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Review Article

A Review on Bioactive Phytochemical Constituents and Pharmacological Activities of *Aegiceras corniculatum*: A Pharmaceutically Important Mangrove Plant

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Aegiceras corniculatum, commonly referred to as Khalsi, is a member of the mangrove Myrsinaceae family. The various parts of this plant have been used in traditional medicinal systems for their potential therapeutic effects in conditions such as asthma, microbial infections, diabetes, pain relief, inflammation, cancer, and arthritis. A diverse array of bioactive phytochemicals such as flavonoids, benzoquinones, triterpenes, polyphenolic acids, stilbenes, tannins, and macrolides have been identified in different parts of this plant. The aim of this review was to summarize the bioactive phytoconstituents reported from this plant that are accountable for the observed different pharmacological effects of the plant and further elucidate the possible underlying mechanisms by which these chemicals exert their actions. The search was conducted on various widely used database platforms, including Google Scholar, Scopus, Web of Science, SciFinder, and PubMed. Articles published until July 2023 were extracted and all the information was sorted based on the inclusion and exclusion criteria. The data revealed that anti-inflammatory compounds from this plant suppress iNOS, myeloperoxidase, COX, LOX, and cytokines (like TNF-alpha, IL-1β, LTB_4, IL-12, and IL-6) to reduce inflammation. 5-O-Butyl-embelin, 2-hydroxy-5-ethoxy-3-nonyl1, 4-benzoquinone, 5-O-methylembelin, 5-O-methyl-rapanone, s-saponin, and 5-O-ethylembelin are some phytochemicals of *A. corniculatum* with anticancer properties, although their mechanism is unclear. *A. corniculatum* has antibacterial, parasitic, and antifungal effects, but no antiviral effects were reported. The plant-isolated coumaric acid and fatty acids interact with bacterial DNA/RNA and limit protein formation, making them antibacterial. Gallocatechin, epicatechin, epigallocatechin-3-O-gallate, epigallocatechin, and other tannins, as well as flavonoids like kaempferol, quercetin, and isorhamnetin, are some of the compounds in *A. corniculatum* that may depolarize and change bacterial membranes, showing antibacterial effect. These phenolic chemicals also reduce oxidative stress and help treat cancer and other inflammatory diseases. The extract of this plant activates the κ-opioid receptor, causing central antinociception. Catechol components, such as epigallocatechin-3-O-gallate, protect against CNS illnesses including Parkinson's disease and amnesia. Despite numerous studies demonstrating various pharmacological advantages of this plant and its constituents, the number of clinical trials conducted on humans remains significantly limited.

1. Introduction

Since ancient times, in pursuit of a cure for their illness, humans have sought to nature for drugs. The initial usage of medicinal plants was instinctual, similar to that of animals. Over time, it became clear why people were turning to different plants for the treatment of different illnesses; as a result, the practice of using medicinal plants to combat disease moved away from an empirical basis [1]. The global market for herbal medicines was assessed at a financial value of 170 billion United States dollars in the year 2022 and calculations indicate that this market is anticipated to

expand to USD 600 billion by the year 2033, exhibiting a compound annual growth rate (CAGR) of 15% during the period spanning from 2023 to 2033 [2]. Natural product utilization in medicine is an important resource for pharmaceutical businesses worldwide that are working to find new therapies [3]. Approximately 6,500 plant species are believed to inhabit Bangladesh, and among them, over 500 species are recognized for their medicinal properties, with 250 routinely employed in the formulation of healthcare remedies. Yet, most of these plants are not being investigated chemically, pharmacologically, or toxicologically to find out what parts of them are useful [4].

Mangrove and mangrove associates have long been widely used as medicinal and nonmedicinal purposes throughout the world. There are reports of extracts from plants of mangrove origin to have proven activity against human, animal, and plant pathogens [5]. The diversity in activity of these plants could be due to the peculiar environment (high moisture, large tidal difference, high salinity, etc.) in which they exist, producing stressful conditions, which might change their morphology, physiognomy, and biosynthetic pathways to survive [5]. Bangladesh has the largest single block of Sundarbans mangrove forests in the world, which is a globally significant ecosystem rich in plant biodiversity [5]. However, the scientific information about the biological effects of these plants and active substances is scarce and poorly documented. *Aegiceras corniculatum*, a Myrsinaceae mangrove plant, is called Khalsi in Bengali and grows in India, China, Singapore, Australia, Papua New Guinea, and Singapore. Traditional medicine has used the plant's fruits, leaves, and stem bark to treat asthma, arthritis, diabetes, inflammation, cancer, hepatic diseases, and many others [6]. In different portions of this plant such as leaves, bark, root, stem, and twig, researchers have identified a number of bioactive secondary metabolites. These metabolites include, but are not limited to, flavonoids, polyphenolic chemicals, terpenoids, tannins, alkaloids, and various glycosides [7–17]. These compounds may be accountable for the plant's antimicrobial, antidiabetic, analgesic, anti-inflammatory, anticancer, and antiarthritis effects. As a part of our continuing search for new insight of Bangladeshi traditional medicinal plants, here we report the bioactive phytoconstituents and pharmacological potential of *A. corniculatum* as well as the possible mechanism of action behind the pharmacological effects.

2. Materials and Methods

2.1. Methodology for Conducting the Search. For the start of this review, a thorough literature search was undertaken on 11th March 2023. The search was conducted on various widely used database platforms, including Google Scholar, Scopus, Web of Science, SciFinder, and PubMed. The search terms employed were "*Aegiceras corniculatum*" along with "pharmacological use," "folk medicinal uses," "mechanism of action," and "isolated compounds."

2.2. The Process of Study Selection. This review encompassed various types of investigations. The research encompasses various methodologies, including (a) investigations conducted on animal models (*in vivo*), (b) studies conducted in a controlled laboratory environment (*in vitro*), (c) computational studies that use computer models and simulations, (d) investigations that examine the pharmacological effects of plant extract and various phytochemicals derived from *A. corniculatum*, (e) studies that provide information on the specific concentrations, doses, and routes of administration for the extract and its individual compounds, and (f) investigations that elucidate the underlying mechanisms of action of the isolated phytochemicals.

2.3. The Process of Extracting Information. The articles that were examined underwent a comprehensive evaluation process that considered various factors such as the surname of the first author, the year of publication, the specific substance being studied, the experimental framework employed, the observations made, the outcomes observed, the proposed mechanism of action, and the concentrations that were evaluated. The searches revealed 949 records, of which around 84 studies met the criteria and rest of others are excluded. This document presents an overview of the fundamental stages involved in conducting a data search, including the processes of data exclusion and inclusion, as well as other pertinent details.

3. Discussion

3.1. Chemical Constituents of A. corniculatum. Various studies have identified that *A. corniculatum* extract contains a spectrum of naturally occurring chemical constituents, including flavonoids (such as kaempferol, quercetin, and isorhamnetin), benzoquinones (such as embelin), triterpenes (including aegiceradienol, genin-A, protoprimulagenin, and aegicerin), polyphenolic acids (such as gallic acid, coumaric acid, and syringic acid), stilbenes (such as resveratrol), and other compounds which have been isolated and are believed to contribute to the diverse medicinal properties associated with different solvent extracts (Table 1) [27–29].

3.2. Pharmacological Effects of A. corniculatum

3.2.1. Antioxidative. An imbalance between ROS (like $O_2\bullet-$, H_2O_2, $\bullet OH$) generation and detoxification in cells and tissues causes oxidative stress which arises as by-products of metabolic processes in biological systems [30, 31]. A study found that extracts derived from *A. corniculatum*, namely, n-hexane, EtOAc, and MeOH (Table 2), demonstrated proficiency in efficiently neutralizing different free radicals (like $O_2\bullet-$, H_2O_2, $\bullet OH$) in more than one in vitro experimental tests [27]. The potential explanation for the antioxidant property of *A. corniculatum* leaves may be attributed to their comparatively higher total phenolic content [38]. A noteworthy correlation was observed between the total phenol content and the outcomes of various antioxidant assays, including the DPPH and ABTS radical scavenging assays, as well as the FRAP and phosphomolybdenum assays (Table 2) [32]. The key phenolic constituents (Figure 1) found in

Table 1: Phytoconstituents from different parts of *A. corniculatum*.

Parts used	Chemical	Reference
Leaves	3-O-[α-L-Rhamnopyranosyl-(1 $\longrightarrow$ 2)-α-L-rhamnopyranosyl- (1 $\longrightarrow$ 2)-β-D-galactopyranosyl-(1 $\longrightarrow$ 3)-β-D-glucopyranosyl- (1 $\longrightarrow$ 2)-β-D-(6′-O-methyl) glucuronopyranosyl]-13β, 28- epoxy-3β, 16α-dihydroxy-olean; (3β, 16α, 20α)-3, 16, 28-trihydroxyolean-12-en-29-oic acid 3-{O-β-D-glucopyranosyl (1 $\longrightarrow$ 2)-O-[β-D-glucopyranosyl (1 $\longrightarrow$ 4)]-α-L-arabinopyranoside}; aegicoroside A; sakurasosaponin	[14]
	2-O-Acetyl-5-O-methylembelin; delphinidin-3-O-beta-glucopyranoside; rutin; rhodojaponin I; isoschaftoside; kaempferol-3-rhamnoside-4″-rhamnoside-7-rhamnoside; isobutyryl-coenzyme A; rebaudioside C; aegicerin saponin; protoprimulagenin saponin; sakurasosaponin; ganoderic acid H; 25S-Inokosterone; decumbesterone A; fructose 1,6-diphosphate	[10]
	Arachidic acid; heneicosanoic acid; myristoleic acid; linolelaidic acid; linoleic acid and cis-4,7,11,14,17-eicosapentaenoic acid	[18]
	Aegicoroside A; sakurasosaponin; sakurasosaponin methyl ester; (3β, 16α, 20α)-3, 16, 28-trihydroxyolean-12-en-29-oic acid 3-{O-β-D-glucopyranosyl (1 $\longrightarrow$ 2)-O-[β-D-glucopyranosyl (1 $\longrightarrow$ 4)]-α-L-arabinopyranoside}; rutin; nicotiflorin	[19]
	Oleanolic acid β-D-glucopyranosyl ester; isoquecitrin; quercitrin; isomyricitrin; hyperoside; myricitroside; astragalin; quercetin-3-D-xy-loside; chondrillasterol; stigmasterol	
	Palmitic acid; α-linolenic acid; linolenic acid; palmitoleic acid; stearic acid; oleic acid; heptadecanoic acid	[20]
	4,4′-(Tetramethylenebisoxy) bis (2-nitro-5-methoxybenzoic acid methyl) ester; ethyl 2,2-diethoxyacetate; pentadecan-4-yl cyclopentanecarboxylate; 2-O-(2-methylpropyl) 1-O-pentyl oxalate; N-(4- nitrobenzilidene)-tert-butylamine	[21]
Bark	Acornine 1; acornine 2	[7]
	16-alpha-Hydroxy-13,28-epoxyoleanan-3-one; protoprimulagenin; aegicerin; embelinone; syringic acid; gallic acid; isorhamnetin	[22]
	3-O-a-l-rhamnopyranosyl-(1Y6)-h-d-glucopyranoside	
	Palmitic acid; α-linolenic acid; linolenic acid; oleic acid; stearic acid	[20]
Root/pneumatophore	Gallic acid	[11]
	Methyl cis-5, 8, 11, 14- eicosatrienoic acid; linoleic acid; palmitic acid; lignoceric acid; Cis-10 heptadecanoic acid; stearic acid; oleic acid; palmitoleic acid	[20]
Stem and twigs	2-Hydroxy5-ethoxy-3-nonyl-1,4-benzoquinone; 5-O-butyl-embelin; 2,5-dihydroxy-6-methyl-3-pentadecyl-1,4-benzoquinone; 2,5-dihydroxy-3-methyl-6-nonyl-1,4-benzoquinone; 2,5-dihydroxy-3-methyl-6-undecyl-1,4-benzoquinone; 2,5-dihydroxy-6-methyl-3-tridecyl-1,4-benzoquinone; 2-hydroxy-5-methoxy-3-nonyl-1,4-benzoquinone; 5-O-methylembelin; 5-O-methyl-rapanone; 5-O-ethylembelin	[23]
	Myristic acid; palmitic acid; linolenic acid; cis-11, 14, 17-eicosatrienoic acid and arachidonic acid	[18]
	2-Methoxy-3-nonylresorcinol; 5-O-ethylembelin; 2-O-acetyl-5-O-methylembelin; 3,7-dihydroxy2,5-diundecylnaphthoquinone; 2,7-dihydroxy-8-methoxy-3,6-diundecyldibenzofuran-1,4-dione; 2,8-dihydroxy-7-methoxy-3,9-diundecyldibenzofuran-1,4-dione; 10-hydroxy-4-O-methyl-2,11-diundecylgomphilactone; 5-O-methylembelin; 3-undecylresorcinol, and 2-dehydroxy-5-O-methylembelin	[16]
	Sitosterol; protocatechuic acid; vanillic acid; daucterol; schimpefinone; primulagenin A	[22]

Table 1: Continued.

Parts used	Chemical	Reference
Unidentified	4-Hydroxy-2-methoxybenzamide; 1. 2,5-didehydroxy-6-methylembelin; embelin; 5-O-Ethylembelin; 5-O-Methylembelin; acetylation of 5-O-methylembelin; 4-methoxyresorcinol	[24]
	Gallocatechin; epigallocatechin; Epigallocatechin-3-O-gallate; Epicatechin-3-O-gallate; epicatechin	[25]
	Falcarindiol; P-hydroxyphenethyl anisate; phthalic acid; bis (2-ethylhexyl) ester; 1-hentriacontanol; resveratrol; 1,5-dihydroxy-3-methoxy-7-methylanthraquinone; 1,3,5-trihydroxy-7-methylanthraquinone; quercetin; lupeol; benzodiazepines; kaempferol; quercetin; isorhamnetin; aegicerin; aegiceradienol; Genin-A	[15]
	Vanillic acid; stigmasterol; β-sitosterol; syringic acid; alpha-spinasterol; embelinone; 5-O-methylembelin; protocatechuic acid; 3,28-dihydroxy-16-oxo-12-oleanene; fucosterol	[26]

Aegiceras corniculatum are predominantly present in the ethyl acetate extract, include flavonoids such as kaempferol, flavonol compounds like quercetin and isorhamnetin, polyphenolic acidic compounds including gallic and syringic acid, and sterol compounds like resveratrol [27, 28, 33]. The antioxidant properties are also shown by the MeOH extract of the plant which could be related to phenols and tannins (such as gallocatechin, epicatechin, epigallocatechin-3-O-gallate, and epigallocatechin) present in it [25, 38]. So, it can be said that *A. corniculatum* plant extracts possess free radical scavenging abilities, which aligns with its traditional application as an antioxidative agent.

3.2.2. Anti-Inflammatory. Diseases including diabetes, cardiovascular disease, cancer, and asthma all are involved with inflammation in some way [39]. Inflammation is a sophisticated immunological response that causes the consecutive release of proinflammatory cytokines. Therefore, the mitigation of inflammation-associated ailments can be achieved by suppressing the excessive production of inflammatory mediators, particularly proinflammatory cytokines such as IL-1b, IL-6, and TNF-alpha [40]. Based on a recent study, it was observed that the administration of *A. corniculatum* extracts at dosages of 250 and 500 mg/kg resulted in a significant reduction in paw edema in Swiss albino mice [6]. By combining different in vivo and in vitro models (Tables 2 and 3), a study indicates that extracts obtained from *A. corniculatum*, specifically methanol and ethyl acetate extracts, exhibit notable inhibitory effects on the chronic inflammatory phase and these effects are observed through the suppression of mononuclear cell infiltration, fibroblast proliferation, collagen fiber production, and connective tissue formation, all of which contribute to the development of granuloma [45]. Carrageenan-induced pleurisy is a very common method used to test anti-inflammatory therapeutics [49]. Methanol and ethyl acetate extract of *A. corniculatum* protects against acute lung inflammation by lowering nitrate/nitrite concentrations and MPO enzyme levels and also decreases neutrophils and mononuclear infiltration at a higher dose (100 mg/kg) in a mice model of pleurisy [47] (Table 3). Different classes of phytochemicals are isolated from different parts of *A. corniculatum* (Table 4) which is the potential causative factor for the observed anti-inflammatory effect [51, 52]. In accordance with the outcomes of a research, it has been found that the ethyl acetate extract of plant demonstrates inhibitory effects on the production of eicosanoids like LTB_4 (IC_{50}: 0.86 ± 0.03 g/ml), 5-HHT (IC_{50}: $3.4 \pm 0.04\,\mu$g/ml), and 12-HHT (IC_{50}: $0.08 \pm 0.002\,\mu$g/ml), with only a minor effect on 12-HETE (IC_{50}: $8.0 \pm 0.18\,\mu$g/ml), thus demonstrating that it has comparatively strong binding preference towards the 5-lipoxygenase and cyclooxygenase-1 in relation to the 12-lipoxygenase [43]. The ethyl acetate extract derived from plants contains a diverse range of triterpenes and phenolic compounds (like flavonoids), which have the potential to exhibit anti-inflammatory properties [14, 28, 32, 43]. Ethyl extract of this plant contains two triterpenoid saponins (3β, 16α, 20α)-3,16,28-trihydroxyolean-12-en-29-oic acid 3-{O-β-D-glucopyranosyl $(1 \longrightarrow 2)$-O-[β-D-glucopyranosyl $(1 \longrightarrow 4)$]-α-L-arabinopyranoside} and aegicoroside A (Figure 2) which show anti-inflammatory effect by inhibiting the production of TNF-α, IL-6, and IL-12 p40 [14]. The presence of flavonoids, specifically quercetin, kaempferol, and isorhamnetin (Figure 1), in the ethyl acetate extract may be associated with its dual anti-inflammatory effects. These flavonoids have the ability to inhibit both cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, which play a crucial role in the synthesis of various inflammatory mediators including cytokines, chemokines, and adhesion molecules [43, 53]. At a maximal oral dose of 50 mg/kg, methanol extract reduced paw swelling in a rat arthritic model by approximately 67%, but it had no effect on LTB_4-induced cell infiltration, further demonstrating its preference for the COX pathway [43, 45]. Triterpenes, phenols, and tannins previously reported in the methanol extract may be responsible for its anti-inflammatory properties [25, 38, 54]. Epicatechin, a tannin, is found in the methanol extract of the plant [25]. (−)-Epicatechin exhibits a greater negative binding affinity compared to CA, leading to the enhancement of various proteins such as HSP-30, HSP-70, HSP-90, interleukin-10, and FOXP3. Additionally, (−)-Epicatechin demonstrates the ability to inhibit interleukin-6, peptidoglycan, flagellin, and dectin *in silico* [55]. Also, a study reveals that epicatechin decreases iNOS, COX-2, NO, PGE_2, and proinflammatory cytokines (TNF-α, IL-1β, and IL-6) in LPS-stimulated RAW264.7 cells, making it a potent anti-inflammatory compound [56]. An investigation about n-hexane extract of the plant demonstrated a decrease in 12-

Table 2: *In vitro* pharmacological effect of *A. corniculatum* extract.

Reported activity	Test model	MIC/IC_{50}/EC_{50} (μg/ml)	Mechanism	Reference
Antituberculosis	Against Mtb H37Rv strain	MIC using resazurin microtiter assay, Soxhlet, and maceration techniques, respectively (19.53 μg/ml, 39.06 μg/ml, and 1250 μg/ml)	Through oxidation	[28]
Antioxidation	Using DPPH (2,2-diphenyl-1-picrylhydrazyl)	MIC using microwave and SEAF (IC_{50}: 86.31 μg/ml and 165.75 μg/ml)	By scavenging free radicals	
Antioxidant	DPPH radical scavenging activity	Methanolic, water, and ethyl acetate extract of leaf (EC_{50} value: 55.77, 58.43, and 59.73 μg/ml) Methanolic and water extract of bark (EC_{50}: 80.73 and 82.02 μg/ml) Petroleum ether extracts of bark and leaf (EC_{50}; 328 and 201 μg/ml)	By scavenging free radicals	[32]
	ABTS + radical scavenging activity	Water extract of leaf and bark (EC_{50}: 84.38 and 87.89 μg/ml) Methanolic extract of leaf and bark (EC_{50}: 89.33 and 102.34 μg/ml) Petroleum ether extract of leaf and ethyl acetate extract of bark (EC_{50}: 93.59 and 93.44 μg/ml)		
	Hydrogen peroxide radical scavenging activity	Water and petroleum ether extract of bark (EC_{50}: 94.19 and 96.09 μg/ml) Water and methanol extract of leaf (EC_{50}: 97.07 and 95.05 μg/ml)		
Antioxidant	DPPH assay	Aqueous ethanol extract of bark and leaves (IC_{50}: 20.49 ± 2.14 μg/mL)	By scavenging free radicals	[33]
Anti-inflammation	LOX inhibition assay	Aqueous ethanol extract of bark and leaves (IC_{50}: 23.58 ± 1.75 μg/mL)	Inhibition of lipoxygenase enzyme	
Anticoagulation	Prothrombin time (PT) determination assay	*A. corniculatum* bark needed 18.19 ± 0.13 min at highest concentration (800 μg/mL)	N/A	
Neuroprotective	MTT pretreatment method using SK-S-NH neuroblastoma cell lines	Methanol extract of concentration 5 μg/ml showed 70.02% cell viability	Hinders lipid peroxidation, DNA damage, and the production of reactive oxygen species (ROS)	[34]
Cytotoxicity	On Vero cell lines	Silver nanoparticles using a mangrove extract of *Aegiceras corniculatum* (IC_{50} was 18.79 ± 0.9 μg/mL)	N/A	[35]
Anthelmintic	Using adult earthworms (*Pheretima posthuma*)	Petroleum ether, chloroform, methanol, and aqueous extract of *Aegiceras corniculatum* stem are used in 50 and 100 mg/ml concentration	N/A	[36]
Antidiabetic	Alpha glycosidase enzyme activity inhibition	IC_{50} of ethyl acetate and water extract of the *Aegiceras corniculatum* leaves was 40.59 μg/mL and 60.79 μg/mL, respectively	α-Glucosidase inhibition	[37]

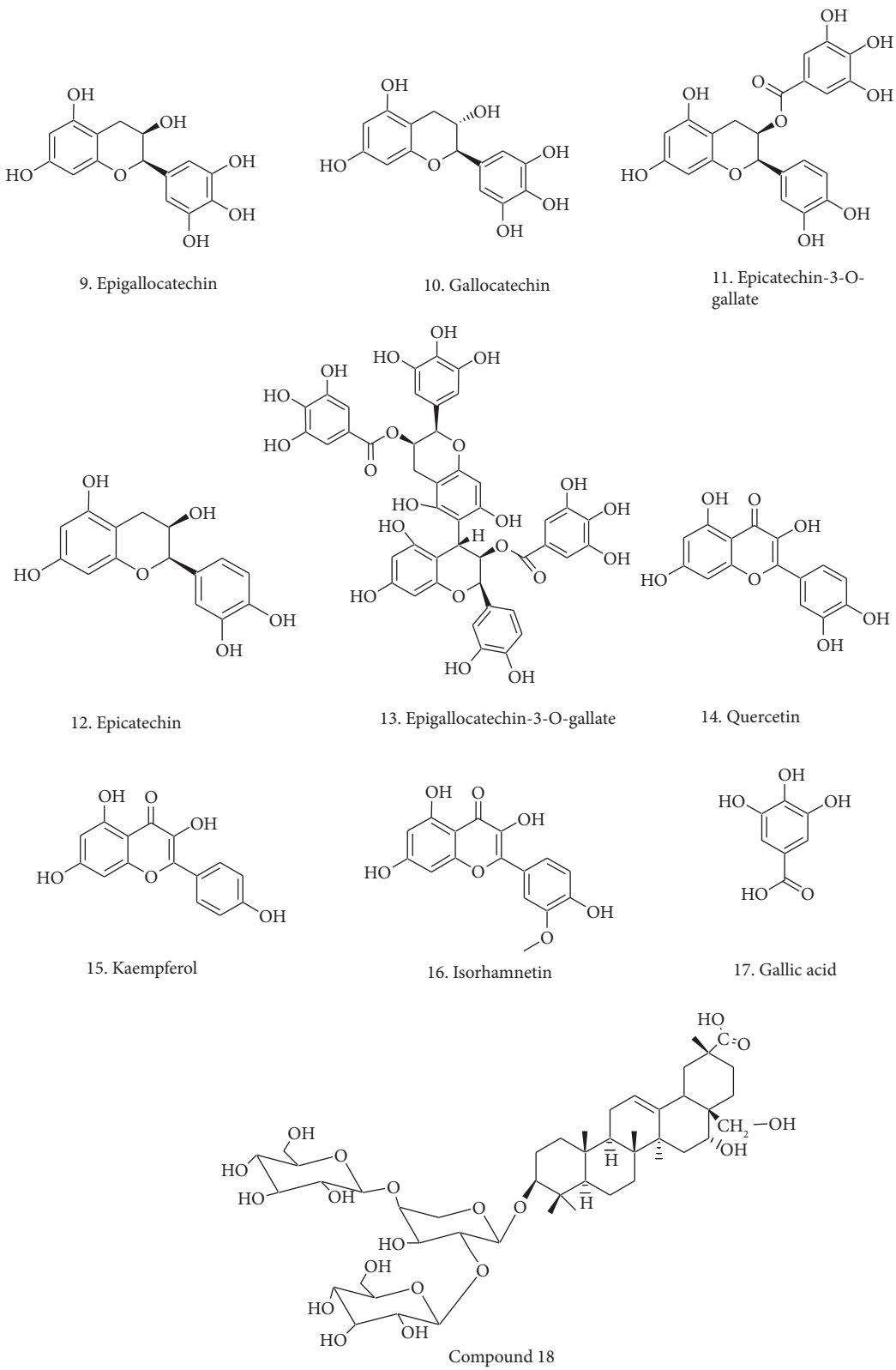


Figure 1: Anti-inflammatory and antioxidant compounds isolated from *A. corniculatum*.

HETE formation with an IC_{50} value of $0.36 \pm 0.12\,\mu$g/ml and simultaneously an increase in 12-HHT and also exhibited an antagonistic effect on the synthesis of 5-LOX metabolites, specifically LTB_4 and 5-HETE, in rat neutrophils, indicating a selectivity towards lipoxygenases pathway [43]. It is possible that the presence of benzoquinones is responsible for the

selectivity of hexane extract towards lipoxygenases [16, 43, 57, 58]. Oxidative stress plays a significant role in the development of chronic inflammation [59]. Current research aimed to replicate the anti-inflammatory response to oxidative stress in an *in vivo* model of glucose oxidase-induced paw edema in mice revealed that extracts derived from *A. corniculatum* possess the ability to inhibit the production of proinflammatory mediators in the presence of oxidative stress, owing to their capacity to scavenge OH radicals [27]. Thus, it can be inferred that n-hexane, EtOAc, and MeOH extracts derived from the *A. corniculatum* possess anti-inflammatory properties that are exerted through various mechanisms of action (Figure 3). Hence, *A. corniculatum*, a species of mangrove plant, has been employed for numerous years in the management of various inflammatory and autoimmune conditions, such as coronary artery disease, rheumatoid arthritis, and allergies and asthma, and its utilization as a traditional remedy has garnered significant recognition.

3.2.3. Antiproliferative. Cancer indicates a significant global public health concern, exerting a considerable influence on nations across the spectrum of development. In the year 2018, there was a global estimation of approximately 18.1 million newly diagnosed cases of cancer and it is projected that by the year 2030, this figure will increase to reach approximately 23.6 million cases [60]. The significance of identifying medicinal plants with notable cytotoxic potential for the advancement of cancer therapies has experienced a notable increase in the past decade, and progress in this domain is currently expanding [61]. The methanolic extract obtained from *A. corniculatum* demonstrated pronounced cytotoxic effects on healthy, colon, and breast cancer cells, as evidenced by IC_{50} values ranging from 0.02 to 0.66 mg·mL^{-1}. However, the cytotoxicity against gastric cancer cells was notably low [62]. Different classes of phytochemicals are isolated from different parts of *A. corniculatum* (Table 1) which may be responsible for anticancer or cytotoxic effect [51, 52]. 3-O-[α-L-Rhamnopyranosyl-(1 ⟶ 2)-α-L-rhamnopyranosyl-(1 ⟶ 2)-β-D-galactopyranosyl-(1⟶3)-β-D-glucopyranosyl-(1⟶2)-β-D-(6′-O-methyl)glucuronopyranosyl]-13β, 28-epoxy-3β, 16α-dihydroxy-olean and sakurasosaponin (Figure 2) are two triterpenoid saponins isolated from the EtOAc extract of *A. corniculatum* leaves showing apoptosis of B16F10 melanoma cells [14]. A study said that significant cytotoxic effects have been reported for sakurasosaponin and sakurasosaponin methyl ester (Table 4) against MCF7, A549, and HCT116 cell lines, with IC_{50} values ranging from 2.89 ± 0.02 to 9.86 ± 0.21 μM [63]. A research suggested that sakurasosaponin shows antitumor effect through decreasing mitochondrial membrane potential, increasing cytochrome C release into the cytoplasm, and elevating caspase-3 activity that causes apoptosis [50]. Various benzoquinones are extracted from various parts of the plant, potentially contributing to its anticancer properties [16, 23, 64]. 2-Hydroxy-5-ethoxy-3-nonyl1, 4-benzoquinone, 5-O-butyl-embelin, 5-O-methylembelin, 5-O-methyl-rapanone, and 5-O-ethylembelin are some of the benzoquinone phytoconstituents (Figure 2) of A. *corniculatum* plant, and they show selective cytotoxicity against HL-60, HepG2, BGC-823, and A2780 cell lines [23]. The benzoquinone derivatives, namely, 5-O-ethylembelin and 5-O-methylembelin (Table 4), which have been extracted from *A. corniculatum*, have been found to induce cell cycle arrest in HL-60 cells specifically in the G_1/G_0 phase, and this effect is believed to be mediated through their interaction with microtubular proteins [16, 65]. However, the precise mechanism underlying this interaction remains to be elucidated.

Higher levels of reactive oxygen species (ROS) produced through persistent aerobic glycolysis, subsequent pyruvate oxidation in mitochondria, receptor and oncogene activation, and activation of growth factor-dependent pathways or oxidizing enzymes contribute to the induction of genetic instability [66]. Various studies have proposed that the protective effect of antioxidants against cancer is manifested through the inhibition of the generation of carcinogenic metabolites [67, 68]. Also, epigallocatechin-3-O-gallate inhibits DNA methyltransferase activity and controls histone acetylation, which increases apoptosis and also activates mitogen-activated protein kinases to boost anticancer action [69]. Therefore, *A. corniculatum* has anticancer benefits against various cancers through a variety of methods and may serve as a future source of anticancer drugs.

3.2.4. Analgesic. A study suggested that *A. corniculatum*'s ethanolic and water-soluble extracts (200 and 400 mg/kg, p.o.) had a substantial analgesic effect, increased latency in Eddy's hot plate, and reduced the writhing caused by acetic acid in a dose-dependent way [70]. According to another investigation, the extract derived from *A. corniculatum* demonstrated notable inhibition of writhing impulse (Table 3). Specifically, at doses of 250 mg/kg and 500 mg/kg body weight, the extract exhibited inhibitory effects of 54.78% and 75.60%, respectively, and these findings indicate that the extract's potency is comparable to that of a 25 mg/kg dose of diclofenac sodium [6]. The potential mechanism underlying the antinociceptive effect of methanol plant extract appears to involve the activation of the κ-opioid receptor. On the other hand, the n-hexane extract may exert its effects by acting as an opioid agonist on the peripheral opioid receptor, thereby counteracting withdrawal abstinence syndrome through the GABAB receptor. In contrast, the neurogenic analgesic action of the EtOAc extract was not found to be mediated by the opioidergic system. Instead, it is possible that the extract exerts its effect by inhibiting the biosynthesis of proinflammatory PGs [41]. Different investigations found that flavonoids, flavonols, benzoquinones, triterpenes, polyphenolic acids, stilbenes, and others are some naturally occurring chemical constituents isolated from plant extract and may be responsible for reducing both central and peripheral pain effect through different mechanisms [27–29, 71].

3.2.5. Antimicrobial. Several investigations have demonstrated that *A. corniculatum* possesses antimicrobial properties against different microorganisms (Table 2)

Table 3: *In vivo* pharmacological effect of *A. corniculatum* extract.

Test model	Dose (mg/kg)	Route	Mechanism of action	Reference
Model of nociception based on the writhing response generated by acetic acid, formalin-induced paw licking test, and hot plate test in mice	MeOH, n-hexane, and EtOAc extracts of *A. corniculatum* (stem) (1–100 mg/kg)	Intraperitoneal	The MeOH extract may potentially elicit a central antinociceptive effect through the activation of κ-opioid receptors and the inhibition of prostaglandin biosynthesis The n-hexane extract functions by activating the peripheral opioid receptors as an opioid agonist, thereby counteracting the symptoms of withdrawal abstinence syndrome through the GABAB receptor The neurogenic analgesic effect of the EtOAc extract was not attributed to the opioidergic system, but it may exert its impact by inhibiting the synthesis of proinflammatory PGs	[41]
CCl4-induced hepatotoxicity in rats	MeOH, n-hexane, and EtOAc extracts of *A. corniculatum* (stem) (250–1000 mg/kg)	Oral	The n-hexane and ethyl acetate extracts have the potential to sequester harmful substances such as trichloromethyl and its peroxy radicals, thereby reducing cellular damage. Additionally, these extracts may exhibit a hepatoprotective effect by inhibiting drug-metabolizing enzymes, specifically cytochrome P-450.	[27]
Glucose oxidase-induced paw edema in mice	MeOH, n-hexane, and EtOAc extracts of *A. corniculatum (stem)* (10, 50, and 100 mg/kg)	Oral	Suppression of proinflammatory mediator synthesis under conditions of oxidative stress	[27]
Alloxan-induced diabetic male albino rats	ACEt extract of *A. corniculatum* leaves (25, 50, and 100 mg/kg body weight) for 60 days	Oral	The activity of hexokinase has been observed to be elevated, while the activities of glucose 6-phosphatase and fructose-1,6-bisphosphatase have been found to be reduced	[42]
Carrageenan-induced rat paw edema and glycogen-induced peritonitis models	MeOH, n-hexane, and EtOAc extracts (1–100 mg/kg) derived from *A. corniculatum* (stems)	Intraperitoneal	MeOH extract inhibits the COX-1 metabolite, 12-HHT, while increasing the 12-LOX metabolite, 12-HETE Hexane extract reduced 12-HETE synthesis while increasing 12-HHT, and it inhibited the development of 5-LOX metabolites such as leukotriene B_4 and 5-HETE The EtOH extract demonstrated inhibitory effects on both COX and 5-LOX enzymes, leading to a notable reduction in the production of 12-HHT and LTB4	[43]
Antiplasmodial activity in adult male albino rats	15, 30, 60, 120, and 200 mg/kg of polyherbal extracts of *A. corniculatum*	Oral	N/A	[44]
Antitumor activity in HT-29 colon cancer cell injected male nude mice	n-Butanol extract of *A. corniculatum* leaves (25 mg/kg) once daily for 18 consecutive days	Oral	The activation of forkhead box proteins by the extract regulates cell cycle checkpoint pathways that are associated with caspase-dependent mitochondrial apoptotic cascades and Bcl-2 family proteins. This leads to cellular apoptosis and arrest of the cell cycle.	[10]

Table 3: Continued.

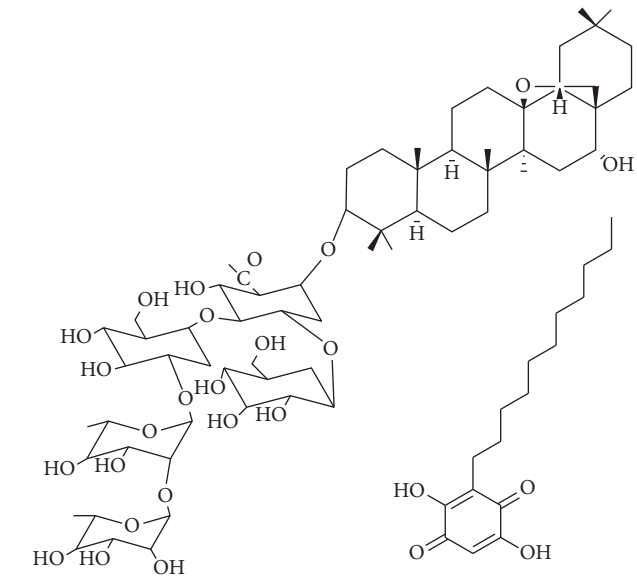
Test model	Dose (mg/kg)	Route	Mechanism of action	Reference
Chronic granulomatous inflammation and arthritis test in albino rats	MeOH extract (10, 25, 50, and 100 mg/kg) and acetyl acetate extract (10, 25, 50, 100, and 200 mg/kg) derived from *A. corniculatum* leaves	Oral	Both extracts effectively decrease chronic inflammation, preventing mononuclear cell infiltration, fibroblast proliferation, collagen fiber production, and granuloma progress	[45]
Acetic acid-induced writhing test and tail immersion test in Swiss albino mice	MeOH extract of *A. corniculatum* (leaves) (125, 250, and 500 mg/kg)	Oral	Inhibit the enzyme prostaglandin synthetase	[46]
Carrageenan-induced lung injury in Swiss mouse using pleurisy model	MeOH and EtOAc extract (10, 50, and 100 mg/kg)	Oral	The decline of nitrate/nitrite concentrations and MPO enzyme levels and reduction of neutrophils and mononuclear infiltration	[47]
MWM test for scopolamine-induced amnesia in aged Swiss albino mice	MeOH extract *of Aegiceras corniculatum* (AC) leaves at doses of 50 and 100 mg/kg for 7 days	Oral	The activity of acetylcholinesterase (AChE), the levels of thiobarbituric acid reactive substances (TBARS), and reactive oxygen species (ROS) were notably reduced	[48]

Table 4: Pharmacological effect of compounds reported from *A. corniculatum*.

Compound	Chemical class	Test model	Possible mechanism	Reference
(1) (3β, 16α, 20α)-3, 16, 28-Trihydroxyolean-12-en-29-oic acid 3-{O-β-D-glucopyranosyl (1 ⟶ 2)-O-[β-D-glucopyranosyl (1 ⟶ 4)]-α-L-arabinopyranoside} (2) Aegicoroside A	Triterpenoid saponin	In vitro anti-inflammatory test using female C57BL/6 mice bone marrow	Inhibitors of cytokines TNF-α, IL-6, and IL-12 p40	[14]
(1) 3-O-[α-L-Rhamnopyranosyl-(1 ⟶ 2)-α-L-rhamnopyranosyl-(1 ⟶ 2)-β-D-galactopyranosyl-(1 ⟶ 3)-β-D-glucopyranosyl-(1 ⟶ 2)-β-D-(6′-O-methyl) glucuronopyranosyl]-13β, 28-epoxy-3β, 16α-dihydroxy-olean (2) Sakurasosaponin	Triterpenoid saponin	In vitro apoptosis test using B16F10 melanoma cells	N/A	
(1) 2,5-Didehydroxy-6-methylembelin (2) Embelin (3) 5-O-Ethylembelin (4) 5-O-Methylembelin (5) Acetylation of 5-O-methylembelin	Benzoquinone	In vitro antimalarial activity using chloroquine-sensitive (3D7) and resistant (*K*1) strains	N/A	[24]
(1) Acornine 1 (2) Acornine 2	Triterpenoid saponin	In vitro antifungal effect using *S. cerevisiae* and *T. clypeatus* and antimicrobial effect using *Bacillus subtilis* and *Bacillus coagulans*	N/A	[7]
(1) 2-Hydroxy-5-ethoxy-3-nonyl1,4-benzoquinone (2) 5-O-Butyl-embelin (3) 5-O-Methylembelin (4) 5-O-Methyl-rapanone (5) 5-O-Ethylembelin	Benzoquinones	In vitro cytotoxic activities against HL-60, HepG2, BGC-823, NCI-H1650, and A2780 cell lines by the MTT assay	N/A	[23]
(1) Gallic acid	Polyphenolic acid	In vitro allelopathic effects on *Cyclotella caspia*	Through oxidation it damages cell membrane and cellular components	[11]
(1) 5-O-Ethylembelin (2) 5-O-Methylembelin	Benzoquinone	In vitro cytotoxicity test against the HL-60, Bel7402, Hela, and U937 cell lines	N/A	[16]
(1) Sakurasosaponin (2) Sakurasosaponin methyl ester	Triterpenoid saponin	In vitro cytotoxic activities of the isolated compounds against MCF7 (breast), HCT116 (colon), B16F10 (melanoma), and A549 (adenocarcinoma) cancer cell lines	N/A	[19]
(1) Gallocatechin (2) Epigallocatechin (3) Epigallocatechin-3-O-gallate (4) Epicatechin-3-O-gallate (5) Epicatechin	Tannin	DPPH radical scavenging	By scavenging free radicals	[25]
		Ferric reducing antioxidant assay	By reduction of TPTZ-Fe (III) to TPTZ-Fe (II)	

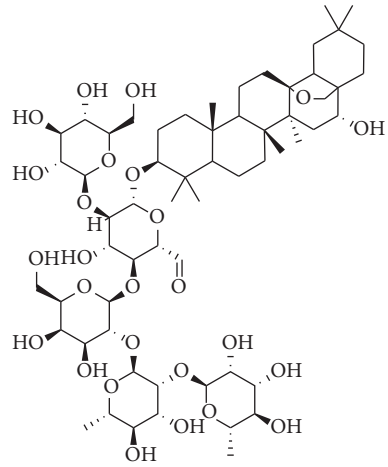
Table 4: Continued.

Compound	Chemical class	Test model	Possible mechanism	Reference
(1) Methyl cis-5, 8, 11, 14- eicosatrienoic acid (2) Linoleic acid (3) Palmitic acid (4) Lignoceric acid (5) cis-10-Heptadecanoic acid (6) Stearic acid (7) Oleic acid (8) Palmitoleic acid	Fatty acid	Antimicrobial assay of fatty acids through using disk diffusion method using *S. aureus*, *E. coli*, *K. pneumonia*, and *P. aeruginosa*	Due to the metabolic oxidation products of fatty acids	[20]
(1) Quercetin (2) Kaempferol (3) Isorhamnetin	Flavonoid	In vitro anti-inflammatory activity through cytokine inhibition	Suppressed the activity of both cyclooxygenase (COX) and 5-lipoxygenase (5-LOX), resulting in a significant reduction in the synthesis of 12-hydroxyheptadecatrienoic acid (12-HHT) and leukotriene B_4 (LTB_4)	[43]
(1) Sakurasosaponin	Saponin	In vivo S-saponin induced AR deficiency to check suppression of tumor growth	Decreased mitochondrial membrane potential, increased cytochrome c release into the cytoplasm, elevated caspase-3 activity, and induced apoptosis	[50]
(1) 2-O-(2-Methylpropyl) 1-O-pentyl oxalate	Oxalate	In silico antidiabetes test	DPP-IV inhibition	[21]

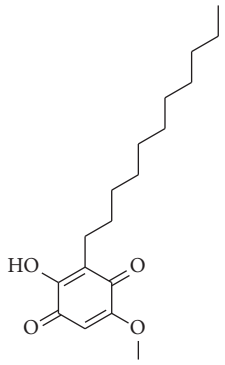


Compound 1

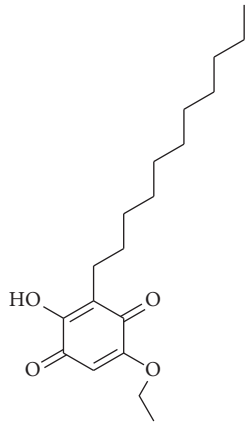
2. Embelin



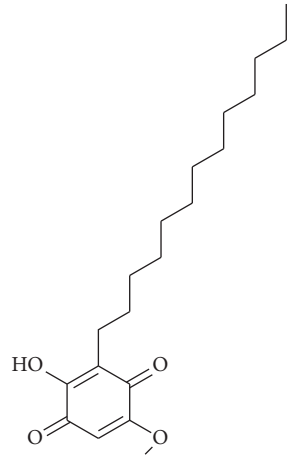
3. Sakurasosaponin



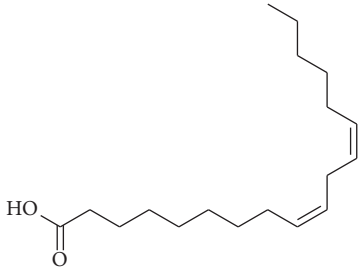
4. 5-O-Methylembelin



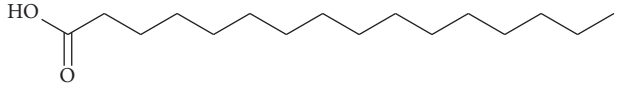
5. 5-O-ethylembelin



6. 5-O-methyl-rapanone



7. Linoleic acid



8. Palmitic acid

(a)

Figure 2: Continued.

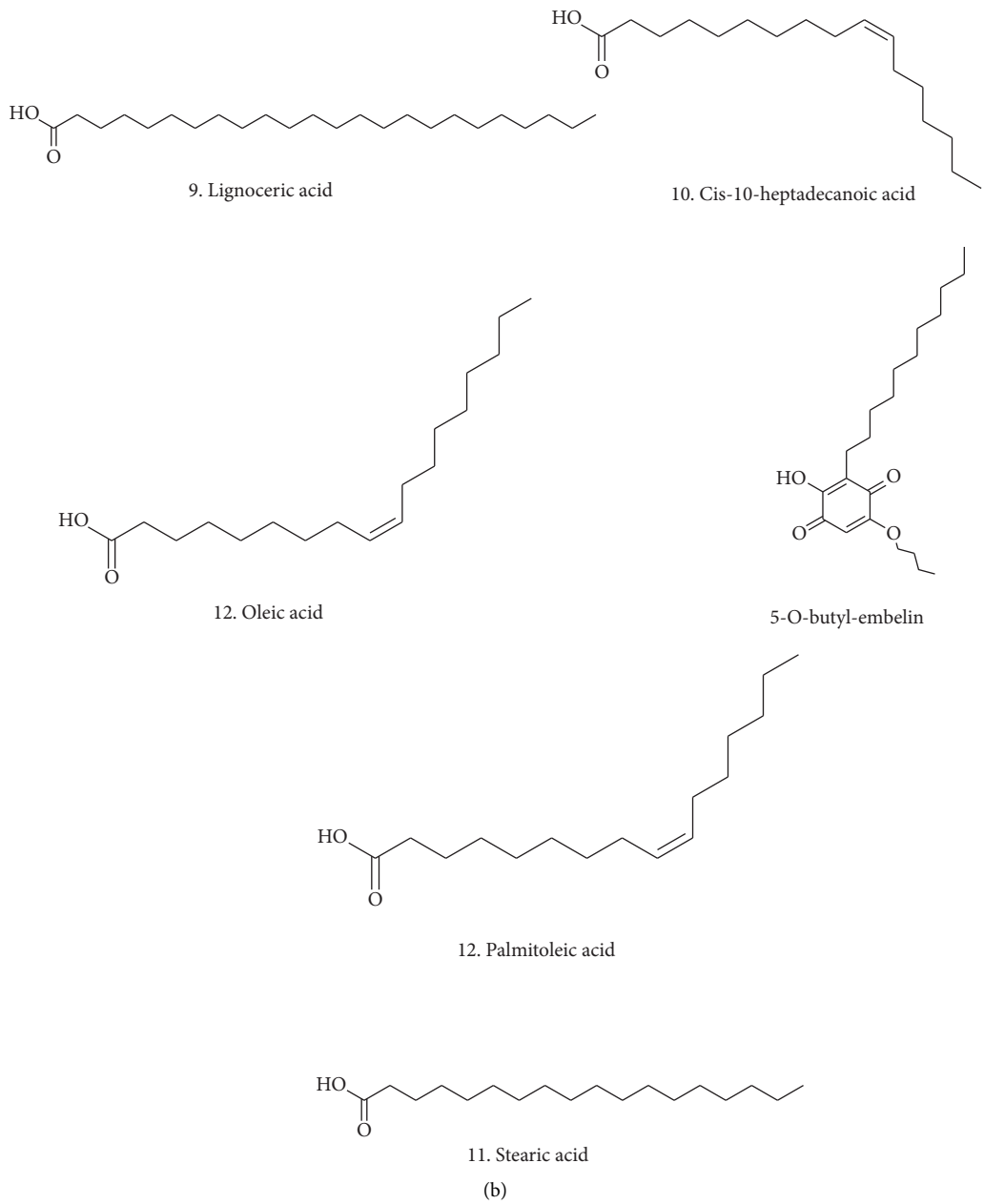


Figure 2: Anticancer and antimicrobial compounds isolated from *A. corniculatum*.

[7, 20, 36, 55]. An antimicrobial refers to any substance that has the ability to eliminate microorganisms or inhibit their proliferation or development. There are primarily four types of antimicrobial drugs, including antibacterial, antifungal, antiviral, and antiparasitic drugs [72, 73]. An in vitro study found that *A. corniculatum* stems are used to inhibit adult earthworms (*Pheretima posthuma*) showing anthelmintic effect [36]. Also methanol extract of polyherbal mixture containing *A. corniculatum* and *Chaetomorpha antennina* demonstrated a suppressive effect of approximately $63.50 \pm 0.408\%$ on *P. falciparum*, a parasite that causes malaria, when tested at a concentration of 1.5 mg/ml [44]. The plant contains various benzoquinones (embelin), including 2,5-didehydroxy-6-methylembelin, embelin, 5-O-ethylembelin, and 5-O-methylembelin (Table 4). These have exhibited antimalarial activity in laboratory tests against both chloroquine-sensitive (3D7) and resistant (*K*1) strains of the malaria parasite [24]. Benzoquinones are the most cytotoxic substances presumably because of their higher electrophilicity and autooxidation potential [74]. These findings suggest potential antimalarial activity of *A. corniculatum's* phytoconstituents.

Methanol extract derived from *A. corniculatum* exhibits in vitro inhibitory effects on the growth of *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans* in the disk diffusion method, and the observed effect can be attributable to the existence of (−) epicatechin and coumaric acid within the extract [55]. There

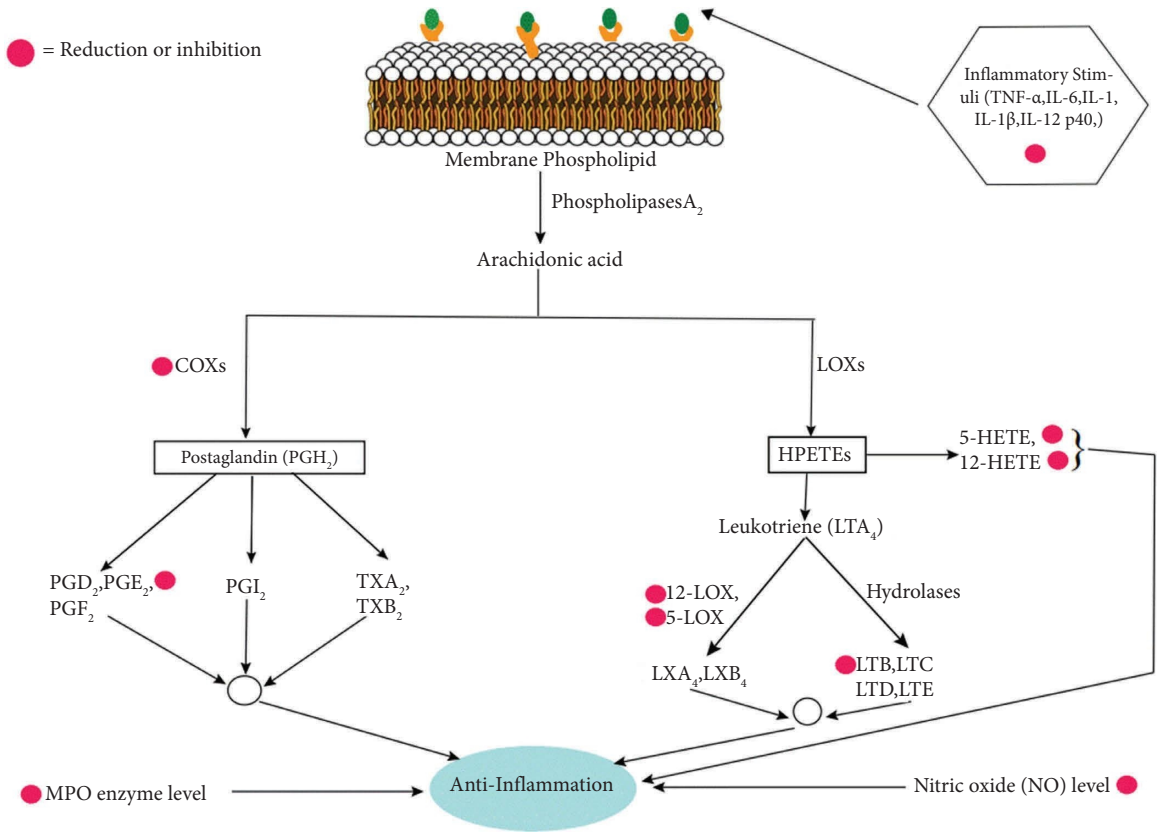


Figure 3: Proposed mechanism of action for *A. corniculatum* extracts in reducing inflammation.

is a possibility that coumaric acid can bind to the phosphate anion present in the DNA double helix. Moreover, it can potentially insert itself into the groove of the DNA double helix, and these interactions have the potential to affect the production of proteins and the growth of bacteria [75]. A recent study has demonstrated that the EtOAc fraction exhibited the most potent antituberculosis activity, with a minimum inhibitory concentration (MIC) of 6.25 μg/ml, with the highest total phenolic content and antioxidant activity. A clear correlation was observed between the amounts of phenolic content and the effectiveness of the antituberculosis activity [28]. Different extracts of *A. corniculatum* contain phenolic compounds (Figure 1) such as polyphenolic acid (like gallic acid and coumaric acid); tannins (such as gallocatechin, epicatechin, epigallocatechin-3-O-gallate, and epigallocatechin); and flavonoids (like kaempferol, quercetin, and isorhamnetin) which may be responsible for antimicrobial activity [11, 25, 38, 43, 55, 76]. The existing literature suggests that the inhibition of pathogenic bacteria by phenolic compounds is attributed to the depolarization and alteration of membrane fluidity [77]. Moreover, the fatty acids derived from the pneumatophore of *A. corniculatum* exhibited significant efficacy against GNB *Klebsiella pneumoniae* and a medium efficacy against GPB *Staphylococcus aureus*. The results suggest that the ability of the fatty acid fractions to kill bacteria depended on the presence of long-chain unsaturated fatty acids [20]. Possible mechanisms by which antibacterial fatty acids exert their effects include the potential to hinder DNA/RNA replication, impede cell wall formation, disrupt the integrity of the cytoplasmic membrane, and interfere with metabolic pathways [78]. Macrolides such as isocorniculatolide A; 11-O-methylisocorniculatolide A; 11-O-methylcorniculatolide A; 12-hydroxy-11-O-methylcorniculatolide A; and corniculatolide A are isolated from *A. corniculatum* which may show antibacterial activity through their ability to bind the bacterial 50S ribosomal subunit causing the inhibition of bacterial production of protein [12, 79]. These findings point to the possibility of antibacterial action on the part of the phytoconstituents found in *A. corniculatum*. Two compounds, called as Acornine 1 and Acornine 2 (Table 4), were extracted from *A. corniculatum*, and both of them demonstrated growth inhibitory activity against the fungus *T. clypeatus* [7]. Both of the Acornines are triterpenoid saponins, which have been found to possess the ability to disrupt the structural integrity of the cell membrane, resulting in the release of cellular contents and afterwards inhibition of fungal growth [7]. Therefore, it is obvious that this plant is effective against a wide spectrum of microorganisms through different mechanisms.

3.2.6. Effect on CNS Diseases. Phenolic compounds capable of traversing the blood-brain barrier have been observed to elicit beneficial health outcomes within the brain [80]. As different extracts of *A. corniculatum* contain phenolic compounds, it may have effect on CNS [11, 25, 43, 81, 82].

Tolcapone and entacapone are inhibitors of COMT, a novel category of pharmaceuticals employed in the therapeutic management of Parkinson's disease, both of which are catechol analogues [83]. Epigallocatechin-3-O-gallate (Figure 1), a catechol analogue that is derived from *A. corniculatum*, exhibits strong inhibitory effects on human catechol-O-methyltransferase (COMT), potentially impeding the progression of Parkinson's disease [25, 84]. A study also shows that strong antioxidant activities in *A. corniculatum* have been shown to improve cognitive performance in both adult and elderly rats and can be used to treat amnesia [48]. Furthermore, it has been reported that the methanol plant extract elicits a central antinociceptive effect by activating the κ-opioid receptor [41]. Only a few studies have been carried out on the central nervous system (CNS) to explore the neuropharmacological impacts of this specific plant. Further research is required to investigate the neuropharmacological activity of this plant and elucidate its mechanism of action.

3.2.7. Antidiabetic Effect. According to a research study, it was discovered that the ACEt extract derived from the leaves of *A. corniculatum* exhibits antidiabetic properties in male albino rats. This effect is achieved by enhancing the activity of hexokinase (Table 3) while simultaneously reducing the activities of glucose 6-phosphatase and fructose-1,6-bisphosphatase [42]. Alpha-glucosidase inhibitors reduce postprandial blood glucose and insulin by inhibiting small intestine carbohydrate absorption in diabetic patients [85]. The results of an in vitro study demonstrated that the ethyl acetate portion and water portion extracts derived from the leaves of *A. corniculatum* exhibited inhibitory effects on the alpha-glucosidase enzyme. The IC_{50} values for the ethyl acetate portion and water portion were determined to be 40.59 μg/mL and 60.79 μg/mL, respectively [37]. Further research is warranted to identify the specific molecules underlying the antidiabetic effect and to comprehensively understand the precise mechanism of action, and this necessitates a comprehensive investigation utilizing both in vivo and in vitro approaches.

4. Conclusion

The primary sources for the development of medical drugs are active ingredients derived from medicinal plants. Different classes of compounds, including flavonoids, benzoquinones, tannins, triterpenes, polyphenolic acids, stilbenes, and macrolides, are present in *A. corniculatum* that are responsible for a wide range of pharmacological effects. Quercetin, (3β, 16α, 20α)-3,16,28-trihydroxyolean-12-en-29-oic acid 3-{O-β-D-glucopyranosyl (1 $\longrightarrow$ 2)-O-[β-D-glucopyranosyl (1 $\longrightarrow$ 4)]-α-L-arabinopyranoside}, isorhamnetin, aegicoroside A, kaempferol, and (−)-epicatechin are some of the chemicals isolated from this plant that may be responsible for anti-inflammatory activity. The compounds present in this plant exhibit inhibitory effects on iNOS, myeloperoxidase, COX, and LOX enzymes and additionally reduce the production of various cytokines including TNF-α, IL-1β, IL-6, and LTB4, resulting in an anti-inflammatory response. A specific substance called S-saponin, derived from this plant, has been identified to induce cell death through mitochondrial-mediated pathways in both androgen-dependent and castration-resistant cells, by modulating androgen receptor (AR) mechanisms. Also, 2-hydroxy-5-ethoxy-3-nonyl1, 4-benzoquinone, 5-O-butylembelin, 3-O-[α-L-rhamnopyranosyl-(1 $\longrightarrow$ 2)-α-L-rhamnopyranosyl-(1 $\longrightarrow$ 2)-β-D-galactopyranosyl-(1 $\longrightarrow$ 3)-β-D-glucopyranosyl-(1 $\longrightarrow$ 2)-β-D-(6′-O-methyl)glucuronopyranosyl]-13β, 28-epoxy-3β, 16α-dihydroxy-olean, 5-O-methylembelin, 5-O-methyl-rapanone, and 5-O-ethylembelin are some of the other phytochemicals of *A. corniculatum* showing anticancer effect, but their exact mechanism is still unknown. Multiple studies have revealed that *A. corniculatum* exhibits antimicrobial properties against a variety of microorganisms, including both types of bacteria, parasites, and fungi. However, no evidence of antiviral effects has been observed. Different in vitro and in vivo studies found that different extracts of *A. corniculatum* are used to inhibit adult earthworms (*Pheretima posthuma*) showing anthelmintic effect and inhibit *P. falciparum* showing an antimalarial effect. Plant-isolated coumaric acid and fatty acids have the capacity to interact with bacterial DNA/RNA and to inhibit protein production through a variety of mechanisms and can show antimicrobial effect. Macrolides from *A. corniculatum* may inhibit bacterial protein production by binding the bacterial 50S ribosomal subunit. Gallocatechin, epicatechin, epigallocatechin-3-O-gallate, epigallocatechin, and other tannins, as well as flavonoids like kaempferol, quercetin, and isorhamnetin, constitute some of the phenolic compounds found in *A. corniculatum* that may be responsible for antibacterial activity by depolarizing and changing the fluidity of bacterial membranes. These phenolic compounds are also responsible for acting as antioxidants by reducing oxidative stress which will assist to diminish a variety of inflammatory disorders (such as asthma and arthritis), cancer, and various other ailments. Two triterpenoid saponins, Acornine 1 and Acornine 2, were isolated from *A. corniculatum*, and both exhibited growth inhibitory action against *T. clypeatus*. One possible explanation for this is the capacity of the triterpenoid saponin to limit fungal development by compromising the structure of the cell membrane. Evidence has been discovered supporting the idea that this particular plant possesses a central antinociceptive effect through the activation of the κ-opioid receptor. In addition, the neuroprotective properties of this plant against several central nervous system (CNS) disorders like Parkinson's disease and amnesia could potentially be ascribed to the existence of catechol compounds, including epigallocatechin-3-O-gallate. In addition, certain scholars have also discovered the plant's potential antidiabetic properties through the inhibition of the alpha-glucosidase enzyme. However, additional investigation is necessary to determine the exact neuropharmacological and antidiabetic effects. In summary, *A. corniculatum* exhibits a diverse range of pharmacological

properties, including antibacterial, antioxidant, anticancer, anti-inflammatory, antidiabetic, analgesic, and neuroprotective effects. This finding provides evidence for the utilization of this botanical species as a traditional remedy.

Abbreviations

COX: Cyclooxygenase
IL-6: Interleukin-6
TNF-α: Tumor necrosis factor-α
ROS: Reactive oxygen species
PG: Prostaglandin
TXA2: Thromboxane A2
LTB4: Leukotriene B4
LOX: Lipoxygenase
HPETE: Hydroperoxyeicosatetraenoic acid
MPO: Myeloperoxidase
Bcl-2: B-cell lymphoma 2
DPPH: 2,2-Diphenyl-1-picrylhydrazyl
TBARS: Thiobarbituric acid reactive substances
MIC: Minimal inhibitory concentration
PLA: Polylactic acid
iNOS: Nitric oxide synthase
ICAM-1: Intercellular adhesion molecule 1
PMNs: Polymorphonuclear neutrophils
FOXP3: Forkhead box protein 3
12-HHT: 12-Hydroxyheptadecatrienoic acid
EtOAc: Ethyl acetate
MeOH: Methanol
ACEt: Acetic acid
GNB: Gram-negative bacteria
GPB: Gram-positive bacteria
Compound 1: 3-O-[α-L-Rhamnopyranosyl-(1 $\longrightarrow$ 2)-α-L-rhamnopyranosyl-(1 $\longrightarrow$ 2)-β-D-galactopyranosyl-(1 $\longrightarrow$ 3)-β-D-glucopyranosyl-(1 $\longrightarrow$ 2)-β-D-(6′-O-methyl)glucuronopyranosyl]-13β, 28-epoxy-3β, 16α-dihydroxy-olean
Compound 18: (3β, 16α, 20α)-3,16,28-Trihydroxyolean-12-en-29-oic acid 3-{O-β-D-glucopyranosyl (1 $\longrightarrow$ 2)-O-[β-D-glucopyranosyl (1 $\longrightarrow$ 4)]-α-L-arabinopyranoside}
COMT: Catechol-O-methyltransferase
IC: Inhibitory concentration
GABAB receptors: G-Protein coupled receptors
DPP-IV: Dipeptidyl peptidase-4.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

PS and TRA accumulated the literature and systematically analyzed the data. PS and RR drafted and revised the manuscript. JAS and SJU supervised the project and provided helpful comments and revisions.

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References

[1] B. B. Petrovska, "Historical review of medicinal plants' usage," *Pharmacognosy Reviews*, vol. 6, no. 11, p. 1, 2012.
[2] D. Silveira and F. Boylan, "Medicinal plants: advances in phytochemistry and ethnobotany," *Plants*, vol. 12, p. 1682, 2023.
[3] J. B. Calixto, "The role of natural products in modern drug discovery," *Anais da Academia Brasileira de Ciências*, vol. 91, Article ID e20190105, 2019.
[4] M. H. Rahman, B. Roy, G. M. Chowdhury, A. Hasan, and M. S. R. Saimun, "Medicinal plant sources and traditional healthcare practices of forest-dependent communities in and around Chunati Wildlife Sanctuary in southeastern Bangladesh," *Environmental Sustainability*, vol. 5, no. 2, pp. 207–241, 2022.
[5] S. J. Uddin, *Screening of bangladeshi medicinal plants for the isolation and structural elucidation of novel anti-cancer compounds (phd thesis)*, [PhD Thesis], Griffith University, Queensland, Australia, 2010.
[6] S. L. Debnath, P. Kundu, M. Golder, B. Biswas, and S. K. Sadhu, "Phytochemical characterization and evaluation of pharmacological activities of leaves of a mangrove plant species-Aegiceras corniculatum (L.)," *Tropical Journal of Natural Product Research (TJNPR)*, vol. 4, no. 9, pp. 516–522, 2020.
[7] A. Roy, V. Gupta, and K. Mukherjee, "Two novel antifungals, acornine 1 and acornine 2, from the bark of mangrove plant *Aegiceras corniculatum* (Linn.) Blanco from Sundarban Estuary," *Pharmacognosy Magazine*, vol. 10, no. 38, p. S342, 2014.
[8] H. Jiang, Y. Zhang, Y. Zhang, X. Wang, and X. Meng, "An updated meta-analysis based on the preclinical evidence of mechanism of aconitine-induced cardiotoxicity," *Frontiers in Pharmacology*, vol. 13, Article ID 900842, 2022.
[9] Y. Li, C. Dong, M. J. Xu, and W. H. Lin, "New alkylated benzoquinones from mangrove plant *Aegiceras corniculatum* with anticancer activity," *Journal of Asian Natural Products Research*, vol. 22, no. 2, pp. 121–130, 2020.
[10] H. Luo, E. Hao, D. Tan et al., "Apoptosis effect of *Aegiceras corniculatum* on human colorectal cancer via activation of FoxO signaling pathway," *Food and Chemical Toxicology*, vol. 134, Article ID 110861, 2019.
[11] Y. Liu, F. Li, and Q. Huang, "Allelopathic effects of gallic acid from *Aegiceras corniculatum* on Cyclotella caspia," *Journal of Environmental Sciences*, vol. 25, no. 4, pp. 776–784, 2013.
[12] M. G. Ponnapalli, S. C. V. A. R. Annam, S. Ravirala, S. Sukki, M. Ankireddy, and V. R. Tuniki, "Unusual isomeric corniculatolides from mangrove, *Aegiceras corniculatum*," *Journal of Natural Products*, vol. 75, no. 2, pp. 275–279, 2012.
[13] I. Podolak, K. Grabowska, D. Sobolewska, D. Wróbel-Biedrawa, J. Makowska-Wąs, and A. Galanty, "Saponins as cytotoxic agents: an update (2010–2021). Part II—triterpene saponins," *Phytochemistry Reviews*, vol. 22, no. 1, pp. 113–167, 2023.

[14] L. B. Vinh, N. V. Phong, I. Ali et al., "Identification of potential anti-inflammatory and melanoma cytotoxic compounds from *Aegiceras corniculatum*," *Medicinal Chemistry Research*, vol. 29, no. 11, pp. 2020–2027, 2020.

[15] J. Wang, M. Dong, W. Zhang, X. Shen, and Y.-W. Guo, "Chemical constituents of mangrove plant *Aegiceras corniculatum*," *Chinese Journal of Natural Medicines*, vol. 4, pp. 275–277, 2006.

[16] M. Xu, Z. Deng, M. Li et al., "Chemical constituents from the mangrove plant, Aegiceras corniculatum," *Journal of Natural Products*, vol. 67, no. 5, pp. 762–766, 2004.

[17] D. Zhang, J. Wu, S. Zhang, and J. Huang, "Oleanane triterpenes from *Aegiceras corniculatum*," *Fitoterapia*, vol. 76, no. 1, pp. 131–133, 2005.

[18] D. Priya, A. Patil, S. Niranjana, and A. Chavan, "Potential testing of fatty acids from mangrove *Aegiceras corniculatum* (L.) Blanco," *International Journal of Pharmacy and Pharmaceutical Sciences*, vol. 3, pp. 569–571, 2012.

[19] N. X. C. Thanhb, N. H. Namb, C. Van Minhb, I. Hwanga, and Y. H. Kima, *Cytotoxic Triterpene Saponins from the Mangrove Aegiceras corniculatum*, 2019.

[20] A. Gopi, P. Stephy, K. K. Jacob, and C. Kumar, "In vitro antibacterial screening of fatty acid from *Aegiceras corniculatum* against human pathogens," *Journal of Pharmacognosy and Phytochemistry*, vol. 8, no. 1, pp. 448–451, 2019.

[21] P. Geegi and N. Manoharan, "In silico screening of phytochemicals identified from aegiceras corniculatum (l.) Blanco for its anti-diabetic activity," *Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences*, vol. 5, no. 4, pp. 81–91, 2019.

[22] D. Zhang and W. Jun, "Chemical constituents from mangrove: Aegiceras corniculatum," *Chinese Traditional Patent Medicine*, vol. 11, 1992.

[23] Y. Li, C. Dong, M.-J. Xu, and W.-H. Lin, "New alkylated benzoquinones from mangrove plant *Aegiceras corniculatum* with anticancer activity," *Journal of Asian Natural Products Research*, vol. 22, no. 2, pp. 121–130, 2019.

[24] S. P. R. Thota, N. S. Sarma, and Y. Murthy, "A new embelin from the mangrove *aegiceras corniculatum*," *Indian Journal of Chemistry*, vol. 55B, pp. 123–127, 2016.

[25] S. D. Wei, Y. M. Lin, M. M. Liao, H. C. Zhou, and Y. Y. Li, "Characterization and antioxidative properties of condensed tannins from the mangrove plant *Aegiceras corniculatum*," *Journal of Applied Polymer Science*, vol. 124, no. 3, pp. 2463–2472, 2012.

[26] M. Grg, *Chemical Constituents from the Bark of Aegiceras Corniculatum*, Guangdong Chemical Industry, Guangzhou, China, 2014.

[27] T. Roome, A. Dar, S. Ali, S. Naqvi, and M. I. Choudhary, "A study on antioxidant, free radical scavenging, anti-inflammatory and hepatoprotective actions of *Aegiceras corniculatum* (stem) extracts," *Journal of Ethnopharmacology*, vol. 118, no. 3, pp. 514–521, 2008.

[28] H. Janmanchi, A. Raju, M. Degani, M. Ray, and M. Rajan, "Antituberculosis, antibacterial and antioxidant activities of *Aegiceras corniculatum*, a mangrove plant and effect of various extraction processes on its phytoconstituents and bioactivity," *South African Journal of Botany*, vol. 113, pp. 421–427, 2017.

[29] S. Bidve, V. Kadam, and N. Malpathak, "Metabolite profiling and principle component analysis of a mangrove plant *Aegiceras corniculatum* L (Blanco)," *International Journal of Pharmaceutics and Pharmacology*, vol. 2, no. 1, pp. 1–9, 2018.

[30] H. Sato, M. Shibata, T. Shimizu et al., "Differential cellular localization of antioxidant enzymes in the trigeminal ganglion," *Neuroscience*, vol. 248, pp. 345–358, 2013.

[31] G. Pizzino, N. Irrera, M. Cucinotta et al., "Oxidative stress: harms and benefits for human health," *Oxidative Medicine and Cellular Longevity*, vol. 2017, Article ID 8416763, 13 pages, 2017.

[32] S. Bidve, V. Kadam, M. Shindikar, and M. Np, "Antioxidant potential of bark and leaves extracts of mangrove plant *Aegiceras corniculatum* L," *World Journal of Pharmaceutical Research*, vol. 6, no. 13, pp. 495–505, 2017.

[33] R. Biswas, S. Rahman, K. M. Didarul Islam et al., "Antioxidant, anti-inflammatory, and anticoagulation properties of *Aegiceras corniculatum* and *Acanthus ilicifolius*," *Pharmaceutical and Biomedical Research*, vol. 5, no. 3, pp. 35–44, 2019.

[34] A. Vedamurthy, B. Kulkarni, and J. Hoskeri, "Neuroprotective and anti-inflammatory activities of *Aegiceras corniculatum* (L.) blanco," *Pharmacognosy Research*, vol. 11, no. 3, p. 260, 2019.

[35] S. Dinesh Kumar, G. Singaravelu, K. Murugan et al., "Aegiceras corniculatum-mediated green synthesis of silver nanoparticles: biophysical characterization and cytotoxicity on vero cells," *Journal of Cluster Science*, vol. 28, no. 1, pp. 277–285, 2017.

[36] N. Raju and L. Patro, "Anthelmintic activity of black mangrove of aegiceras corniculatum," *World Journal of Pharmaceutical Research*, vol. 6, no. 8, pp. 1173–1180, 2017.

[37] J. Cai, Y. Gu, X. Huang, J. Huang, Y. Li, and C. Wu, "Study on α-glucosidase inhibitory activity of the ethyl acetate extract from leaves of *Aegiceras corniculatum*," *Food Research and Development*, vol. 36, no. 24, pp. 1–6, 2015.

[38] R. Ark and G. Jr, "In vitro evaluation of antioxidant activity of methanolic extracts of selected mangrove plants," *Medicinal & Aromatic Plants*, vol. 05, no. 03, p. 250, 2016.

[39] S. J. Maleki, J. F. Crespo, and B. Cabanillas, "Anti-inflammatory effects of flavonoids," *Food Chemistry*, vol. 299, Article ID 125124, 2019.

[40] F. Zhu, B. Du, and B. Xu, "Anti-inflammatory effects of phytochemicals from fruits, vegetables, and food legumes: a review," *Critical Reviews in Food Science and Nutrition*, vol. 58, no. 8, pp. 1260–1270, 2018.

[41] T. Roome, A. Dar, S. Naqvi, and M. I. Choudhary, "Evaluation of antinociceptive effect of *Aegiceras corniculatum* stems extracts and its possible mechanism of action in rodents," *Journal of Ethnopharmacology*, vol. 135, no. 2, pp. 351–358, 2011.

[42] S. Gurudeeban, K. Satyavani, T. Ramanathan, and T. Balasubramanian, "Antidiabetic effect of a black mangrove species *Aegiceras corniculatum* in alloxan-induced diabetic rats," *Journal of Advanced Pharmaceutical Technology and Research*, vol. 3, no. 1, pp. 52–56, 2012.

[43] T. Roome, A. Dar, S. Naqvi, S. Ali, and M. I. Choudhary, "*Aegiceras corniculatum* extract suppresses initial and late phases of inflammation in rat paw and attenuates the production of eicosanoids in rat neutrophils and human platelets," *Journal of Ethnopharmacology*, vol. 120, no. 2, pp. 248–254, 2008.

[44] S. Ravikumar, G. Ramanathan, S. Jacob Inbaneson, and A. Ramu, "Antiplasmodial activity of two marine polyherbal preparations from Chaetomorpha antennina and *Aegiceras corniculatum* against Plasmodium falciparum," *Parasitology Research*, vol. 108, no. 1, pp. 107–113, 2011.

[45] T. Roome, A. Razzak, P. Ali, S. Aziz, A. Dar, and S. Naqvi, "Therapeutic effect of *Aegiceras corniculatum* in chronic granulomatous inflammation and arthritis," *Journal of the Dow University of Health Sciences (JDUHS)*, vol. 8, no. 3, pp. 98–103, 2014.

[46] B. Kulkarni, J. Hoskeri, and A. Vedamurthy, "Evaluation of Analgesic activity of A. corniculatum L. Blanco. leaves extracts," *Journal of Pharmaceutical Sciences and Research*, vol. 11, no. 8, pp. 2862–2865, 2019.

[47] S. Aziz, T. Roome, P. Ali, and A. Razzak, "Inhibitory effect of *Aegiceras corniculatum* against lung injury in carrageenan-induced mouse pleurisy model," *Madinat Al-Hikmah*, vol. 59, no. 1, p. 52, 2016.

[48] L. Bulbul, S. Kamruzzaman, and M. Mostafizur Rahman, "Relationship of brain antioxidant protection of aged mice with memory enhancing efficiency of *Aegiceras corniculatum* leaves," *Oriental Pharmacy and Experimental Medicine*, vol. 17, no. 4, pp. 397–407, 2017.

[49] T. Hou, M. Yang, K. Yan, X. Fan, X. Ci, and L. Peng, "Amentoflavone ameliorates carrageenan-induced pleurisy and lung injury by inhibiting the NF-κB/STAT3 pathways via Nrf2 activation," *Frontiers in Pharmacology*, vol. 13, Article ID 763608, 2022.

[50] I.-S. Song, Y. J. Jeong, J. Kim et al., "Pharmacological inhibition of androgen receptor expression induces cell death in prostate cancer cells," *Cellular and Molecular Life Sciences*, vol. 77, no. 22, pp. 4663–4673, 2020.

[51] W. Deng, H. Du, D. Liu, and Z. Ma, "Editorial: the role of natural products in chronic inflammation," *Frontiers in Pharmacology*, vol. 13, Article ID 901538, 2022.

[52] R. Narayanaswamy and V. Veeraragavan, "Natural products as antiinflammatory agents," *Studies in Natural Products Chemistry*, vol. 67, pp. 269–306, 2020.

[53] M. Tunon, M. Garcia-Mediavilla, S. Sanchez-Campos, and J. González-Gallego, "Potential of flavonoids as anti-inflammatory agents: modulation of pro-inflammatory gene expression and signal transduction pathways," *Current Drug Metabolism*, vol. 10, no. 3, pp. 256–271, 2009.

[54] O. Hensens and K. Lewis, "Extractives of the bark of *Aegiceras corniculatum*," *Australian Journal of Chemistry*, vol. 19, no. 1, pp. 169–174, 1966.

[55] A. P. Nugraha, M. T. Sibero, A. P. Nugraha et al., "Anti-periodontopathogenic ability of mangrove leaves (*Aegiceras corniculatum*) ethanol extract: in silico and in vitro study," *European Journal of Dermatology*, vol. 17, no. 01, pp. 046–056, 2022.

[56] D. J. Yang, S. C. Liu, Y. C. Chen, S. H. Hsu, Y. P. Chang, and J. T. Lin, "Three pathways assess anti-inflammatory response of epicatechin with lipopolysaccharide-mediated macrophage RAW 264.7 Cells," *Journal of Food Biochemistry*, vol. 39, no. 3, pp. 334–343, 2015.

[57] T. Yoshimoto, C. Yokoyama, K. Ochi et al., "2, 3, 5-Trimethyl-6-(12-hydroxy-5, 10-dodecadiynyl)-1, 4-benzoquinone (AA861), a selective inhibitor of the 5-lipoxygenase reaction and the biosynthesis of slow-reacting substance of anaphylaxis," *Biochimica et Biophysica Acta*, vol. 713, no. 2, pp. 470–473, 1982.

[58] E. Gomez, O. de la Cruz-Giron, A. A. De La Cruz, B. S. Joshi, V. Chittawong, and D. H. Miles, "Toxicants from mangrove plants, V. Isolation of the piscicide, 2-Hydroxy-5-methoxy-3-undecyl-1, 4-benzo-quinone (5-O-methylembelin) from *Aegiceras corniculatum*," *Journal of Natural Products*, vol. 52, no. 3, pp. 649–651, 1989.

[59] T. Finkel and N. J. Holbrook, "Oxidants, oxidative stress and the biology of ageing," *Nature*, vol. 408, no. 6809, pp. 239–247, 2000.

[60] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA: A Cancer Journal for Clinicians*, vol. 68, no. 6, pp. 394–424, 2018.

[61] J. Z. Al-Kalaldeh, R. Abu-Dahab, and F. U. Afifi, "Volatile oil composition and antiproliferative activity of Laurus nobilis, Origanum syriacum, Origanum vulgare, and Salvia triloba against human breast adenocarcinoma cells," *Nutrition Research*, vol. 30, no. 4, pp. 271–278, 2010.

[62] S. J. Uddin, I. D. Grice, and E. Tiralongo, "Cytotoxic effects of Bangladeshi medicinal plant extracts," *Evidence-based Complementary and Alternative Medicine*, vol. 2011, Article ID 578092, 7 pages, 2011.

[63] L. B. Vinh, N. T. M. Nguyet, S. Y. Yang et al., "Cytotoxic triterpene saponins from the mangrove *Aegiceras corniculatum*," *Natural Product Research*, vol. 33, no. 5, pp. 628–634, 2019.

[64] A. Ahmad, R. K. Mishra, A. Vyawahare et al., "Thymoquinone (2-Isopropyl-5-methyl-1, 4-benzoquinone) as a chemopreventive/anticancer agent: chemistry and biological effects," *Saudi Pharmaceutical Journal*, vol. 27, no. 8, pp. 1113–1126, 2019.

[65] M. Xu, J. Cui, H. Fu, P. Proksch, W. Lin, and M. Li, "Embelin derivatives and their anticancer activity through microtubule disassembly," *Planta Medica*, vol. 71, no. 10, pp. 944–948, 2005.

[66] B. Perillo, M. Di Donato, A. Pezone et al., "ROS in cancer therapy: the bright side of the moon," *Experimental and Molecular Medicine*, vol. 52, no. 2, pp. 192–203, 2020.

[67] A. D. Rahimtula, P. K. Zachariah, and P. J. O'Brien, "The effects of antioxidants on the metabolism and mutagenicity of benzo [a] pyrene in vitro," *Biochemical Journal*, vol. 164, no. 2, pp. 473–475, 1977.

[68] N. Sharifi, "Commentary: antioxidants for cancer: new tricks for an old dog?" *The Oncologist*, vol. 14, no. 3, pp. 213–215, 2009.

[69] K.-J. Min and T. K. Kwon, "Anticancer effects and molecular mechanisms of epigallocatechin-3-gallate," *Integrative medicine research*, vol. 3, no. 1, pp. 16–24, 2014.

[70] J. Karthi and M. Purushothaman, "Anti-nociceptive effect of alcoholic and aqueous extracts of *Aegiceras corniculatum*," *Journal of Global Trends in Pharmaceutical Sciences*, vol. 8, no. 2, pp. 4006–4009, 2017.

[71] G. Bin, C. Yanping, Z. Hong et al., "Isolation, characterization and anti-multiple drug resistant (MDR) bacterial activity of endophytic fungi isolated from the mangrove plant, *Aegiceras corniculatum*," *Tropical Journal of Pharmaceutical Research*, vol. 13, no. 4, pp. 593–599, 2014.

[72] M. L. Grayson, S. E. Cosgrove, S. Crowe, W. Hope, J. S. McCarthy, and J. Mills, *Kucers' the Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic, and Antiviral Drugs-Three Volume Set*, CRC Press, Boca Raton, FL, USA, 2017.

[73] D. Greenwood, *Antimicrobial Chemotherapy*, Oxford University Press, Oxford, United Kingdom, 2007.

[74] P. O'brien, "Molecular mechanisms of quinone cytotoxicity," *Chemico-Biological Interactions*, vol. 80, no. 1, pp. 1–41, 1991.

[75] Z. Lou, H. Wang, S. Rao, J. Sun, C. Ma, and J. Li, "p-Coumaric acid kills bacteria through dual damage mechanisms," *Food Control*, vol. 25, no. 2, pp. 550–554, 2012.

[76] M. Daglia, "Polyphenols as antimicrobial agents," *Current Opinion in Biotechnology*, vol. 23, no. 2, pp. 174–181, 2012.
[77] M. D. C. Lima, C. Paiva de Sousa, C. Fernandez-Prada, J. Harel, J. Dubreuil, and E. De Souza, "A review of the current evidence of fruit phenolic compounds as potential antimicrobials against pathogenic bacteria," *Microbial Pathogenesis*, vol. 130, pp. 259–270, 2019.
[78] G. Casillas-Vargas, C. Ocasio-Malavé, S. Medina et al., "Antibacterial fatty acids: an update of possible mechanisms of action and implications in the development of the next-generation of antibacterial agents," *Progress in Lipid Research*, vol. 82, Article ID 101093, 2021.
[79] P. H. Patel and M. F. Hashmi, *Macrolides. StatPearls*, StatPearls Publishing, St. Petersburg, FL, USA, 2022.
[80] D. Velásquez-Jiménez, D. A. Corella-Salazar, B. S. Zuñiga-Martínez et al., "Phenolic compounds that cross the blood–brain barrier exert positive health effects as central nervous system antioxidants," *Food and Function*, vol. 12, no. 21, pp. 10356–10369, 2021.
[81] A. A. Zanwar, S. L. Badole, P. S. Shende, M. V. Hegde, and S. L. Bodhankar, "Antioxidant role of catechin in health and disease," *Polyphenols in Human Health and Disease*, pp. 267–271, Elsevier, Amsterdam, Netherlands, 2014.
[82] J. A. Joseph, B. Shukitt-Hale, and G. Casadesus, "Reversing the deleterious effects of aging on neuronal communication and behavior: beneficial properties of fruit polyphenolic compounds," *The American Journal of Clinical Nutrition*, vol. 81, no. 1, p. 313S, 2005.
[83] C. De Santi, P. Giulianotti, A. Pietrabissa, F. Mosca, and G. Pacifici, "Catechol-O-methyltransferase: variation in enzyme activity and inhibition by entacapone and tolcapone," *European Journal of Clinical Pharmacology*, vol. 54, no. 3, pp. 215–219, 1998.
[84] B. Zhu, J.-Y. Shim, M. Nagai, and H.-W. Bai, "Molecular modelling study of the mechanism of high-potency inhibition of human catechol-O-methyltransferase by (–)-epigallocatechin-3-O-gallate," *Xenobiotica*, vol. 38, no. 2, pp. 130–146, 2008.
[85] F. A. Van De Laar, P. L. Lucassen, R. P. Akkermans, E. H. van de Lisdonk, G. E. Rutten, and C. van Weel, "α-Glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis," *Diabetes Care*, vol. 28, no. 1, pp. 154–163, 2005.