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MULTIDIMENSIONAL PHYTOPHARMACOLOGICAL EVALUATION OF THE GENUS *SYMPLOCOS* (SYMPLOCACEAE): A REVIEW

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ABSTRACT

The Symplocos genus, comprising more than 300 species of flowering plants, has garnered significant attention in both traditional and modern medicine. This genus, commonly found in tropical and subtropical regions, has a rich history of use in traditional medicinal systems worldwide. Extracts from these plants have been employed to treat various ailments, including digestive disorders, diabetes, cancer and respiratory issues. In the realm of modern medicine, Symplocos species have undergone extensive phytochemical analysis. However, to date, there is no collective information on the pharmacognostical and pharmacological significance of this genus as a whole. Hence, this review article aims to highlight the phytochemical, ethnobotanical, pharmacognostical, pharmacological, and molecular aspects that have been studied in the Symplocos genus, providing a deeper understanding of recent literature relating to the phytochemical and pharmacological attributes of various Symplocos species. Researchers have tapped various bioactive entities, including alkaloids, flavonoids, and terpenoids, which contribute to their therapeutic properties. These phytochemical investigations have laid the foundation for further exploration of Symplocos-derived compounds as potential pharmaceutical agents. Pharmacognostical studies in this genus have explored the further characterisation and standardisation of Symplocos extracts, ensuring their quality and safety in medicinal applications. Additionally, pharmacological investigations have provided valuable insights into the mechanism of action of these extracts, revealing their potential in treating various diseases. Notably, Symplocos extracts have displayed anti-inflammatory, anticancer, antimicrobial and antioxidant activities, and gene expression studies have shed light on the molecular mechanism underlying the pharmacological effects of Symplocos compounds. This review article emphasises the importance of the Symplocos genus, which holds great medicinal potential, with studies confirming its diverse bioactive compounds and therapeutic properties. The pharmacological and molecular investigations on this genus have provided valuable insights into its mechanisms of action. Continued research in this field holds greater promise of unveiling novel therapeutic agents and expanding novel exposure of their mechanism of action in the discovery of novel drug leads.

Keywords: Medicinal Plants, Phytochemistry, Pharmacognosy, Phytochemical Constituents, Pharmacology, Ethnobotany, Phytomedicine, Therapeutic

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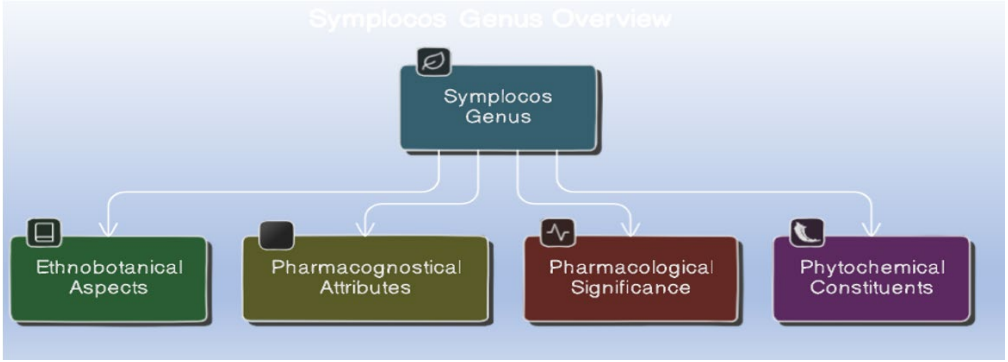
Graphical abstract



1. INTRODUCTION

Symplocos is the only known genus in the family Symplocaceae; most commonly found in tropical and subtropical Asia, Malaysia and America. Symplocos is a genus of flowering plants belonging to the order Ericales. There are approximately 318 species, and about 25 of these have been identified as dioecious. and most of the species have been recorded to have specific medicinal and economic importance. Genus Symplocos has been found to have various chemical constituents such as flavonoids, alkaloids, iridoids, lignans, triterpenoids and terpenoids. In this era of increasing interest towards traditional plant-based medicine, the Symplocos genus has promising effects as it is known for its medicinal importance, particularly in traditional and herbal medicinal systems. Different species of the Symplocos genus have been used in traditional medicinal systems, such as Ayurveda and Traditional Chinese Medicine, for centuries. Various parts of the plants, including the bark, leaves, and roots, are widely used for their therapeutic properties in the treatment of various ailments like bacterial diseases, diarrhoea, dysentery, eye infections, hemorrhagic gingivitis, uterine disorders, ulcers, bowel complaints, enteritis, malaria, snake bite and so on. In recent years, this genus has been gaining popularity due to its diverse biological properties, especially in antitumor and phosphodiesterase inhibitory activities.

The majority of the species within this genus with high medicinal importance are Symplocos racemosa, S. caudata, S. chinensis, S. glomerata, S. paniculata, S. confusa, S uniflora, S vaccinifolia, S. lucida etc. All these plants have unique and promising therapeutic effects. So, the Symplocos genus has garnered greater attention in the field of medicine and drug delivery systems due to its varied pharmacological properties and the presence of bioactive compounds in different species and some Symplocos species are known for their antioxidant properties. They combat oxidative stress and inflammation, which are linked to various chronic diseases. Beyond their direct medicinal properties, Symplocos-based formulations can serve as a search engine for drug delivery vehicles. They can enhance the solubility and bioavailability of poorly water-soluble drugs, making them more effective. Ongoing scientific research also continues to explore the potential medicinal compounds present within Symplocos species. This review contributes to our deeper understanding of phytochemical constituents, pharmacological action and furthermore mechanisms of action and their potential applications in modern medicine Acharya et al. (2016).

2. REVIEW OF LITERATURE

2.1. GEOGRAPHIC DISTRIBUTION

The *Symplocos* genus is mainly distributed in Asia, North America, South America, Africa and Australia. They are abundant in various parts of Asia, including India, China, Japan, and Southeast Asian countries Figure 1. Mostly present in tropical and subtropical forests. In North America, *Symplocos* species are found in regions such as the southeastern United States, especially in places with warm and humid climates. Some *Symplocos* species are native to South America, particularly in countries like Brazil and Colombia, where they grow in montane and rainforest habitats. While not as widespread as in other continents, a few *Symplocos* species are found in African countries, particularly in tropical and subtropical regions. Limited distribution of this species of *Symplocos* can be found in parts of Australia, mostly in northern and eastern regions. The distribution of *Symplocos* species can vary within these regions, depending on factors such as climate, elevation, and habitat type Wang et al. (2004).

Figure 1

Figure 1 Geographical Distribution of the Genus *Symplocos*

2.2. TAXONOMIC DESCRIPTION

The genus *Symplocos* is a single taxonomic group within the family *Symplocaceae*, which belongs to the order Ericales. The diverse distribution of the genus includes both evergreen and deciduous trees and shrubs. The taxonomic classification of the genus *Symplocos* is:

Kingdom: Plantae
Phylum : Angiosperms
Class : Eudicots
Order : Ericales
Family : Symplocaceae
Genus : Symplocos

2.3. TAXONOMIC CHARACTERISTICS

Symplocos species are mostly woody shrubs or small to medium-sized trees. Leaves are typically simple, alternate and usually evergreen. The leaves are leathery and have entire margins, usually glandular, apex acute to acuminate, midvein abaxially prominent, and adaxially raised. Flowers are small, inconspicuous, and

often fragrant flowers and usually bisexual. Sepals imbricate, Petals imbricate and white or yellow in colour, filaments glabrous and anthers round ovate to spherical. The flowers are arranged in various types of inflorescences, such as spikes or panicles. The fruits are typically a drupe, which is a fleshy fruit with a hard stone-like pit inside. Usually crowned by persistent calyx and endocarp celled Wu and Nooteboom (1996).

2.4. MEDICINAL AND HEALTH EFFECTS

The genus *Symplocos* holds significant importance in traditional medicine and healthcare practices in various regions. *Symplocos* species have a long history of use in traditional medicinal practices, such as Ayurveda in India, Traditional Chinese Medicine (TCM), and indigenous healing practices in Southeast Asia and other parts of the world Figure 2. Different parts of *Symplocos* plants, including leaves, bark, roots and fruits, are utilised for a wide range of medicinal purposes. These uses include treating inflammation, wounds, gastrointestinal issues, diabetes and oral health issues. *Symplocos* plants contain bioactive compounds like alkaloids, flavonoids, tannins and terpenoids, which contribute to their medicinal properties.

Plants in this genus have been employed as remedies for a wide spectrum of ailments, including leprosy, gynaecological disorders, ulcers, leucorrhea, menorrhagia, malaria and tumefaction, etc. For instance, S. chinensis, a herb found in Guangxi Province, South China, has served as a folk remedy for conditions like malaria, tumefaction, enteritis, nephritis, and snake bites Li et al. (2003). S. racemosa has been historically used to address menstrual disorders and to provide relief for spongy and bleeding gums. Its decoction has found applications in treating bowel complaints and ulcers Dhaon et al. (1990). In Ayurveda, the astringent bark of S. racemosa has been chiefly regarded as a potent treatment for diarrhoea, dysentery, eye diseases, gum bleeding, menorrhagia, and uterine disorders Watt (1972). The bark has also been applied in managing 'Kapha' blood diseases, leprosy, dropsy and liver complaints. It remains a prominent Ayurvedic remedy, particularly for gynaecological disorders, including abortion, miscarriages, and vaginal ulcers. In the Unani system of medicine, it functions as an emmenagogue and aphrodisiac, while also being a valuable remedy for inflammation, uterine cleaning, leucorrhea, and menorrhagia Bhutani et al. (2004). The roots of S. caudata have been traditionally used in Chinese folk medicine to treat icterus and arthritis. Local populations have also relied on their roots to address jaundice, dysentery, and excessive uterine bleeding Badoni et al. (2010). S. cochinchnensis is widely applied for the treatment of diverse disorders such as leprosy, tumours, diarrhoea, dysentery, menorrhagia, inflammation, and uterine issues. Furthermore, S. spicata has been used as a source of Ayurvedic crude drug known as 'Lodhara' in Travancore, Cochin, South India Badoni et al. (2010). Some of the major medicinal plants in this genus are listed in Table 1.

Figure 2

Figure 2 Medicinal and Health Benefits of Various Parts of the Genus Symplocos

Table 1

Table 1 List of Important Medicinal Plants of the Genus Symplocos and Their Ethnomedicinal Significance

SL.No	Scientific name	Part used	Ethno-Medicinal Uses	Reference
1.	Symplocos racemosa Roxb.	Bark	Gum and teeth infection, abortion, stomatitis, wound healing, paralysis, conjunctivitis, micro fracture or dislocation of bone, diarrhea, pelvic pain, diabetes	Aiyar et al. (1975)
2.	Symplocos cochinchinensis (Lour.) S. Moore.	Leaf& bark	Diabetes, Antimicrobial, Inflammation, leprosy, tumor, dysentery, diarrhea, menorrhagia, uterine issues	Khan et al. (2001), Sunil and Ignacimuthu (2011), Vadivu and Lakshmi (2008)
3.	Symplocos tanakana Nagai.	Bark, leaf&root	Enteritis, malaria, leprosy, tumefaction, diabetes	Seong et al. (2023)
4.	Symplocos lucida Wall.ex G.Don.	Bark	Antibacterial, antioxidant, menstrual disorders, uterine issues	Shrestha et al. (2017)
5.	Symplocos caudata Wall.ex G.Don.	Bark&roots	Jaundice, dysentery, profuse uterine bleeding, skin diseases and diabetes	Huo et al. (2008)
6.	Symplocos paniculata Miq.	Root	Dysentery, bowel complaints, inflammation, snake bite, miscarriages	Kusuma et al. (2018)
7.	Symplocos setchuensis Brand ex Diels.	Leaves, bark, roots	Malaria, nephritis, snake bite, diarrhea, dysentery, menorrhagia, and asthma.	Wang and Yan (2018)
8.	Symplocos Sumuntia Buch-Ham ex D. Don.	Leaf	Anti-inflammatory	Huong et al. (2017)
9.	Symplocos anomala Brand.	Bark	Skin diseases, digestive problems, gynecological health	Huang et al. (2016)
10.	Symplocos lancifolia Zucc.	Leaf	Antimicrobial, antiseptic and digestive problems	Acebey-Castellon et al. (2011)

2.5. ETHNOBOTANICAL SIGNIFICANCE

The ethnobotanical uses of the genus Symplocos are diverse, and various indigenous tribes and communities have incorporated these plants into wide use in their traditional practices. The Gond tribe, primarily found in Central India, including states like Madhya Pradesh, Chhattisgarh and Maharashtra, is known to use Symplocos species viz S.racemosa and S.cochinchinensis for their traditional medicinal purposes. The Kondh tribe, residing particularly in the hilly regions of Odisha and Andhra Pradesh, uses Symplocos species like S.racemosa for their

medicinal and cultural purposes. The Bhil tribe, found in various states across western and central India, including Rajasthan and Gujarat, also incorporates S. racemosa into their traditional medicinal practices. The Santhal tribe, residing in the states of West Bengal, Jharkhand and Odisha, has extensive knowledge of local flora, including Symplocos species, which they use for medicinal or cultural purposes. In the northeastern state of Meghalaya, the Khasi tribe has a rich tradition of using local plants, including Symplocos species, for their ethnobotanical claims. The Toda tribe, residing in the Nilgiri Hills of Tamil Nadu, uses S.cochinchinensis for various purposes, and they have traditional knowledge related to Symplocos species Sharma et al. (1993).

2.6. PHARMACOGNOSTICAL ASPECTS

Pharmacognostical studies on the genus Symplocos typically focus on the morphological, anatomical, and chemical characteristics of the plant within the genus. These studies can help to identify and understand the medicinal properties and credible uses of Symplocos species.

Powder microscopic studies on the stem bark of Symplocos racemosa Roxb indicate a yellowish-brown colour with slightly astringent characteristics and soft texture. An in-depth study reveals that cork cells of the stem bark are polygonal in shape and larger in size, up to 70 to 110 µm, and anticlinal walls are slightly wavy. Fibres are long and the lumen is narrow, thick-walled, lignified and blunt on one end. Sclereids are mostly brachysclereids, and some are rectangular and lignified with thick spiny outgrowths and sclerotic phellem cells or phelloids, while some others are rectangular and tubular with simple pits in the lumen that are about 320 µm long and 130 µm wide. There are numerous starch grains found in the stem bark, which are simple as well as compound, having 2 to 6 components. A Y-shaped hilum is present in the centre, which is about 4 to 13 µm in diameter. Furthermore, abundant prismatic crystals of calcium oxalate were also found in the stem bark.

Similarly, the organoleptic analysis of the stem bark of Symplocos crataegoides Ham. indicates light brown colour with a slightly sour to slightly bitter taste and soft texture. The cork cells are smaller in size, with about 50 to 70 µm, polygonal in shape, and have straight anticlinal walls filled with brownish content. Fibres are libriform with tertiary thickening. Lumen is very narrow, long, cylindrical, thick-walled, lignified, and tapering at both ends. Sclereids are polyhedral, more or less isodiametric, lignified, thick-walled, and 80 to 100 µm in size. Simple, round to oval-shaped starch grains were also found, which are about 4 to 25 µm in diameter, and further scarce prismatic crystals of calcium oxalate were also found in the stem bark Govindarajan et al. (2016).

Another comprehensive study on the root bark of Symplocos racemosa Roxb. evidenced that they are reddish-brown powders with a distinct spicy aroma and a slightly bitter taste. Key identifying characters of this powdered drug include stone cells, rectangular cells containing colouring matter, thin-walled oil cells, and cork tissue sheets, some of which contain lignin and tannin. Additionally, rosette calcium oxalate crystals and numerous starch grains (both simple and compound) are the prominent features. In the cross-sectional view of S. racemosa root, there are sclerides and a thread-like, single-cell arrangement alongside the phloem and phelloderm. The upper and lower pericycle zones, stone cells, two layers of thickened lignified cells, cork cells with thickening, and a secondary cortex housing bast mucilage cells and thick oil glands are also notable in this region. Furthermore, medullary rays and occasional soft bast are also found within them Hyder et al. (2017).

2.7. MAJOR PHYTOCONSTITUENTS OF THE GENUS *SYMPLOCOS*

Phytoconstituents, also known as phytochemicals, are naturally occurring chemical compounds found in plants. These compounds are responsible for various biological activities and functions within the plant. The genus Symplocos contains various phytoconstituents. While the specific phytochemical composition can vary among different species within the genus, some of the major phytoconstituents commonly found in Symplocos plants include alkaloids, flavonoids, triterpenoids, phenolic compounds, saponins, lignans, and essential oils. Important phytoconstituents present in Symplocos species are listed in Table 2, and the chemical structural information of some of the major phytochemical compounds is depicted in Figure 3.

Figure 3

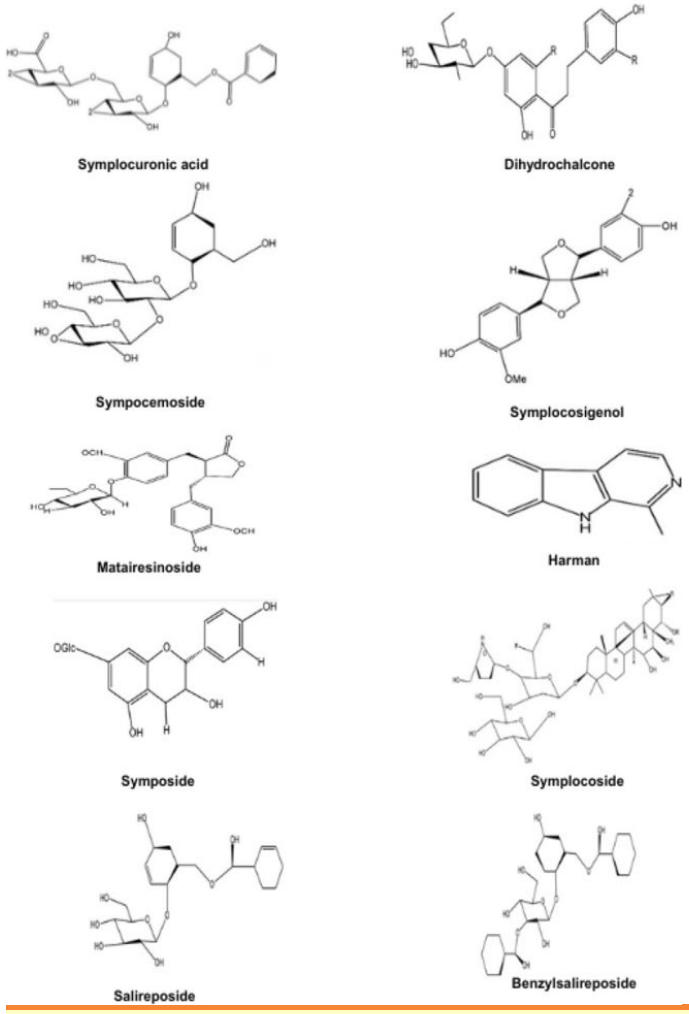


Figure 3 Major Phytochemical Compounds of the Genus *Symplocos*

Table 2

Table 2 List of Phytochemical Constituents Present in Different Symplocos Species

SL.No	Plant	Constituents	Reference
1.	S. paniculata Miq.	Trilobatin , Ursolic acid, Corosolic acid.	Na et al. (2006)

2.	S. racemosa Roxb.	Saponin glycosides, carbohydrate, 1-Ethyl brachiose-30-acetate, ketochaulmoogric acid, nonaeicosanol, triacontyl palmitate, and methyl triacontanoate. symplocuronic acid, sympocemoside, and salirepin, harmine, alkaloids, Phenolic glycoside benzoylsalireposide and salireposide, Dithiadiazetidin derivative, Symplonate, Symconosides A and B, Locoracemosides A –C, Symploracemoside and Symplomoside, Symposide, Epiafzelechin Oleanolic acid. Symplocomoside, Symponoside, Symplososide, and symploveroside.	Kambhoja and Keshava (2004), Ahmad et al. (2007)
3.	S. spicata Var.	3,28-O-bis-D-glucopyranosides, 19-hydroxyasiatic acid, Spinasterol and Flavanol glycoside.	Tiwar et al. (1976), Higuch et al. (1982)
4.	S. tinctoria Linn.	Sugars, polysaccharides and polyol.	Hussain et al. (1990)
5.	S. uniflora Benth.	Flavanol glycoside (Symplocoside), Epicatechin	Tschesche et al. (1980)
6.	S. vacciniifolia Chen.	Dihydrochalcone glucoside, vacciniifolin, confusoside, trilobatin and sieboldin	Ling et al. (2004)
7.	S. caudata Wall. ex G.Don.	Glucopyranosyl, Symplolignanoside A, Glucopyranoside, Neolignan	Huo et al. (2008)
8.	S. celastrinea Mart. ex Miq.	N-methyllaurelliptin, Isoboldin, and 5-hydroxy-6-methoxynor-aporphine	Li et al. (2006)
9.	S. chinensis f.pilosa.	Symplocososides A–F, Symplocososides G–K, Triterpenoids, Glucuronide triterpenoid saponins.	Li et al. (2006)
10.	S. confusa Brand.	Dihydrochalcone glucoside: confusoside	Tanaka et al. (1982)
11.	S. glauca Thunb.	Verbenalin, 6-Dihydroverbenalin.	Iida et al. (1990)
12.	S. glomerata King ex. C.B Clarke.	Bidesmosidic 3-O-glucuronide, Oleanane triterpenoid saponins, Salsoloside C and Copteroside E, Lignans, Pinoresinol. Glucopyranoside	Waffo-Téguo et al. (2004)
13.	S. lancifolia Zucc.	Ursolic acid, Quercetin, Kaempferol, Syringaresinol, Dimethoxycinnamic acid, Gallic acid, Phloridin.	Lin et al. (1996)
14.	S. lucida Wall. ex G.Don.	Symplocosigenol, Pinoresinol glucoside	Huo et al. (2007)
15.	S. microcalyx Hayata.	Confusoside and trilobatin	Miura et al. (1985)
16.	S.cochinchinensis Moore.	Triterpenoids, alkaloids, anthraglycosides, flavonoids, anthocyanosides, proanthocyanidins, polyphenols, tannins, saponins, polyuronics, and reducing agents.	Ly et al. (2022)
17.	S.sumuntia Buch. Ham ex. D.Don	Arctigenin, Matairesinol, Monomethylpinoresinol, Pinoresinol	Huong et al. (2017)
18.	S.anomala Brand.	Terpene alkaloid glucosides, Apocarotenoids, Iridoid, Phenylpropanoids, Coumarin	Huang et al. (2016)
19.	S.setchuensis Brand ex Diels.	Phenolics, Glucoside, Sucrose	Wang and Yan (2018)
20.	S. sawafutagi Nagam.	Quercetin, Galactopyranoside, Tellimagrandin	Seong et al. (2023)

2.8. PHARMACOLOGICAL ASPECTS OF THE GENUS SYMPLOCOS

The genus *Symplocos* holds great significance in pharmacology for several reasons; Many species within the *Symplocos* genus have a long history of traditional medicinal use in various parts of the world. Their pharmacological properties, such as antioxidant, anti-inflammatory, anticancer, antidiabetic, and antimicrobial effects, make them a valuable candidate for drug discovery and development Figure 4. *Symplocos* plants produce a wide range of bioactive compounds, including alkaloids, flavonoids and polyphenols. These natural compounds have the potential

to serve as the basis for developing new pharmaceuticals or herbal remedies. Bioprospecting in this genus may uncover novel treatments for various medical conditions. In regions where *Symplocos* plants are traditionally used, they provide an alternative or complementary approach to healthcare, and to integrate traditional medicine with modern healthcare practices. Important pharmacological attributes of the *Symplocos* genus are:

Figure 4

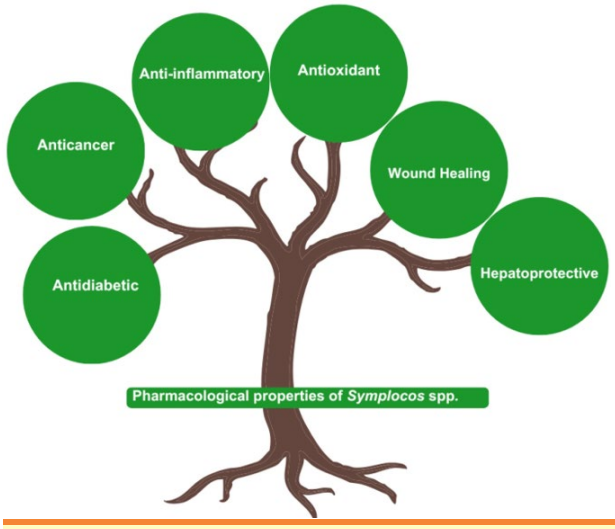


Figure 4 Major Pharmacological Properties of the Genus *Symplocos*

2.8.1. ANTIOXIDANT ACTIVITY

Plant-derived antioxidants are bioactive compounds found naturally in a range of plant sources, including fruits, vegetables, nuts, seeds, and herbs. The methanolic extract obtained from S. paniculata was primarily evaluated for its ability to neutralise 1,1-diphenyl-2-pyrylhydrazyl (DPPH) free radicals. The results demonstrated that the extract displayed a significant DPPH free radical scavenging effect, with an IC50 value of 23.0 mg/ml Kim et al. (2003).

The ethanolic extract of leaves and flowering tops of S. racemosa, at the dose levels of 100 and 300 mg/kg, exhibited notable antioxidant properties in Swiss albino mice. This was evident through the reduction of lipid peroxidation levels, as well as enhancement in superoxide dismutase and catalase activity Devmurari (2010) and the ethanolic extract obtained from the bark of S. racemosa demonstrated strong ABTS radical scavenging activity, along with moderate scavenging activity against DPPH, nitric oxide, and hydroxyl radicals. These effects were compared with the standard antioxidant drugs, ascorbic acid and rutin Vijayabaskaran et al. (2010).

The methanol extract from the leaves of S. cochinchinensis Moore was assessed for its antioxidant activity both in vitro and in vivo, and the extract exhibited high total phenolic content, measuring 230 mg of gallic acid equivalents per gram of the extract. Notably, it demonstrated strong scavenging activity against 2,2-diphenyl-picrylhydrazyl (DPPH) radicals Sunil and Ignacimuthu (2011). The ethanol extracts obtained from the leaves of S. sawafutagi Nagam. and S. tanakana Nakai was found to possess a potent radical scavenging effect. These extracts exhibited potent antioxidant effects, demonstrating impressive radical scavenging capabilities, and they also functioned as inhibitors of non-enzymatic advanced glycation end-product (AGEs) formation Seong et al. (2023).

2.8.2. ANTICANCER ACTIVITY

A growing interest in natural chemicals is demonstrated by the investigation of plant extracts in anticancer investigations. In a comprehensive study on S.chinensis, the extract derived from the root of S. chinensis, along with an isolated triterpenoid compound ursane, displayed notable cytotoxic effects against B16 and BGC-823 cells, with an IC50 value of 0.025 and 0.068 mM, respectively Li et al. (2003). Six triterpenoid saponins, known as symplocososides A to F, isolated from S. chinensis, were evaluated for their antiproliferative effects on KB, HCT-8, A549, BGC-823, and HELF cells. Among these compounds, symplocososide A exhibited significant activity against KB cells (IC50, 1.72 mg/ml), HCT-8 cells (IC50, 4.31 mg/ml), A549 cells (IC50, 0.67 mg/ml), and HELF cells (IC50, 4.62 mg/ml). Symplocososide C demonstrated cytotoxic effects against HCT-8 cells (IC50, 2.86 mg/ml) and BGC-823 cells (IC50, 7.29 mg/ml), while symplocososide F exhibited cytotoxicity against HCT-8 cells (IC50, 4.04 mg/ml) Tang et al. (2004). The butanolic and ethyl acetate extracts derived from S. racemosa exhibited significant cytotoxic potential where the cell proliferation assays indicated a dose-dependent inhibition of cell growth. Specifically, the butanolic extract demonstrated cytotoxicity against HL 60 (human leukaemia cell line) with an IC50 of 27183 mg/ml and HeLa (human cervix cancer cell line) with an IC50 of 22,861 mg/ml Bhuvan et al. (2009). The methanolic extract of the leaf and bark of S.cochinchinensis exhibited potent activity against three cell lines, viz U87, Hep G2 and MCF7 Abida et al. (2016).

2.8.3. ANTI-HIV ACTIVITY

Studies on plant extracts' anti-HIV properties reveal a developing area in which natural substances show promise as inhibitors, opening up new options for HIV treatment research when tested the ethanolic extract obtained from the stem bark of S. setchuensis displayed notable HIV replication-inhibitory activity, with an EC50 value of 20 mg/ml and a therapeutic index (TI) of 5, when tested with H9 lymphocyte cells. Subsequent bioassay-directed fractionation of this extract led to the identification of matairesinol and harman as anti-HIV compounds. These two compounds exhibited IC50 values of 21.9 and 111.5 mM, respectively. In terms of their EC50 values (2.0 and 10.7 mM, respectively), they demonstrated TI values of 11.0 and 10.4, respectively Ishida et al. (2001).

2.8.4. ANTIDIABETIC ACTIVITY

According to studies, some members of the Symplocos genus may contain substances that can prevent diabetes. It is thought that these substances affect glucose absorption, insulin sensitivity, and pancreatic function. When administered to streptozotocin-induced diabetic rats, the methanolic extract derived from S. racemosa bark at a dose level of 250 and 500 mg/kg b.w. lead to a reduction in both blood glucose and triglyceride levels. This effect is potentially attributed to an insulin-like mechanism acting on peripheral tissues. It may involve either the promotion of glucose uptake and metabolism or the inhibition of hepatic gluconeogenesis Venkidesh et al. (2012). In another study on hexane extract of S. cochinchinensis leaves in diabetic rats, it exhibited a significant reduction in plasma insulin, plasma and hepatic total cholesterol (TC), triglycerides (TG) and free fatty acids (FFA) levels Sunil and Ignacimuthu (2011). In-vitro studies on ethyl acetate fractions of S. cochinchinensis evidenced the highest inhibitory potential in both α-amylase and α-glucosidase activities Ly and Le (2021). The ethanolic extract derived

from S. cochinchnensis bark, as well as its varied fractions (hexane, dichloromethane, ethyl acetate, and 90% ethanol), were investigated for its in-vitro assessments targeting multiple factors, including the control of postprandial hyperglycemia, insulin resistance, oxidative stress, pancreatic beta cell proliferation, inhibition of protein glycation, protein tyrosine phosphatase-1B (PTP-1B), and dipeptidyl peptidase-IV (DPPxxi IV) Antu (2014).

2.8.5. ANTI-INFLAMMATORY ACTIVITY

Symplocos species have shown strong anti-inflammatory qualities, indicating great potential in using it for therapy in the treatment of inflammatory diseases due to their capacity to alter important inflammatory pathways. Sapinasterol, derived from the stem bark of S. spicata, demonstrated strong anti-inflammatory effects in a rat model of carrageenin-induced acute paw oedema Frotan et al. (1983). The in vitro assessment of the methanol extract from S. cochinchnensis bark for anti-inflammatory activity was conducted using the human red blood cell (HRBC) membrane stabilisation method, and it revealed a remarkable 67% protection of HRBC in a hypotonic solution at a concentration of 1000 mg/ml Vadivu and Lakshmi (2008).

The anti-inflammatory potential of S. racemosa bark was evaluated in Wistar Albino rats using a carrageenan-induced hind paw oedema model. The ethanolic extract of leaf and bark demonstrated notable inhibitory effects in the formalin-induced paw licking model. This suppression was comparable to the standard drug, diclofenac sodium (5 mg/kg), The extended anti-inflammatory action of the ethanolic extract is attributed to its inhibition of prostaglandin and kinin synthesis/release Sharma et al. (2013). The ethanolic extract of S.paniculata manifested significant anti-inflammatory activity in carrageenan-induced paw oedema in rats Semwal et al. (2011). Studies on the methanolic extract of S. sumuntia on its inflammatory responses in lipopolysaccharide (LPS)-treated BV2 cells exhibited a pronounced inhibitory effect on the LPS-stimulated inducible nitric oxide synthase and cyclooxygenase-2 expression, as well as the production of nitric oxide (NO), a proinflammatory mediator Lim et al. (2022).

2.8.6. ANTIMICROBIAL ACTIVITY

Through agar well diffusion method, petroleum ether and ethanolic extracts of S. racemosa bark showed pronounced inhibitory effect against the growth of gram-positive bacteria, Staphylococcus aureus, Enterococcus faecalis, Bacillus cereus, and gram-negative bacteria Klebsiella pneumoniae, Pseudomonas aeruginosa, and Escherichia coli showed significant antimicrobial activity by inhibiting the growth of these organisms Devmurari (2010). The antimicrobial activity of the methanolic extracts from the leaf, root, and stem bark of S. cochinchinensis, were further partitioned using petroleum ether, dichloromethane, and ethyl acetate, and the results demonstrated a wide range of antibacterial activity in both the crude and its fractions Khan et al. (2001).

2.8.7. HEPATOPROTECTIVE ACTIVITY

The ethanolic extract obtained from S. racemosa bark, administered orally at the dose range of 100 and 200 mg/kg b.w., exhibited potent hepatoprotective activity in rats induced with DMBA hepatocellular carcinoma. This activity was characterized by a substantial decrease in hepatic enzyme levels and total bilirubin

levels accompanied by a dose-dependent increase in total proteins, reduced glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) levels Vijayabaskaran et al. (2010). The methanolic extract from S. racemosa bark was administered at doses of 250 and 500 mg/kg b.w. demonstrated high hepatoprotective effects against carbon tetrachloride (CCl4)-induced liver toxicity in rats. These effects included a substantial reduction in hepatic enzyme levels and total bilirubin, as well as a dose-dependent increase in total protein levels. Notably, these results were, however, comparable with those achieved with the standard drug, silymarin (100 mg/kg) b.w. Venkidesh et al. (2011).

2.8.8. ANTIULCER ACTIVITY

The aqueous and ethanolic extracts derived from S. racemosa bark, administered at doses of 250 and 500 mg/kg b.w, were evaluated for their antiulcer activity using pylorus ligation and aspirin-induced ulcer models in rats. The results of the experiments evidenced that both the extracts significantly reduced the ulcer index in both the models, comparable to the effects of the standard drug, Lansoprazole (8 mg/kg) b.w. Krishna et al. (2013).

2.8.9. PHOSPHODIESTERASE INHIBITORY ACTIVITY

Four phenolic glycosides were extracted from S. racemosa bark and leaves, namely benzoyl salireposide, salireposide, symploracemoside, and symplomoside. These compounds were assessed for their inhibitory effects on snake-venom phosphodiesterase I. Among them, symploracemoside displayed moderate inhibitory activity with an IC50 value of 590 mM, while symplomoside exhibited weaker activity with an IC50 value of 998 mM. In comparison, benzoyl salireposide demonstrated strong inhibitory potential with an IC50 value of 171 mM, and salireposide exhibited moderate inhibitory activity with an IC50 of 544 mM Ahmad et al. (2003). In another study, four glycosides, namely symplocomoside, symponoside, symplocoside, and symploveroside were extracted from S. racemosa which exhibited in vitro inhibitory activity against phosphodiesterase I and their respective IC50 values were 122 mM, 698 mM, 722 mM, and 909 mM Abbasi et al. (2004).

2.8.10. ANTIPYRETIC ACTIVITY

Ethanolic extract of S. racemosa bark was treated with brewer's yeast-induced pyrexia in rats, The extract demonstrated a notable antipyretic effect, effectively maintaining normal body temperature and reducing the elevated rectal temperature induced by brewer's yeast in rats. The activity of the extract was highly comparable with the standard antipyretic drug, paracetamol (100 mg/kg b. w.) Vijayabaskaran et al. (2010).

2.8.11. WOUND HEALING ACTIVITY

Jatyadi taila is a medicated oil preparation that includes S. racemosa and is well-known for its topical wound-healing properties. It contains essential oils, flavonoids, alkaloids, steroids, tannins, and glycosides. In studies, it has been observed to significantly reduce wound area in a dose-dependent manner. Additionally, it has led to an increased amount of protein, hydroxyproline, and hexosamine content in the granulation tissue when tested in an excision wound model in rats. These effects were comparable to those of the reference standard topical drug, Neosporin

Shailajan et al. (2011). Additional studies have also explored the burn wound healing capabilities of both Jatyadi taila and Jatyadi ghrita using experimentally induced burn injuries in rats. The results indicated their promising credences, which were comparable to the effects of 1% silver sulfadiazine cream Dhande et al. (2012).

2.8.12. ANTI-SNAKE VENOM STUDIES

Researchers conducted investigations on the anti-snake venom properties of different extracts from S cochinchinensis leaves. These studies involve both in vitro assessments, using human RBC lysis, and in vivo experiments conducted on Swiss albino mice. The results revealed a substantial reduction in the mortality rate induced by snake venom toxicity in mice when administered at a dose range of 400 mg/kg b.w.. This underscores the significant anti-snake venom activity of the plant, thereby validating its traditional use in indigenous medicinal systems Lakshmi, and Vadivu (2010). Phenolic glycosides, namely symplocomoside, symponoside, symplososide, and symploveroside, were obtained from S. racemosa and exhibited inhibitory activity against snake venom phosphodiesterase-I in vitro with respective IC50 values, viz. 122 mM, 698 mM, 722 mM, and 909 mM Choudhary et al. (2004).

2.9. GENE EXPRESSION AND MOLECULAR LEVEL STUDIES

Gene expression (GE) involves creating a functional gene product based on the information stored in DNA. The process of transcription, which is part of GE, converts DNA into Ribonucleic acid (RNA). As an organism grows or reacts to environmental changes, cells can adapt the type and quantity of GE Perdew et al. (2006). In plants, the response to stress signals is precisely managed by transcriptional regulators. Post-translational modification plays a crucial role in regulating the actions of these transcription factors Li and Loake (2016). Gene expression studies on the Symplocos genus involve analysing how genes within these plants are activated or deactivated in response to various conditions or stimuli that will be helpful in further research in the fields of medicine, agriculture and ecology of the genus.

Recent research on the ethanolic extract of S. cochinchinensis on high fructose and saturated fat (HFS) fed insulin resistant rat model was carried out to study and elucidate the molecular mechanism underlying the insulin-sensitising effects of S. cochinchinensis, and the plant extract enhances insulin sensitivity in HFS rat model through the downregulation of SCD1 gene expression and can modulate SREBP-1c dependent and independent hepatic lipid accumulation or simply lipogenesis Antu et al. (2016).

In another study, five compounds, namely Ellagic acid, Damphetamide, Odoroside, RD1 and RD2, were isolated from S. cochinchinensis, and they have shown the ability to alter the mitochondrial gene expression in cervical cancer cells by the induction of oxidative stress. The isolated compounds obtained from the plant induced apoptosis of cancer cells through the downregulation of BCL2, upregulation of BAX and the activation of Caspase 3 in HeLa cells. These studies offer promising results for future studies on S. cochinchinensis in drug development against cervical cancer Rajeshkumar and Dhanabal (2020). A comprehensive study on the antidiabetic properties of S. cochinchinensis extract on high fructose-fed rat models has shown that the extract can inhibit alpha-glucosidase and enhance insulin sensitivity by modifying the gene expression in vivo in rats Antu (2014).

In a study conducted on the methanolic extract from S. sumuntia (SSME) impact on the inflammatory responses in BV2 cells treated with lipopolysaccharide (LPS), the SSME demonstrated significant inhibition of LPS-induced expression of inducible nitric oxide synthase and cyclooxygenase-2, along with a reduction in the production of nitric oxide (NO), a proinflammatory substance. The mechanism responsible for these anti-inflammatory effects of SSME involves suppressing the LPS-triggered activation of mitogen-activated protein kinases (MAPKs), specifically JNK. Additionally, SSME reduced the LPS-induced nuclear translocation of the nuclear factor-κB (NF-κB)/p65 protein, leading to decreased IκB degradation. These findings collectively suggest that SSME holds great promise as a potential and prominent therapeutic candidate for various inflammatory diseases Lim et al. (2022).

2.10. MOLECULAR DOCKING STUDIES

In an ongoing investigation on potential insulin-mimetic agents derived from medicinal plants, 70% ethanolic extract derived from S. cochinchinensis exhibits a stimulating effect on glucose uptake in 3T3-L1 adipocyte cells. Through a targeted isolation process, they identified ten novel hydroxyoleoside-type compounds linked to phenolic acids and monoterpenes, along with four previously known compounds. The structural elucidation of these new compounds relied on extensive spectroscopic analysis, including 1H and 13C NMR, HSQC, HMBC, NOESY, and MS. The researchers determined the absolute configuration of these isolated compounds by employing electronic circular dichroism (ECD) analysis after various chemical reactions, including reactions with dirhodium (II) tetrakis (trifluoroacetate) and dimolybdenum (II) tetraacetate. In an in vitro experiment conducted, novel compounds demonstrated moderate enhancements in the uptake of 2-deoxy-2-[(7-nitro-2,1,3-benzoxadiazol-4-yl) amino]-D-glucose (2-NBDG) in differentiated 3T3-L1 adipocytes. Subsequent investigations assessed their impact on the expression of glucose transporter-4 (GLUT4), its translocation, inhibition of protein tyrosine phosphatase 1B (PTP1B), and the expression of phosphorylated Akt. These findings strongly support the traditional uses of the plant and its active constituents, particularly hydroxyoleoside-type compounds Lee et al. (2019).

3. CONCLUSION

This review article delves into the multiple facets of the Symplocos genus, shedding light on its significance in various domains. It covers phytochemical analysis, ethnobotanical applications, pharmacological credences, gene expression and molecular docking investigations. By synthesising a wealth of research, this review highlights the diverse medicinal and ethnobotanical contributions of Symplocos plants, emphasising their vital role in contemporary society and their relevance, which underscores how Symplocos species are pivotal for the well-being and environmental sustainability. By presenting the multidimensional facts of this genus, it illuminates the relevance of Symplocos genus, serving as a valuable search engine for researchers and herbal practitioners.

AUTHOR CONTRIBUTIONS

All the listed authors contributed to this study and agreed to publish it. JM did the conceptualisation, investigation, and writing of the original draft and KT was involved in review, editing, supervision, and validation. The author(s) read and approved the final manuscript.

CONFLICT OF INTERESTS

None.

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