REVIEW ARTICLE

Agarwood's Role in Inflammatory-related Conditions: A Systematic Review of Animal Models

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ABSTRACT

Agarwood (*Aquilaria* spp.) is a resinous wood traditionally used in various medicinal systems across Asia for treating inflammation-related ailments. Despite its longstanding ethnopharmacological use, scientific validation of its anti-inflammatory effects remains fragmented. This scoping review aims to systematically evaluate and synthesize current evidence from animal studies investigating the anti-inflammatory potential of agarwood. A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science. Inclusion criteria focused on original animal studies assessing the anti-inflammatory effects of agarwood extracts, essential oils, or derivatives. Data on study design, animal models, agarwood species, treatment dosage, duration, biomarkers, and outcomes were extracted and summarized narratively due to methodological heterogeneity. Eight studies met inclusion criteria, involving models of inflammation-related conditions such as pain, neuroinflammation, gastrointestinal injury, cancer, and toxicity. Agarwood treatment consistently reduced pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α), modulated oxidative stress markers (e.g., NO, SOD, GSH), and regulated signalling pathways including NF-κB, p38 MAPK, and Nrf2–ARE. Notably, improvements were observed in behavioural and histological outcomes across models, with evidence of dose-dependent effects in several studies. In conclusion, preclinical evidence supports agarwood's broad-spectrum anti-inflammatory and antioxidant properties across multiple organ systems. These findings provide mechanistic insights and a scientific basis for its traditional use. However, variability in species, extraction methods, and study designs highlights the need for standardised protocols and clinical validation to advance agarwood as a potential therapeutic agent.

Keywords:
agarwood, Aquilaria, anti-inflammation, inflammatory, oxidative, animal model

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INTRODUCTION

Agarwood (*Aquilaria* spp., *Thymelaeaceae*) is a highly valued, fragrant, resinous wood with a history dating back to approximately 1400 BCE. Revered in religious texts, classical literature, cultural rituals, and historical trade, agarwood is most prized for the aromatic heartwood formed, which forms in response to injury and emits a distinctive scent when burned.[1] While widely known for its role in perfumery, agarwood is also used in wood chips, carvings, resins, and traditional medicine.[2]

Due to high demand and overharvesting, wild agarwood populations have declined significantly. The International Union for Conservation of Nature (IUCN) has classified several species as threatened, including *Aquilaria malaccensis* (Critically Endangered), *A. microcarpa* (Endangered), *A. sinensis* (Vulnerable), and *A. subintegra* (Data Deficient).[3] Consequently, international trade is regulated under the Convention on International Trade in Endangered Species (CITES), spurring interest in sustainable cultivation and alternative products such as seedlings, inducers, fertilizers, hydrosols, and leaf-based extracts.

Traditionally, agarwood has held therapeutic value in Chinese, Ayurvedic, Unani and Malay medicine for ailments including coughs, rheumatism, jaundice, and postpartum disorders, often serving as stimulant, tonic,

and carminative agent.[2,4] Historical medical texts such as Avicenna's *Canon of Medicine* and China's *Compendium of Materia Medica* document its medicinal applications.[5,6] In Malay traditional medicine, *A. malaccensis* (locally known as *kayu gaharu* or *kayu gaharu lempong*) is used in boiled preparations and liniments for treating pain, inflammation, and female reproductive conditions.[2] Historical Malay medical manuscripts such as *Kitab Tib MSS 2515*, *MSS 2999 Kitab Tib: Pandangan dan Tafsiran Perubatan Moden Terhadap Manuskrip Perubatan Melayu* (Modern Medical Perspectives and Interpretations of Malay Medical Manuscripts), and *Kitab Tib Muzium Terengganu* document its therapeutic significance and integrate spiritual practices such as Quranic recitations alongside herbal remedies, underscoring agarwood's deep cultural and medicinal significance in Malay ethnomedicine.[7]

Recent research has focused on the phytochemical constituents of agarwood and their pharmacological potential, particularly anti-inflammatory effects.[2,8,9] Inflammation is a vital physiological defence mechanism through which the immune system identifies and eliminates harmful or foreign stimuli to promote tissue repair and healing.[10,11] However, chronic or dysregulated inflammation contributes to numerous diseases, including cancer, atherosclerosis, rheumatoid arthritis, and sepsis.[12,13]

Despite an extensive body of research particularly those using *in vitro* approach, the anti-inflammatory effects of agarwood remain inconclusive due to variability in study design, extraction methods, and bioactive compound characterization. While *in vitro* models offer efficiency and ethical advantages, they lack the complexity of whole organisms.[14] Animal models, by contrast, provide essential insights into systemic effects and therapeutic relevance.[15] Nevertheless, animal-based studies on agarwood remain limited, hindering translational progress towards developing a modern therapeutic agent. Therefore, this scoping review aims to assess existing animal studies investigating agarwood's anti-inflammatory effects, elucidate underlying mechanisms, and provide a scientific foundation for the development of agarwood-derived therapeutic agents.

MATERIALS AND METHODS

This review was conducted in accordance with the framework established by a previous benchmark study and adhered to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines.[16,17] The methodology consisted of the following steps: (1)identifying the research questions, (2)identifying relevant studies, (3) selecting studies, (4)charting the data, and (5)collating, summarising, and reporting the results.

Identification of research questions

The central research question guiding this review was: "What are the effects of agarwood on inflammation-related conditions in animal models?" This broad approach includes studies in which agarwood was evaluated as a potential therapeutic agent for inflammation-related conditions, ranging from mild inflammation to more severe diseases such as arthritis and cancer.[2,13]

Identification of relevant studies

A systematic literature search was conducted on three electronic databases: PubMed, Scopus, and Web of Science. No restriction was set on publication year, and all available studies up to the date of the search were considered. The included studies retrieved spanned from 2003 to 2023. Several keyword combinations were used to ensure comprehensive coverage of relevant studies. For PubMed, the search string was: "((agarwood OR agilawood OR aloeswood OR eaglewood) AND (cancer OR (Inflammation OR inflammatory OR antiinflammatory OR anti-inflammatory)))". The same search string was applied in Scopus. For Web of Science, the following string was used: "((ALL=(agarwood OR agilawood OR aloeswood OR eaglewood)) AND ALL=(cancer OR inflammation OR inflammatory OR antiinflammatory OR anti-inflammatory))".

Article selection process

The Endnote software (version 20.4.1, Clarivate, London, UK) was used to sort the references and eliminate

duplicates, followed by a manual verification step. Following initial screening by title and abstract, full-text articles were assessed for eligibility using predefined inclusion and exclusion criteria. The inclusion and exclusion criteria are listed in Table I.

Table I: Article identification and selection was based on these defined inclusion-exclusion criteria.

Criterion	Characteristics
Inclusion	Original/research articles published in peer-reviewed journals
	Studies that included animal models
	Studies using any type of agarwood as sample
	Studies which were compliant to animal study ethics
	English written articles
Exclusion	Reviews, perspectives, commentaries, letters to the editor, case study, proceedings, early access type articles, books and book chapters
	In vitro only articles
	Out of scope articles
	Non-English written articles

Only peer-reviewed, English-language original research articles involving animal models and agarwood samples were included. Reviews, commentaries, conference abstracts, *in vitro*-only studies, and non-English articles were excluded. A manual search of references from selected articles was also conducted to identify any additional relevant studies. Discussions were held between the authors to resolve any disagreements and to finalise the selection of articles.

Data charting and quality assessment

Data were extracted into a standardised Excel spreadsheet, capturing details such as authorship, publication year, animal model, disease type, agarwood sample, dosage, administration route, duration, and outcomes. Study quality was assessed using the ARRIVE guidelines (Animal Research: Reporting of *In Vivo* Experiments), with each criterion scored from 0 (inaccurate) to 2 (accurate). Risk of bias was evaluated using the SYRCLE tool (Systematic Review Centre for Laboratory Animal Experimentation), focusing on elements like randomisation, blinding, and selective reporting.

Collating, summarizing and reporting the results

Due to substantial heterogeneity in study designs, disease models, intervention protocols, and reported outcomes, a meta-analysis was not feasible. Instead, a scoping review approach was employed to map the existing evidence and summarise the progress in the field. Findings were synthesized narratively, with studies grouped by disease category and discussed in relation to agarwood dosage, treatment duration, affected cytokines, and relevant signalling pathways.

RESULTS

Article identification and selection

From a total of 231 articles identified through PubMed (47), Scopus (94), and Web of Science (90), 110 duplicates were removed. Title and abstract screening were conducted on the remaining 121 articles, of which 111 were excluded based on the inclusion and exclusion criteria. Ten articles proceeded to full-text screening, after which two non-English articles and one with questionable methodology were excluded. One additional article was included via manual reference checking, resulting in a final selection of eight studies. The selection process is illustrated in Figure 1.

A total of eight animal studies were included in this review. Considerable variation was noted in the reported *Aquilaria* species, extraction methods, sample applied on animal model, and inoculation status. In several studies, species identification or inoculation status was not provided, which may affect reproducibility, and the phytochemical consistency of the extracts used. These details are summarized in Table II.

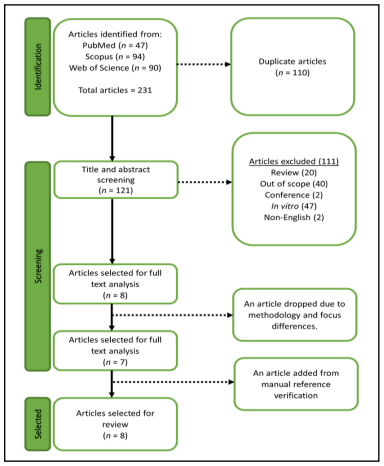


Figure 1: Summary of process of article identification, screening, and selection.

Quality and risk-of-bias assessment

All eight included studies scored above 80 % on the ARRIVE checklist, indicating high reporting quality as shown in Table III. Consistently high scores were seen in areas such as study design, ethical statement, and

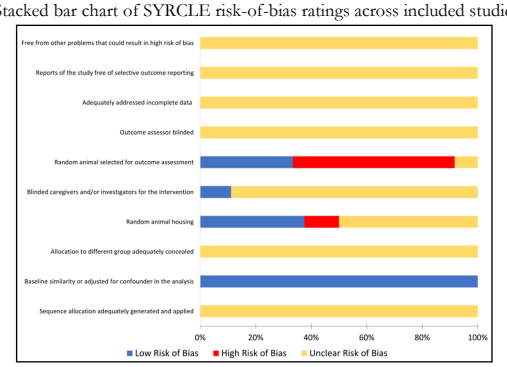
outcome reporting. However, the implementation of blinding was rarely reported, with only one study referencing it, and even then, the application was unclear. This resulted in a blinding score of just 6.25% across the included studies. Risk-of-bias assessment using the SYRCLE tool showed that while baseline group similarity (n=8;100%) and outcome measures were generally well-handled, most studies lacked detailed reporting on randomisation, allocation concealment, and selective outcome reporting, as illustrated in Figure 2.

Table II: Aquilaria species, extraction methods, and inoculation status reported in the included studies.

Included articles	Aquilaria species	Extraction method	Sample applied on animal model	Inoculation status
Article 1[18]	Sinensis	2-h reflux with ethanol (50% v/v).	Extract was dissolved in dimethylsulfoxide (DMSO)	NR
Article 2[18]	Crassna	Hydrodistillation (48h)	Essential oil and essential oil extract (suspended in 1% Tween-80)	NR
Article 3[19]	Not specified	Hydrodistillation (12h)	Essential oil suspended in 1% Tween-80	Artificial inoculation reported
Article 4[20]	Agallocha	Methanol extraction (3×1h)	Extract was dissolved in distilled water	NR
Article 5[21]	Not specified	Absolute ethanol extraction (2 days)	Ethanolic extract.	NR
Article 6[9]	Not specified	95% ethanol extraction (2h) + reflux (3×1h)	Alcoholic extract.	Artificial inoculation reported
Article 7[22]	Not specified	95% ethanol extraction (2h) + reflux (2 ×1h)	Ethanolic extract.	Artificial inoculation reported
Article 8[23]	Crassna	Ethanol extraction	Ethanolic extract.	NR

*NR-not reported

Figure 2: Stacked bar chart of SYRCLE risk-of-bias ratings across included studies.



Anti-inflammatory effects of agarwood in animal models

Eight studies evaluated the anti-inflammatory effects of agarwood using various animal models involving conditions such as analgesia, toxicity, cancer, psychiatric disorders, neurodegenerative diseases, and gastrointestinal injury. Agarwood was administered in different forms including ethanolic extracts, essential oils, and powdered heartwood from species such as A. crassna, A. sinensis, and A. agallocha. Details on experimental designs, dosages, durations, and outcomes are summarized in Table IV.

Despite variability in disease models, sample types, and experimental protocols, consistent reductions in inflammatory readouts were reported. The following subsections outline the pharmacological effects and molecular mechanisms identified across these studies.

Analgesic and anti-inflammatory effects

The earliest study reviewed demonstrated the analgesic and anti-inflammatory effects of A. sinensis leaf ethanolic extract in mice. Using inflammatory models such as writhing, hot plate, ear and paw oedema, and leukocyte migration, the extract (424 and 848 mg/kg) showed significant in vivo activity.[8] These findings were supported by in vitro LPS-stimulated assays (50-200 µg/mL), marking one of the first studies to validate agarwood's traditional use through both in vivo and in vitro approaches.

Toxicity and anti-cancer effects

Additionally, article 2 assessed the safety and anticancer potential of *A. crassna* essential oil (EO) in Swiss mice.[18] Acute (2000 mg/kg) and sub-chronic (100 and 500 mg/kg for 28 days) toxicity tests showed no treatment-related mortality. In tumour-xenografted mice (HCT 116 model), EO treatment significantly reduced tumour size and vascularization, with histological evidence of necrosis and decreased cell density.

Article 5 examined the protective effects of agarwood chip ethanolic extract (100 mg/kg daily for 35 days) against methanol-induced brain and liver toxicity.[21] Detoxification of alcohols, xenobiotics, and drugs elevates reactive oxygen species (ROS), contributing to oxidative stress, inflammation, apoptosis, and tissue damage.[24] In this case, methanol-exposed models increased levels of oxidative and inflammatory markers, including nitric oxide (NO), malondialdehyde (MDA), acetylcholinesterase (AChE), cyclooxygenase-2 (COX-2), lipoxygenase (LOX), caspase-3, tumour necrosis factor-alpha (TNF-α), monoamine oxidase (MAO), and DNA fragmentation. Agarwood treatment restored these biomarkers to near-control levels, suggesting its utility in mitigating ROS-driven tissue damage in hepatic and neurodegenerative contexts.[25]

Table III: Assessment of agarwood animal model inflammatory related **study using ARRIVE framework.**

ARRIVE Framework	Article 1[8]	Article 2[18]	Article 3[19]	Article 4[20]	Article 5[21]	Article 6[9]	Article 7[22]	Article 8[23]	Framework total percentage (%)
Abstract	2	2	2	2	2	2	2	2	100
Introduction or background	2	2	2	2	2	2	2	2	100
Objectives	2	2	2	2	2	2	2	2	100
Ethical statement	2	2	2	2	2	2	2	2	100
Housing and husbandry	2	2	2	2	2	2	2	2	100
Animal care and monitoring	2	2	2	2	2	2	2	2	100
Interpretation or scientific implications	2	2	2	2	2	2	2	2	100
Generalizability or translation	1	1	1	1	1	1	1	1	50
Protocol registration	1	1	1	1	1	1	1	1	50
Data access	2	1	1	1	1	1	2	1	62.5
Declaration of interests	2	2	2	2	2	2	2	2	100
Study designs	2	2	2	2	2	2	2	2	100
Sample size	2	2	2	2	2	2	2	2	100
Inclusion and exclusion criteria	1	1	1	1	1	1	1	1	50
Randomization	2	1	2	1	2	1	2	1	75
Blinding	0	0	1	0	0	0	0	0	6.25
Outcome measures	2	2	2	2	2	2	2	2	100
Statistical method	2	2	1	2	2	2	2	1	87.5
Experimental animals	2	2	2	2	2	2	2	2	100
Experimental procedures	2	2	2	2	2	2	2	2	100
Results	2	2	2	2	2	2	2	2	100
Article total percentage (%)	88.1	83.33	85.71	83.33	85.71	83.33	88.1	80.95	

Stress-related disorders

In addition to its effects on systemic toxicity and tumour growth, agarwood has also shown promise in modulating central nervous system inflammation. Article 3 demonstrated that Aquilaria EO exhibits anxiolytic and antidepressant effects in a restraint stress-induced mouse model. EO was administered daily at 10, 20, and 40 mg/kg for 10 days, 5 minutes prior to a 3-hour stress exposure.[19] Restraint stress elevated pro-inflammatory cytokines and NO, contributing to hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, a key pathway in stress-related disorders.[26] EO treatment dose-dependently suppressed serum levels of interleukin-1α (IL-1α), IL-1β, and IL-6, while also reducing nNOS expression in both the cerebral cortex and hippocampus. It also significantly downregulated corticotropin-releasing factor (CRF), CRF receptors (CRFR), adrenocorticotropic hormone (ACTH), and corticosterone (CORT), indicating suppression of HPA axis activity.[27]

Neurodegenerative disorders

Article 8 investigated the effects of agarwood on Alzheimer's disease and dementia by measuring beta-amyloid (Aβ) and tau protein (τ) levels in brain tissue.[23] The accumulation of Aβ and τ is known to trigger neuroinflammation and oxidative stress, as activated microglia release pro-inflammatory cytokines and reactive oxygen species, ultimately contributing to neuronal dysfunction and cell death.[28] Neurofibrillary tangles formed by τ-protein disrupt synaptic transmission, impairing cognition.[29] In a high-fat diet-induced dementia mouse model, agarwood supplementation (1 mL/day for 16 weeks) significantly reduced Aβ and τ expression. Markers of microglial activation and oxidative stress were also lower in treated groups compared with controls.

Gastrointestinal disorders

Several studies have explored agarwood's protective effects on gastrointestinal tissues under inflammatory and chemotherapeutic stress. Article 6 successfully demonstrated that different types of agarwood extracts wild (WAAE), burning-chisel-drilling (FBAAE), and whole-tree inducing technique (WTAAE) effectively ameliorated intestinal injury induced by 5-fluorouracil (5-FU) in a murine model.[9] Over 14 days, treated animals showed improved body weight, intestinal propulsion, and tissue architecture. Biochemically, agarwood reduced NO, IL-17, and IL-33, while increasing antioxidant enzymes (GSH, SOD) and IL-10. Upregulation of Nrf2, Keap1, HO-1, and NADPH-related genes was observed. Concurrently, pro-inflammatory mediators were reduced in agarwood-treated groups relative to controls, including TNF-R, TRAF6, MyD88, IKKβ, IκB-β, and NF-κB.

Table IV: Summary of agarwood inflammatory-related studies using animal model administered either orally or injected intraperitoneally (IP).

Author	Sample	Animal	Model and sample dose	Administration route and duration	Sample size [group(n)]	Outcome measured	Findings
Article 1[8]	Aquilaria sinensis leaf ethanolic extract (50 % v/v twice reflux)	Male and female 18-22 -gram ICR mice	Acetic-acid-induced writhing response in mice. Sample dose: 424 mg/kg 848 mg/kg	1 hour before acetic acid injection. Route: Oral	n =10	Frequency of writhing occurring was recorded 15 min after the injection of acetic acid. Indomethacin was administered to mice to the positive control group.	Agarwood samples group (424 and 848 mg/kg)) showed restrained writhing with inhibition rate of 62.2 % and 66.9 %, respectively. Positive control (20mg/ kg) also markedly reduced writhing time.
			Hot plate latency assay in mice Sample dose: 424 mg/kg 848 mg/kg	1 hour and 2 hours before hot plate latencies recording. Route: Oral	n =10	The time that elapsed until the occurrence of either a hind paw licking or a jump off the plate surface was recorded as the hot-plate latency (5< t <30 seconds). Measurement was conducted at 1 and 2 hours after oral administration of samples.	Agarwood sample (848 mg/kg) increased pain threshold by 57.1 % measured at 2 hours after oral administration. Indomethacin (20 mg/ kg) also markedly increased mice latency.
			Xylene-induced ear swelling in mice Sample dose: 424 mg/kg 848 mg/kg	1 hour before xylene injection on anterior and posterior right ear lobe. Route: Oral	n = 10	Ear swelling degree caused by xylene induced injection was measured Indomethacin was administered to the positive control group. Left lobe as control.	At a dose of 848 mg/kg, the sample reduced xylene-induced ear swelling in a dose-dependent manner, with a 51.0% inhibition rate. Positive control (20 mg/ kg) also showed potent swelling reducing effect.
			Carrageenan-induced paw oedema in mice Sample dose: 424 mg/kg 848 mg/kg	1 hour before subcutaneous injection of carrageenan. Route: Oral	n = 10	Paw oedema caused by 2 % (v/v) carrageenan solution was measured using plethysmometer. Indomethacin was administered to the positive control group.	Sample at 848 mg/kg notably inhibited paw oedema in mice administered orally at 1, 3, and 5 hours after carrageenan injection showing similar effect as positive control (20 mg/kg).
			Carboxymethyl-cellulose-sodium (CMC-Na) induced leukocyte emigration in mice Sample dose: 424 mg/kg 848 mg/kg	1 hour before the injection of the CMC-Na solution. Route: Oral	n =10	An hour after oral administration of drugs, leukocyte cell count (stained with 0.01% crystal violet in 3% acetic acid) was conducted to observe whether the treatment enhances or reduced the leukocyte emigration in the mice peritoneal cavity. Dexamethasone was introduced as positive control in this test.	CMC-Na (375 mg/kg) significantly enhanced leukocyte emigration in the mice peritoneal cavity. Sample dose-dependently inhibited leukocyte emigration with inhibition percentage of 90.6 % (848 mg/kg) comparable to dexamethasone, 96.84 % (20 mg/kg).
			lipopolysaccharide (LPS)-stimulated NO release from macrophages in vitro Sample dose for assay: 50 µg/mL 100 µg/mL 200 µg/mL	48 hours	N/A	All assays were performed on thioglycolate-elicited mouse peritoneal macrophages. Measuring the LPS-induced massive amount of NO in macrophages. Also, the test was meant to observe the toxicity effect after 48 hours of exposure to samples. 0.1 µM hydrocortisone as positive control.	Agarwood sample dose-dependently reduced the NO-induced release at concentration of 50, 100, and 200 µg/ mL resulting in IC_{50} of 80.4 µ/mL. Additionally, samples showed no obvious toxicity effect on the viability of macrophages during 48 hours period of incubation.
Article 2[18]	Essential oil hydrodistillated from Aquilaria crassna stem bark (after 1 week maceration in distilled water at room temperature)	Male and female 8 to 12 weeks Swiss mice	Acute toxicity. Sample dose: 2000 mg/kg	Single dose and observed for 16 days. Route: Oral	n = 9	Mortality and toxicity signs such as apathy, hyperactivity, dizziness, vomiting, diarrhoea, excessive salivation, loss of fur, anxiety, convulsions, lethargy, and morbidity	Agarwood samples showed no treatment-related mortality at the limit test dose (2000 mg/kg). No significant changes in mice behaviour during the 14 days observation period. Also, no abnormal changes attributable to treatment had been noticed in body weights and treatment related changes like respiration rate and heart rate.
			Sub-chronic toxicity Sample dose: 100 mg/kg 500 mg/kg	Daily dose over 28 days. Route: Oral	3(n = 10)	Observations were made on general behaviour, hematological, and biochemical parameters. Signs such as piloerection, diarrhoea, sedation, loss of fur, and alterations in locomotor activity or mortality were recorded.	Swiss mice showed no signs of toxicity recorded during the 28 consecutive days of treatment at the doses of 100 and 500 mg/kg. Also, no changes had been recorded in the hematological and biochemical indices.
		6 to 8 weeks Athymic-NCR nu/nu mice	In vivo anti-tumour (HCT-116 cell) Sample dose: 50 mg/kg 100 mg/kg 200 mg/kg	Daily dose over 6-8 weeks period. Route: Oral	4(n = 6)	Cross-section of xenografted tumour to measure size and observe any histological changes when treated	Treatment caused significant reduction in the tumour size compared to those in the untreated group. Apparent differences in the extent of necrotic regions. Histological feature showed loss of cell compactness and severe necrosis with areas of low density of blood vessels, as well as many pools of tumour cells compared to control group.
Article 3[19]	Hydrodistillated agarwood essential oil from whole tree agarwood-inducing technique (species not mentioned)	Adult male ICR mice	Elevated Plus Maze (EPM) Test Sample dose: 10 mg/kg 20 mg/kg 40 mg/kg	Daily dose for 10 days before stress induction. Route: IP	7(n = 12)	Time spent, distance moved, and number of entries in the open arms from the central elevated platform was recorded.	Agarwood treated group and positive control group showed markedly increased the time spent, distance moved and entries in open arms. 20 and 40 mg/kg agarwood showed comparable effects as 2.5 mg/kg diazepam suggesting anxiolytic effect.
			Light Dark Exploration (LDE) Test Sample dose: 10 mg/kg 20 mg/kg	Daily dose for 10 days before stress induction. Route: IP		Time spent, distance moved, and number of transitions between dark and light compartment were recorded.	Agarwood treatment increased the time spent and distance in light compartment including increased the transition to light compartment. 40 mg/kg agarwood displayed comparable effects to 2.5 mg/ kg diazepam indicating the anxiolytic effect.
			Open Field (OF) Test Sample dose: 10 mg/kg 20 mg/kg 40 mg/kg	Daily dose for 10 days before stress induction. Route: IP		Mice placed in an open field cage for 2 mins for acclimatization. Then, the next 10 mins, the movement were recorded with a threshold selected at 6.5 cm/s. Time spent and distance moved were recorded.	Agarwood treatment (20 and 40 mg/kg) increased time in the center/open arms compared with control; values were comparable to diazepam.

cont'd

			Tail Suspension (TS) Test Sample dose: 10 mg/kg 20 mg/kg 40 mg/kg	Daily dose for 10 days before stress induction. Route: IP		A system consists of eight suspension units divided by walls where mouse was suspended by the tail using an adhesive tape for 6 min, and the immobility time during the final 4 min was recorded automatically by software.	Depressed mice showed increased immobility, while paroxetine significantly decreased immobility. Agarwood at 20 and 40 mg/kg also reduced immobility compared with control, with effects comparable to paroxetine (10 mg/kg).
			Forced Swimming (FS) Test Sample dose: 10 mg/kg 20 mg/kg 40 mg/kg	Daily dose for 10 days before stress induction. Route: IP		Mice were individually placed into a plastic cylinder (20 cm height, 18 cm diameter) filled with 12 cm high water (24 ± 1 ℃). All animal were forced to swim for 6 mins. The immobility time during the final 4 mins was recorded.	Immobility time was described as time spent by mouse floating in the water without struggling and making only small movement to keep its head above water. Agarwood at 40 mg/kg and paroxetine at 10 mg/kg showed similar immobility inhibitory effect suggesting the potential anti-depressant effect.
			RT-PCR Sample dose: 10 mg/kg 20 mg/kg 40 mg/kg	N/A	N/A	This method evaluates the mRNA levels of neuronal nitric oxide synthase (nNOS), corticotropin releasing factor (CRF), and corticotropin releasing factor receptor (CRFR).	Repeated restraint stress increased the nNOS gene and protein expression in the cerebral cortex and hippocampus. Agarwood treatment (40 mg/kg) markedly inhibited the mRNA levels of nNOS in cerebral cortex and hippocampus. The treatment also significantly inhibited the nNOS protein level in the hippocampus but unobvious in the cerebral cortex.
			Western blot Sample dose: 10 mg/kg 20 mg/kg 40 mg/kg	N/A	N/A	This method measures the protein levels of nNOS and CRFR.	Agarwood treatment significantly reduced the expression of CRF and protein CRFR in the cerebral cortex and hippocampus. Also, the concentrations of ACTH and CORT downstream of the HPA axis were reduced.
Article 4[20]	Methanolic extract of Aquilaria agallocha heartwood	250 to 280 grams of Wistar rats	Blood analysis Sample dose: 3 g/kg	Pre and post treatment (1 hour after) Route: Oral	n = 6	Blood samples of rats were collected pre-dose and 1-hour post-dose after oral administration of methanolic agarwood extract (3g/kg). Samples were analyzed by UHPLC-Q-TOF/MS.	10 compounds detected in rat blood plasma out of the 22 compounds identified from the methanolic extract of Aquilaria agallocha heartwood.
		22 to 25 grams of Kunming mice	5-fluorouracil (5-Fu) intestinal mucositis induction Sample dose: 200 mg/kg 400 mg/kg 800 mg/kg	Sample daily dose 30 minutes prior to 5-Fu. Total duration of 7 days Route: Oral	6(n = 10)	Body weight, food intake, and stool scoring were recorded to assess the severity of intestinal mucositis. The following tests includes histopathological evaluation, immunohistochemical analysis, superoxide dismutase (SOD) and malondialdehyde (MDA) analysis including cytokines evaluation via RT-PCR and western blot. IM induce using 5-Fu dose at 60 mg/kg/day for 5 days Loperamide 4 mg/kg.	Agarwood reduced the severity of 5-Fu induced IM displayed by the improvement in body weight, food intake, and diarrhoea status. Agarwood treated mice showed relatively intact mucosa structure with notably better villus height and crypts depth. SOD levels were increased while MDA levels were significantly reduced by the treatment. The treatment also reduced the COX-2 and TNF-α expression. These agarwood effects recorded were similar to the effects shown by the positive control, loperamide.
Article 5[21]	Ethanolic extract of agarwood chip (species not mentioned)	Male 100-110 grams of Sprague -Dawley rats	Agarwood protective effects against methanol toxicity Sample dose: 100 mg/kg	Sample daily dose for 35 days Route: Oral	4(n = 10)	Animal separated into 4 groups i.e., control (untreated), methanol (model), agarwood, and agarwood-methanol groups. Methanol (3 g/kg) was injected once per week for three weeks. Agarwood was orally administered daily at 100 mg/kg. After 35 days, feeding was stopped for 12 hours prior to anesthetized and sacrificed for brain and liver tissue collection.	Methanol caused elevation of NO, MDA, ACHE, COX-2, LOX, TNF-α, Caspase-3, MAO and DNAF in brain and liver compared to control. Treatment with agarwood pre, during, and post-methanol administration managed to improve the liver and brain biological parameters compared to the control.
Article 6[9]	Alcohol extract of wild agarwood extract, whole tree inducing agarwood extract, and burning-chisel-drilling agarwood extract. Species not mentioned	Male 18 to 20 grams of ICR mice	Agarwood protective effect against intestinal injury by fluorouracil (5-Fu) Sample dose: WAAE 2.84 g/kg FBAAE 2.84 g/kg WTAAE: 0.71 g/kg 1.42 g/kg 2.84 g/kg	Sample daily dose. Model 5-Fu once/2 day. 14 days duration. Route: Oral	7(n = 10)	Animals divided into 7 groups i.e., Control Model 5-Fu (25 mg/kg) Wild agarwood (WAAE) treated (2.84 g/kg) + 5-Fu (25 mg/kg) Burning-chisel-drilling agarwood (FBAAE) treated (2.84 g/kg) + 5-Fu (25mg/kg) Whole tree inducing agarwood (WTAAE) treated group (0.71, 1.42, and 2.84 g/kg) + 5-Fu (25 mg/kg). Analysis conducted includes body weight observation, intestinal propulsion rate analysis, colon tissue histopathological evaluation, lipid peroxidation analysis (NO, GSH, and SOD), cytokines analysis (IL-17, IL-33, and IL-10), and RT-PCR for anti-oxidant and inflammation.	Agarwood treated group showed increased body weight in the 13th day (especially WTAAE treated). Model group showed loss of body weight. Intestinal propulsion rate of agarwood treated groups were significantly increased (WTAAE and WAAE showed better rates than FBAAE). Model group showed low intestinal propulsion rate. Agarwood significantly relieves the colon histopathological injury caused by 5-Fu. Treatment protected colon from damage characterized by villi shortening and crypt disruption, inflammatory cell infiltration, goblet cell reduction, mucosa and muscle layer thinning as shown by model group. NO level was reduced while GSH and SOD levels were significantly increased by agarwood treatment. Agarwood markedly reduced the levels of IL-17 and IL-33 while significantly increased the level of IL-10. Increased expression of Nrf2-ARE–related genes and proteins was observed following agarwood treatment. NF-κB activation and downstream targets were reduced in treated groups compared with controls.

cont'd

Article 7[22]	Alcohol extract of wild agarwood extract, whole tree inducing agarwood extract, and burning-chisel-drilling agarwood extract. Species not mentioned	Male 4 to 6 weeks of ICR mice	Agarwood protective effect against gastric ulcer Sample dose: WAAE 2.84 g/kg FBAAE 2.84 g/kg WTAAE: 0.71 g/kg 1.42 g/kg 2.84 g/kg	Daily pre-treatment with sample for 7 days Route: Oral	7(n = 10)	Animals were divided into 7 groups.[9] Pre-treatment with agarwood was done daily for 7 days while control and model groups were pre-treated with distilled water (20 mL/kg). After pre-treatment and 24 hours food deprivation with water ad libitum, mice were infected by oral gavage absolute ethanol at 0.015 mL/g except for normal group. An hour after that, blood was collected for analysis and sacrificed. Stomach was immediately removed and fixed with formaldehyde solution for gastric lesion index and histopathological analysis.	Pre-treatment with agarwood reduced ethanol-induced mucosal damage and ulcer index. The model group exhibited severe gastric ulcers with linear haemorrhages and ulceration craters. Agarwood protected against gastric lesions, preventing submucosal oedema, haemorrhagic injury, mucosal degradation, epithelial loss, inflammatory infiltration, and necrosis. Dose-dependent treatment decreased NO levels while increasing GSH and SOD, highlighting antioxidant effects. Agarwood reduced proinflammatory cytokines (IL-1β, IL-6) and elevated anti-inflammatory IL-10 levels. Immunohistochemical analysis showed downregulation of NF-κB and p-38 MAPK phosphorylation, confirming its potent anti-inflammatory activity.
Article 8[23]	Aquilaria crassna ethanolic extract (sample type not mentioned).	Female 6 weeks of ICR mice	Agarwood effect against Alzheimer's and other dementia related diseases. Working under the hypothesis of critical association between obesity, diabetes, and Alzheimer's. Sample dose: 1 mL/day added to high-fat energy diet.	Ad lib food supply with sample for 16 weeks. Route: Oral	2(n = 10)	Mice were fed with high-fat energy diet plus agarwood ethanolic extract (1 mL/day) for the treated group. Control was fed with high-fat energy diet only. Body weight changes were measured weekly. Blood analysis was conducted at the termination point of experiment. Aβ and τ-protein expression analysis (western blot)	Agarwood treatment increased body weight over time. However, the difference was not significant at the end of 16 weeks. Weight changes after week 9 were almost asymptotically plateau. Blood analysis showed slightly higher levels of HDL, LDL, and cholesterol values which were unexpected. Aβ and τ-protein expression were reduced (>50%) versus control.

Similarly, in an ethanol-induced gastric ulcer model, agarwood pre-treatment reduced mucosal damage, oedema, and hemorrhage.[22] Levels of GSH and SOD were elevated, while IL-1β, IL-6, and NO were suppressed. IL-10 was upregulated, alongside inhibition of phosphorylated NF-κB and p38 MAPK.

Another study using powdered A. agallocha extract (200-800 mg/kg) confirmed protection against 5-FU-induced intestinal mucositis, with improved clinical symptoms, structural preservation, and decreased COX-2 and TNF-α levels.[20]

Selection of agarwood sample and animal model

Agarwood sample selection often reflected the researchers' geographic location; studies from Indochina primarily used A. crassna, while those from China used A. sinensis. However, several studies did not specify species or inoculation status, the latter being critical as artificial inoculation alters phytochemical profiles.[30, 31]

Animal model selection aligned with study objectives. For example, mice were used for stress models due to their heightened sensitivity, while rats were chosen for procedures requiring larger blood volumes. Figure 3 summarises animal and sample types. Rats are preferred for surgical and imaging studies due to their size, while mice are commonly used in pharmacological research for cost-efficiency and lower dosing requirements.[32]

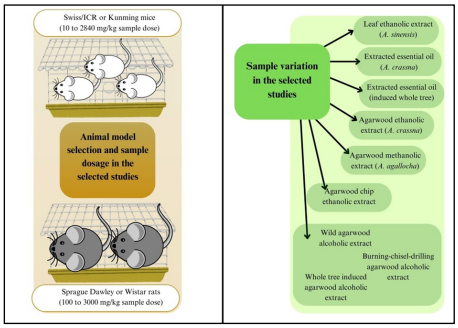


Figure 3: (a) On the left: Animal models used in the selected studies, predominantly Swiss/ICR or Kunming mice and Sprague Dawley or Wistar rats. Agarwood sample dosages ranged from 10 to 2840 mg/kg in mice and 100 to 3000 mg/kg in rats. (b) On the right: Variations in agarwood sample types, including extracts from different plant parts and essential oils. Sample selection was influenced by research objectives and the geographical affiliations of the researchers.

DISCUSSION

Inflammation is a physiological response to harmful stimuli such as infection, injury, or certain pathological conditions, often presenting with symptoms like fever, sore throat, and nasal congestion. Under normal conditions, these responses are self-limiting, and tissue homeostasis is restored. However, in chronic inflammatory diseases, this process becomes dysregulated, preventing resolution and leading to persistent tissue damage.[33] Chronic inflammation is now widely recognized as a key contributor to a range of non-communicable diseases commonly associated with modern lifestyles and aging, including cancer, obesity, cardiovascular disorders, and neurodegenerative conditions.[34]

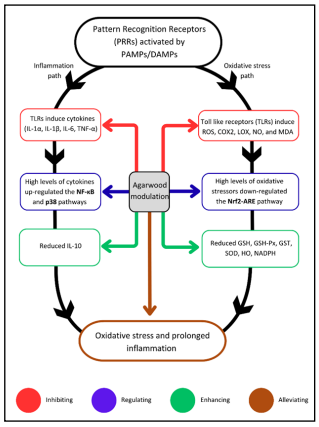


Figure 4: Proposed mechanisms underlying the anti-inflammatory effects of agarwood. Agarwood may modulate inflammation directly or indirectly through oxidative stress-related pathways. These effects may involve inhibition, regulation, or activation of molecular signalling cascades associated with immune and oxidative responses. Color codes: red=inhibition, purple=regulation, green=enhancement, brown=alleviation.

The current review highlights consistent findings from animal models indicating that agarwood exerts anti-inflammatory effects through multiple biological pathways, including the Nrf2–ARE and NF-ϰB signalling cascades (Figure 4), which are central to oxidative stress and inflammation control.

Bioactive phytochemicals in agarwood are postulated to modulate inflammation by influencing key molecular signals. One major pathway involves the activation of pattern recognition receptors (PRRs) by pathogen or damage associated molecular patterns (PAMPs/ DAMPs),[35] triggering downstream cascades that recruit immune cells and stimulate cytokine production.[36] This leads to the release of pro-inflammatory mediators such as TNF-α, IL-1, IL-6, and type I interferons. These cytokines also influence neuroendocrine and neurotransmitter function, contributing to illness behaviours and psychiatric conditions, including anxiety and anhedonia.[37] These substances can induce fever, decrease food intake, sexual activity, and social exploration, as well as provoke anxiogenic-like effects, interfering with the brain's ability to respond to pleasurable stimuli.[38]

In stress-induced models, agarwood treatment suppressed HPA axis hyperactivity that was activated by cytokines production by downregulating CRF expression in the cerebral cortex and hippocampus, and reducing ACTH secretion from the pituitary and adrenocortical hormone excretion from the adrenal cortex, indicating effective modulation of cytokine-driven stress responses.[39] These behavioural changes are consistent with an anxiolytic-like profile, as agarwood treatment increased time spent in the centre or open arms compared with controls, with values comparable to diazepam. Findings also align with an antidepressant-like effect, as agarwood reduced immobility times in a manner comparable to paroxetine. In addition, stress-related cytokine levels (IL-1α, IL-1β, IL-6) were reduced with treatment, further supporting anti-inflammatory contributions to these behavioural outcomes. Overall, these patterns are consistent with anxiolytic and antidepressant like effects, though their clinical relevance remains to be established. In neurodegeneration models, agarwood reduced microglial activation and oxidative stress. These findings motivate more targeted studies on neuroinflammatory pathways to clarify the mechanisms underlying its neuroprotective potential.

In gastrointestinal models, agarwood mitigated ethanol- and drug-induced mucosal injury by restoring antioxidant levels (GSH, SOD, IL-10) and reducing pro-oxidant and pro-inflammatory markers (NO, IL-1β, IL-6).[19] These molecular changes included upregulation of Nrf2, Keap1, HO-1, and NADPH-related genes, along with suppression of NF-ϰB and p38 MAPK signalling.[40, 41] The concurrent antioxidant and anti-inflammatory responses support a dual-action hypothesis for agarwood's effects in gastrointestinal inflammation, although confirmation across different models is still needed. Similar protective effects were observed in chemotherapy-induced intestinal damage, where agarwood enhanced the expression of Nrf2, Keap1, HO-1, GST, and NADPH, thereby reducing oxidative stress, promoting mucosal protection, and modulating immune responses.[42] This is particularly relevant given the bidirectional relationship between inflammation and oxidative stress, in which elevated cytokines such as TNF-α and IL-1β promote ROS production, while oxidative stress further amplifies inflammatory signalling.[43] The molecular evidence also supports this dual action: agarwood enhanced the expression of Nrf2–ARE–related genes, consistent with antioxidant activation, while suppressing NF-ϰB signalling, a central regulator of inflammatory responses. Together, these shifts provide a mechanistic basis for its observed antioxidant and anti-inflammatory effects. By

modulating both cytokine levels and antioxidant enzymes such as SOD and GSH, agarwood appears to act on this interlinked pathological axis. NF-ϰB inhibition, in particular, contributed to reduced inflammation and tissue damage across both gastrointestinal and neuroinflammatory models. Given that NF-ϰB regulates cytokines involved in stress and mood-related pathways, its downregulation may underlie agarwood's observed effects on neuroendocrine modulation, particularly in anxiety and depression-like behaviours.[44] Likewise, the suppression of p38 MAPK phosphorylation an important mediator of cytokine production and epithelial injury further supports agarwood's therapeutic potential in addressing gastric ulceration and systemic inflammatory responses.[41]

Despite variability in disease models, agarwood type, and experimental protocols, several consistent outcomes were observed across the reviewed studies:

- Reduction in pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) indicating suppression of key mediators involved in acute and chronic inflammatory responses.
- Modulation of oxidative stress markers (e.g., GSH, SOD, NO) highlighting agarwood's antioxidant capacity in mitigating reactive oxygen species (ROS)-induced damage.
- Regulation of inflammatory signalling pathways (NF-ϰB, p38-MAPK, Nrf2-ARE) suggesting a mechanistic basis for agarwood's systemic anti-inflammatory and cytoprotective effects.

In addition to these anti-inflammatory and antioxidant outcomes, one study demonstrated reduced tumour growth in HCT116 xenograft models following agarwood essential oil treatment. These results point to possible anti -tumour activity that warrants further investigation in preclinical cancer studies.

Taken together, these outcomes across different models suggest that agarwood's effects are mediated, at least in part, through shared inflammatory pathways such as NF-ϰB and Nrf2, which play central roles in inflammation and oxidative stress. Overall, the evidence indicates that agarwood exhibits broad-spectrum anti-inflammatory and antioxidant activities across multiple organ systems and disease contexts. This highlights its promise as a candidate for the development of novel therapeutics targeting inflammation-driven disorders.

Beyond efficacy, safety is an equally important consideration for the clinical translation of agarwood. Only a few of the included studies reported toxicity outcomes. For example, *A. crassna* essential oil showed no acute toxicity at 2,000 mg/kg or sub-chronic toxicity at 100–500 mg/kg for 28 days in mice, with no treatment-related mortality or notable behavioural or biochemical changes.[18] Another study found that agarwood ethanolic extract actually improved liver and brain biomarkers in a methanol-induced toxicity model, suggesting possible protective rather than harmful effects.[21] While these results are encouraging, most studies did not evaluate standard safety parameters such as liver enzymes, kidney function, or histopathology. This gap is particularly relevant for solvent-based extracts like ethanol, which may have toxicological implications in humans.

It is also worth noting that many of the included studies had methodological shortcomings. Randomization, blinding, and allocation concealment were rarely reported, which points to a moderate–high risk of bias. These weaknesses limit how confidently the results can be interpreted and underline the need for better reporting and study design in future preclinical work. Future studies should prioritize the use of random allocation, allocation concealment, and blinded outcome assessment to reduce bias and strengthen the robustness and reproducibility of findings. In addition, species identification and inoculation status were not consistently reported across studies, which hinders reproducibility and complicates cross-study comparisons. Addressing this gap will require future studies to provide complete details on species, extraction protocols, and inoculation status to ensure reproducibility and phytochemical consistency.

Although the preclinical findings are promising, moving agarwood-based therapies into human use presents several challenges. At present, little is known about their pharmacokinetics, making it difficult to predict how these

extracts are absorbed, distributed, metabolized, or excreted in humans. Without such data, establishing safe and effective dosing remains speculative.[45] Extrapolating dosing from animals to humans is not straightforward due to physiological differences; robust methods such as allometric scaling or physiologically based pharmacokinetic modeling are preferred over simple weight-based formulas.[46] Finally, regulatory approval of herbal therapies demands standardized preparations, reproducible phytochemical profiles, and comprehensive safety testing, including genotoxicity and long-term toxicity assessments. In several countries, including Malaysia, herbal products must also comply with GMP and registration procedures to be legally marketed.[47] These considerations underscore the need for well-designed pharmacological and clinical studies before agarwood can be confidently advanced as a therapeutic option.

LIMITATIONS

While this review supports the anti-inflammatory potential of agarwood, several limitations should be noted. There is considerable variability in species, extraction methods, and phytochemical content, and many studies lacked details such as plant origin, inoculation status, and standardization. As highlighted in Table II, incomplete reporting of species and inoculation status represents a significant limitation that hinders reproducibility and cross-study comparisons. Future studies should ensure detailed reporting of Aquilaria species, extraction protocols, and inoculation status to improve reproducibility and maintain phytochemical consistency across studies. Most data were derived from preclinical models, limiting clinical relevance, and only a few studies conducted dose response or long-term evaluations.

Although the included studies generally achieved high scores on the ARRIVE checklist, the limited use of blinding and randomization raises concerns about internal validity. The absence of these measures increases the potential for performance and detection bias, which may lead to an overestimation of treatment effects.[48, 49] Consequently, the findings should be interpreted with caution, as the robustness of the reported outcomes may be reduced. Future studies should integrate rigorous methodological safeguards, including random allocation, allocation concealment, and blinded outcome assessment. These practices are essential to reinforce study rigor, minimize bias, and improve the reproducibility and translational value of preclinical research.[50]

Information on safety and toxicity was also limited. While a small number of studies reported no obvious adverse effects or even protective outcomes, most did not include standard assessments such as liver enzymes, renal function, or histopathology. This gap makes it difficult to draw firm conclusions about the safety profile of agarwood extracts, particularly those prepared using solvents like ethanol, which may pose toxicological risks if translated to humans. Comprehensive toxicity evaluation should therefore be incorporated into future preclinical work alongside efficacy testing.

To ensure broad coverage, three major databases (PubMed, Scopus, and Web of Science) were searched; however, relevant studies from other platforms may have been missed. In addition, journal indexing can change over time, potentially affecting study inclusion. Finally, as is typical of scoping reviews, no formal quality appraisal was conducted, since the objective was to map available evidence rather than assess study rigor.[17]

CONCLUSIONS

Although limited in number, existing preclinical studies provide promising evidence for the anti-inflammatory effects of agarwood across diverse animal models, including those simulating analgesic, anticancer, neurodegenerative, psychiatric, and gastrointestinal conditions. These findings support its traditional medicinal use and highlight its potential for future therapeutic development targeting inflammation-related disorders.

Further research is essential to validate these findings, identify optimal dosing strategies, and assess the long-term safety and efficacy of agarwood-based interventions. Mechanistic studies and standardized formulations will be

crucial in advancing its clinical applicability.

To date, no registered clinical trials have evaluated agarwood or its derivatives in humans. While some botanical trials exist, the composition and relevance to agarwood remain unclear. Given its pharmacological potential, well-designed clinical studies are urgently needed to confirm efficacy, establish safety profiles, and explore its role in modern therapeutic settings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article are available from the corresponding author upon reasonable request and will be provided in Excel format.

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CONFLICT OF INTEREST

The authors declare that the research was conducted without any commercial or financial relationships that could be perceived as a potential conflict of interest.

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