Tabebuia Impetiginosa

Subjects: Plant Sciences

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Tabebuia impetiginosa, a plant native to the Amazon rainforest and other parts of Latin America, is traditionally used for treating fever, malaria, bacterial and fungal infections, and skin diseases.

Keywords: Tabebuia impetiginosa, ; pharmacological activities, anti-inflammatory

1. Introduction

Historically, people have used natural products such as plants, animals, microorganisms, and other biological resources to assuage and cure diseases [1]. Many of the commercial drugs (such as atropine, teniposide, aescin, digoxin, silymarin, and so on) available today were initially developed from plants and other biological resources used in traditional medicines [2][3]. Therefore, knowledge of the traditional use of natural products plays a large role in drug discovery and development.

Tabebuia impetiginosa (Mart. Ex DC. Mattos) is a plant belonging to the family Bignoniaceae, which is mainly distributed in the Amazon rainforest and other tropical regions of Central and Latin America [4]. It is not only a decorative plant but also has high pharmaceutical value. *T. impetiginosa* has been used as a traditional medicine to treat various diseases and has antinociceptive, anti-edematogenic, antibiotic, and antidepressant effects [5][6][7]. Moreover, the inner bark of this tree can be made into poultice or concentrated tea to treat various skin inflammatory diseases [8]. Several categories of compounds have been isolated and identified from *T. impetiginosa,* principally quinones, flavonoids, naphthoquinones, and benzoic acids [9][10][11][12]. In recent years, many investigations have demonstrated that extracts or compounds isolated from *T. impetiginosa* reveal an extensive range of pharmacological activities such as anti-obesity, antifungal, anti-psoriatic, antioxidant, anti-inflammatory, and anti-cancer activities [4][7][13][14][15][16][17][18]. It is particularly prominent in immunopharmacology. Typically, the mechanism of anti-inflammatory activity of extract from the inner bark of *Tabebuia* was studied through a molecular biological approach. Nevertheless, the clinical applications of *T. impetiginosa* have been poorly researched, and there is a void of information on its mechanisms of action.

2. Traditional Uses

T. impetiginosa has been used traditionally to treat cancer [19], obesity [20], depression [21], viral, fungal, and bacterial infections [22], and inflammatory symptoms such as pain [23], arthritis [15], colitis [24], and prostatitis since the Inca civilization. The Callawaya Tribe makes a concentrated tea out of the tree's inner bark for treating skin inflammatory diseases [8]. Moreover, it can be used as an astringent and diuretic [25]. Caribbean folk healers utilize the bark and leaves of *T. impetiginosa* to cure toothaches, backaches, and sexually transmitted diseases [26]. Latino and Haitian populations were also reported to use this plant for the treatment of infectious disease [27]. Brazilian people have traditionally used this plant for anti-inflammatory, analgesic, and antiophidic purposes against snake venom [28]. Traditional healers in Brazil prescribed *T. impetiginosa* for cancer and tumor prevention or treatment; 69.05% for the treatment of tumors and cancer in general and 30.95% for specific tumors or cancers [29]. Such ethnomedicinal uses of *T. impetiginosa* led us to pay attention to it for a full understanding of its immunopharmacological properties for the future development of an effective drug against ethnopharmacologically targeted diseases with this plant.

3. Phytochemistry

Several categories of phytochemicals have been identified in the leaves, bark, and wood of *T. impetiginosa.* From *T. impetiginosa* bark, 19 glycosides comprised of four iridoid glycosides, two lignan glycosides, two isocoumarin glycosides, three phenylethanoid glycosides, and eight phenolic glycosides were methanol-extracted [30]. Major constituents of *T. impetiginosa* are furanonaphthoquinones, naphthoquinones, anthraquinones (e.g., anthraquinone-2-carboxylic acid (Compound **1** in Figure 1)), quinones, benzoic acid, flavonoids, cyclopentene dialdehydes, coumarins, iridoids, and phenolic glycosides [4][8][31]. The presence of naphthoquinones attracted scientific attention, with lapachol (**2**) and β-

lapachone (**3**) especially piquing the interest of professionals in the medical field. Lapachol inhibits proliferation of tumor cells, while β-lapachone exhibits strong toxicity in murine and human cells. Lapachol has been shown to reduce the number of tumors caused by doxorubicin in *Drosophila melanogaster* heterozygous for the tumor suppressor gene. Lapachol can also decrease the invasion of HeLa cells, which could represent an interesting scaffold for the development of novel antimetastatic compounds [4].

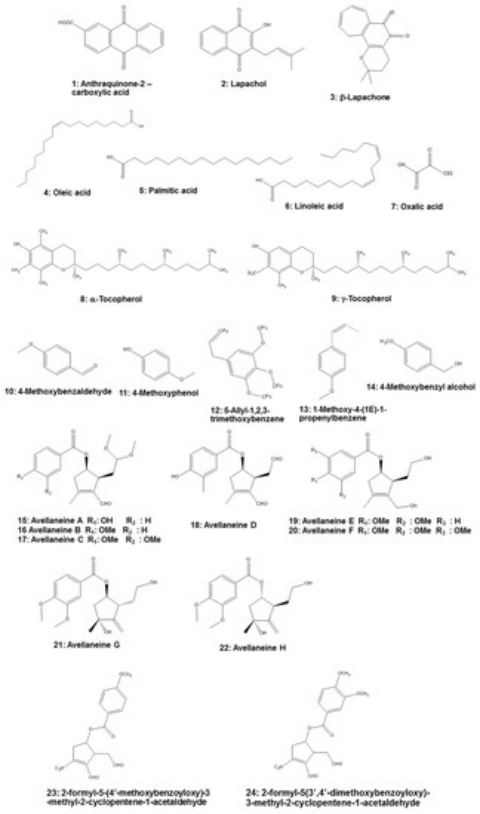

Figure 1. Chemical structures of *Tabebuia impetiginosa*-derived components.

Fatty acids, especially oleic acid (**4**), palmitic acid (**5**), and linoleic acid (**6**), are found in the bark of *T. impetiginosa*. Free sugars also were identified in the bark, with glucose being the most abundant, followed by fructose and sucrose. Organic acids, especially oxalic acid (**7**), are present, as well as the fat-soluble alcohols α-tocopherol (**8**) and γ-tocopherol (**9**). α-Tocopherol can reduce cardiovascular disease risk and neurodegenerative disorders [4]. In addition, *T. impetiginosa* has some volatile constituents that exhibit antioxidant activity. The major volatile constituents in *T. impetiginosa* include 4-methoxybenzaldehyde (**10**), 4-methoxyphenol (**11**), 5-allyl-1,2,3-trimethoxybenzene (**12**), 1-methoxy-4-(1*E*)-1-propenylbenzene (**13**), and 4-methoxybenzyl alcohol (**14**) [32].

Cyclopentene derivatives are secondary metabolites of plants, and this constituent from *T. impetiginosa* contained six known cyclopentenyl esters (avallaneine A–F (**15–20**)), two new cyclopentyl esters (avallaneine G (**21**) and H (**22**)), and two known cyclopentenyl esters. These cyclopentene derivatives may provide a significant anti-inflammatory effect on the lipopolysaccharide (LPS)-mediated inflammatory response by blocking the production of NO and PGE_2; therefore, it is important to determine the molecular mechanism whereby cyclopentenyl esters from *T. impetiginosa* inhibit inflammatory responses [16]. Moreover, Koyama et al. [33] isolated two cyclopentene dialdehydes, 2-formyl-5-(4′-methoxybenzoyloxy)-3-methyl-2-cyclopentene-1-acetaldehyde (**23**) and 2-formyl-5-(3′,4′-dimethoxybenzoyloxy)-3-methyl-2-cyclopentene-1-acetaldehyde (**24**), that exert anti-inflammatory activity in human leukocytes. Thus, it is necessary to further investigate their activities.

3. Pharmacological Activities

Previous research has indicated various pharmacological effects of *T. impetiginosa* and its crude extracts and chemical compounds in a series of in vitro and animal models. It exhibits antibacterial, antioxidant, antifungal, antinociceptive, antidiabetic, anti-edema, anti-inflammatory, and anti-cancer activities at different concentrations or doses. The main pharmacological activities of extracts or compounds isolated from *T. impetiginosa* reported in in vitro and in vivo studies are briefly summarized in Table 1 and described in detail in the following subsections.

Table 1. Immunopharmacological effects of *Tabebuia impetiginosa.*

Pharmacological Activity	Extract/Isolated Compounds	Model	Concentration/Dose	Results	Ref.
Immunomodulatory	Water extract	RAW264.7 (murine macrophage cell), U937 (human promonocytic cell)	50, 100, 200, and 400 µg/mL	Maintained cluster formation of RAW264.7 cells even after lipopolysaccharide (LPS) treatment. Downregulated the phagocytic uptake of FITC-labeled dextran. Upregulated cell-cell interactions by decreasing migration of cells and enhancing CD-29-mediated cell-cell adhesion and the surface levels of adhesion molecules and costimulatory molecules linked to macrophage stimulation, as seen in upregulation of reaction oxygen species (ROS) release. Suppressed an alteration in the membrane level of macrophages (phagocytic uptake and morphological changes).	[34]
	Ethanol extract	IL-2-independent T-lymphocyte	0.25, 0.5, 0.75, 0.9, and 1.0, mg/mL	Inhibited activation and proliferation of IL-2-independent T-lymphocyte	[35]
Anti-inflammatory	Water extract	LPS-stimulated macrophages, arachidonic acid, or croton oil-induced mouse ear edema models	0–400 µg/mL, 100–400 mg/kg	Inhibited the production of NO and PGE_2 and suppressed the mRNA levels of COX-2 and iNOS. Curative effect in an in vivo PGE_2-based inflammatory symptoms model induced by arachidonic acid.	[8]
	Ethanol extract	TPA- or arachidonic acid-induced ear edema, hot plate, acetic acid-induced vascular permeability in rats	100, 200, or 400 mg/kg	Inhibited inflammation of paw edema, ear inflammation, and dye leakage in the vasculature using various animal models including acetic acid-induced vascular permeability, 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced ear edema, arachidonic acid-induced mouse ear edema, and carrageenan-induced paw.	[23]
	Five novel compounds	Human myeloma THP-1 cells	25 µM	Showed inhibitory activity on production of the inflammatory cytokines, such as TNF-α and IL-1β.	[36]
	Cyclopentene derivatives	RAW264.7 cells	12.5, 25, 50 µg/mL	Suppressed the production of NO and PGE_2.	[16]

Pharmacological Activity	Extract/Isolated Compounds	Model	Concentration/Dose	Results	Ref.
Anti-cancer	Naphthoquinones	MDA-BB-231, MCF7, and A549 cells	0–30 µM	Inhibited growth of cancer cell lines and STAT3 phosphorylation activity.	[14]
	Water extract	Estrogen receptor $(ER)^+$ human mammary carcinoma MCF-7 cell line	0.05, 0.125, 0.25, 0.5, 0.75, 1.5 mg/mL	Exhibited dose-dependent growth inhibition of MCF-7 cells.	[19]
	β-lapachone	A549 human lung carcinoma cells		Inhibited growth of A549 cells and telomerase activity; induced apoptosis by reducing the expression of Bcl-2, increasing the expression of Bax, and activating caspase-3 and caspase-9.	[13]
Antinociceptive	β-lapachone	HepG2 hepatoma cell line		Inhibited the activity of HepG2 by inducing apoptosis; downregulation of Bcl-2 and Bcl-X_L, upregulation of Bax expression; induced apoptosis by activating caspase-3 and caspase-9 and degrading poly (ADP-ribose) polymerase protein.	[37]
	Methanol extract	Human tumor cell lines MCF-7, NCI-H460, HeLa, and HepG2; porcine liver primary cells (PLP2).	GI50 values: 110.76 ± 5.33 µg/mL (MCF-7), 76.67 ± 7.09 µg/mL (NCI-H460), 93.18 ± 1.46 µg/mL (HeLa), 83.61 ± 6.61 µg/mL (HepG2), and >400 µg/mL (PLP2).	Showed cytotoxic effects on MCF-7, NCI-H460, HeLa, and HepG2 cells.	[4]
	Ethanol extract	Acetic acid-induced writhing response in rats	100, 200, or 400 mg/kg	Increased the pain threshold in a mouse model when assessed through the hot plate test and inhibited the number of writhes compared to controls in the acetic acid-induced writhing responses mouse model.	[23]
Osteoarthritis	Ethanol extract	RAW264.7 cells and chondrosarcoma cell line (SW1353); monoiodoacetate (MIA)-induced osteoarthritis in rats	75, 150, and 300 µg/mL	Showed a chondroprotective effect by preventing cartilage degradation through targeting of NF-κB and AP-1 signaling pathways in macrophage and chondrocyte cells. Downregulated MMP2, MMP9, and MMP13 in a PMA-induced, dose-dependent manner; no effect on the gene expression of COL2A1 and CHSY1.	[15]

Pharmacological Activity	Extract/Isolated Compounds	Model	Concentration/Dose	Results	Ref.
Colitis	Water extract	RAW264.7 cells Dextran sulfate sodium (DSS)-induced colitis in mice	100, 300, 900, and 2700 μg/mL 2 mg/day, a total of 5 days	Activated DC to produce immunosuppressive IL10; upregulated anti-inflammatory Th2 and Foxp3$^+$ Treg cells in mesenteric lymph node (MLN) and downregulated pro-inflammatory Th1 and Th17 cells. By upregulating type II T-assisted immune response, weight loss and inflammation of colon tissue were downregulated in DSS-induced colitis mice.	[24]
Antioxidant	Methanol extract		EC50 values: 0.68 ± 0.03 (DPPH scavenging activity), 0.27 ± 0.01 (Reducing power), 0.23 ± 0.04 (β-carotene bleaching inhibition), 0.14 ± 0.01 (thiobarbituric acid Thiobarbituric acid reactive substances (TBARS) inhibition).	Showed the highest antioxidant activity, which may be related to its total phenol content.	[4]
	Methanol, butanol, and water extracts	H_2O_2-induced NIH3T3 cells	0–2 mg/mL	Regenerated superoxide dismutase (SOD), catalase, and glucose 6-phosphate dehydrogenase activities; enhanced the concentration of glutathione in the cell; protected proteins from oxidative attack of H_2O_2, reduced formation of malondialdehyde in the cell, and protected NIH3T3 cells from H_2O_2-induced oxidative stress.	[38]
	Volatile constituents		5, 10, 50, 100, and 500 μg/mL	Displayed dose-dependent activity in antioxidant assays	[32]
	Phenylpropanoid glycosides		Compound 5 had the highest antioxidant activity, with an IC_{50} of 0.12 μM	Had inhibitory effects on cytochrome CYP3A4 enzyme	[18]
Anti-obesity	*n*-butanol extract	Ovariectomized (OVX) mice. 3T3-L1 cells	A total of 16 weeks	Preventing the accumulation of adipocyte in mice, weight loss and fat mass ↓ in ovariectomized mice.	[17]
	Ethanol extract	Triton WR-1339-treated Wistar rats	A total of 24,700 kJ/kg energy	Decreased postprandial triglycerides in rats given a fatty meal.	[20]
Anti-allergic	Five novel compounds	RBL-2H3 cells	100 μM	Inhibited release of β-hexosaminidase of the allergy marker.	[36]

Pharmacological Activity	Extract/Isolated Compounds	Model	Concentration/Dose	Results	Ref.
Antidepressant	Ethanol extract	Forced swimming test (FST) and tail suspension test (TST) in mice.	100 mg/kg, p.o. (in the FST) and 10–300 mg/kg, p.o. (in the TST)	Produced antidepressant effects in the tail suspension test and forced swimming test.	[21]
Antiplatelet	Methanol extract	Rabbit platelets and cultured rat aortic vascular smooth muscle cells (VSMCs)	10, 50, 100, and 200 μg/mL	Reduced platelet aggregation by inhibiting arachidonic acid release and ERK1/2 MAPK activation.	[25]

4. Conclusions

T. impetiginosa has been used as a traditional medicine in Central and South America to treat edema, arthritis, diuretic, and infections. Based on its traditional use, in vivo and in vitro experiments examining its pharmacological potential have been conducted. In vivo experiments were conducted using edema, osteoarthritis, animal paw edema, and writhing (and other) models to screen effects of *T. impetiginosa*. Moreover, there are numerous studies confirming that extracts or compounds isolated from *T. impetiginosa* have various pharmacological activities such as anti-obesity, antibacterial, antifungal, antiviral, anti-psoriatic, antioxidant, anti-inflammatory, and anti-cancer activities.

Currently, substantial progress has been made in exploration of the phytochemistry and pharmacological activity of *T. impetiginosa.* Nonetheless, there are still challenges and gaps in published research papers that should be further explored to establish its clinical application value. Firstly, the extracts and compounds isolated from *T. impetiginosa* possess multiple pharmacological activities, though most functional mechanisms remain unclear and need to be further explored through in vivo and in vitro experiments. Furthermore, most studies on *T. impetiginosa* are still in the in vitro and in vivo mouse model stages. Toxicological research can be conducted on other animals such as rabbits in the future to evaluate its safety, which will pave the way for further clinical trials. In addition, further comprehensive experiments are needed to enrich the data and discover other pharmacological uses of *T. impetiginosa* and to find the exact mechanisms by which its extracts bind to target proteins.

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