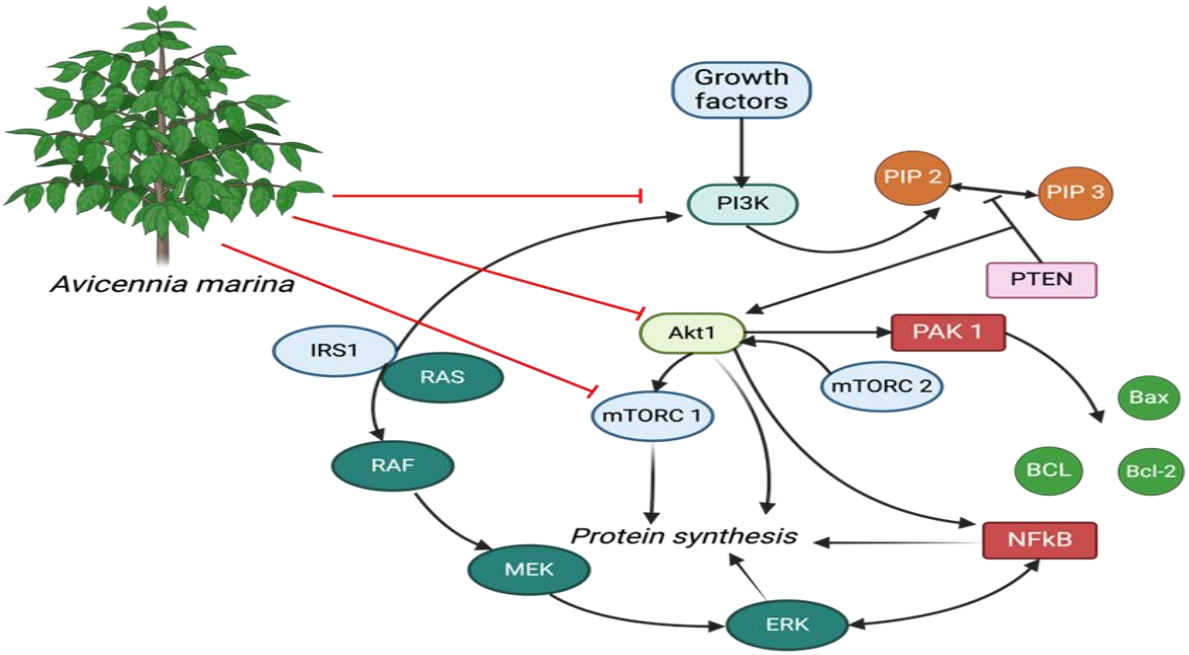

Figure 2. Suggested anti-inflammatory pathway of *Avicennia marina*. (PIP: Phosphatidylinositol; PTEN: Phosphatase and tensin homolog; PAK: p21-activated kinase; PI3K: Phosphatidylinositol 3-Kinase; IRS: Insulin receptor substrate; RAS: Rat sarcoma; RAF: Rapidly accelerated fibrosarcoma; MEK: mitogen-activated protein kinase; ERK: Extracellular signal-regulated kinase; NF-kB: Nuclear factor kappa B; BCL: B-cell lymphoma; Bax: Bcl-2-associated X protein).

Additionally, the *Akt-1/mTOR* pathway not only plays a role in the inflammatory process, but also contributes to cancer development through the inhibition of apoptosis. Its persistent activation gives cancer cells a survival advantage and promotes growth, making it a key target for anti-cancer therapies (Glaviano et al. 2023; Manning and Toker 2017; Peng et al. 2022). *Avicennia* leaves are known to be toxic to cancer cells. Polyisoprenoids extracted from *A. marina* reduced the expression of *PI3k*, *Akt1*, *Egfr*, and *mTOR* gene expressions in WiDr cells (human colon cancer cell line) (Qurrohman et al. 2020). *A. marina* leaf extract was known to be cytotoxic to HeLa cell (cervical cancer cell) viability with IC50 value of 1115.345 g/ml (Rahman 2021).

The anti-inflammatory potentials of *Avicennia* are further supported by studies demonstrating its inhibitory effects on NO production (Okla et al. 2019; Pereira et al. 2019; Victoria et al. 2012; Yassien et al. 2021; Yi et al. 2020). Nitric oxide is an inflammatory mediator generated by

activated macrophages during the inflammatory response. This is produced by inducible nitric oxide synthase (iNOS) during inflammation. Furthermore, NO reacts with superoxide (O_2^-) to form peroxy-nitrite ($ONOO^-$), a highly reactive molecule that contributes to oxidative stress, cell damage, and apoptosis. Nitric oxide physiologically functions both as an anti-inflammatory agent and pro-inflammatory mediator. The primary effects of NO are mediated through the production of cyclic guanosine monophosphate. It plays a role in innate immunity as a toxic agent against pathogens but can also influence or control the death and function of host immune cells, thereby modulating adaptive immunity (Papi et al. 2019; Sharma et al. 2007). Figure 3 summarizes the mechanism of *Avicennia* plants in inhibiting NO production.

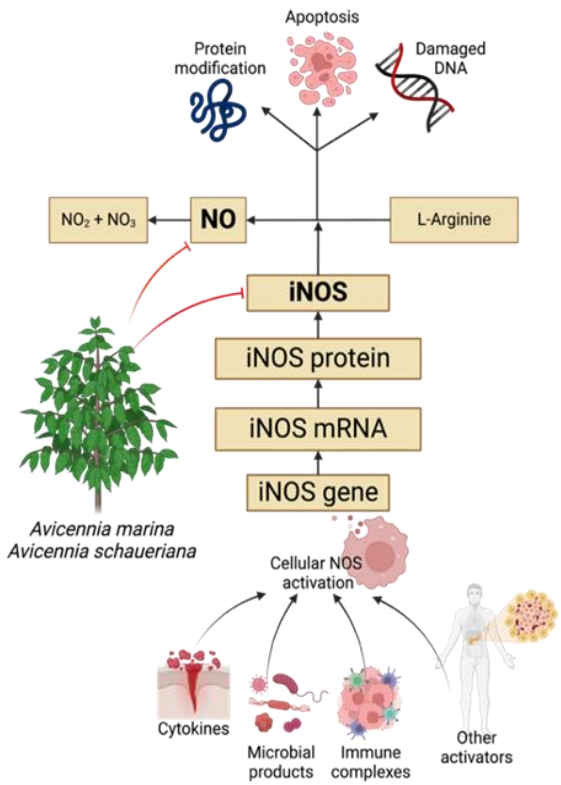

Figure 3. *Avicennia* plants inhibit nitric oxide (NO) production. (NO: Nitric oxide; iNOS: inducible nitric oxide synthase; mRNA: messenger ribonucleic acid).

The immunomodulatory effect of *Avicennia* plants represent another potential mechanism through which may impact inflammatory diseases and oxidative stress. Studies suggest that *A. marina* can boost the immune response, especially by enhancing the activity of B lymphocytes (Fang and Chen 2013). Lymphocytes are essential components of adaptive and innate immunity (Hira 2022; Vivier et al. 2018). They combat infections, regulate immune responses, and contribute to both acute and chronic inflammation. Activated lymphocytes release pro-inflammatory cytokines that enhance immune cells recruitment and promote further inflammation (Abbas et al. 2015). However, this result requires further in-depth research to determine the extent to which, *Avicennia* can modulate the immune system, particularly under more severe infection conditions such as tuberculosis, HIV, or coronaviruses. For example, the herb *Phyllanthus niruri*, well known for its immunomodulatory properties, has been proven to possess immunomodulatory activity in tuberculosis infection, as evidenced by increased proliferation of mononuclear cells, enhanced phagocytic activity, and elevated nitric oxide release by macrophages (Putri et al. 2018).

Excessive free radicals produced from the destruction of microorganisms by macrophages, as part of the immune response, can further lead to lipid peroxidation. Malondialdehyde (MDA), a key by-product of lipid peroxidation, interacts with lipids, proteins, and nucleic acids—leading to enzyme dysfunction, structural damage, membrane instability, and ultimately, cell death (Ayala et al. 2014; Forrester et al. 2018). High concentrations of MDA indicate oxidative processes in cell membranes. Erythrocyte and plasma MDA levels have been used as markers of tissue damage caused by free radicals in *in vivo* studies. Chemically, MDA is stable, making it more commonly used as an oxidative stress marker compared to other compounds (Grotto et al. 2009). Naturally, the human body has an endogenous antioxidant system to

neutralize and scavenge free radicals, such as catalase (CAT) and superoxide dismutase (SOD). Superoxide dismutase acts by converting O^{2-} into H_2O_2 and oxygen, which are subsequently detoxified by CAT and glutathione peroxidase (GPx). Higher SOD activity reduces ROS levels, lowering oxidative stress. Meanwhile, GPx uses reduced glutathione (GSH) to convert H_2O_2 into water (H_2O), preventing ROS build-up. Thus, low GSH/GPx levels causing the increase of oxidative stress (Ighodaro and Akinloye 2018; Zhao et al. 2019). An excessive production of ROS can result in the oxidation of proteins (Nouri et al. 2021). The ROS are primarily generated in intracellular organelles such as the mitochondria, endoplasmic reticulum, peroxisomes, nucleus, cytosol, and the extracellular matrix (Javaid and Jabeen 2025).

The antioxidant potentials of secondary metabolites in *Avicennia* plants may be attributed to the following mechanisms; phenolics donate hydrogen atoms or electrons to neutralize free radicals, thereby stopping chain reactions causing oxidative damage to cells. Some phenolics (like flavonoids and tannins) can chelate metal ions like Fe^{2+} and Cu^{2+}, which prevent radical generation. Additionally, phenolics can enhance the activity of various antioxidant enzymes (Pannucci et al. 2023; Zhang et al. 2022). In the present review, *Avicennia* plants are shown to enhance the production of GSH, SOD, GPx, and CAT, while simultaneously suppressing the production of NO, lipid peroxidation, MPO, MDA, and H_2O_2 in *in vitro* and *in vivo* studies (Al-Jaghthmi et al. 2020; Okla et al. 2019; Sadoughi and Hosseini 2020; Vellimalai et al. 2019; Victoria et al. 2012; Yassien et al. 2021; Yi et al. 2020).

Inflammation and oxidative stress are closely linked, with a rise in one often triggering an increase in the other (Abbasnia et al. 2024). Figure 4 implies that the anti-inflammatory and antioxidant potentials of *Avicennia* species are closely interconnected in pathophysiological processes. The antioxidant properties of *Avicennia* are demonstrated through the inhibition of lipid peroxidation and myeloperoxidase, as well as the regulation of antioxidant production or activity and glutathione-related parameters. Additionally, the immunomodulatory effects of *Avicennia* include suppressing the production of cytokines, stimulating lymphocyte proliferation, and reducing clinical symptoms in animal models. The inflammatory signaling pathways affected by *Avicennia* involve the induction of the *PI3K/ mTOR* pathway. Studies on *Avicennia* species have highlighted their notable anti-inflammatory and antioxidant properties, which support a range of therapeutic uses.

The limitation of this review is the inconsistent presentation of information across studies, particularly in those with "unclear" or "high" risk of bias in their design. This raises the possibility that some findings from the included studies may have been misinterpreted by the authors. Challenges in accessing specific data were not entirely accounted for, and not all journals offer consistent or comprehensive information. Limited studies were found to isolate active compounds from *Avicennia* plants using a phytochemical approach. Therefore, further isolation of the secondary metabolites contained in *Avicennia* is still needed, such as utilizing bioassay-guided isolation approach along with the signaling pathways involved. Future clinical trials on human with clearly-defined symptoms are essential to assess the therapeutic potential of the *Avicennia* genus, as animal studies cannot fully replace clinical trials in determining therapeutic efficacy. Additionally, it is crucial to investigate and address potential adverse interactions in polypharmacy and polyherbal formulations involving *Avicennia*.

Avicennia species, particularly *Avicennia marina*, *Avicennia alba*, *Avicennia schaueriana*, and *Avicennia officinalis*, have been reported to possess

anti-inflammatory and antioxidant properties in preclinical studies, supporting their traditional use in folk medicine for treating inflammation. Additional preclinical research, including a deeper investigation into the mechanisms of action and pharmacokinetic studies on bioactive compounds isolated from *Avicennia* plants is needed before advancing to clinical trials. *Avicennia* genus holds significant potential for development as a medicinal agent for immunomodulatory supplements targeting oxidative stress and inflammation.

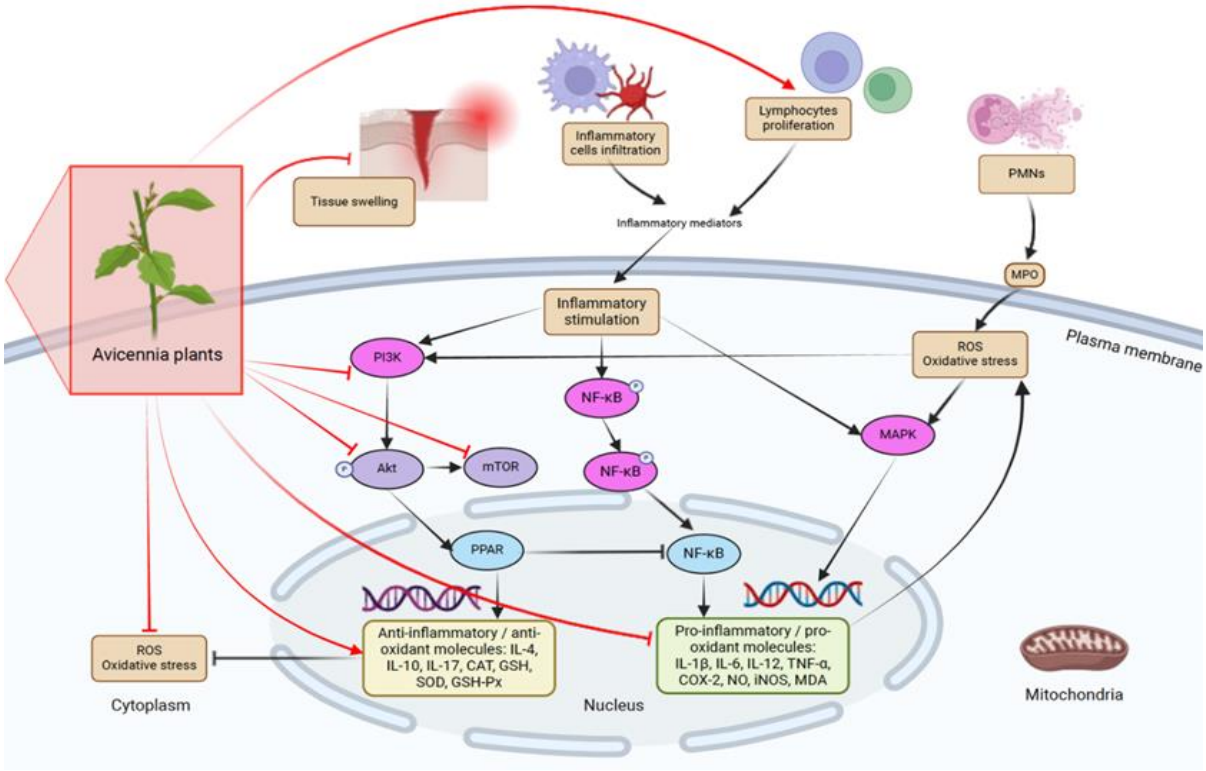

Figure 4. A schematic illustrating signaling pathways affected by *Avicennia* species. (PMN: Polymorphonuclear; NF-kB: Nuclear factor kappa B; PPAR: Peroxisome proliferator-activated receptor; *mTOR*: mammalian target of rapamycin; IL: Interleukin; CAT: Catalase; GSH: Glutathione; SOD: Superoxide dismutase; GSH-Px: GSH-Peroxidase; TNF: Tumor necrosis factor; COX: Cyclooxygenase; NO: Nitric oxide; iNOS: inducible nitric oxide synthase; MDA: Malondialdehyde).

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Conflicts of interest

The authors have declared that there is no conflict of interest.

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