Traditional Medicine Research
doi: 10.12032/TMR20201128209

The coastal medicinal plant *Vitex rotundifolia*: a mini-review on its bioactive compounds and pharmacological activity

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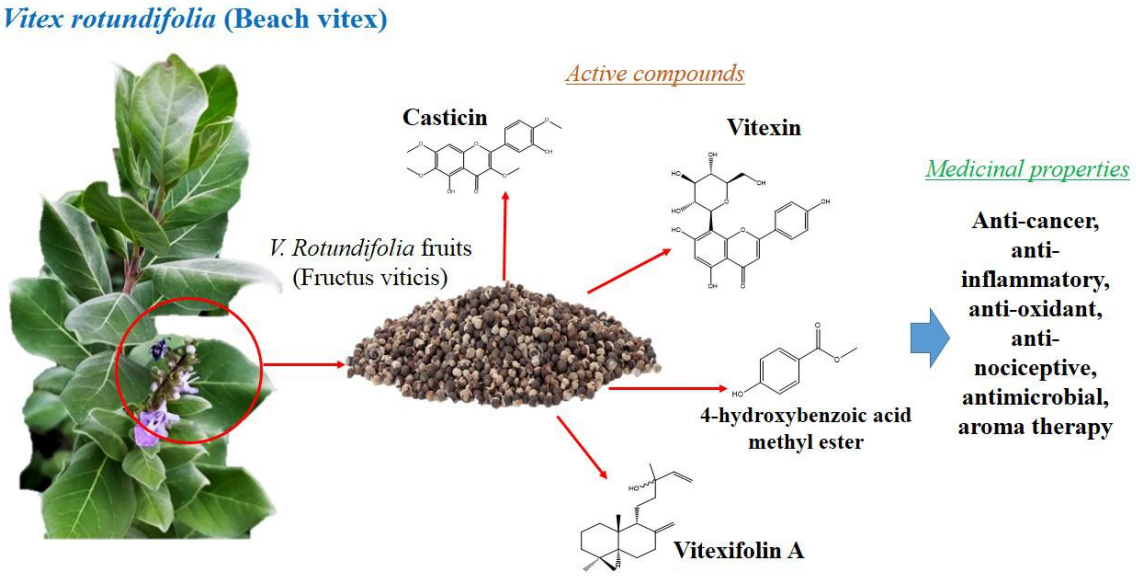
Highlights

This review focuses on *Vitex rotundifolia* as a medicinal plant and its bioactive compounds and current pharmacological activity.

Tradition

The Vitex species has been used as medicine for 2,000 years, and throughout the Middle Ages and the Renaissance era. Botanist and herbalist Christopher Hobbs described the use of *Vitex rotundifolia* throughout history, stating that Hippocrates (400 B.C.E.) recommended it for injuries and inflammation. *V. rotundifolia* has also been listed in well-known European pharmacopoeias, including *Pharmacopoeia Londinensis* which dates back to the year 1618. In 1633, a renaissance herbalist recommended *V. rotundifolia* for inflammation of the uterus. In China, it is widely used in traditional Chinese medicine and as a crude drug of the fruits of *V. rotundifolia*, *Fructus viticis*. It is also recorded as a Manjingzi in the *Pharmacopoeia of the People's Republic of China*.



Abstract

Humans have long used natural remedies like plants and herbs to treat disease. Furthermore, research has been ongoing to find alternative pharmaceutical drugs based on traditionally used plants, as natural products show fewer side effects compared to synthetic drugs. Medicinal plants have long been targeted in drug development due to their bioactive compounds like alkaloids, flavonoids, and terpenoids. This is not only the case for terrestrial plants, but marine environments also provide a larger diversity of flora and fauna with medicinal bioactive compounds. *Vitex rotundifolia*, also known as Beach Vitex, is a coastal plant that has been traditionally used to treat a variety of diseases including premenstrual syndrome, headaches, migraines, colds, and eye pain. There have been many review papers on *V. rotundifolia*, emphasizing its taxonomy, distribution, and biological activity. Our current mini-review not only summarizes the pharmacology and bioactivity of *V. rotundifolia*, but it also provides new information on the main bioactive compounds of *V. rotundifolia* such as flavonoids, phenolic acid, and terpenes and their current pharmacological activity in vitro and in vivo research. This information can be useful for developing new pharmaceutical and nutraceutical agents to treat and manage disease.

Keywords: *Vitex rotundifolia*, *Fructus viticis*, Marine plants, Anti-inflammation, Anti-nociception, Antioxidant

***Author contributions*:**

Suvik Assaw and Wan Amir Nizam Wan Ahmad developed the idea for the study and coordinated and directed the article; Nurul Laili Rosli did the data collection on the history, taxonomy and general plant description; Muhammad Aniq Hamzah Mohd Azmi, Choo En Liang, and Noor Wini Mazlan did the comprehensive data collection on compound isolation, chemicals structure and its bioactivities from *V. rotundifolia*; Nurul Husna Azizul collected most of the provided data and drafted the manuscript; and all authors read and approved the final version of manuscript.

***Competing interests*:**

The authors declare no conflicts of interest.

***Acknowledgments*:**

Author would like to thank School of Health Sciences, Universiti Sains Malaysia and Universiti Malaysia Terengganu for providing the facilities to support this project. This project is fully supported by Fundamental Research Grant Scheme Vot No. 59479 from Ministry of Higher Education Malaysia.

***Abbreviations*:**

MIC, minimum inhibitory concentration; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

***Citation*:**

Azizul NH, Ahmad WANW, Rosli NL, et al. The coastal medicinal plant *Vitex rotundifolia*: a mini-review on its bioactive compounds and pharmacological activity. *Tradit Med Res*. 2021;6(2):11. doi: 10.12032/TMR 20201128209.

***Executive editor*:** Rui-Wang Zhao.

***Submitted*:** 15 August 2020, ***Accepted*:** 27 October 2020, ***Online*:** 22 December 2020.

doi: 10.12032/TMR20201128209

Background

The coastal plant *Vitex rotundifolia* has a long history of ethnopharmacological use in both European and Asian countries, such as China, Korea, and Japan [1–3]. In European herbalism, the plant was used to treat various diseases related to female the reproductive system and menstrual cycle [4, 5]. The exact date when human use of the Vitex species for natural remedies began is not known, however, the prominent botanist and herbalist Christopher Hobbs described the Vitex species as being used medicinally starting 2,000 years ago and throughout the Middle Ages and the Renaissance (the herbalism age) [6]. He also described the history of the medicinal use of Vitex, where Hippocrates (400 B.C.E.) recommended it for injuries and inflammation. Moreover, Dioscorides (50 C.E.) recommended its use for stimulating mother's milk. Vitex has also been listed in well-known European pharmacopoeias including *Pharmacopoeia Londinensis* which dates back to the year 1618. In 1633, a renaissance herbalist recommended Vitex for inflammation of the uterus [6]. In China, it is used extensively in traditional Chinese medicine and as a crude drug of the fruits *V. rotundifolia Fructus viticis*. It is even recorded as a Manjingzi in the *Pharmacopoeia of The People's Republic of China* [3, 7]. However, due to overexploitation, the species is listed in the *List of The Important Wild Plants for Conservation in China and Japan* [8, 9]. The fruits of *V. rotundifolia* were also used in indigenous medicine to cure migraines, colds, eye pain, headaches, asthma, and gastrointestinal infections [10].

The genus Vitex L. belongs to the family Verbenaceae and is widely distributed in tropical and temperate regions of China, Japan, Southeast Asia, the Pacific Islands, and Australia [11]. In addition, out of the 250 species of Vitex, the most common species known for their medicinal properties are *V. agnus-castus*, *V. rotundifolia* (synonyms of *V. trifolia*), and *V. negundo*. This mini-review describes the pharmacology and bioactivity of the widely found coastal medicinal plant *V. rotundifolia*, also known to Malaysians local to its environment as *Legundi or Lemuni* [12, 13] and to the Siamese people of Malaysia as "Bai Khun Thi". *V. rotundifolia,* also known as Beach Vitex is an important coastal and medicinal plant. It is a deciduous sprawling shrub with round leaves and a spicy fragrance [14–16]. *V. rotundifolia* belongs to the Verbenaceae family (Table 1) of angiosperms, and is also placed the in Lamiaceae family. It is a low-growing, salt-tolerant, shoreline/seaside shrub [17, 18]. *V. rotundifolia* has been used in traditional medicine to treat diarrhea, gastrointestinal disorders, sprain, rheumatic pain, inflammation, cancer, respiratory infections, migraine, premenstrual problems, depression, allergies, and wounds [19, 20].

Table 1 Current taxonomy of *V. rotundifolia*

Taxon: *Vitex rotundifolia* L. f.
Kingdom: Plantae-plants
Subkingdom: Tracheobionta-vascular plants
Superdivision: Spermatophyta-seed plants
Division: Magnoliophyta-angiosperms
Class: Magnoliopsida-dicots
Subclass: Asteridae
Order: Lamiales
Family: Lamiaceae
Subfamily: Viticoideae
Genus: Vitex L.-chastetree
Species: *Vitex rotundifolia* L. f.-Beach Vitex

V. rotundifolia's leaves produce thick, round, waxy cuticles 1–2 inches long with a gray-green to silvery color and have a spicy fragrance. They contain large amounts of diverse n-alkanes and these compounds are transferred to the sand particle surface where they cause intense hydrophobicity in the substratum [21]. *V. rotundifolia* has a nodal root system that allows the plant to form dense mats that spread from mother plants to distances of more than 10 m. Its roots and stems can regenerate quickly [22]. The young stems of *V. rotundifolia* are square and green or purple, fleshy at the tips, and as the stems mature they turn round, brown, and woody. The bark will crack and fissure with age while the branches from running stems are upright [8]. The fruit of *V. rotundifolia* (also known as *Fructus viticis*) is a small succulent drupe, globular or ovoid, 0.2–2 cm in size (usually less than 2 cm), with a hardened endocarp divided into four pyrenees, each with a seed. The ripe pulp of these fruits is characterized by a dark-purple to brown color [23]. Most of the *V. rotundifolia* plant parts such as the leaves, root, flowers, and stem have been reported to have medicinal values, but the fruit, *Fructus viticis* is the most studied (Figure 1).

There have been many review papers on *V. rotundifolia*, emphasizing its taxonomy, distribution, and biological activity. The aim of this mini-review is to further describe and add new information using in vitro and in vivo research on the traditional use of the coastal medicinal plant *V. rotundifolia's* main bioactive compounds such as flavonoids, phenolic acid, and terpenes and its current pharmacological activity. This information can be useful in developing new pharmaceutical and nutraceutical agents to treat and manage disease.

Bioactive compounds of *V. rotundifolia*

Various bioactive compounds with medicinal value can be found in *V. rotundifolia* plants including

flavonoids, alkaloids, saponins, iridoids (eucommiol, iridolactone, pedicularis-lactone, 1-oxo-eucommiol, agnuside, VR-I (10-o-vanilloyl aucubin) 16, viteoid i, viteoid ii, and trans- and cis-eurostoside), phenolics, mono- and diterpenes, α-pinene, α-terpineol, 1,8-cineole and manoyl oxide, phenylnapthalene, polymethoxyflavonoids, dehydroabietane, biformene, rotundiferan, vitexicarpin, prerotundifuranne and rotundifuranne, aucubin, thunbergol, mussaenosidic acid, trans-phytol, and sabinene [24]. Although, many bioactive compounds that have been isolated from *V. rotundifolia*, flavonoids, phenolic acids, and terpenes are frequently reported to have various biological and pharmacological activity in vitro and in vivo.

Flavonoids

A category of natural substances with varying phenolic structures, flavonoids are present in fruit, plants, grains, bark, roots, stems, flowers, tea, and wine. They are well known for their positive health effects, and efforts are made to isolate flavonoids from their sources. Flavonoids are now accepted as essential components of a variety of nutraceutical, pharmaceutical, medicinal, and cosmetic products. They contain antioxidant, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties combined with their ability to modulate cellular enzymes' key functions. Based on previous studies, various types of flavonoids have been isolated from *V. rotundifolia* (as shown in Figure 2) such as casticin, known as the major flavonoid presence in *V. rotundifolia*, which is reported to inhibit various biological activities with its antioxidant, anti-inflammatory, anti-viral, anti-osteoporosis, anti-cancer, [25] and anti-atherosclerotic effects [26]. Other discovered flavonoids are vitexin, isovitexin, artemetin, hesperidin, orientin, luteolin, and 5,3'-dihydroxy-6,7,4'-trimethoxyflavanone, some of which were also shown to have antioxidant effects on 1,1-diphenyl-2-picrylhydrazyl scavenging tests in previous studies [26–28].

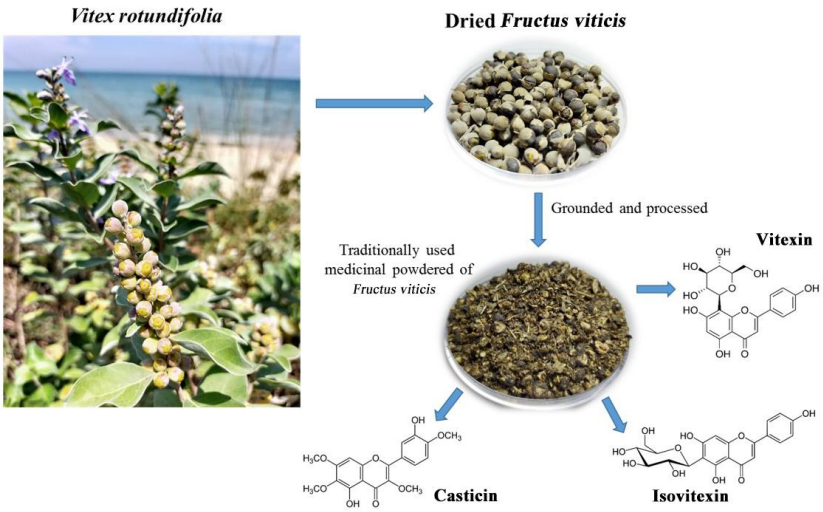


Figure 1 *V. rotundifolia* whole plant and its dried processed powdered fruits, *Fructus viticis*, used in traditional medicine

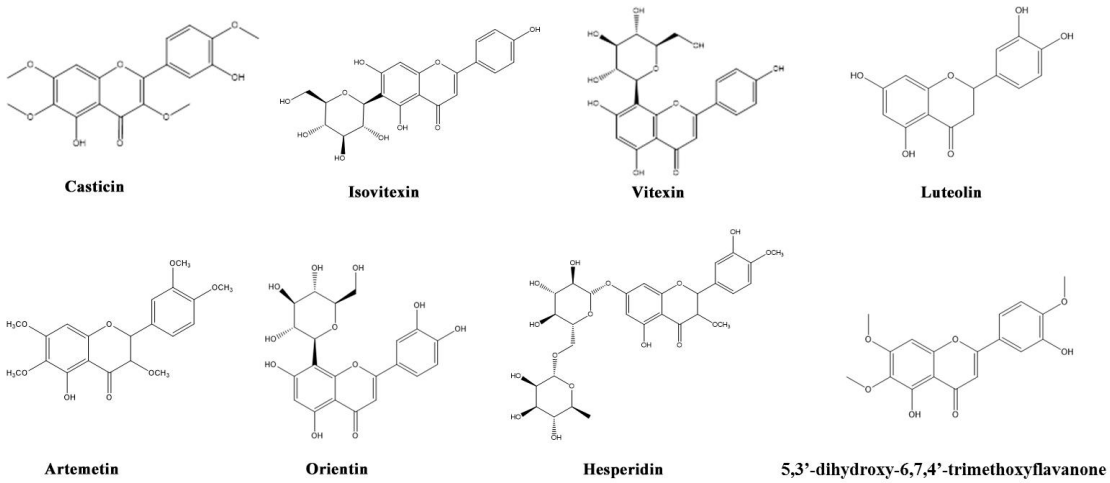


Figure 2 Flavonoid isolated from *V. rotundifolia*

doi: 10.12032/TMR20201128209

Phenolic acid

Phenolic compounds are known as secondary metabolites derived from the cinnamic acid skeleton or benzoic carboxylic acid, which are widely distributed among plants, fruits, and cereal grains. Previous studies have found several types of phenolic acid in the Vitex plant, as shown in Figure 3, such as castusic acid [29], 4-hydroxybenzoic acid methyl ester, vanilic acid methyl ester, 4-hydroxy benzaldehyde, and 4-hydroxy-benzoic acid that were isolated from the fruits and leaf of *V. rotundifolia* L. [30].

Terpenes

Terpenes are known as secondary metabolites that are mostly found in plants, including *V. rotundifolia*. The secondary metabolite presence in aromatic organic hydrocarbon form developed to attract pollinators and helpful herbivores. Previous studies showed that many types of terpenes were present in *V. rotundifolia*, as shown in Figure 4. The terpenes that have been found in *V. rotundifolia* are vitexifolin A, vitexifolin B, vitexifolin C, vitexifolin D, vitexifolin E, vitetrifolin D, trisnor-gamma-lactone, iso-ambreinolide, vitexolin A, and vitexolin B [28, 31].

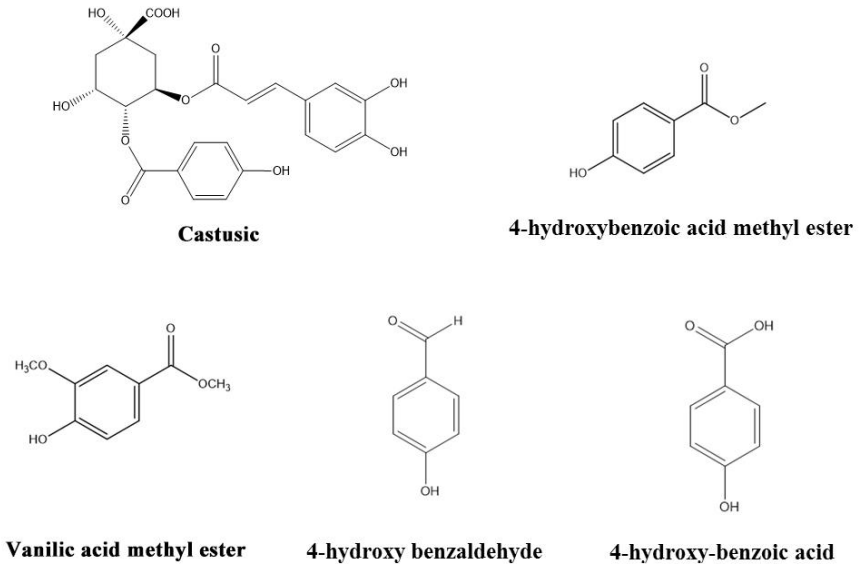


Figure 3 Phenolic acid isolated from *V. rotundifolia*

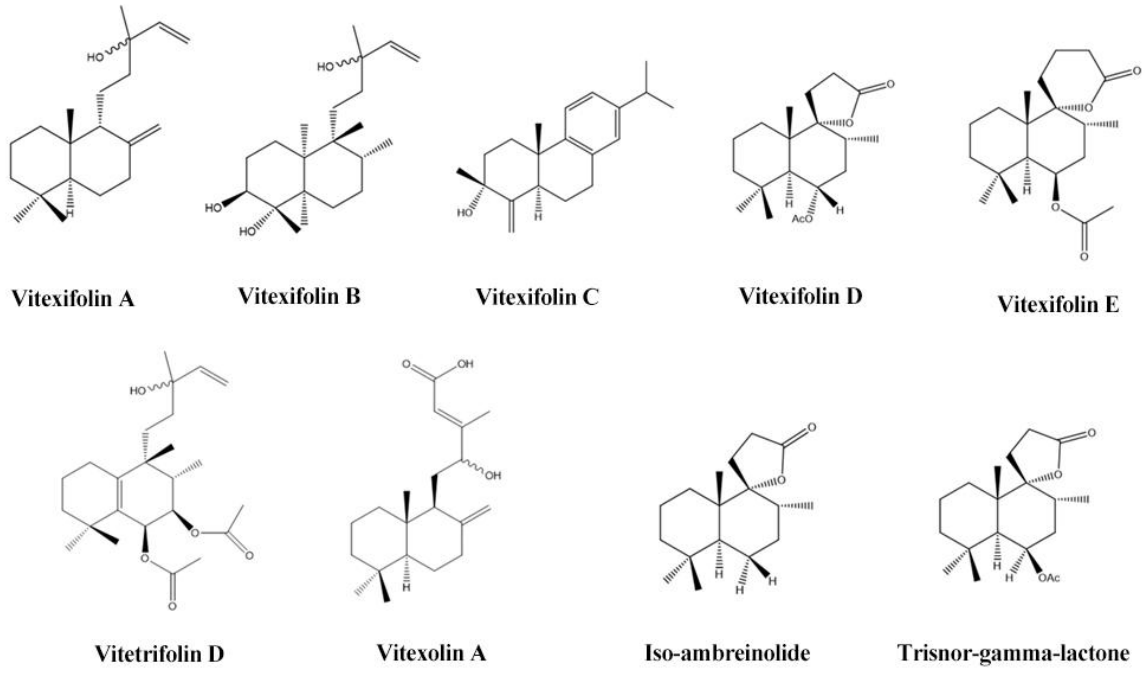


Figure 4 Terpenes isolated from *V. rotundifolia*

General pharmacological activity of *V. rotundifolia*

V. rotundifolia is used in traditional medicine to treat headaches, colds, eye pain, asthma, chronic bronchitis, inflammation, allergic diseases, and gastrointestinal diseases [32]. Furthermore, *V. rotundifolia* exhibits various pharmacological effects such as anti-microbial, anti-nociceptive, cytotoxic, anti-inflammatory, and anti-hyperprolactinemia activity [33, 34]. One of the main components of *V. rotundifolia*, casticin (3',5-dihydroxy-3,4',6,7-tetramethoxyflavone) has several pharmacological properties, including anti-inflammatory, hepatoprotective, and anti-cancer activity [35]. Casticin, also known as vitexicarpin or casticine, is shown to contain anti-cancer and anti-inflammatory properties, as well as anti-asthmatic, tracheospasmolytic, analgesic, anti-hyperprolactinemia, immunomodulatory, opioidergic, oestrogenic, anti-angiogenic, and anti-glioma effects. It is also shown to protect against lung injury, improve symptoms of rheumatoid arthritis, and reduce liver fibrosis [36–38]. From the perspective of disease treatment, the *V. rotundifolia* is a useful agent for treating female health issues [39–41], where previous report has found that essential oils and specific compounds such as casticin, leteolin, rotundifuran, and agnuside from *V. rotundifolia* contain estrogen-like biological activity with the potential to treat hormone-related diseases and premenstrual syndrome [42].

Anti-inflammatory and analgesic effects

The *V. rotundifolia* plant is well known for its anti-cancer and anti-proliferative activity. However, there are limited in vitro and in vivo studies focusing on the plant's extracts and isolated compounds as potential anti-inflammatory and analgesic agents. Here we summarized the potential compounds or extracts from *V. rotundifolia* as anti-inflammatory and anti-nociceptive agents, as shown in Table 2.

Table 2 Anti-inflammatory and analgesic effects of isolated compounds from *V. rotundifolia* and their mechanisms of action

Bioactivity	Compound/extract	Mechanisms of action	Ref
Anti-inflammatory	Casticin	Inhibited interleukin-1β-induced nitric oxide and prostaglandin E2 production, inducible nitric oxide synthase and cyclooxygenase-2 expression in human osteoarthritis chondrocytes and suppressed the levels of tumor necrotic factor alpha, interleukin-6 and metalloproteinases.	[32]
		Suppressed eotaxin production in cytokine activated A549 lung epithelial cells. Casticin also suppressed the mRNA expression levels of eotaxin, regulated upon activation, normal T-cell expressed and secreted, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1, which subsequently contributed to the inhibition of eosinophil migration.	[35]
		Suppressed the inflammatory effect by blocking the nuclear factor kappa B and mitogen-activated protein kinase pathways in lipopolysaccharides-induced RAW264.7 macrophage cells and ulcerative colitis.	[43, 44]
	Compounds 3, 4, 7, 13, 15, 19, and 24	Inhibits nitric oxide production with the inhibitory concentration values ranging from 11.3 to 24.5 μM.	[45]
	Methanolic extract	Inhibitory effect on the nitric oxide production in RAW264.7 macrophage cells.	[46]
	Agnuside	Possible development of agnuside as a potential treatment of arthritis through its modulatory effects on the host immune response.	[47]
	Aucubin	Able to inhibit tumor necrotic factor alpha production in RAW264.7 cells.	[48]
Analgesic anti-nociceptive	Casticin	Significantly inhibited xylene-induced mouse ear edema, egg albumen-induced rat paw edema and acetic acid-induced mouse vascular permeability.	[49]

Antioxidant Activity

V. rotundifolia has been shown to possess high antioxidant activity [50]. A study showed that the methanolic extract of the twigs of *V. rotundifolia* possesses potent antioxidant activity when measuring the radical scavenging effect on 1,1-diphenyl-2-picrylhydrazyl. Two flavonoids, orientin and 3,4-di-O-caffeoylquinic acid, a quinic acid derivative showed significant antioxidative effects [27]. The study revealed that vitexilactone, a labdane diterpenoid that can be isolated *V. rotundifolia* appears to be a safe and efficacious alternative treatment for kidney injury on cisplatin-induced nephrotoxicity in rats, probably due to its high antioxidant activity [50, 51]. Furthermore, ferruginol, an abietane-type diterpenoid isolated from *V. rotundifolia* showed higher antioxidant activity than 3-tert-butyl-4-hydroxyanisole using the ferric thiocyanate method [30]. An in vivo study is needed to assess the antioxidant activity of *V. rotundifolia* in animal tissues or blood. The most common in vivo methods used to study an extract's antioxidant activity are by lipid peroxidation assays, catalase, and superoxide dismutase methods [52].

Antibacterial activity

Various studies have examined the antibacterial activity of the *V. rotundifolia* either from the extract of the species or the isolated compounds. The methanol extracts from the *Vitex negundo* leaf have shown a possible antibacterial agent. The extracts have been shown to inhibit the growth of bacteria and exhibit the lowest minimum inhibitory concentration (MIC) values against *Staphylococcus aureus* and *Pseudomonas aeruginosa* [53, 54]. From previous studies, vitrofolal C, vitrofolal D, and detetrahydroconidendrin, isolated compounds from the subterranean part of *V. rotundifolia* are shown to be active against methicillin-resistant *Staphylococcus aureus* with a MIC of fewer than 64 µg/mL against 8 out of 18 strains [54]. The chloroformic and ethyl acetate fractions from the fruits of another Vitex species, *Vitex mollis* have been recorded as having the highest antibacterial activity ranging from 4 to 8 mg/mL of MIC against gram-positive and gram-negative bacteria [55].

Other pharmacological activity

Agnuside, an iridoid glycoside is shown to regulate menopause symptoms and is used in the treatment of premenstrual disorders. A study revealed that agnuside exhibits dose-dependent estrogenic activity through its interaction with estrogen receptors and progesterone receptors [56]. Furthermore, a study revealed that diterpenes from *Fructus viticis* inhibits prolactin release in vivo and in vitro by acting as dopamine agonists, and the current study indicated that casticin counteracted the stimulating effects of estrogen to reduce the production of prolactin, as it was reported that women with severe premenstrual syndrome have higher mid-cycle estrogen levels [57]. Studies found that *Fructus viticis* substantiated the anti-tumor properties in a variety of human cancer cells and their xenograft models in mice due to the presence of large amounts of flavonoids, including casticin, luteolin, apigenin, isoorientin, hesperidin, and isovitexin [58, 59]. Additionally, luteolin can inhibit the proliferation of human myeloid leukemia HL-60 cells by apoptosis induction [60]. A recent study on the anti-atherosclerotic effects of *V. rotundifolia* fruits revealed that casticin and luteolin suppressed the oxidation of low-density lipoprotein (LDL) and high-density lipoprotein (HDL), showing inhibition of lipid peroxidation, decrease of negative charges in lipoproteins, reduction of hyperchromicity, decrease in carbonyl contents, and prevention of apoA-I aggregation. The potent inhibitory effect on the oxidation of LDL and HDL suggests the fruit's protective role against atherosclerosis via inhibition of LDL and HDL oxidation [25]. In addition, known for its anti-cancer properties, the current study showed that *V. rotundifolia* methanolic extract and fractions (dichloromethane and dichloromethane-hexane) induced apoptosis in human breast cancer T-47D and MCF-7 cell lines by activating the extrinsic and intrinsic pathways such as caspases-8, -9, and -3/7 and upregulating Bax and down-regulating B cell lymphoma-2 protein [61, 62]. Recently, the diterpenoids from *V. rotundifolia* have been found to have antimalarial activity with inhibitory concentration values ranging from 1.2 to 11.0 µM [63]. Interestingly, the *V. rotundifolia* plant parts not only have high medicinal values but also provide other good microorganisms that symbiotically live with the plant. For example, an endophytic fungus *Neofusicoccum parvum* JS-0968 has been isolated and cultured and its secondary metabolites, (3R)-5-hydroxymellein were also isolated [64]. In addition, this compound has been shown to have anti-atherosclerotic activity by inhibiting the lipoproteins oxidations and foam cells formation.

Conclusion

The coastal medicinal plant *V. rotundifolia* has been used traditionally worldwide due to its valuable bioactive compounds. Through this mini-review, we examined its pharmacological activity in vivo and in vitro and described its mechanisms of action. It can be concluded that *V. rotundifolia* is a valuable medicinal plant that can be developed into pharmaceutical and nutraceutical products to treat a variety of diseases.

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