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Integrated Comparative Analysis of Three Medicinal Combretaceae Species for Phytochemical Composition and Therapeutic Implications

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ABSTRACT: The Combretaceae family comprises numerous medicinal plants that produce bioactive compounds with various healing properties and are useful in traditional medicine. This study compares three medicinal species, viz. *Anogeissus latifolia* (Roxb. ex DC.) Wall. Ex Guill. & Perr., *Terminalia paniculata* B. Heyne ex Roth., and *Terminalia arjuna* (Roxb.) Wight & Arn. with respect to their phytochemical composition, biological mechanisms, therapeutic effects, and research evidence. The three species have similar polyphenolic profiles, including tannins, flavonoids, and phenolic acids, but they function differently because they contain varying amounts of these compounds. *A. latifolia* contains high levels of tannins, which yield wound-healing properties and antibacterial activity of extract of the plant. In contrast, *T. paniculata* contains various hepatoprotective and anti-inflammatory phenolic compounds, whereas *T. arjuna* contains high levels of triterpenoids, which underline its cardioprotective effects. This review found that *T. arjuna* appears comparatively more investigated and demonstrates broader pathway engagement based on available evidence (half-maximum inhibition concentration/inhibition constant to measure binding affinity [IC_{50}/K_i]) than the other two species because of its ability to target multiple pathways via nuclear factor kappa B, mitogen-activated protein kinases, and nuclear factor erythroid 2-related factor 2 pathway, whereas *T. paniculata* and *A. latifolia* have limited research. The clinical application of *T. arjuna* has received human research support, whereas the other two treatments lack clinical research and standardised treatment protocols. However, several fundamental challenges remain to be addressed. Research needs to focus on three main areas: omics research, advanced drug delivery systems, and clinical testing methods. This review provides a comprehensive framework for developing Combretaceae species into phytopharmaceuticals and novel drug candidates.

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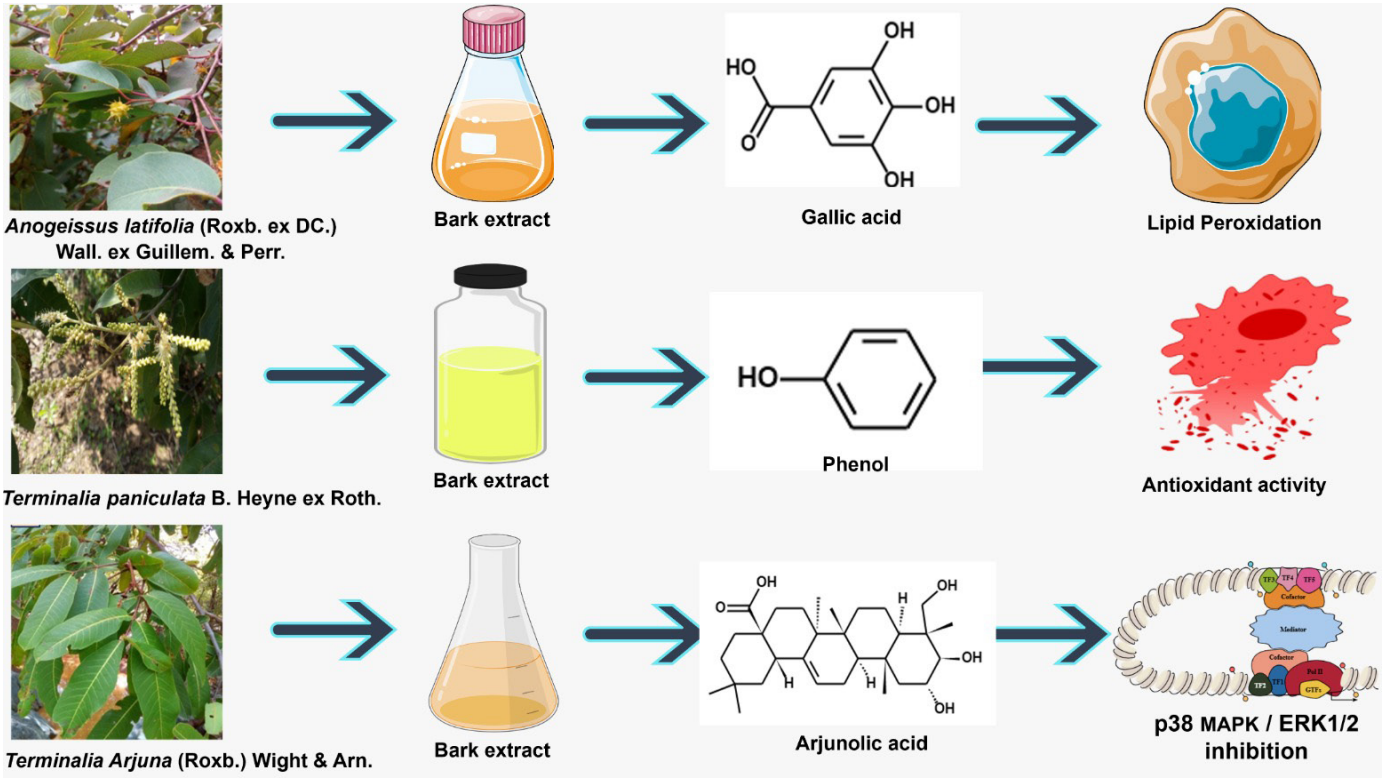
GRAPHICAL ABSTRACT



1. INTRODUCTION

Medicinal plants remain essential for drug discovery as they provide diverse natural compounds utilised in modern pharmacotherapy. The Combretaceae family has become a focus of scientific research because its plants contain multiple secondary metabolites used in traditional healing systems, including the Ayurveda and Siddha medicine (Cock, 2015). The family contains species that produce high levels of polyphenols, tannins, flavonoids, and triterpenoids, which exhibit multiple pharmacological effects, including antioxidant, anti-inflammatory, antimicrobial, hepatoprotective, and cardioprotective properties (Lawal et al., 2016). There is a lack of comprehensive studies correlating phytochemical composition with pharmacological efficacy and clinical applications. *Anogeissus latifolia* (Roxb. ex DC.) Wall. Ex Guill. & Perr., *Terminalia paniculata* B. Heyne ex Roth., and *Terminalia arjuna* (Roxb.) Wight & Arn. are three medicinal plants belonging to the Combretaceae family and exhibiting distinct functions that define their importance as medicinal plants. *A. latifolia* has traditional uses for wound healing, antimicrobial treatments and management of skin disorders because of its high tannin content and astringent properties (Khan et al., 2024). The diverse phenolic profile of *T. paniculata*, together with its antioxidant capacity, drives its application as a treatment for liver disorders, inflammation, and metabolic conditions (Younus et al., 2025). The traditional and modern medical fields recognise *T. arjuna* as an effective treatment for heart protection because of its bioactive triterpenoid content, including arjunolic acid, and its clinical and experimental evidence (Ramesh and Palaniappan, 2023). The three species share a common phytochemical profile, yet recent research shows that their distinct metabolite patterns, along with their tissue-specific distribution, yield diverse therapeutic effects. The existing research reports focus on a single species, creating a barrier that prevents scientists from understanding how the species compare in their medicinal properties. The process of developing evidence-based therapeutics from these plants faces major challenges, such as inconsistent phytochemical standardisation, differences in research methods, and limited clinical validation.

The present review provides a narrative overview of *A. latifolia*, *T. paniculata*, and *T. arjuna*, integrating evidence from phytochemical profiling, reported biological pathways, pharmacological findings, and available clinical insights. Rather than establishing a formal structure–activity relationship

framework, the review qualitatively examines the existing literature to highlight comparative trends and identify translational gaps. It also outlines potential future research directions, including the application of omics-based approaches and network pharmacology as well as advanced formulation strategies. Through this integrative narrative approach, the selected species are positioned as promising candidates for multi-target therapeutics and polyherbal formulations, thus underscoring relevance of the Combretaceae family in contemporary phytopharmaceutical research.

2. NARRATIVE REVIEW METHODOLOGY

This review used a structured approach to examine *A. latifolia*, *T. paniculata*, and *T. arjuna* with respect to their phytochemical properties and molecular mechanisms to determine their medical applicability. Literature was obtained from PubMed, Scopus, Web of Science, and Google Scholar by using Boolean search methods with the following keywords: Combretaceae; phytochemistry; IC_{50}; mechanism; NF-κB; MAPK; Nrf2; pharmacological activity. The inclusion criteria included that studies were published in peer-review journals and presented phytochemical information along with *in vitro*, *in vivo*, or clinical pharmacological findings. Meta-analysis was not performed because the included studies used different experimental models and reported various units (viz. dissociation constant/inhibition constant/half-maximum inhibition concentration [K_i/K_d/IC_{50}]). Mechanistically, comparisons of pharmacological efficacy were based on normalised results from each assay comparison, categorising literature values into three potency levels (high, moderate, and low) based on IC_{50} ranges within similar assay contexts.

2.1. Methodology limitations

The review confronts several methodological constraints. Firstly, the study relies on a non-systematic literature selection which may introduce selection bias despite efforts to include relevant and recent studies. The included data shows high heterogeneity because different experimental models, assay conditions, and reporting units (e.g. µM, µg/mL, and mg/kg) were used to collect information across various species. The included evidence lacks proper evaluation because there is no established method for assessing quality or risk of bias. The semi-quantitative potency classification system, which uses high, moderate, and low levels, requires cautious interpretation because it provides only approximate assessments across similar assay contexts. The research findings have limited translational value because there are insufficient high-quality clinical studies available to evaluate *A. latifolia* and *T. paniculata*.

3. BOTANICAL AND ETHNOMEDICINAL OVERVIEW

Medicinally important Combretaceae family members, *A. latifolia*, *T. paniculata*, and *T. arjuna*, are found in tropical and subtropical regions of the Indian subcontinent and have a significant position in the traditional system of medicine, viz. Ayurveda and Siddha. *A. latifolia*, or the axle wood tree, is a medium-sized deciduous tree with smooth grey bark, small clusters of flowers, and winged fruits. The tree is found growing in dry deciduous forests, especially in the central and southern parts of India. Ethnomedicinal parts of *A. latifolia* include the bark, leaves, and gum, called "ghatti," used for their strong astringent activity in treating diarrhoea, dysentery, wounds, ulcers, and skin infections, possibly because of their high tannin content and antimicrobial activity (Khan et al., 2024). *T. paniculata* has been traditionally used to manage liver-related ailments, inflammation, diabetes, and intermittent fever. The extracts of its bark and heartwood are of significant importance in the Siddha medicine because of their hepatoprotective and detoxification properties (Talwar et al., 2011). Conversely, *T. arjuna*, one of the most studied and documented species, is a tall evergreen or semi-deciduous tree with a common habitat on riverbanks. The plant is characterised by its smooth, pinkish-grey bark, which exfoliates in thin sheets. *T. arjuna*, revered in the classical Ayurvedic literature, is primarily used as a cardiotonic. The bark of the plant is traditionally used for hypertension, angina, heart failure, and hyperlipidemia (Thakur et al., 2021). The plant is also used for wound healing and management of fractures.

4. COMPARATIVE PHYTOCHEMICAL COMPOSITION

The comparative phytochemical analysis of *A. latifolia*, *T. paniculata*, and *T. arjuna* reveals a common polyphenolic framework characteristic of the Combretaceae family, comprising tannin, flavonoids, and phenolic acids, while also showing specific differences between the species. *A. latifolia* is predominantly a tannin-rich plant with condensed phenolic compounds and proanthocyanidins, which explains its antimicrobial and wound-healing properties (Ray et al., 2024). This chemical distinction provides a direct rationale for the pharmacological gradient documented in Table 1. Shifts in the dominance of compound types correspond to quantitative changes in heterogeneous unit values such as, (model in vitro/in vivo/clinical) and therapeutic potency. *T. arjuna* shows higher tannin content than other tested classes, which

Table 1
Functional and potency-based evaluation of major phytochemical classes in three Combretaceae species.

Phytochemical class	Plant	Active compounds	Target/assay	Heterogeneous units	Potency range	Functional significance	References
Tannins	*T. arjuna*	Gallic acid, ellagic acid	DPPH scavenging	1.6–28.4 µM *in vitro*	High–moderate	Antioxidant activity	Meena et al., 2021
	T. paniculata	Hydrolysable tannins	DPPH	~20– 40 µg/mL *in vitro*	Moderate	Hepatoprotection	Talwar et al., 2013
	A. latifolia	Gallic acid derivatives	Antimicrobial (MIC-based)	50 µg/mL *in vitro*	Moderate	Antibacterial activity	Patil and Gaikwad, 2010
	T. paniculata	Gallic acid	Liver	541.26 ± 22.44 µg/mL *in vitro*	Low	Apoptotic pathway in CCl_4	Talwar et al., 2013
Flavonoids	*T. arjuna*	Quercetin, luteolin	Lipid peroxidation	57.7 µg/mL *in vitro*	Moderate	ROS scavenging	Khan et al., 2022
	T. arjuna	Quercetin	Standard antioxidant	25.18 µg/mL *in vitro*	Moderate	Benchmark antioxidant	Shahriar et al., 2012
Triterpenoids	*T. arjuna*	Arjunic acid	CYP450 inhibition	<50 µg/mL *in vitro*	Moderate	Drug interaction potential	Varghese et al., 2015
	T. paniculata	Aqueous extract	Paw edema	200 mg/kg *in vitro*	Moderate	Chronic inflammation and arthritis	Talwar et al., 2011
Saponins	*T. arjuna*	Saponin fractions	Antioxidant	>200 µg/mL *in vitro*	Low	Membrane stabilisation	Nadeem and Abrar, 2026
	T. paniculata	Ethanolic extract	Antioxidant	5 mg/mL *in vitro*	Low	Liver and renal function	Mopuri and Meriga, 2014
Phenolic acids	*T. arjuna*	Gallic acid	Antioxidant	52.16 ± 3.94 µg/mL *in vitro*	Moderate	Free radical scavenging	Pugazhendhi et al., 2018
	A. latifolia	Phenolic-rich extract	Antioxidant	~30–80 µg/mL *in vitro*	Moderate	Antimicrobial	Govindarajan et al., 2006
Glycosides	*T. arjuna*	Cardiac glycoside-like compounds	Cardioprotection	500 mg/mL *in vivo*	Low	Cardiotonic	Dwivedi and Chopra, 2014
	T. paniculata	Crude extract	Hepatic enzymes	200 mg/kg *in vivo*	Low	Hepatoprotective activity	Eesha et al., 2011

makes it the most important source of antioxidant power in this study. Gallic acid and ellagic acid exhibit strong radical-scavenging activity, with low IC_{50} values (1.6–28.4 µM) in 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging test, because they can quickly donate electrons to neutralise reactive oxygen species (ROS) (Meena et al., 2021). *T. paniculata* exhibits moderate antioxidant activity in the range of 20–40 µg/mL. Still, its tannin fraction appears to mitigate liver damage by modulating apoptosis in carbon tetrachloride (CCl_4)-induced hepatotoxicity experiments (Talwar et al., 2013). *A. latifolia* uses tannin derivatives to fight microbes, demonstrating that the plant has evolved to protect itself from pathogens instead of using its antioxidants for oxidative stress defence alone (Patil and Gaikwad, 2010).

Flavonoids boost antioxidant protection. *T. arjuna* research shows that quercetin- and luteolin-based compounds inhibit lipid peroxidation at moderate levels (IC_{50} ~57.7 µg/mL) (Khan et al., 2022). The isolated quercetin compound exhibits higher antioxidant activity, with an IC_{50} of ~25.18 µg/mL, serving as a reference point for measuring antioxidant activity (Shahriar et al., 2012). Inhibition of cytochrome P450 enzymes (IC_{50} < 50 µg/mL) indicates that the compound affects drug metabolism and pharmacokinetic interactions (Varghese et al., 2015). Triterpenoid-rich extracts of *T. paniculata* exhibit significant anti-inflammatory effects in an experimental model and demonstrate their effectiveness to treat paw oedema at a 200-mg/kg dosage in chronic inflammatory diseases (Talwar et al., 2011).

The examination of saponins in *T. arjuna* and *T. paniculata* shows that these compounds exhibit weak antioxidant activity (IC_{50} > 200 µg/mL) and high *in vivo* efficacy at high doses (Mopuri and Meriga, 2014; Nadeem and Abrar, 2026). Saponins exert their therapeutic effect through diverse biochemical interactions, such as alterations in membrane dynamics, modulation of signalling cascades, and modulation of enzyme function, thereby impacting physiological processes. Phenolic acids demonstrate stable antioxidant effects, as demonstrated by the testing of *T. arjuna*, which has an IC_{50} value of approximately 52 µg/mL, and *A. latifolia*, which has an IC_{50} value between 30 µg/mL and 80 µg/mL (Govindarajan et al., 2004; Pugazhendhi et al., 2018). These compounds are widely distributed in nature and exhibit moderate activity, making them a fundamental part of basic antioxidant defence systems. At the same time, they work together with stronger agents, such as tannins, to enhance their efficacy.

Clinical and *in vivo* tests show that *T. arjuna*'s cardiac glycoside-like compounds exhibit medicinal properties by improving cardiac functioning and blood flow (Dwivedi and Chopra, 2014). The extract from *T. paniculata* contains glycosides that act as hepatic detoxifiers, demonstrating their essential role in regulating human metabolic activities (Eesha et al., 2011). The IC_{50} values are insufficient as assessment tools because clinical effectiveness depends on three factors: bioavailability, metabolism, and multi-target interactions. The hepatoprotective effects of crude extracts from *A. latifolia* demonstrate that multiple phytochemicals act synergistically to confer medicinal benefits that cannot be attributed to any single active component. The evidence indicates that whole-plant extracts offer better medical treatment options because they can modulate multiple biological pathways, aligning with traditional healing methods.

The basic biological activity of direct ROS scavenging shows (in Table 2) its highest value with *T. arjuna*; the

Table 2
Integrated mechanistic profiling of Combretaceae-derived phytochemicals across cellular signaling pathways.

Mechanism	Plant	Active compound/ extract	Specific pathway/target	Heterogeneous units	Potency range	References
ROS scavenging	*T. arjuna*	Phenol	DPPH radical (electron transfer)	4.1 µg/mL *in vitro*	High	Kumar et al., 2018
	T. arjuna	Flavonoid	Nitric oxide (NO•) scavenging	3.3 µg/mL *in vitro*	High	Kumar et al., 2018
	T. paniculata	Phenol	DPPH/ABTS pathways	2.15 mg/g *in vitro*	Low	Agrawal et al., 2011
	A. latifolia	Aqueous extract	ROS neutralisation	65–110 mg/kg *in vivo*	Moderate	Ramachandran et al., 2012
	A. latifolia	Gallic acid and ellagic acid	Lipid peroxidation	100 and 200 mg/kg *in vivo*	Moderate	Govindarajan et al., 2006
NF-κB inhibition	*T. arjuna*	Flavonoids	NF-κB (p65 nuclear translocation), cardioprotective effects	500 mg *in vitro*	Low	Kapoor et al., 2015
	A. latifolia	Bark extract	IL-6, IL-1β, TNF-α, MMP-1, and MMP-13	400 mg/kg *in vivo*	Low	Sirsath Patil et al., 2026
MAPK suppression	*T. arjuna*	Arjunolic acid	p38 MAPK/ERK1/2 inhibition	25 and 50 µM *in vitro*	Moderate	Hasan et. al., 2023
	A. latifolia	Bark extract	MAPK modulation	200 mg/kg *in vivo*	Moderate	Sirsath Patil et al., 2026
Nrf2 activation	*T. arjuna*	Polyphenols	Nrf2–Keap1 pathway	80 mg/kg *in vitro*	Moderate	Nasir et al., 2026
	A. latifolia	Crude extract	Anti-ulcer activity	100 mg/mL *in vitro*	Moderate	Singhal et al., 2022
Apoptosis modulation	*T. arjuna*	Arjunolic acid	Mitochondrial (Bax/Bcl-2, caspase-3), H9c2 cells	111.88 and 196.66 µg/mL *in vitro*	Moderate	Gouthamchandra et al., 2024
	A. latifolia	Extract	HepG-2, Caco-2/ATB-37, and MCF-7/HTB-22	203.3 ± 5.33, 81.78 ± 0.43, and 288 ± 20.1 µg/mL *in vitro*	Moderate	Hasan et al., 2023
Immunomodulation	*T. arjuna*	Bark extract	Cytokine regulation (TNF-α, IL-6)	~30 µg/mL (IC_{50}) *in vitro*	Moderate	Meena et al., 2024

phenolic and flavonoid fractions show strong capacity to neutralise radicals, as evidenced by their DPPH and nitric oxide scavenging tests. Low IC_{50} values, such as 4.1 µg/mL and 3.3 µg/mL, demonstrate their ability to donate electrons and rapidly terminate free-radical chain reactions (Kumar et al., 2018). The strong *in vitro* activity of *T. arjuna* functions as a key redox control element, protecting against macromolecular damage and destruction. *A. latifolia* shows moderate ROS-scavenging capability *in vivo*, requiring 65–110 mg/kg doses to produce equivalent results (Ramachandran et al., 2012). The activity of gallic acid and ellagic acid at 100–200 mg/kg against lipid peroxidation processes shows a transition from direct radical scavenging to protective mechanisms against membrane oxidative damage (Govindarajan et al., 2006). The phytochemicals present in *T. paniculata*, although active against DPPH and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radicals, do not yield precise IC_{50} values, indicating that its antioxidant capacity is assessed qualitatively rather than quantitatively (Agrawal et al., 2011).

This review established three potency categories, which divided pharmacological data into two groups: high-potency drugs, moderate-potency drugs, and low-potency drugs. Owing to heterogeneity in experimental conditions, values are presented for qualitative comparison only. The potency classification was performed within assay-specific contexts and should not be interpreted as a direct cross-model comparison.

5. SUPPRESSION OF INFLAMMATORY SIGNALLING VIA NUCLEAR FACTOR KAPPA B (NF-κB) AND MITOGEN-ACTIVATED PROTEIN KINASES (MAPK) PATHWAYS

The anti-inflammatory activity of the three species is primarily mediated by modulation of key signalling pathways, notably NF-κB and MAPKs, including p38, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK) (as shown in Figure 3). In *T. arjuna*, flavonoids inhibit NF-κB (p65) nuclear translocation, thereby reducing the expression of pro-inflammatory cytokines and contributing to cardioprotective effects (Kapoor et al., 2015). This mechanism underscores the redox sensitivity of NF-κB activation, linking oxidative stress to inflammatory signalling. Additionally, bioactive polyphenols suppress IkappaB (IκB) kinase (IKK) activation, thereby preventing IκB degradation and subsequent NF-κB activation, which leads to decreased production of inflammatory mediators, such as tumour necrosis factor-α (TNF-α), interleukin 6 (IL-6), interleukin 1β (IL-1β), and cyclooxygenase-2 (COX-2) (Khan et al., 2020).

In contrast, *A. latifolia* exhibits pronounced anti-inflammatory effects *in vivo*, where bark extracts significantly reduce cytokine levels (TNF-α, IL-6, and IL-1β) and matrix metalloproteinases (MMP-1 and MMP-13) at a dose of 400 mg/kg (Sirsath Patil et al., 2026), indicating broader modulation of inflammatory and extracellular matrix pathways. Furthermore, anti-inflammatory activity is reinforced through inhibition of MAPK signalling. Arjunolic acid from *T. arjuna* suppresses p38 MAPK and ERK1/2 within a micromolar range (25–50 µM) (Hasan et al., 2023), while *A. latifolia* demonstrates systemic regulation of MAPK pathways *in vivo*. Collectively, these findings suggest that coordinated inhibition of NF-κB and MAPK pathways underlines the anti-inflammatory efficacy of these species, supporting a multi-target mechanism of action (Figure 1).

6. ACTIVATION OF TRANSCRIPTION FACTOR NRF2 AS A SECONDARY ANTIOXIDANT DEFENCE MECHANISM

The nuclear factor erythroid 2-related factor 2–Kelch-like epichlorohydrin (ECH)-associated protein 1 (Nrf2–Keap1) signalling pathway functions as a critical secondary defence system, safeguarding cells against oxidative damage by complementing direct ROS scavenging mechanisms. Phytoconstituents, such as gallic acid, ellagic acid, and flavonoids, induce Nrf2 dissociation from its cytoplasmic inhibitor Keap1 during oxidative stress, leading to Nrf2 nuclear translocation and subsequent activation of antioxidant response elements (AREs) (Fakhri et al., 2020). The process increases the production of protective enzymes, including heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which together restore redox balance. The Nrf2 signalling pathway is activated when researchers administer 80 mg/kg of bark extract from *T. arjuna*, leading to increased expression of ARE-regulated genes (Nasir et al., 2026). The extracts from *A. latifolia* show increased expression of antioxidant genes, but the available data is insufficient to quantify this effect (Singhal et al., 2022). Phytochemicals exhibit two distinct antioxidant activities: firstly, they eliminate ROS, and secondly, they activate Nrf2-dependent protective systems within the body. The system provides ongoing defence against oxidative damage because oxidative stress is a key factor in the development of inflammatory disorders, cardiovascular diseases, and liver diseases (Figure 2).

7. REGULATION OF APOPTOSIS: BALANCING CYTOPROTECTION AND CYTOTOXICITY

The process of apoptosis modulation varies across contexts, resulting in both protective and harmful effects on cells. Arjunolic acid from *T. arjuna* controls mitochondrial apoptotic

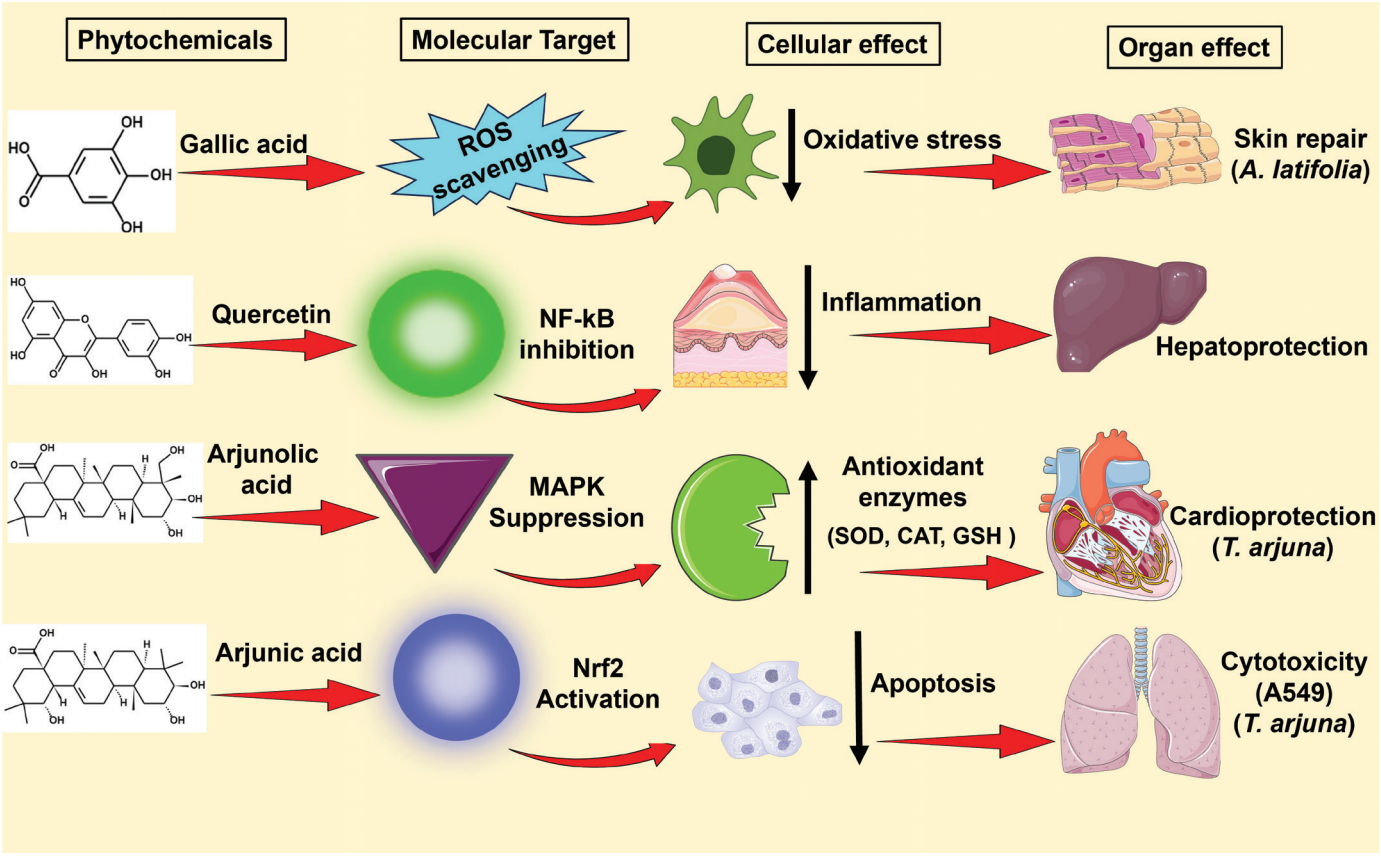


Figure 1. Phytochemicals, such as gallic acid, quercetin, arjunolic acid, and arjunic acid, exert therapeutic effects through a coordinated multilevel mechanism involving ROS scavenging, NF-κB inhibition, MAPK suppression, and Nrf2 activation. These molecular interactions reduce oxidative stress and inflammation, enhance antioxidant enzyme systems (SOD, CAT, and GSH), and regulate apoptosis, ultimately leading to organ-level outcomes, including skin repair (*A. latifolia*), hepatoprotection, cardioprotection, and anticancer activities (*T. arjuna*).

pathways by affecting Bax/Bcl-2 balance and caspase-3 pathway in H9c2 cardiomyocytes (Gouthamchandra et al., 2024). The research shows that cardiac cells develop a protective mechanism to withstand stress by preventing apoptosis. *A. latifolia* extracts exhibit harmful effects on cancer cell lines, including HepG-2, Caco-2, and MCF-7, with IC_{50} values ranging from approximately 81 to 288 µg/mL (Hassan et al., 2024). The phytochemicals exhibit two distinct effects: they prevent normal cells from dying while killing cancer cells, a property that is beneficial for developing effective medical treatments.

8. IMMUNOMODULATORY EFFECTS AND CYTOKINE REGULATION

The immunomodulatory effects of these species are most pronounced in *T. arjuna*, as its bark extracts inhibit cytokine production at an approximate IC_{50} value of 30 µg/mL (Meena et al., 2024). This mechanism controls immune reactions by preventing excessive inflammation while maintaining immune system function. This system links NF-κB suppression to antioxidant functions, forming a three-way system that controls redox, inflammatory, and immune processes.

9. INTEGRATED MECHANISTIC MODEL

The therapeutic effects of *A. latifolia*, *T. paniculata*, and *T. arjuna* arise from coordinated regulation of oxidative stress, inflammation, and cell-survival pathways (shown in Figure 1). Despite sharing a common phytochemical base (polyphenols, tannins, flavonoids, and triterpenoids), species-specific efficacy reflects differential targeting of molecular pathways, including ROS scavenging, NF-κB, MAPK, and Nrf2 signalling. Key compounds, including gallic acid, quercetin, and arjunolic acid, enhance antioxidant defences (SOD, CAT, and GSH), suppress inflammation, and regulate apoptosis,

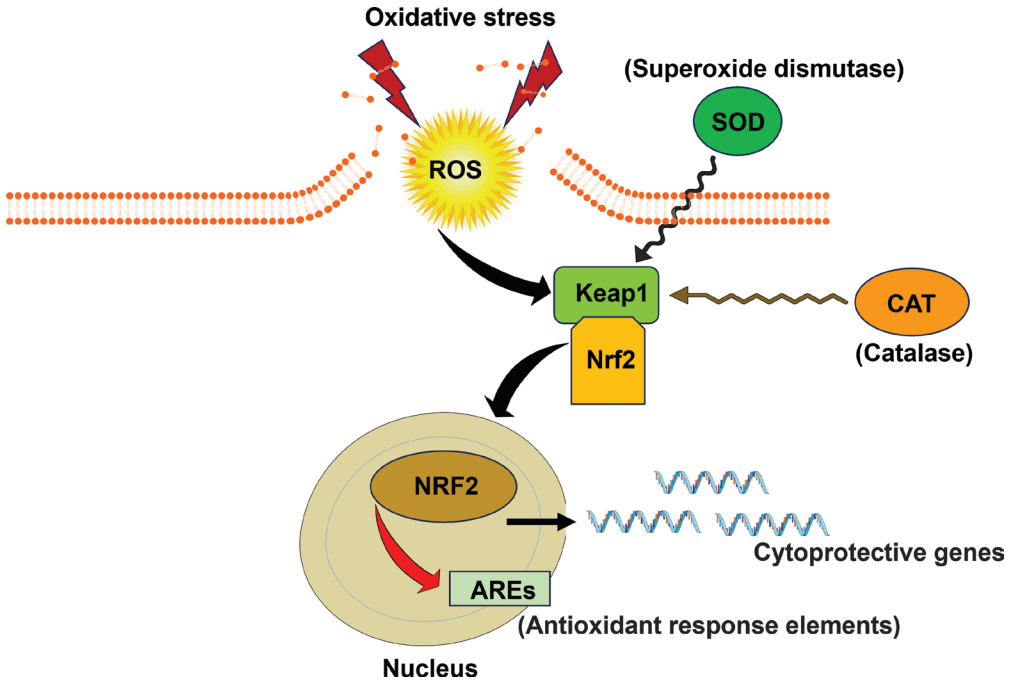


Figure 2. Schematic illustration of oxidative stress regulation via the Nrf2-Keap1 pathway. Under basal conditions, Nrf2 resides in the cytoplasm because Keap1 sequesters it; however, increased ROS levels disrupt this interaction, allowing Nrf2 to stabilise and translocate into the nucleus. The activated Nrf2 protein binds to antioxidant response elements (AREs), which trigger the production of cytoprotective proteins, including the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT). The coordinated response increases cellular capacity to produce antioxidants, decreases oxidative damage, and restores the internal balance of redox processes.

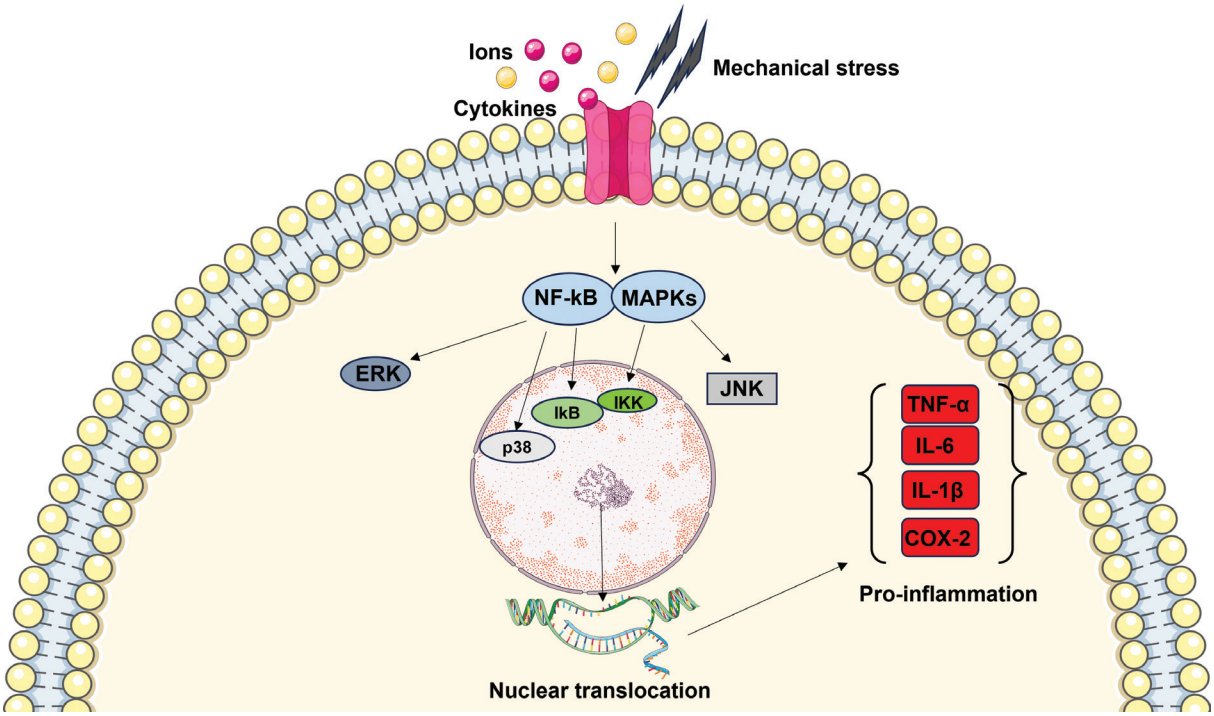


Figure 3. The diagram shows how inflammatory the NF-κB and MAPK pathways process signals. The process begins when extracellular signals bind to membrane receptors, which initiate intracellular signalling that activates MAPKs (ERK, JNK, and p38) and the NF-κB pathway via IKK-mediated phosphorylation and degradation of IκB. This mechanism enables NF-κB to move into the nucleus, where it initiates the production of pro-inflammatory mediators, such as TNF-α, IL-6, IL-1β, and COX-2.

leading to tissue-specific therapeutic outcomes (Ghosh et al., 2011; Yaidikar and Thakur, 2015). *T. arjuna* exhibits cardioprotective effects through triterpenoid-mediated modulation of mitochondrial apoptosis (↑Bcl-2, ↓Bax, and caspase-3) and improved nitric oxide (NO) bioavailability, thereby preserving myocardial and endothelial functioning (Chen et al., 2018; Ghosh et al., 2011). *T. paniculata* confers hepatoprotection via antioxidant and anti-inflammatory actions, reducing alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) levels while restoring liver integrity (Talwar et al., 2013; Younus et al., 2025). In contrast, *A. latifolia* demonstrates antimicrobial and wound-healing activity through tannin-mediated inhibition of microbes and enhanced tissue repair (Huang et al., 2024; Singhal et al., 2022; Smith et al., 2019). Collectively, these species illustrate a multi-target, network-based pharmacological model with potential for both targeted and polyherbal therapeutic strategies.

10. COMPARATIVE PHARMACOLOGY

T. paniculata demonstrates a wider range of medicinal properties which extend to multiple systems in the body while showing their active effects through hepatoprotective, anti-inflammatory, antidiabetic, and antioxidant functions. The substance demonstrates anti-inflammatory properties by blocking pro-inflammatory mediators and reducing inflammation in animal studies. The research findings demonstrate that *T. paniculata* can lower blood sugar levels and reduce fat accumulation, which indicate its potential use as a treatment for metabolic syndrome and diabetes (Ganjayi et al., 2017). The research currently indicates that, in early-stage studies, *T. paniculata* shows both cytoprotective and toxic effects (Talwar et al., 2013).

T. arjuna stands as the relatively more investigated medicinal species, which possesses the highest level of pharmacological development and clinical validation among the three studied species. The plant demonstrates its cardioprotective properties through comprehensive scientific research, including laboratory and animal studies and clinical trials, making it one of the few traditional medicinal plants that have proven their effectiveness in treating heart disease (Dwivedi, 2007). Preclinical studies demonstrate that it effectively reduces myocardial damage, enhances cardiac performance, and protects against ischemia-reperfusion injury (Maulik and Talwar, 2012). The bark extracts of *T. arjuna* are shown to be clinically effective for treating chronic stable angina, congestive heart failure, hypertension, and dyslipidemia if used in combination with standard medical treatments (Maulik et al., 2016). The substance provides cardiovascular benefits through its cardioprotective properties, which include antioxidant, anti-inflammatory, antithrombotic, and endothelial protection effects. *T. arjuna* has better dose standardisation, safety assessment, and human research, compared to its two counterpart species. However, researchers still need to conduct extensive randomised controlled trials to confirm its safety.

The species share a common mechanism that operates through antioxidant and anti-inflammatory pathways, but their main biological targets differ: *A. latifolia* utilises tannin-based antimicrobial and wound-healing methods; *T. paniculata* employs multiple hepatoprotective and metabolic pathways; and *T. arjuna* uses triterpenoid-based heart-protection methods. The integrative mechanistic framework demonstrates how phytochemicals interact with multiple pathways to produce combined effects while also identifying specific molecular targets for different species, thereby creating unique medical uses.

11. CLINICAL EVIDENCE: COMPARATIVE ANALYSIS AND CURRENT STATUS

Clinical studies on *T. arjuna* have demonstrated beneficial effects for heart protection, helping patients with angina and improving exercise capacity (Dwivedi and Chopra 2014). However, the overall clinical evidence remains limited because the research used small sample sizes, weak study designs, and failed to follow standardised research methods. The clinical evidence presented in Table 3 demonstrates that *T. arjuna* shows multiple cardioprotective effects, which depend on particular circumstances, to different cardiovascular diseases that include chronic stable angina, coronary artery disease, and chronic heart failure (CHF). Human research studies demonstrate that functional capacity and lipid parameters show consistent improvements, while the structural cardiac outcomes remain inconclusive. Patients with chronic stable angina demonstrate increased exercise tolerance, as confirmed by multiple studies. A randomised crossover study conducted by Kapoor et al. (2014) demonstrated that participants who received 500 mg every 8 h showed better treadmill exercise performance, resulting in improved functional abilities. The findings of Dutta and Das's (2023) clinical assessments showed that patients experienced a 20–30% increase in routine performance after taking doses of 500mg to 1g per day. *T. arjuna* shows potential to enhance myocardial efficiency and oxygen utilisation through mechanisms, which include greater coronary blood flow, antioxidant functioning, and regulation of endothelial functions.

A randomised controlled trial tested 750 mg of the drug, which patients used twice daily for 12 weeks, to evaluate its

Table 3
Summary of the Clinical Studies Evaluating the Cardioprotective Effects of *T. arjuna.*

Study design	Population (n)	Dose & duration	Clinical parameter	Quantitative value	Clinical interpretation	References
Randomised crossover (chronic stable angina)	58 patients (NYHA II–III)	500 mg every 8 h	Exercise tolerance	Increased treadmill time	Improved functional capacity	Kapoor et al., 2014
Randomised controlled trial (coronary heart disease)	105 patients	Not uniform	Total cholesterol	Decreased	Improved lipid profile	
Randomised controlled trial (chronic heart failure)	100 patients (LVEF ≤ 40%)	750 mg twice daily (12 weeks)	LVEF	24.3 ± 7.1–25.5 ± 7.7 (p = 0.4)	No significant change	
Stable angina	Patients with chronic stable angina	500 mg–1 g/day	Exercise tolerance (treadmill test)	20–30% increase	Improved functional capacity	Dutta and Das, 2023
Coronary artery disease (CAD)	Patients with CAD	Variable	Total cholesterol	10–20% reduction	Lipid-lowering effect	
Chronic heart failure	Patients (reduced LVEF)	750–1500 mg/day	LVEF	~1–3% increase (not significant)	Limited structural improvement	
Case study	Hypertension, type 2 diabetes	6 g twice daily (oral) for 12 weeks	Cardiovascular risk grade	Improved	Reduced cardiovascular risk	Parveen et al., 2025

Note: LVEF: left ventricular ejection fraction.

effects in CHF patients with left ventricular ejection fraction (LVEF) ≤ 40%. The treatment produced a small increase in LVEF from 24.3 ± 7.1 to 25.5 ± 7.7, which was not statistically significant (p = 0.4). Results from other studies show that *T. arjuna* produces slight LVEF increase of 1–3%, which indicates that the treatment has limited power to restore normal cardiac functions. The distinction between these two factors creates a critical restriction on treatment options that exist for patients suffering from advanced heart failure. Another study (Parveen et al., 2025) presents a current case study which delivers basic clinical knowledge about the topic. A patient with multiple health conditions, including hypertension and type 2 diabetes, showed better cardiovascular risk assessment results after receiving high-dose treatment, which included 6 g of medication twice each day over 12 weeks. Single-case designs have control and generalizability problems, limiting the generalizability of promising findings. The discrepancy between functional improvement and limited structural recovery suggests a predominantly metabolic or endothelial mechanism rather than direct myocardial remodelling.

The current clinical research conducted on *T. paniculata* and *A. latifolia* remains limited, as these plants have been studied primarily through laboratory and animal testing. The existence of preclinical evidence demonstrating high treatment effectiveness prevents clinics from using these treatments, which should follow evidence-based medical standards. Research needs to focus on developing multicentre randomised controlled trials that include standardised phytochemical testing and dose determination, as well as long-term safety studies, to demonstrate clinical effectiveness and reproducibility. The research must demonstrate the validity of traditional medicine's uses while enabling scientists to develop new phytopharmaceuticals from these species, which can become valid candidates for modern integrative medicine.

12. FUTURE PERSPECTIVES AND CHALLENGES

Future investigations should emphasise translational validation by advancing these species into well-designed clinical trials to substantiate their therapeutic efficacy and safety. The therapeutic efficacy and safety of *T. arjuna* in cardiovascular disorders require confirmation through large-scale, multicentre, randomised controlled trials. Well-designed early-phase clinical studies are needed to establish traditional claims about *A. latifolia* and *T. paniculata* as they could identify optimal dosing and safety profiles. The integration of biomarker-driven endpoints with pharmacodynamic assessments increases clinical testing accuracy and support regulatory approval processes. The research direction needs to focus on developing advanced delivery systems that use nanocarriers, such as liposomes, phytosomes, and hydrogel-based formulations, to improve the bioavailability and stability of phytoconstituents. Future strategies should also emphasise polyherbal and systems-based approaches that leverage the complementary pharmacological profiles of these species to

develop multi-target therapies for complex diseases. The combination of systems pharmacology and network modelling provides robust methods for optimising combination therapies in this research area. Clinical research requires a comprehensive assessment of pharmacokinetics (ADME), herb-drug interactions, and long-term safety to achieve patient acceptance. The plants contain active compounds, which scientists can transform into new substances through partial chemical changes. The integration of artificial intelligence (AI) and molecular docking with computational methods can accelerate lead optimisation and target identification to develop new phytopharmaceuticals.

Despite the promising pharmacological potential of *A. latifolia*, *T. paniculata*, and *T. arjuna*, several critical challenges limit their translational applicability. The lack of standardised phytochemical profiling, with significant variability, arises from differences in plant sources, extraction methods, and the absence of validated marker compounds. In addition, mechanistic understanding remains insufficient as most studies report pathway-level associations without detailed target validation, dose–response relationships, or systems-level integration. Another key challenge is the limited availability of well-designed clinical studies, particularly across different species, which restrict the establishment of clear efficacy and safety profiles. Addressing these challenges through standardised methodologies bridges the existing gaps and enables the effective development of these species into evidence-based therapeutics.

13. CONCLUSIONS

The researchers conducted an integrated comparative review demonstrating that *A. latifolia*, *T. paniculata*, and *T. arjuna* share similar phytochemical profiles, but their medicinal uses differ. The three species share a common polyphenolic and triterpenoid chemical structure, yet they have distinct medicinal uses and properties: *A. latifolia* extracts possess antimicrobial and wound-healing properties; *T. paniculata* extracts exhibit liver-protective and anti-inflammatory effects; and *T. arjuna* extracts exhibit heart-protective properties. The research provides strong preclinical evidence for *T. arjuna*, yet its clinical development has shown inconsistent progress because the plant has not yet achieved adequate clinical backing, while *A. latifolia* and *T. paniculata* require comprehensive clinical research and standardised profiling methods. The functional complementarity of these species supports their potential in multi-target and polyherbal strategies for complex diseases. Future research should focus on standardisation, clinical validation, and integrative approaches, such as omics and advanced delivery systems. This study provides a clear framework for advancing Combretaceae species into scientifically validated phytopharmaceuticals.

AUTHOR CONTRIBUTIONS

Kandavel Dhandayuthapani: Critical revision of the article, and final approval of the article; Panjatcharam Varadharasu: research concept and design, collection and/or assembly of data, and data analysis and interpretation; Pushparaj Annadurai: collection and/or assembly of data and writing the article; and Balamurugan Sundarrajan: critical revision of the article.

CONFLICTS OF INTEREST

Authors declared no conflict of interest for this work.

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