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Comprehensive analysis of the chemical composition, bioactivities, and applications in human health of *Artocarpus tonkinensis* A. Chev. ex Gagnep

Análisis exhaustivo de la composición química, bioactividades y aplicaciones en la salud humana de *Artocarpus tonkinensis* A. Chev. ex Gagnep

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ABSTRACT

Artocarpus tonkinensis A. Chev. ex Gagnep. is an endemic Vietnamese tree that has gained scientific relevance due to its traditional ethnomedicinal uses and emerging nutraceutical potential; however, a comprehensive and systematized synthesis of its chemical composition and biological activities remains limited. This study aimed to critically compile and analyze published scientific evidence on the phytochemical constituents, bioactivities, toxicity, and potential applications of *A. tonkinensis.* A structured review of peer-reviewed literature was conducted, focusing on studies addressing chemical characterization, *in vitro* and *in vivo* biological assays, and pharmacological evaluations. The analysis showed that a wide range of secondary metabolites, including flavonoids, benzofurans, chalconoids, and phenolic acids, have been isolated from different plant tissues. Experimental evidence indicates that extracts and isolated compounds exhibit significant anti-inflammatory, antioxidant, immunomodulatory, and anticancer activities. *In vivo* studies reported reductions in arthritis severity ranging from 30 to 60%, together with decreased serum levels of pro-inflammatory cytokines such as TNF-α and IL-6. This review highlights relevant structure–activity relationships, summarizes available toxicity data, and discusses the therapeutic and pharmacological prospects of this species. Overall, the compiled evidence provides a coherent and verifiable scientific basis supporting the potential of *A. tonkinensis* as a source of bioactive compounds and underscores the need for further biochemical, pharmacological, and applied research.

Palabras clave:
Antiinflamatorio
Artocarpus tonkinensis
Inmunomodulador
Plantas medicinales
Metabolitos secundarios

RESUMEN

Artocarpus tonkinensis A. Chev. ex Gagnep. es un árbol endémico de Vietnam que ha adquirido relevancia científica debido a sus usos etnomedicinales tradicionales y a su emergente potencial nutracéutico; sin embargo, aún es limitada la existencia de una síntesis integral y sistematizada de su composición química y actividades biológicas. El objetivo de este estudio fue recopilar y analizar críticamente la evidencia científica publicada sobre los constituyentes fitoquímicos, las bioactividades, la toxicidad y las posibles aplicaciones de *A. tonkinensis*. Se realizó una revisión estructurada de la literatura científica arbitrada, enfocada en estudios que abordan la caracterización química, ensayos biológicos *in vitro* e *in vivo* y evaluaciones farmacológicas. El análisis mostró que una amplia variedad de metabolitos secundarios, incluidos flavonoides, benzofuranos, chalconas y ácidos fenólicos, han sido aislados de diferentes tejidos de la planta. La evidencia experimental indica que los extractos y compuestos aislados presentan actividades antiinflamatorias, antioxidantes, inmunomoduladoras y anticancerígenas significativas. Estudios *in vivo* reportaron reducciones en la severidad de la artritis que oscilaron entre 30 y 60%, junto con una disminución en los niveles séricos de citocinas proinflamatorias como TNF-α e IL-6. Esta revisión destaca las relaciones estructura–actividad, resume los datos disponibles sobre toxicidad y discute las perspectivas terapéuticas y farmacológicas de esta especie. En conjunto, la evidencia compilada proporciona una base científica coherente y verificable que respalda el potencial de *A. tonkinensis* como fuente de compuestos bioactivos y subraya la necesidad de realizar investigaciones bioquímicas, farmacológicas y aplicadas adicionales.

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The genus *Artocarpus* J.R. Forst. & G. Forst. (Family: Moraceae) comprises more than 50 species widely distributed throughout tropical Asia and Africa. Several species, such as *Artocarpus heterophyllus*, *Artocarpus altilis*, and *Artocarpus integer*, are known for their edible fruits and bioactive compounds, particularly flavonoids and prenylated phenolics with pharmacological potential. Within this genus, *Artocarpus tonkinensis* A. Chev. ex Gagnep. (commonly known in Vietnam as "Chay"), it is endemic to the mountainous regions of Northern Vietnam, especially Lai Chau, Lao Cai, Tuyen Quang, Cao Bang, and Lang Son (Dang et al. 2009).

Morphologically, *A. tonkinensis* produces distinctive fruits with two main variants: red- and yellow-fleshed types. The red-fleshed fruits are typically round with pale green to yellow skin when ripe, while the yellow-fleshed ones are more elongated and irregular with a slightly concave or convex surface (Figure 1). These macroscopic features help distinguish *A. tonkinensis* from other *Artocarpus* species, such as *A. integer* and *A. altilis* (Hộ 2003; Tang et al. 2021).

Beyond fruit morphology, several *Artocarpus* species have been reported to accumulate diverse secondary metabolites in different plant parts, including flavonoids, tannins, stilbenes, and triterpenoids. In particular, bark and root tissues are often rich in condensed and hydrolysable tannins, which are associated with antioxidant, antimicrobial, and anti-inflammatory properties (Lợi 2004; Jagtap and Bapat 2010). These phytochemical features suggest that non-fruit parts of *Artocarpus* species may represent valuable sources of bioactive compounds.

Figure 1. *A. tonkinensis* fruit, and cross-section: **A**. Red-fleshed fruit, and **B**. Yellow-fleshed fruit.

A. tonkinensis is traditionally regarded in Vietnamese ethnomedicine as a medicinal plant, particularly among some ethnic minority communities. According to local traditional practices and ethnobotanical knowledge, its leaves were used as decoctions to treat rheumatoid arthritis, back pain, and joint inflammation. In addition, previous studies have shown that *A. tonkinensis* leaves are rich in flavonoid glycosides and exhibit notable anti-inflammatory, immunomodulatory, and anticancer potential, supporting its traditional medicinal use (Linh et al. 2020). During wartime, decoctions from *A. tonkinensis* leaves were reportedly used to manage autoimmune diseases such as lupus erythematosus (Thủy et al. 2015).

From a pharmacological perspective, tannin-rich extracts from medicinal plants have been reported to modulate inflammatory pathways, inhibit oxidative stress, and contribute to joint-protective effects in chronic inflammatory diseases (Fraga-Corral et al. 2021). The presence of flavonoid glycosides and tannins in *A. tonkinensis* leaves, bark, and roots therefore provides a plausible biochemical basis for its traditional use in treating rheumatoid and autoimmune-related disorders.

Despite these advances, most available research focuses on *in vitro* or preliminary *in vivo* findings, and there remains a lack of systematic data on standardized extraction procedures, dose-response relationships, and long-term toxicity. Furthermore, quantitative studies on antibacterial or anti-inflammatory potency and the potential for industrial-scale applications are limited.

Therefore, this study aims to provide an integrated analysis of the chemical composition, biological properties, and potential pharmacological applications of *Artocarpus tonkinensis* A. Chev. ex Gagnep., highlighting the current knowledge, existing research gaps, and perspectives for future development.

MATERIALS AND METHODS

This study was conducted using a narrative and scoping approach to synthesize and critically evaluate available scientific evidence on *Artocarpus tonkinensis*. Scientific literature was systematically collected from multiple databases, including Scopus, Google Scholar, PubMed, and Vietnam Journals Online (VJOL). Additional records were identified through manual screening of reference lists and relevant documents published by national research institutes, local universities, and Vietnamese regulatory agencies. The primary literature search focused on studies published between 1998 and 2024. When relevant data were scarce, earlier publications were also considered to ensure comprehensive coverage of this relatively underexplored species.

The inclusion criteria comprised peer-reviewed journal articles, academic theses, and authoritative reports written in English or Vietnamese that addressed the botany, ethnomedicinal uses, phytochemical composition, and pharmacological activities of *Artocarpus tonkinensis*. Exclusion criteria included non-scientific sources (e.g., popular media or anecdotal reports), duplicated records, review articles without original data, studies unrelated to *A. tonkinensis*, and publications lacking verifiable experimental methods or results.

The literature search employed combinations of the following keywords: "*Artocarpus tonkinensis*", "phytochemical composition", "bioactive compounds", "anti-inflammatory activity", "traditional medicine", "anticancer", "antioxidant", "nutraceutical", "toxicity", and "pharmacological effects".

After removal of duplicate and non-relevant records, titles and abstracts were screened for relevance, followed by full-text assessment of eligible publications. In total, 34 studies were included in the qualitative synthesis, comprising 19 articles indexed in international journals (Scopus and PubMed), 7 additional records retrieved via Google Scholar, and 8 publications from Vietnamese scientific sources, including VJOL-indexed journals, academic books, and institutional reports.

A narrative review approach was applied to synthesize and critically discuss the collected data, which were organized into thematic sections covering taxonomy and distribution, traditional medicinal uses, chemical constituents, and biological activities, with particular emphasis on anti-inflammatory properties and potential applications in modern medicine.

RESULTS AND DISCUSSION

Phytochemical constituents

To date, only a limited number of studies (approximately 10 publications) have investigated the phytochemical composition of *Artocarpus tonkinensis*. These studies indicate an uneven distribution of secondary metabolites among different plant parts, with the leaves being the most extensively studied. The major classes of compounds identified from the leaves and their associated biological activities are summarized in Table 1. The leaves are the most thoroughly and in-depth studied part, both in terms of the number of isolated compounds and the evaluation of biological activities. From the n-butanol extract of the leaves, two important flavonoids were isolated, the auronol glycosides maesopsin 4-O-glucoside and the alphitonin 4-O-glucoside. They showed significant immunosuppressive effects through inhibition of lymphocyte proliferation and induction of apoptosis in activated T cells, as well as the inhibition of NOS_2 activity and IL-6 expression in macrophages. Among the flavonoid glycosides isolated from the leaves, maesopsin 4-O-glucoside and alphitonin 4-O-glucoside were shown to exert strong immunomodulatory and anti-inflammatory effects. These compounds suppressed osteoclastogenesis via downregulation of the RANK–Src pathway, protected bone and cartilage, and inhibited Th17 lymphocyte proliferation (Thuy et al. 2004; Orecchini et al. 2021). Another flavonoid glycoside from the leaves, artonkin 4′-O-glucoside, was reported to modulate pro-inflammatory cytokines, including TNF-α, IL-6, and IFN-γ, in an experimental arthritis model (Dang et al. 2009). Some prenylated flavonoid compounds, such as cycloartocarpesin and artonin E, were isolated from the aqueous extract of the leaves and have also been reported to possess anticancer and immunomodulatory effects *in vitro*, as evidenced by the inhibition of lymphocyte proliferation and modulation of inflammatory mediator production (Thủy et al. 2015), although data on them are still limited.

Table 1. Secondary metabolites with biological activity isolated from *A. tonkinensis*

Part	Secondary metabolite	Chemical group	Biological activities	References
Leaves	Flavonoid afzelechin 3- O -α rhamnopyranoid	Flavonoid glycoside	Antioxidant, anti-inflammatory	Ha et al. (1994)
	Maesopsin 4-O-glucoside	Flavonoid glycoside	Anti-inflammatory	Thuy et al. (2004); Thuy et al. (2016)
	Alphitonin 4-O-glucoside	Flavonoid glycoside	Apoptosis of an activated T cell	Thuy et al. (2004)
	Artonkin 4'-O-glucoside	Flavonoid glycoside	Modulation of inflammatory cytokines TNF-α, IL-6, IFN-γ	Dang et al. (2009)
	Cycloartocarpesin, Artonin E	Prenylated flavonoids	Antitumoral, immunomodulatory	Thủy et al. (2015)
	Glycoside and aglycone	Polyphenol	Antioxidant potential	Quan et al. (2018)
	Maesopsin 4-O-β-D-glucoside (TAT-2)	Flavonoid glycoside	Anti-inflammatory and anti-arthritic activities	Orecchini et al. (2021)
	2-Arylbenzofuran derivatives	Benzofuran	Antiproliferative potential	Guo et al. (2024)
Bark, roots	Catechin, kaempferol, and ampelopsin	Flavonoid glycoside	Antioxidant, anti-inflammatory	Lien et al. (1998)
Trunk	2-Arylbenzofuran	Benzofuran	Antitumoral potential	Guo et al. (2024)
Roots	Artotonin A, Artotonin B	Prenylated flavonoids	Cytotoxicity against hepatocellular and gastric carcinoma cell lines (SMMC-7721, BGC-823, SGC-7901)	Ma et al. (2010)
Roots	Morusin, Cudraflavone C, Cyclocommunol	Prenylated flavonoids/ Polyphenol	Strong *in vitro* cytotoxicity against human cancer cell lines	Ma et al. (2010)

Notes: "-" not tested

Chemical investigations of *A. tonkinensis* leaves revealed the presence of 2-arylbenzofuran derivatives, a class of benzofuran-type phenolic compounds, mainly isolated from organic solvent extracts and structurally characterized by NMR and MS analyses (Guo et al. 2024). To date, no specific biological activities have been reported for these compounds from *A. tonkinensis*. In addition, polyphenols in both glycoside and aglycone forms were detected in the 70% ethanol leaf extract, including the flavonoid glycosides hovetrichoside C and alphitonin-4-O-β-D-glucopyranoside. These compounds mainly belong to flavonoids and glycosides, as identified by chromatographic and spectroscopic analyses, suggesting a potential contribution to antioxidant properties, although direct bioactivity evaluations remain limited (Quan et al. 2018). Some prenylated flavonoids, such as cycloartocarpesin and artonin E, were isolated from organic solvent extracts of the leaves and were reported to exhibit anticancer and immunomodulatory effects, mainly evaluated through *in vitro* and *in vivo* experimental models (Thủy et al. 2016), although available data remain limited.

Furthermore, ethyl acetate (EtOAc) extracts of the leaves have shown the ability to slow down graft rejection and inhibit the growth of lymphocytes in animal models (Ha et al. 1994; Lien et al. 1998).

Notably, some compounds such as cycloartocarpesin, which is a natural triterpenoid, have been detected in the leaves of *Artocarpus elasticus* (Ramli et al. 2013), also occur in *A. tonkinensis*, suggesting chemical overlap within the genus *Artocarpus*. This is consistent with the observation of Lathiff et al. (2021), indicating that compounds such as cycloartocarpesin, p-hydroxybenzoic acid, and stigmasterol—previously reported to possess anticancer, antioxidant, antimicrobial, and anti-inflammatory

activities—are common constituents in many *Artocarpus* species, especially in the leaves and bark. In addition, EtOAc extracts of different plant parts, including roots, leaves, and bark, were reported to contain various secondary metabolites, such as lectins, the stilbene oxyresveratrol, the triterpenoid β-amyrin acetate, and several flavonoids, including afzelechin 3-O-α-rhamnopyranoside, catechin, kaempferol, and ampelopsin. Specifically, afzelechin 3-O-α-rhamnopyranoside, catechin, kaempferol, and ampelopsin were isolated from the ethyl acetate extracts of the leaves and bark, whereas β-amyrin acetate and oxyresveratrol were mainly identified from root and bark extracts. Ampelopsin (dihydromyricetin), a flavonoid widely reported in other *Artocarpus* species and related genera, has been associated with antioxidant, anti-inflammatory, and hepatoprotective activities in various *in vitro* and *in vivo* models, although its biological activity has not yet been directly evaluated in *A. tonkinensis* (George et al. 2016).

About the roots, although not as extensively investigated as the leaves, be a rich source of valuable prenylated flavonoids, including artotonin A, artotonin B, morusin, cudraflavone C, and cyclocommunol. These compounds exhibited potent *in vitro* cytotoxic activity against various cancer cell lines, such as liver (SMMC-7721) and stomach (BGC-823, SGC-7901) (Ma et al. 2010). The presence of the prenylated flavonoid group in the root demonstrates its biological potential, especially in the field of cancer treatment.

The stem is the least studied part; however, some recent studies have shown the presence of 2-arylbenzofuran derivatives with an uncommon benzofuran scaffold compared to the major phenolic classes typically found in *Artocarpus* (Guo et al. 2024). Although no in-depth evaluation of biological activity has been performed, the biological activities of these compounds remain unexplored.

In contrast, the fruit of *A. tonkinensis* remains poorly investigated, with no reports to date on its chemical composition or biological activity. Despite its traditional consumption by ethnic minority communities in the mountainous regions of Northern Vietnam. Elucidating its phytochemical profile may provide a scientific basis for future applications in medicinal and functional food development.

Immunomodulator activity

Artocarpus tonkinensis has been shown to have potent immunomodulator effects in multiple models *in vitro* and *in vivo* (Table 2). The anti-inflammatory mechanism of this plant is thought to be mainly related to its ability to modulate T-cell-mediated immune responses and pro-inflammatory cytokines (Thuy et al. 2004).

Table 2. Immunomodulator activity of *A. tonkinensis*.

Parts	Extract/Main Compound	Research model	Anti-inflammatory Mechanism/ Effect	References
Leaves	Ethyl acetate (EtOAc) extract	Collagen-induced arthritis (CIA) model in mice	Reduces inflammation, joint edema, tissue damage; inhibits T cell activation and induces apoptosis	Thuy et al. (2004)
	Aqueous decoction (whole leaf extract)	*In vivo* (Collagen-induced arthritis in DBA/1 mice)	Prevents clinical arthritis symptoms; preserves cartilage; inhibits inflammatory cell infiltration; modulates 39 autoimmune-related genes	Rosseto et al. (2015)
	Alphitonin-4-O-β-D-glucopyranoside	*In vitro* (macrophage), *In vivo* (rat model)	Inhibition of IL-2 (1,000 μg mL^{-1}), increase of IL-4 (500 μg mL^{-1}); causes thymic atrophy in mice (18.8% reduction in thymic weight)	Vượng and Dương (2017)

Table 2.

Parts	Extract/Main Compound	Research model	Anti-inflammatory Mechanism/Effect	References
Leaves and root	Ethyl acetate extract	*In vivo* (Collagen-Induced Arthritis mouse)	Reduces the incidence and severity of arthritis; inhibits T cell proliferation; promotes lymph node cell apoptosis; immunomodulatory	Jagtap and Bapat (2010)
	Ethyl acetate (EtOAc) extract	*In vivo* (CIA on Dark Agouti rats), *In vitro* (LN cells)	Reduces the incidence and severity of arthritis; inhibits T-cell proliferation; induces activated lymphocyte apoptosis; regulates immunity through T cells	Ngoc et al. (2005)
Root	Prenylated flavonoids	*In vitro*	Immune regulation supports systemic anti-inflammatory	Ma et al. (2010)

In an *in vivo* collagen-induced arthritis (CIA) mouse model, the leaf extract of *A. tonkinensis*, administered intraperitoneally at 15 mg kg^{-1} per day, significantly reduced inflammation and delayed disease onset through the suppression of TNF-α, IFN-γ, and IL-6. In complementary *in vitro* assays, the extract showed no significant cytotoxicity at therapeutically relevant concentrations, indicating a favorable safety profile.

Studies have shown that *A. tonkinensis* leaf extract has the ability to inhibit lymphocytic cell proliferation and reduce the expression of inflammatory cytokines such as TNF-α, IL-6, and IFN-γ. In a collagen-induced arthritis (CIA) model in mice, ethyl acetate (EtOAc) extract from the leaves significantly reduced the level of inflammation, joint edema, and tissue damage (Thuy et al. 2017). This is explained by the inhibitory effect on T cell activation and apoptosis induction in peripheral lymphocytes, thereby limiting the chronic inflammatory process.

Within this immunomodulatory context, previous studies have demonstrated that the activity of *A. tonkinensis* leaf extracts is mainly attributed to flavonoid glycosides, particularly maesopsin-4-O-glucoside and artonkin-4′-O-glucoside. These compounds were shown to inhibit T-cell proliferation and suppress the production of pro-inflammatory cytokines *in vitro* (Dang et al. 2009).

Furthermore, some prenylated flavonoids isolated from the roots also showed certain immunomodulatory activities (Ma et al. 2010). Besides, ethyl acetate extract from *A. tonkinensis* leaves and roots showed significant immunomodulatory activity in an experimental arthritis model, through T-cell inhibition (Ngoc et al. 2005; Jagtap and Bapat 2010).

Taken together, the present results suggest the potential application of *A. tonkinensis* as a natural source of anti-inflammatory and immunomodulatory agents, particularly for chronic diseases associated with excessive immune responses, such as rheumatoid arthritis. However, further studies are needed to better understand the molecular mechanisms and to evaluate clinical safety and efficacy.

Anti-cancer potential

A. tonkinensis has shown great promise in the field of cancer research due to the presence of prenylated flavonoids that have potent cytotoxic activity against several cancer cell lines. Specifically, artotonins A and B were isolated from the roots, along with other compounds such as morusin, cudraflavone C, and cyclocommunol. The artotonin compounds exhibited significant cytotoxic activity *in vitro* against liver (SMMC-7721), gastric (BGC-823, SGC-7901), and cervical (HeLa) cancer cell lines, with IC_{50} values ranging from 2 to 15 μM (Ma et al. 2010). In addition, morusin was shown to inhibit

proliferation and induce apoptosis in HT-29 colorectal cancer cells through mechanisms involving the p53 and caspase-3 pathways (Pozzesi et al. 2011).

Auronol glycosides and polyphenols in *Artocarpus* species, such as morusin, artocarpin, and artonin E, have been reported to exhibit significant anticancer activity through the inhibition of cancer cell proliferation and the induction of apoptosis in various human cancer cell lines (Somashekhar et al. 2013).

The study of *A. tonkinensis* secondary metabolites with anticancer activity becomes necessary because of the possibility of multitargeted cancer therapeutic applications, including proliferation inhibition, apoptosis induction, and suppression of tumor-associated inflammation.

Antioxidant activity

Although no published studies have directly evaluated the antioxidant activity of *A. tonkinensis* using methods such as DPPH, ABTS, or FRAP, the secondary metabolites identified in this species suggest significant antioxidant potential. Flavonoid glycosides, such as maesopsin-glucoside and alphitonin-glucoside, the polyphenols, and prenylated flavonoids, have been reported to exhibit antioxidant activity in other Artocarpus species, particularly *A. heterophyllus* and *A. altilis*, where compounds such as artocarpin, morusin, and related prenylated flavonoids showed strong radical-scavenging activity and inhibition of oxidative enzymes (Palupi et al. 2020).

For example, the aqueous extract from *A. heterophyllus* exhibited strong DPPH radical scavenging activity with an IC_{50} value of 73.5 μg mL^{-1}, while the aqueous fraction of this species showed the highest efficiency in the FRAP assay with an IC_{50} = 72.0 μg mL^{-1} (Loizzo et al. 2010). Besides, many flavonoids of the genus Artocarpus were reported to scavenge DPPH radicals with IC_{50} values ranging from 18.7 to 42.2 μM, while also exhibiting inhibitory activity against xanthine oxidase, a key enzyme involved in endogenous antioxidant mechanisms, with IC_{50} values between 43.3 and 73.3 μM (Lin et al. 2009).

Data from species in the genus partly support the hypothesis that *A. tonkinesis* may have significant antioxidant activity. However, the lack of specific experimental evidence raises the need for further studies to determine active fractions, active secondary metabolites, the specific activity levels, and mechanisms of action of the compounds in this species.

Toxicity and safety regulations

Preliminary existing toxicity studies show that the extract from *Artocarpus tonkinensis* leaves has a relatively high biosafety profile, especially at doses commonly used in traditional medicine.

In a study by Dang et al. (2009), *in vitro* safety and biological activity were first evaluated using murine splenocytes and macrophage-related immune cell models. The isolated flavonoid glycosides, particularly artonkin-4′-O-glucoside and maesopsin-4-O-β-D-glucoside, showed no significant cytotoxicity at concentrations up to 50 μg mL^{-1} after 48 h of exposure, maintaining cell viability above 95%. These compounds inhibited T-cell proliferation and reduced pro-inflammatory cytokine production under stimulated conditions. Subsequently, *in vivo* evaluation was conducted in a collagen-induced arthritis (CIA) mouse model, where the leaf ethyl acetate extract, administered intraperitoneally at 15 mg kg^{-1} per day for 21 consecutive days, did not induce changes in body weight or abnormal behavior, indicating good tolerability. Together, these results demonstrate that both the isolated flavonoid glycosides and the leaf extract of *A. tonkinensis* exhibit favorable safety profiles *in vitro* and *in vivo*, supporting their further investigation as immunomodulatory agents (Dang et al. 2009).

In an acute toxicity study in mice, the ethanolic residue of chay leaves did not cause any abnormal symptoms or death at a maximum oral dose of 42.9 g kg^{-1} body weight - the highest dose that could be tested. During the 7-day follow-up period, no significant toxic manifestations were observed (Thủy et al. 2016).

In addition, an 8-week subchronic toxicity test on rabbits showed that, at both dose levels (0.6 g kg^{-1} per day and 1.8 g kg^{-1} per day), TAT-2 did not negatively affect general physiological status, growth rate, hematological indices, as well as liver function (AST, ALT, bilirubin, albumin) and kidney function (creatinine). Histological observations of organs such as liver and kidney also did not record any significant damage, confirming the high safety level of TAT-2 under

short- and medium-term use conditions (Thủy et al. 2016). In another study, maesopsin 4-O-β-D-glucoside (TAT-2), isolated from the ethanolic extract of *A. tonkinensis* leaves, did not show signs of acute toxicity at the highest tested dose of 2,000 mg kg^{-1} body weight in tumor-bearing mice. At therapeutic doses of 100 and 200 mg kg^{-1} body weight, TAT-2 exhibited significant antitumor activity, as evidenced by reduced tumor growth, increased survival rate, and improvement of hematological and biochemical parameters, although LD_{50} values and chronic toxicity data have not yet been reported (Thuy et al. 2016). Similarly, Quan et al. (2018) reported that administration of the ethanolic leaf extract in a mouse model of arthritis at 15 mg kg^{-1} per day did not affect behavior, body weight, survival rate, or liver enzyme levels (AST and ALT), indicating good tolerability. Overall, the available toxicity data indicate that the pharmacological activities of *A. tonkinensis*, including anti-inflammatory, immunomodulatory, and anticancer effects, occur at doses that are well tolerated in both *in vitro* and *in vivo* models. This supports the potential of *A. tonkinensis* and its flavonoid glycosides as promising candidates for further preclinical and applied pharmacological research.

Prospects for the application of medicinal herbs - functional foods

With its diverse chemical composition and a wide range of reported biological activities, including anti-inflammatory, anticancer, and antioxidant effects, *Artocarpus tonkinensis* has been regarded as a promising plant for the development of medicinal preparations and functional food products intended to support disease management (Table 3).

Table 3. Traditional uses, experimental evidence, and application prospects of *Artocarpus tonkinensis*.

Plant part	Traditional use/ form of use	Reported dose or preparation	Experimentally supported activity	Level of evidence	Potential application	Reference
Leaves	Decoction for bone and joint pain, rheumatoid arthritis, and general health support	10–20 g per day as a decoction	Anti-inflammatory, immunomodulatory (T-cell inhibition, cytokine suppression)	*In vitro*, *in vivo* (CIA models)	Herbal medicine, an immunomodulatory functional beverage	Dang et al. (2009); Quan et al. (2018); Vượng and Dương (2017)
Leaves (EtOH / EtOAc extract)	Folk medicine, arthritis treatment	15 mg kg^{-1} per day (animal studies)	Reduced joint inflammation, Th17 suppression, cartilage protection	*In vivo* (mouse models)	Standardized phytopharmaceuticals	Ngoc et al. (2005); Adorisio et al. (2019)
Leaves (isolated flavonoids: TAT-2, artonkin-4′-O-glucoside)	—	100–200 mg kg^{-1} (TAT-2)	Antitumor, anti-inflammatory, immunosuppressive	*In vitro*, *in vivo*	Lead compounds for drug development	Pozzesi et al. (2011)
Fruits (ripe)	Consumed fresh or as juice for respiratory and digestive support	5–7 fruits/time; ~16 g dried fruit	No direct pharmacological assays	Ethnomedicinal	Functional food, fermented beverage, jam	Reichart and Nguyen (2008)
Fruits (processed)	Culinary use, digestion aid	Braised dishes, fermented products	High soluble solids (~13°Brix)	Sensory analysis	Functional foods, flavoring ingredients	This study
Roots	Decoction for rheumatis, gynecological disorders	Boiled roots in water	No direct modern validation	Ethnomedicinal	Traditional herbal medicine	Bích et al. (2006)

In Vietnam, *A. tonkinensis* is commonly used in folk medicine with many different uses. The leaves are often boiled to make drinking water to support the treatment of bone and joint diseases and improve overall health (Vượng and Dương 2017). In northern Vietnam, it is used by the Hmong ethnic minority to treat arthritis and back pain (Delfino et al. 2016; Adorisio et al. 2016).

According to Reichart and Nguyen (2008), ripe fruits of *A. tonkinensis* are traditionally consumed fresh or as juice (5–7 fruits per use) to support respiratory and digestive health. When fresh fruits are unavailable, dried fruits (≈ 16 g) or root decoctions are used. The fruit is also incorporated into traditional dishes, and the bark is occasionally added during betel chewing to enhance astringency.

The roots and leaves are commonly used in remedies for bone and joint pain, rheumatism, with a usual dose of about 10–20 g per day in the form of a decoction. To enhance therapeutic efficacy, these remedies are often combined with other medicinal plants, such as Smilax glabra, rather than used alone. In addition, the roots of *A. tonkinensis* are also employed in the treatment of gynecological conditions, including menstrual disorders, menorrhagia, and vaginal discharge (Bích et al. 2006).

As functional foods, a preliminary evaluation of the sensory properties and total soluble solids (TSS) content of two types of *A. tonkinensis* fruit was conducted. The fruits were characterized by red- and yellow-fleshed types. Both types exhibited a distinct sour taste; however, the red-fleshed fruit showed a stronger flavor intensity and a sweeter aftertaste. The TSS values were approximately 13%, indicating a relatively high content of soluble solids, mainly sugars and organic acids. Based on these sensory characteristics, *A. tonkinensis* fruit was considered unsuitable for general fresh consumption but showed potential for processing into value-added products such as jam, dried fruit, fermented beverages, or as a flavoring ingredient in functional food formulations. This processing-oriented utilization was regarded as more appropriate given the intrinsic sensory properties of the raw material and consumer preferences for mildly sour flavors.

Challenges and future

The development of *A. tonkinensis* into medicinal products or functional foods faces many challenges: the lack of information on the importance of seasonality in its biological properties, the instability of raw material sources, the lack of standardized cultivation systems and extraction processes, the limited consumer and market awareness, the lack of clinical data and long-term safety evidence, and the legal barriers and lack of commercialization strategy.

A. tonkinensis trees are often scattered in the high mountainous regions of Northern Vietnam. Most of the current raw material sources still depend on natural exploitation, and there is no concentrated growing area. The fruit usually ripens and is harvested from June to August every year (Lợi 2004). However, due to the uneven distribution of trees and the influence of climatic conditions, annual fruit yields can fluctuate significantly. In addition, harvesting fruit during the rainy season is prone to post-harvest quality risks such as mold or damage, making storage and transportation difficult. These factors make standardization of raw materials and large-scale product development challenging.

Currently, the cultivation, care, harvesting, and processing of *A. tonkinensis* are mainly based on folk experience or scattered instructions, without a systematic, standardized, and strict quality control process. This can affect the quality of input materials, active ingredient content, and stability of the processed product.

Although used in folk medicine, very few people know about the presence of *A. tonkinensis* fruit in Vietnam. Consumer awareness of the value of this plant is limited, while product promotion and development activities in the market have not been focused on.

Some preclinical studies have shown safety at traditional doses, chronic toxicity, and reproductive toxicity; however, human studies are still lacking. This limits the ability to register products as functional foods or standardized herbal medicines, especially in demanding markets such as the EU or the US.

In addition, traditional decoctions prepared from leaves or roots, which are widely used in folk medicine, require further scientific validation to confirm the stability of bioactive compounds, the remaining biological activity after thermal processing, and the reproducibility of pharmacological effects. Systematic studies on optimal preparation methods,

effective dosage ranges, and safety margins of decoctions are therefore necessary.

There are no specific technical regulations or quality standards for raw materials or products from *A. tonkinensis*. At the same time, the lack of connection between scientists, businesses, and localities is also a barrier to developing a closed value chain for this medicinal herb.

In short, the potential for *A. tonkinensis* development is huge, especially in the trend of searching for products from natural herbs with diverse biological activities. However, to exploit it effectively and sustainably, a synchronous strategy is needed from research, cultivation, standardization, to commercialization and consumer education.

CONCLUSION

Artocarpus tonkinensis represents a promising natural source of bioactive compounds. The main identified constituents belong to flavonoid glycosides, prenylated flavonoids, and 2-arylbenzofuran derivatives, including maesopsin 4-O-β-glucoside and related phenolic compounds, which have demonstrated notable anti-inflammatory, immunomodulatory, and anticancer activities in experimental studies. Current research has primarily focused on the isolation and preliminary evaluation of these compounds, while detailed investigations into their mechanisms of action, pharmacokinetics, and safety profiles remain limited. The lack of standardized extraction methods and raw material characterization also constrains the reproducibility and clinical translation of existing findings. Future research should prioritize mechanistic studies, toxicity assessments, and the development of standardized preparations to ensure consistent quality and efficacy. Integration of *A. tonkinensis*-derived compounds into evidence-based pharmaceutical research could provide valuable insights into the development of novel therapeutic agents from indigenous plant resources.

CONFLICT OF INTERESTS

The authors declare no potential conflicts of interest.

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