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Review article

A review of the safety profile, antioxidant, anti-inflammatory, and bronchorelaxant activities of *Waltheria indica* Linn (Malvaceae): A potential antiasthmatic phytomedicine

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ABSTRACT

Introduction: *Waltheria indica* Linn (Malvaceae) is a widely distributed plant in West Africa. It is commonly used in Burkina Faso to treat inflammation-related diseases, including asthma. Previous reviews have focused on the ethnobotanical, traditional uses, phytochemistry, and pharmacological properties of *Waltheria indica*. This report aims to compile the biological and pharmacological activities that highlight the anti-asthmatic properties of *Waltheria indica* L. (*W. indica*).

Method: Electronic databases, such as PubMed, Scopus, Hinari, SciFinder, Google Scholar, and ScienceDirect, were used to gather data on *Watheria indica*. Data on the toxicological, anti-inflammatory, antioxidant, and bronchorelaxant effects of *W. indica* were collected.

Results: Twenty-three studies describing the biological and pharmacological activities relevant to assessing the anti-asthmatic properties of *W. indica* were found. Nine articles investigated the anti-inflammatory effects, and three manuscripts were found to have bronchorelaxant activity. Five publications reported the antioxidant activity of the plant extracts. Research on the extracts revealed a tolerable safety profile in rats and mice with an LD_{50} ranging from 300 to 5000 mg/kg body weight, depending on the parts of the plant used. Phenolic compounds, particularly flavonoids, alkaloids, and saponins, were found to be responsible for the activities involved in the assessment of anti-asthmatic properties.

Conclusion: The results of this review suggest that *W. indica* could be a valuable resource for the treatment of asthma and other respiratory diseases. However, further chemical and pharmacological investigations are needed to understand its mechanism of action in treating asthma.

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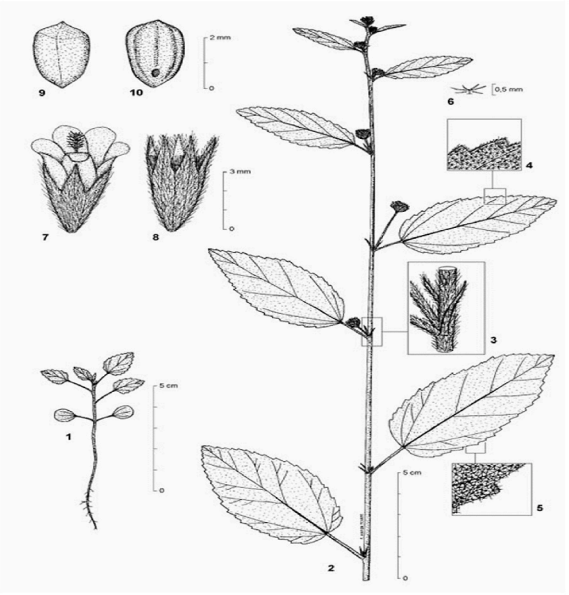
1. Introduction

Respiratory diseases have the highest prevalence, morbidity, and death rates worldwide [1]. The most common respiratory diseases include asthma, bronchitis, common cold, cough, and pertussis [2]. Asthma is characterized by recurrent attacks of paroxysmal dyspnea, wheezing due to spasmodic bronchi contraction, respiratory tract inflammation, or allergic symptoms [3]. Asthma affects approximately 300 million people worldwide, and it is estimated that by 2025, an additional 100 million will be affected [3]. A combination of genetic and environmental factors causes asthma. A significant risk factor for asthma development is an individual's genetic predisposition. Asthma symptoms are developed following the release of endogenous and intrinsic mediators, including histamine, leukotrienes, nitric oxide, chemokines, and endothelins. Asthma can be triggered by various other factors, including viral respiratory infections, allergens, smoke, air pollution, and other chemicals such as medications [4]. Dworski (2000) noted that stress and acute anxiety or extreme emotional arousal can also trigger asthma attacks [5]. The conventional treatment of asthma includes (i) bronchodilators (β2-adrenergic agonists, anticholinergics, and methylxanthines), (ii) anti-inflammatory drugs (corticosteroids, anti-leukotrienes, and mast cell stabilizers), and (iii) the anti-immunoglobulin E drugs [6]. These drugs reduce airway inflammation and reduce the airways' smooth muscle contractions [6,7]. Despite multiple bronchodilators on the market, people in low-income countries still face high costs and, sometimes, unavailability. Moreover, these products induce side effects such as tachycardia, palpitations, tremors (β_2-adrenergic mimetics), and metabolic, endocrine, and digestive disorders (corticoids) [8]. In addition to conventional therapies in Africa, traditional medicine, used by 80 % of the population [9], offers some phytotherapy alternatives for managing asthma.

Several scientific reports have shown the anti-asthmatic potential of African plants [10,11], including *Waltheria indica* L. (*W. indica*). *W. indica* (Figs. 1 and 2) was formerly classified in the family of Sterculiaceae. However, lately, the plant has been re-classified as belonging to the family of Malvaceae. *Waltheria indica* Linnaeus (L), synonym *Waltheria americana*, is generally dispersed in tropical regions worldwide [12].

This ubiquitous plant is frequently used in Burkina Faso traditional medicine [12]. The leaves, root bark, or whole plant oral decoction or maceration are used against asthma, cough, swelling, toothache, rheumatic colic, diarrhea, dysentery, conjunctivitis, wounds, and abscesses. Some pharmacological properties of *W. indica* have been investigated and documented [12–15]. These studies reported several biological and pharmacological activities, including analgesic, antibacterial, antiviral, antiparasitic, aphrodisiac,



1. Seedling
2. Mature plant
3. Stem and stipule
4. Leaf, upper surface
5. Leaf, lower surface
6. Star-shaped hair/trichome
7. Flower
8. Calyx and fruit
9. Seed dorsal view
10. Seed ventral view

Fig. 1. Botanical diagram of *Waltheria indica* Linnaeus http://idao.cirad.fr/content/adventrop/species/w/walam/dessin_walam_fr.html.

Fig. 2. Photo of a young plant of *Waltheria indica* L.

antidiabetic, hematological, sedative, bronchorelaxant, and antifungal activities [16,17]. In addition, an anti-cataract potential was reported [15]. Considering the global impact of asthma on health and the anti-asthmatic potential of *W. indica*, we deemed it important to summarize and discuss the studies reported on this plant that could substantiate the traditional use of *W. indica* as an anti-asthmatic agent. Though *W. indica* has been subjected to two reviews and studies regarding its pharmacological properties [12,15], few reports are strictly related to the antiasthmatic effects. As part of our research on the anti-asthmatic properties of *W. indica* [16,18], we aimed to provide an overview of this subject. In this report, we conduct a systematic review of the biological and pharmacological activities contributing to evaluating the anti-asthmatic properties and toxicity of *W. indica* to lay the groundwork for our investigations into the mechanisms that could justify its traditional use as an anti-asthmatic. Given that oxidative stress and inflammation are known to be involved in asthma [5], all documented anti-asthmatic properties investigations regarding the bronchodilator, antioxidant, and anti-inflammatory effects of *W. indica* were sought. Furthermore, this review attempts to compile the bioactive compounds believed to be responsible for the biological and pharmacological activities contributing to assessing the anti-asthmatic properties.

2. Methods

2.1. Literature search strategy

This report reviews the literature to search, analyze, and synthesize the published works on the biological and pharmacological activities relevant to assessing the anti-asthmatic properties of *W. indica*. To this end, we explored PubMed, Hinari, ScienceDirect, SciFinder, Google Scholar, and Scopus electronic databases.

2.2. Literature search strategy

We used a combination of the following keywords to search: “*Waltheria indica*,” “*Waltheria americana*,” “anti-inflammatory activity,” bronchorelaxant activity, “antioxidant activity,” " anti-hyperactivity,” “anticholinergic activity,” antihistamine activity, “toxicity."

2.3. Study selection

The initial set of articles resulting from the research underwent a rigorous selection process. Initially, articles were examined based on their title and abstract to assess their relevance to the research questions. This step narrowed down the set to a selection of potentially relevant articles. The articles identified as potentially relevant then underwent a comprehensive review to confirm their relevance and assess their quality. The criteria for this comprehensive review included:

1. Publication period: All articles related to the research questions up to July 2023 were included to ensure the review reflected the most recent developments and findings.
2. Document type: Original research and synthesis articles available online were considered.
3. Geographic location: no restrictions were imposed on the country of origin of the articles as long as they were published in English. This inclusive approach ensured a comprehensive understanding of global trends and discoveries. The data obtained throughout the search was summarized and classified in tables.

3. Results

Our search returned 2563 records. After deduplication and screening, twenty-three articles were considered for the present review. Fig. 3 describes the screening process.

3.1. Phytochemistry of W. indica

According to various studies, *W. indica* contains a variety of chemical groups, including flavonoids, alkaloids, terpenes, sterols, tannins, cardiac glycosides, saponins, anthraquinones, and carbohydrates.

In this review, we have summarized the characterized chemical groups and their biological and pharmacological activities, which contribute to evaluating the antiasthmatic properties of *W. indica*. The extraction solvents used in these studies include methanol, ethanol, ethanol-water mixture, hexane, ethyl acetate, and water (Table 1–a). The name and chemical structure of the compounds isolated from the cataloging of biological and pharmacological activities involved in the antiasthmatic properties of *W. indica* are indicated in Table 1–b and Fig. 4.

3.2. Biological and pharmacological activities contributing to the evaluation of the antiasthmatic properties of W. indica

Twenty-three articles were found to likely contribute to evaluating the biological and pharmacological activities of *W. indica* concerning its antiasthmatic properties. These articles have demonstrated the anti-inflammatory, broncho-relaxant, and antioxidant properties of various extracts of *W. indica*, including roots, stems, leaves, and leafy stem extracts.

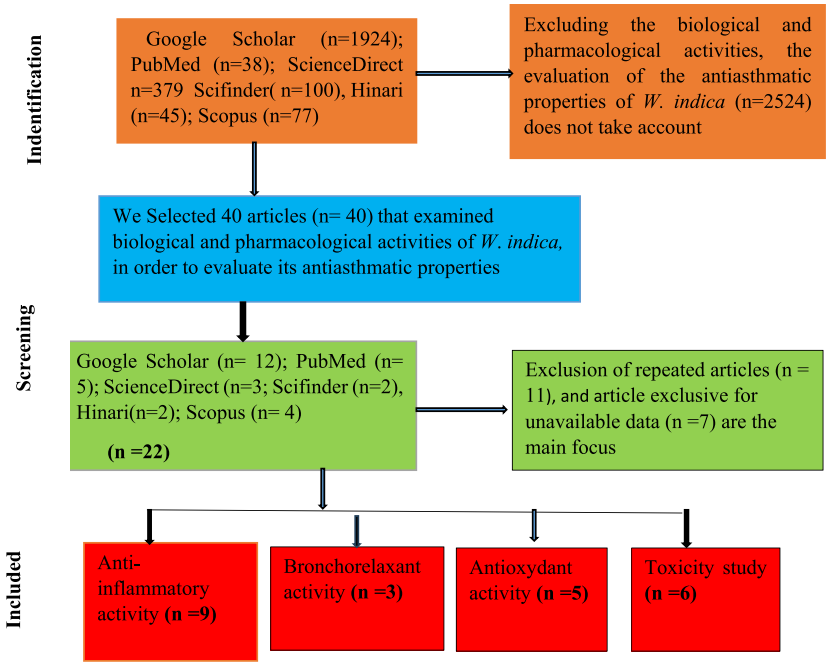


Fig. 3. Diagram describing the articles searched for inclusion in determining the anti-asthmatic properties.

Table 1-a
Phytochemical constituents in different parts of *W. indica*.

Part of the plant	Chemical groups	Reference
Roots	Alkaloids, carbohydrates, cardiac glycosides, saponins, steroids, tannins, phenolic acid, terpenoids	[19]
Leaves	Alkaloids, carbohydrates, cardiac glycosides, phenolic acids, saponins, steroids, tannins, terpenoids	[20]
Leafy stems	Sterols, terpenes, alkaloids, flavonoids, coumarins, tannins, saponosides	[16,21]
Aerial parts	Quinolone alkaloids, polyhydroxymethoxy flavonoids	[22]

Table 1-b
Isolated compounds from cataloging biological and pharmacological activities involved in the antiasthmatic properties of *W. indica*.

Plant part	Isolated compounds	Reference
Roots/hydroalcoolique extract	(−) -Epicatechin	[17]
Whole plant/ethanolic extract	(−)-Epicatechin, quercetin, and tiliroside.	[23]
Leaves/ethanolic extract	Tetradecane, hexadecane, squalene, 2,3-Dihydro-3,5-dihydroxy-6- Methyl-4H-pyran-4-one	[24]
Aerial parts/dichloromethane extract	Methyl (2R,3R)-3,4-dihydro-3,8-dihydroxy-2- methyl-(4-methylpent-3-en-1-yl)-2H-1-benzopyran-6-carboxylate; methyl (R)-2,3-dihydro-7-hydroxy-2-[(S)-2-hydroxy-6-methylhept-5- en-2-yl]-2H-1-benzofuran-5-carboxylate; methyl (R)-2,3-dihydro-7-hydroxy-2- [(2R,5S)-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]-2H-1-benzofuran-5- carboxylate; (2S)- 16 2-[(1S)-1-(5,5-dimethyltetrahydrofuran-2-yl)-1-hydroxyethyl]-2,3-dihydro-2H-1-benzofuran-5-carboxylic acid; methyl (2S,4aR,10aS)-2,3,4,4a,10,10a-hexahydro-6-hydroxy-2-(2-hydroxypropan-2-yl)-4a-methylpyrano [3] [2-b] [1] benzopyran-8-carboxylate.	[25]
Stem/ethanolic extract	6-Oxabicyclo [3.1.0]ʹhex-1-yl) ethenone; 2,3-Dihydro-3,5-dihydroxy- ethyl-4H-pyran-4-one; tridecane; tetradecane; Oxirane; [(dodecyloxy)methyl]-1-Hexadecene; Hexadecane; [1,1′-Bicyclopropyl]-2-octanoic acid; 2′-hexyl-; Methyl ester; 2-Propenoic acid; tridecyl ester; 3-Eicosene; Nonadecane; Nonadecane, 3-methyl- 1-Heneicosanol; 9,12-octadecadienoic acid (Z,Z)- Z,Z-8,10-hexadecadien-1-ol; 2-Bromo dodecane; tetracosane; stigmasterol.	[26]

a Anti-inflammatory Properties of *W. indica*

Among the twenty-three articles on the biological and pharmacological activities contributing to the evaluation of anti-asthmatic properties, nine reports have demonstrated the anti-inflammatory properties of extracts from *W. indica*. The summarized results can be found in Table 2.

b Anti-inflammatory effects of compounds isolated from *W. indica*

Two studies have demonstrated the anti-inflammatory activity of compounds isolated from *W. indica* [23,25].

Rao and his colleagues [23] isolated flavonoid derivatives, including tiliroside, (−) -epicatechin, and quercetin, from a sequentially fractionated ethanolic extract of the whole plant. These compounds were tested on murine peritoneal macrophages activated by lipopolysaccharide and interferon. Quercetin showed the highest activity, followed by tiliroside and (−)-epicatechin in this study. Specifically, at concentrations of 12.5 mM, 50 mM, 200 mM, quercetin, tiliroside, and (−)- epicatechin inhibited NO production by 90 %, 63 %, and 34 %, respectively. The results also demonstrated a dose-dependent inhibition of the inflammatory mediating cytokines, tumor necrosis factor (TNF)-α, nitric oxide (NO), and interleukin 12 (IL-12), without any cytotoxicity [23].

Furthermore, Monteillier and colleagues [25] isolated two quinolone alkaloids, waltherione A and C, from the decoction of the aerial parts of the plant. Their results showed that only the decoction and the alkaloid extract were active at a concentration of 20 μg/ml, with 51 % and 79 % inhibitions, respectively. The walteriones A ($IC_{50} = 56.1 \pm 11.9$ μM at 20 μg/mL) and C ($IC_{50} = 55.5 \pm 8.4$ μM at 20 μg/mL) demonstrated remarkable potency, with no significant decrease in cell viability even at the highest doses. These compounds inhibited the nuclear factor (NF-κB), which is an essential element in inflammation-induced tumors [25]. [31].

3.2.1. Broncho relaxant properties of W. indica

Three of the twenty-three articles demonstrated *in vitro* broncho-relaxant properties of *W. indica* extracts. The extraction solvent used was a mixture of water and aqueous ethanol. The results are summarized in Table 3.

c Antioxidant effects of *W. indica*

Antioxidant properties were observed in five out of the twenty-three articles. A summary of the findings is presented in Table 4.

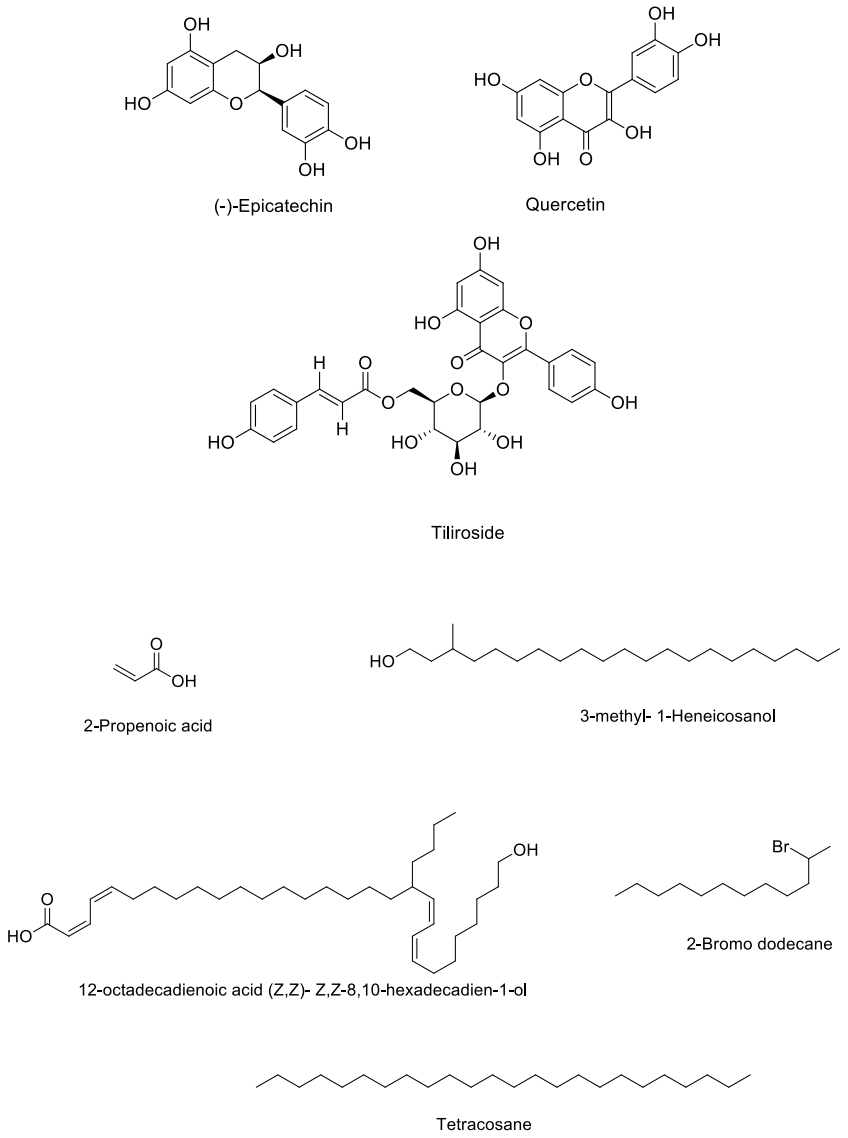


Fig. 4. The chemical structure of the compounds isolated from *W. indica* involved in the assessment of biological and pharmacological activities related to its antiasthmatic properties [17,23–26].

3.3. Toxicological properties of W. indica

The databases listed six *in vivo* studies on the toxicological effects of *W. indica*. These studies utilized extracts from the plant's leaves, stems, and roots. Acute and subacute toxicity studies were conducted on mice and rats. The overall findings suggest that *W. Indica* has low toxicity. A summary of the results can be found in Table 5.

4. Discussion

W. indica is a medicinal plant that treats various diseases, including respiratory conditions. Asthma, a disease characterized by recurrent episodes of difficulty breathing, wheezing, and inflammation of the respiratory passages, is one condition that *W. indica* can help treat [1]. In this review, we have compiled the biological and pharmacological activities of *W. indica* that are relevant to its anti-inflammatory, antioxidant, and relaxant properties.

Studies have shown that preparations of *W. indica* can modulate inflammatory processes by affecting inflammation mediators and cellular processes. *In vitro* studies have shown that the methanol extract from *W. indica* leaves ((20 μg/mL) has COX-2 inhibitory activity, similar to tiliroside (45 μg/mL), a compound known for its anti-inflammatory properties [28]. In rats with

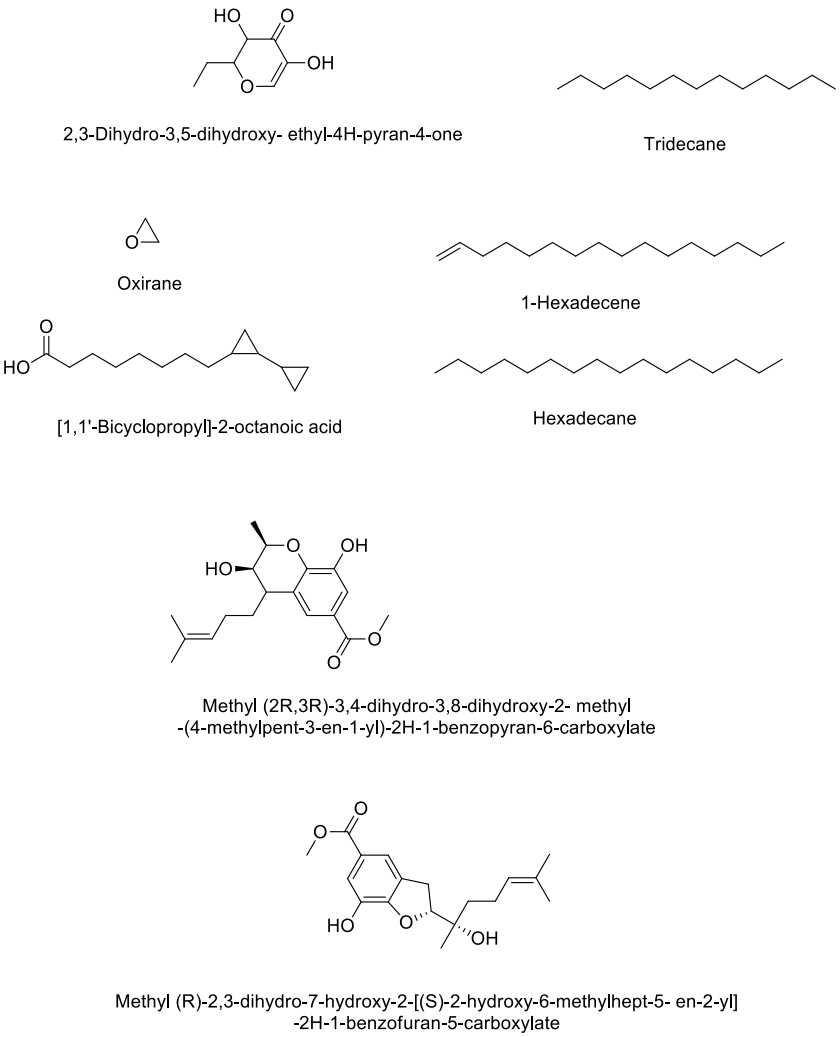


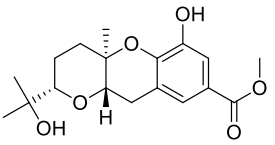
Fig. 4. (*continued*).

carrageenan-induced edema experiments, *W. indica* extracts have demonstrated anti-inflammatory effects by reducing inflammation and swelling. Both the methanol extract (100 and 200 mg/kg) and indomethacin (10 mg/kg) significantly inhibited carrageenan-induced edema ($p < 0.05$) at 2, 3, and 5 h after carrageenan injection compared to the control group [37]. The aqueous extract of *W. indica* stems with leaves has also shown significant anti-edematous effects at different doses. At the dose of 300 mg/kg body weight, there was a significant reduction in edema ($p < 0.05$) of 72.73 % observed in the first hour. Furthermore, during the third and fifth hours, the aqueous extract, at all tested doses, showed a significant reduction in edema compared to salicylic acid (300 mg/kg at 84.09 %) [21].

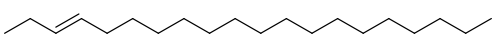
Edema formation is a critical sign of asthma's inflammatory manifestation because it aggravates the condition by causing a buildup of fluid in the bronchial parenchyma, leading to asthma attacks [38,39]. The reduction of edema induced by the extract was observed during the first, third, and fifth hours. It is well-established that the initial phase of inflammation involves releasing mediators such as histamine, serotonin, and bradykinin, followed by the infiltration of leukocytes and prostaglandin production in the later stage.

Therefore, the inhibitory effects of *W. indica* extract occur during both stages of inflammation [40]. These studies suggest that the anti-edematous effects of *W. indica* extract may be explained by the inhibition of cyclooxygenase and various inflammation mediators, including histamine, serotonin, bradykinin, and prostaglandin [21].

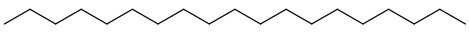
Moreover, hydroethanolic extracts of aerial parts have also shown anti-inflammatory effects by reducing the expression of specific inflammatory cytokines [29]. The root extracts and their fractions have demonstrated inhibitory activity on key inflammatory enzymes, including lipoxygenase (LOX), phosphodiesterase-4A1α (PDE-4A1α), and phospholipase A_2 (PLA_2) [17]. The inhibitory effects of *W. indica* on the nuclear factor (NF-κB), a critical factor in inflammation-induced tumor formation, have also been suggested. Monteillier and collaborators (2017) reported that NF-κB was inhibited by Waltherione A and C, chemical compounds obtained from the decoction of the aerial parts of *W. indica* [25]. Past research has reported that the root extract of *W. indica* and its isolated compound, epicatechin, inhibited lipoxidase and phospholipase A_2 [17].



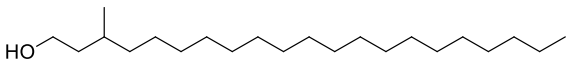
Methyl (2S,4aR,10aS)-2,3,4,4a,10,10a-hexahydro-6-hydroxy-2-(2-hydroxypropan-2-yl) -4a-methylpyrano[3,2-b][1]benzopyran-8-carboxylate



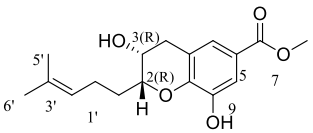
3-Eicosene



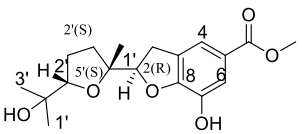
Nonadecane



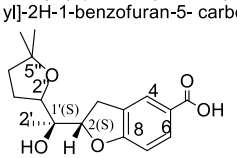
3-methyl- 1-Heneicosanol



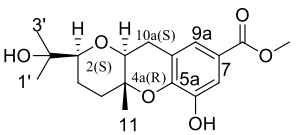
Methyl (2R,3R)-3,4-dihydro-3,8-dihydroxy-2- methyl-(4-methylpent-3-en-1-yl)-2H-1-benzopyran-6-carboxylate



Methyl (R)-2,3-dihydro-7-hydroxy-2- [(2R,5S)-5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]-2H-1-benzofuran-5- carboxylate



2,3-dihydro-2H-1-benzofuran-5- carboxylic acid



Methyl (2S,4aR,10aS)-2,3,4,4a,10,10a-hexahydro-6-hydroxy-2-(2-hydroxypropan-2-yl)-4a-methylpyrano[3,2-b][1] benzopyran-8-carboxylate

Fig. 4. (*continued*).

In addition to the mediators of inflammation discussed above, oxidative stress induced by reactive oxygen species (ROS) is assumed to play an essential mechanistic role in asthma [5]. This stress causes tissue damage and dysregulation of cell signaling, contributing to the pathogenesis of many diseases, including asthma [5,41]. Therefore, asthma is characterized by pulmonary and systemic oxidative stress associated with an inflammatory response [41].

During the inflammatory response, inflammatory cells recruited in the airways produce reactive oxygen species [5,42]. This production causes bronchial hyper-reactivity and stimulates the release of histamine by mast cells and the secretion of mucus by the

Table 2
Summary of the reported anti-inflammatory effects of *W. indica*.

Extraction solvents/parts used	Type of study/model	Results	References
Methanol/leaves	Neurons inflammation in rats	A dose of 200 mg/kg of the extract and 50 mg/kg quercetin administered orally significantly decreased the levels of IL-6 and TNF-α in the striatum, prefrontal cortex, and hippocampus of rats following LPS-induced neuro-inflammation as compared to the control group (LPS + Veh).	[27]
Ethanol, ethyl acetate, methanol, water/ leaves	*In vitro*/inhibition of cyclooxygenases 2 (COX-2)	The M90 extract showed a COX-2 inhibition similar to that of tiliroside at a concentration of 20 μg/mL (75 μM or 45 μg/mL). Similarly, the EA90 and E30 extracts exhibited a COX-2 inhibition similar to that of tiliroside at a concentration of 20 μg/mL (110 μM or 65 μg/mL).	[28]
Water-ethanol/aerial part	TNF-α and IF-γ –induced monocyte-derived macrophage stimulation *in vitro*	The *Waltheria* extract, administered for 48 h at concentrations ranging from 0.9 to 4.5 μg/mL, significantly decreased the levels of IL-1β and TNF-α stimulated by LPS in a concentration-dependent manner. At a concentration of 4.5 μg/mL, the *Waltheria* extract caused a notable reduction in the amount of NF-κB produced by TNF-α/IF-γ-stimulated macrophages after 2 h and 6 h of treatment. Similarly, quercetin (at concentrations of 1–20 μM/mL) also reduced NF-κB in TNF-α/IF-γ-stimulated macrophages.	[29]
Methanol/leaves	carrageenan-induced edema in rats	After administration of carrageenan, the rats treated with the extract (100 and 200 mg/kg) and indomethacin (10 mg/kg) showed a significant decrease ($p < 0.05$) in pain size at 2, 4, and 5 h compared to the control group.	[30]
Water/stems with leaves	carrageenan-induced edema in rats	At a 200 mg/kg dose, the aqueous extract inhibited carrageenan-induced edema of 11.1 %, 39.47 %, and 70.45 % at 1 h, 3 h, and 5 h, respectively. At a dose of 300 mg/kg, the aqueous extract showed inhibition of carrageenan-induced edema of 59,26 %, 60.52 %, and 72.73 % at 1 h, 3 h, and 5 h, respectively.	[21]
	Inhibition of lipoxygenase	The decoction of leafy stems at a concentration of 100 μg/mL inhibited lipoxygenase with a percentage of inhibition of 94.63	
Water-ethanol/roots and their fractions	Inhibition of 5- lipoxygenase (5-LOX)	The 5-LOX inhibition by the extract and fractions appears to be dose-dependent, ranging from 60 % to 80 % at a 10 μg/mL concentration. The inhibition by the fractions at a concentration of 5 μg/mL appears to be just as potent as the inhibition observed with zileuton at a concentration of 0.12 μg/mL.	[17]
	inhibition of phosphodiesterase-4A1α (PDE-4A1α)	At a concentration of 50 μg/mL, the fractions of the extract inhibit PDE-4A1 α by 22–42 % compared to the aminophylline control, which inhibits by 55 %	
	inhibition of phospholipase A_2 (PLA_2)	Both the extract and fractions at a concentration of 100 μg/mL inhibit PLA_2 by 42–94 %. The inhibition by the fractions at a concentration of 100 μg/mL is as significant as that observed with indomethacin at a concentration of 18 μg/mL. The effect of the extract and fractions at a concentration of 500 μg/mL is significantly more important than the effect indometacin control	

TNF-α: Tumor Necrosis Factor alpha; IF-γ: Interferon gamma; IL 6: Interleukin 6; IL-1β: Interleukine 1 bêta; *W90: Water at 90 °C; M90: Methanol at 90 °C; E30-E90-E150: Ethanol at 30-90-150 °C; EA90: Ethyl acetate at 90 °C: LPS: Lipopolysaccharide.*

Table 3
Summary of the reported broncho-relaxant effects of *W. indica* extracts.

Extraction solvents/parts used	Type of study/model	Results	References
Water-ethanol/ leafy stems	*In vitro* acetylcholine (Ach) or barium chloride (BaCl2)-induced contractions of isolated rat trachea	The EC_{50} values for acetylcholine-induced contraction and barium chloride-induced contraction were 3.711 ± 0.823 μM and 9.502 ± 12.354 mM, respectively, for 1.92 mg/mL extract	[18]
Water, water-ethanol/leafy stems	*In vitro* acetylcholine (Ach) or potassium chloride (KCl)-induced contractions of isolated rat trachea	The aqueous decoction and hydroalcoholic extract showed a significant bronchorelaxant response, with EC_{50} values of 1.517 ± 0.002 mg/mL and 1.200 ± 0.002 mg/mL, respectively. The maximum bronchorelaxant effect (Emax) was 88.54 ± 12.44 % for the aqueous decoction and 88.86 ± 10.38 % for the hydroalcoholic extract	[16]
Water-ethanol/ root	*In vitro* Ach-induced contractions of isolated rat trachea	The hydroalcoholic extract reduced the contraction induced by acetylcholine with an IC_{50} of 1051 μg/mL. F1, F2, and F4 did not significantly inhibit the contraction induced by acetylcholine. However, F3 and its fractions had an inhibitory effect. The IC_{50} of the fractions derived from F3 was compared to the IC_{50} of F3 itself (IC_{50} = 563 μg/mL) on the rat trachea. F36 (IC_{50} = 181 μg/mL) and F37 (IC_{50} = 283.7 μg/mL) were more active than F3 ($p < 0.01$). However, the activity of the other fraction was similar to F3	[17]

ACh: Acetylcholine; KCl: Potassium chloride; *Emax:The maximum bronchorelaxant effect (Emax); F1: n-hexane; F2: dichloromethane.*
F3: ethyl acetate; F4: residual fraction of hydroalcoholic extract.

Table 4
Summary of the reported antioxidant effects of *W. indica* extracts.

Extraction solvent Parts used	Type of study/model	Results	References
Methanol and aqueous extract/stem	Cationic free radical scavenging (ABTS) *in vitro*	The antiradical activity shows a linear increase with the concentration of both gallic acid and the extracts. Gallic acid reaches 100 % antiradical activity at a concentration of 0.84 μg/mL, with an IC_{50} of 0.35 μg/mL. The aqueous stem extract exhibits 100 % antiradical activity at 25 μg/mL, with an IC_{50} of 2.5 μg/mL. Similarly, the methanolic stem extract demonstrates 100 % antiradical activity for concentrations greater than or equal to 25 μg/mL, with an IC_{50} of 6 μg/mL.	[32]
Ethanolic extract of the whole plant	Superoxide anion scavenging activity in *vitro*	The ethanolic extract exhibited a maximum superoxide anion scavenging activity of 58.76 % at a concentration of 1000 μg/ml, whereas quercetin (standard) showed a scavenging activity of 98.01 % at the same concentration. The IC_{50} values for the ethanolic extract and quercetin were found to be 410 and 60 μg/mL, respectively.	[33]
	In vitro DPPH radical inhibition	The ethanolic extract showed a maximum DPPH radical scavenging activity of 48.40 % at a concentration of 1000 μg/ml, whereas for rutin (standard), it was found to be 69.83 % the same concentration. The IC_{50} values for the ethanolic extract and rutin were 1020 and 480 μg/ml, respectively.	
Aqueous extract of stems with leaves	*In vitro* DPPH radical inhibition	The IC_{50} value for the inhibition is 79.5 μg/mL of the DPPH radical, compared to the reference product, quercetin, which has an IC_{50} of 0.69 μg/mL.	[21]
	In vitro Lipid peroxidation inhibition	The extract at a concentration of 100 μg/mL inhibited lipid peroxide production by 74.31 %.	
Methanol/whole plant	*In vitro* inhibition of lipid peroxidation (LPO)	The extract at a 400 mg/kg dosage significantly inhibited lipid peroxidation (LPO) in the liver and kidney tissues of rats with alloxan-induced diabetes.	[34]
Methanol/roots	*In vitro* DPPH free radical scavenging activity	At the lowest concentrations (0.06–0.25 mg/100 mL), the methanol extract (10.71 ± 1.35 to 37.07 ± 1.46) demonstrates superior or comparable inhibition compared to ascorbic acid (9.9 ± 1.7 to 38.2 ± 2.06). While ascorbic acid completely inhibits (100 %) DPPH at a concentration of 0.5 mg/100 mL, the methanol extract inhibits 65.71 ± 2.32 % at a similar concentration	[35]

Table 5
Summary of the reported toxicological effects of *W. indica*.

Extraction methods/parts used	Model/type of study	Results	Références
Methanol/leaves	Acute and subacute toxicity in rats	The LD_{50} by oral route was greater than 5000 mg/kg of body. No significant statistical differences were observed in any of the biochemical parameters. There was no significant difference in alkaline phosphate, AST/SGOT, and ALT/SGPT at a dose of 250 mg/kg and 500 mg/kg, respectively. There was no significant effect on the blood cells. Histological examination revealed histopathological changes in the various organs (heart, spleen, liver, and kidney) examined at 1000 mg/kg	[36]
Ethanol/aerial parts	Subacute toxicity/ albino Wistar rats	There was no sub-acute toxicity observed at a dose of 400 and 800 mg/kg/day. Hematological parameters showed no significant differences in female rats treated with various extract doses compared to the control group ($p > 0.05$). However, male rats treated with 1600 mg/kg for 28 days exhibited a significant decrease in MCH values ($p > 0.05$). Additionally, high doses of the extract (800 and 1600 mg/kg) administered over 28 days resulted in a noticeable decrease in MCHC, MCH, and MCV	[37]
Aqueous, water-éthanol/ leafy stems	*In vivo* acute toxicity/ mice	The LD_{50} was greater than 5000 mg/kg of body weight when administered orally	[16]
Methanol/leaves	*In vivo* acute toxicity/ rats	The LD_{50} was greater than 5000 mg/kg of body weight when administered orally	[37]
Water/leafy stems	*In vivo* acute toxicity/ mice	The LD_{50} was greater than 5000 mg/kg of body weight when administered orally	[21]
Hydroethanolic/roots	*In vivo* acute toxicity/ rats	When administered orally, the LD50 was greater than 2000 mg/kg of body weight.	[17]

LD_{50}: lethal dose 50 %; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MCH:Mean Corpuscular Hematocrit; MCV: Mean Corpuscular Volume.

epithelial cells [42]. Therefore, it is rational to assume that oxidative stress could play an essential mechanistic role in asthma.

Natural antioxidants can protect the human body against free radicals, delay the progression of many chronic diseases, and prevent oxidative rancidity of lipids in food or medicinal materials [5,42]. In this regard, several studies have reported the antioxidant properties of *W. indica*. Mongalo and colleagues (2012) demonstrated that the methanolic extract of *W. indica* roots inhibited the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical by 75.45 ± 2.76 % at a concentration of 0.06–0.25 mg/100 mL [35]. The freeze-dried aqueous extract at 100 μg/mL dose prevented lipid peroxidation with a percentage inhibition of 74.31 % [21]. The ethanolic extract of the entire plant also showed an antiradical effect against the nitric oxide radical and hydroxyl radicals [33,43]. These results attest to the antioxidant properties of *W. indica*. Phenolic compounds like flavonoids and tannins in *W. indica* extracts could act as free

radical scavengers. Overall, the antioxidant activity of *W. indica* could have therapeutic potential in preventing oxidative stress implicated in various inflammatory diseases, such as asthma.

In addition to its antioxidant activities, *W. indica* could also have anti-inflammatory properties. It is claimed to have an anti-asthmatic effect, which may be due to its bronchodilator effect.

Bronchoconstriction is a key manifestation of asthma. Various broncho-dilating products are used to treat asthma and chronic obstructive disease. The main drugs used for asthma treatment are beta-adrenergic agonists, anticholinergics, and methylxanthines [44]. Short- or long-acting beta-2 stimulants induce bronchodilation by selectively activating bronchial smooth muscle beta-2 receptors [6]. Anticholinergic compounds competitively target muscarinic M_3 receptors, resulting in a parasympatholytic effect that promotes bronchodilation [6].

Methylxanthines have multiple mechanisms of action for their bronchorelaxant effect, including inhibition of phosphodiesterase (e.g., PDE-4 A1α), which increases cAMP levels, inhibition of calcium ion influx into smooth muscle, prostaglandin antagonism, adenosine receptor antagonism and inhibition of the release of mediators from mast cells and leukocytes [6,45]. These drugs directly affect the airway smooth muscle or inhibit neural pathways, leading to bronchodilatation [45].

Table 3 presents intriguing evidence of the inhibitory effect of *W. indica* on acetylcholine (ACh), potassium chloride (KCl), or barium chloride ($BaCl_2$) induced contractions in isolated rat trachea. Extracts obtained from the stems and leaves [16,18] and roots [17] demonstrated a dose-dependent inhibition of ACh or KCl/$BaCl_2$-induced contractions. Therefore, there appeared to be no significant difference in bronchorelaxant activity between the two parts of the plant [16–18].

Furthermore, the chemical components of the extracts from the roots, stems, and leaves were similar [16,17]. Based on these results, it can be suggested that the same chemical compounds could be present in different parts of the plant, resulting in the same type of bronchorelaxant activity regardless of the plant's part. These findings could support the traditional use of *W. indica* in treating asthma in traditional medicine.

Finally, our review research delved into the toxicity of *W. indica*. The literature inventory led to eight *in vivo* studies assessing acute toxicity and two evaluating subacute toxicity. Adedokun and collaborators [36] studied the methanolic extract of *W. indica* leaves and reported a lethal dose (LD_{50}) greater than 5000 mg/kg orally, suggesting that the plant presents no toxic effects when used in acute conditions. Furthermore, it has been reported that the aqueous and hydroalcoholic extracts of *W. indica* leafy stems have a lethal dose higher than 5000 mg/kg when administered orally [16], confirming the absence of acute toxicity. Hamidu et al. (2018) also determined an intraperitoneal LD_{50} of 875 mg/kg body weight in mice using the hydroethanolic extract derived from the aerial parts of *W. indica* [37]. These results indicate the plant is safe when used orally in acute conditions [37].

Subacute toxicity of *W. indica* has also been studied. Hamidu and colleagues (2018) assessed the toxicological impacts of subacute exposure to the ethanolic extract of *W. indica* aerial parts on body weight, hematological, and biochemical parameters in albino rats [37]. The results showed no behavioral changes in rats treated with a dose of 400 mg/kg body weight (b.w)/day of the extract. However, a general reduction in activity was observed in rats receiving doses of 800 and 1600 mg/kg b. w per day of the extract. Additionally, LD_{50}-treated rats exhibited hypoactivity, grooming, prostration, and irritation during the third and fourth weeks of the treatment [37].

Moreover, the ethanolic extract of the aerial part also did not affect the hematological and biochemical parameters in albino rats. However, increased levels of certain enzymes were observed during the continuous oral administration of *W. indica* for 21 days at high doses [37]. These enzymes include alanine transaminase (ALT), total bilirubin, and creatinine, which significantly increased at doses of 800 and 1600 mg/kg body weight/day of the extract compared to control rats ($p < 0.05$). Therefore, Hamidu and colleagues (2018) recommend exercising caution during prolonged plant use [37]. Overall, the toxicity results indicate that *W. indica* preparations could be safely used under appropriate conditions for treating asthma.

5. Conclusion

Our bibliographic research on the *in vitro* and *in vivo* biological activities that could partly contribute to the anti-asthmatic properties demonstrates that *W. indica* possesses anti-asthmatic potential. Thus, the traditional use of plant preparations in asthma treatment could find its scientific basis through its anti-inflammatory, antioxidant, and bronchorelaxant effects. Furthermore, existing data on the toxicity of *W. indica* seem to indicate that these therapeutic effects are associated with a toxicity profile that does not cause serious adverse effects during treatment. However, since asthma is a chronic disease, further investigations should focus on describing the chronic toxicity of the plant.

Overall, additional in-depth studies are needed to fully validate the scientific basis for using *W. indica* for asthma treatment. These studies should include examining the plant's anti-allergic, anti-mast cell degranulation, and antihistamine properties and understanding broncho-relaxant mechanisms. This would open the path for the medical exploitation of this botanical species, such as developing a phytomedicine based on *W. indica* extracts. Furthermore, conducting a more in-depth chemical analysis of the plant could provide new perspectives on asthma treatment.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

CRediT authorship contribution statement

Zakaline Yabré: Writing – original draft, Conceptualization. **Rainatou Boly:** Writing – review & editing, Conceptualization. **Raogo Ouédraogo:** Writing – review & editing. **Abdul Gafar Victoir Coulidiaty:** Validation. **Gaétan D. Somda:** Writing – review & editing. **Rasmané Semdé:** Investigation, Funding acquisition. **Noufou Ouédraogo:** Writing – review & editing, Supervision. **Estelle Noëla Hoho Youl:** Validation, Supervision, Project administration, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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