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Hibiscus syriacus L.: A Critical Review of Medicinal Utility & Phytopharmacology with Mechanistic Approach

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ABSTRACT

Herbal medicine is an ancient form of medicine that has been used by humans for thousands of years. The vital systems of primordial medicines include Ayurveda, Siddha, Unani, and folk medicine and, the most developed and widely practiced medicinal system in India is Ayurveda. Hibiscus species are commonly shrubs, herbs or trees with many useful properties, of which H. syriacus is one of the prime species of the genus. It is endowed as the national flower of South Korea, commonly known as 'Rose of Sharon' and is found along valleys, open slopes, roadsides and sea cliffs. The plant species is used as a medicine in many diseases such as amoebic colitis, hemorrhoids, hemorrhoidal bleeding, migraine, headache, cold, cough, nausea, vomiting, abdominal pain, ascariasis, colitis, diarrhea, dysentery, dyspepsia, gas, stomach ache, hematochezia, ascariasis etc. Several biological activities of the plant are attributed to the presence of various active compounds like botulin, coumarins, fumaric acid, hydroquinone, is vitexin, linoleic acid, nonanoic acid, naringenin acid, Para hydroxybenzaldehyde, palmitic acid, Syracusans A-C, triterpenoids and vanillic acid. Some phytochemicals, including linolenic acid, palmitic acid, hydroxyhibiscone A, hibiscuses D, Syracusans A, pentacyclic triterpene esters, triterpenoid, nonanoic acid, anthocyanins, and others, are responsible for its biological importance like anti-cancer, anti-aging, anti-depressant, anti-fungal, anti-melanogenic, anti-oxidant, cytoprotective, neuroprotective, etc., Detailed information extracted by reviewing the medicinal utilities & Phyto-pharmacological properties, provide elaborated evidences for the application of H. syriacus in many ailments.

Keywords: Hibiscus Syriacus, Phytoconstituents, Ethno-Medicinal, Pharmacology, Medicinal Uses.

INTRODUCTION

In the modern world, as people become more aware of the strength and side effects of synthetic pharmaceuticals, there is an increasing interest in natural product cures. Throughout history, herbal-based medicines have been used to treat a variety of infectious illnesses, and several scientific investigations have underlined the importance and contribution of various plant species. Ayurvedic as well as, natural herbs had been used since ancient times by all the civilizations in history. Herbal remedies have shown modest growth in recent decades [1]. According to the World Health Organization, traditional medicines are used by more than 80% of the world's population for primary healthcare [2]. *Hibiscus* has around 250 species that are extensively dispersed throughout the world's tropical and subtropical climates, with approximately 40 species found in India. Many species are grown for their decorative value. *H. syriacus* is an important species in the genus, which have great economic and medicinal value and is also used in beverages, in Asian countries [3]. It is used against many diseases such as amoebic colitis, ascariasis, abdominal pain, cold, cough, colitis, dermophytes, diarrhoea, dysentery, dyspepsia, gas, haemorrhoids, haematochezia, haemorrhoidal bleeding, headache, itchiness, migraine, nausea, psoriasis, painful skin diseases, stomach ache, scabies, ulcers, vomiting, vertigo etc. It also contains numerous secondary metabolites which have anti-inflammatory, anti-bacterial, anti-fertility, anti-fungal, anti-oxidative, anti-hypertensive and hypoglycemic like biological activities [4].

Currently, the anti-proliferative effect of root bark against cancer cells has recently been discovered, and various triterpenoids have been identified as active chemicals responsible for the activity [5]. Although, several research works have been already performed previously, but a comprehensive review is still lacking which may aid in future research. The current study has been attempted to summarise the most recent knowledge on pharmacological actions, ethnomedicinal and phytochemical properties of *H. syriacus*, which in-turn will be valuable for future implications. The study will deliver detailed authentication for the application of the plant in various maladies.

METHODOLOGY

This review article was created by combining and evaluating existing studies on therapeutic applications, Phyto-constituents, and scientific validation of *H. syriacus* L. A total of 70 published publications were consulted using several data sources, including PubMed, Google Scholar, Science Direct, Web of Science, Scopus, and among others. Only published publications in English were chosen for performing search targets across several databases using a combination of key phrases including, *H. syriacus*, ethno-pharmacology, Phyto-chemistry, pharmacological terms such as anti-microbial, anxiolytic, and anti-oxidant capabilities, etc. The literature search in this paper was limited to scientific publications included in the above-mentioned databases that may be available to the scientific community for reference, though we acknowledge that there may be some additional data in less accessible forms such as unpublished thesis and reports that were not included in this study. All of the previously published data is presented in two tables (Phyto-constituents construction and pharmacological activity) and five figures. Chemical components reported from the species are provided, together with their IUPAC names, chemical and structural formulas, and are drawn and validated by PubChem.

COMPREHENSIVE LITERATURE-BASED INFORMATION ON *HIBISCUS SYRIACUS L.*

Morphological description

It is a shrub or small tree, 4 m tall. Stems erect or ascending, sparsely to moderately hairy when young, becoming globous or nearly so with age. Leaves stipulate, petiole densely hairy adaxially. Inflorescence has solitary flowers or few-flowered clusters in the axil of distal leaves. Flowers horizontal or ascending, sometimes double, pedicel 1.5 cm long, minutely, densely, stellate-hairy, epicalyx bracts 7 or 8, 0.9-2.2 cm long, linear or narrowly oblanceolate, margin not ciliate, densely stellate-hairy throughout, calyx lobed, widely campanulate, 1.6-2 cm long, lobes triangular, apices sharp or short-acuminate, minutely and thickly stellate-hairy throughout, corolla broadly funnel shape, staminal column 2.5-3.5 cm long, white, carrying filaments virtually throughout, free section of filaments not secund, generally 1.5-3 mm long, style 8 mm long, white, branches sometimes of unequal lengths, stigma white. Fruits capsules, 1.5-2.5 cm long, greenish tan, ovoid, apex apiculate, minutely, densely stellate-hairy. Seeds 5-8 per locule, 4-5 mm long, reniform-ovoid, laterally flattened, reddish brown, laterally globous, dorsally long, hairy, hair straight, reddish orange in colour [6,7].

Distribution and Habitat

This species of *Hibiscus* is native to China & Taiwan and widely distributed in Belgium, Cameroon, Cuba, Ecuador, France, Georgia, Greece, India, Italy, Japan, Korea, Mexico, Tadzhikistan, Uzbekistan, United States of America, Vietnam and Yugoslavia [7,8]. It has been grown in Fujian, Guizhou, Hainan, Hebei, Henan, Hubei, Hunan, Jiangxi, Shaanxi, Shandong, and Xizang since ancient times [9]. This species is found along streams, disturbed areas, forest edges, hillsides, in valleys, open slopes, roadsides and sea cliffs, at an elevation range of 2600 m [8-11]. The detailed taxonomical features are shown in Figure 1.

Vernacular names of *Hibiscus syriacus* L.

H. syriacus has various vernacular names, which vary area, region and country-wise. Linnaeus called *H. syriacus* or Althea frutex, sweet job in Bengali, after claiming that the plant was native to Syria. The wonderful name 'Rose of Sharon' was most likely given for the same purpose, but it is now thought to have originated in China. Shrubby Althea is another name for it that is used in some areas. It grows to approximately 2.7 metres and has gorgeous white, blue, or mauve blooms that are either solitary or double. They appear in the axils of the leaves, much like hollyhocks. It has been widely planted, even as far north as Ontario, and given various descriptive names, as have other *Hibiscus* species [12]. Figure 2 depicts some of the World's Vernacular names, along with their respective languages and nations.

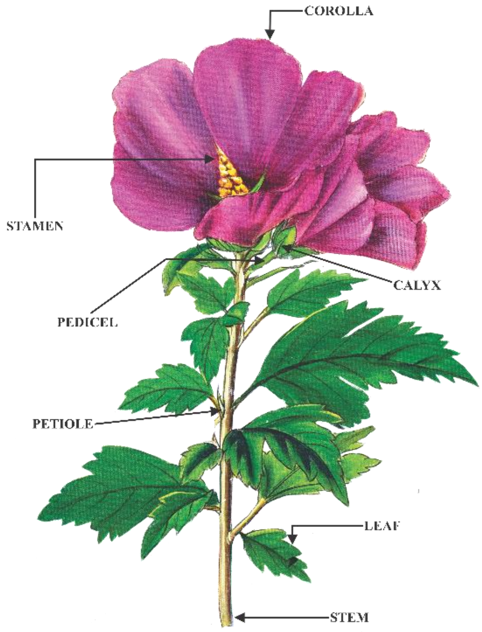


Figure 1: Foliage of *H. syriacus*

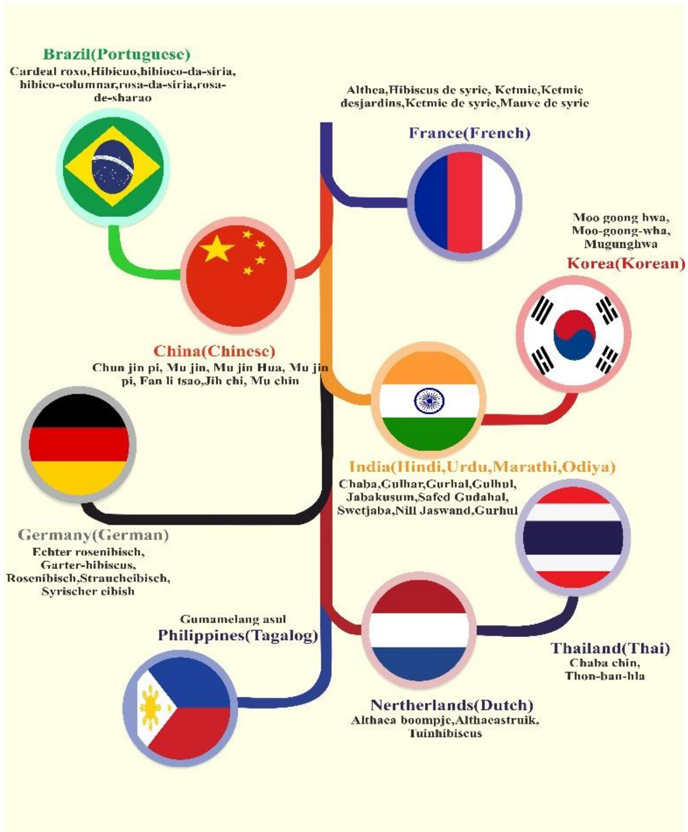
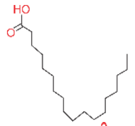
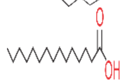
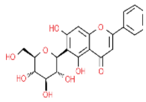
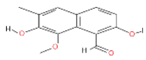
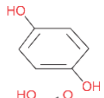
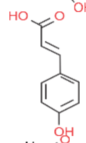
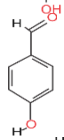
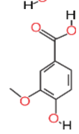
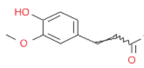
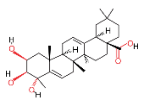
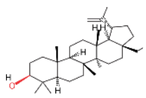
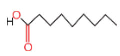
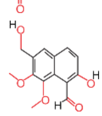
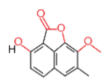
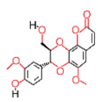


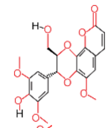
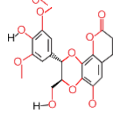
Figure 2: Vernacular names of *H. syriacus* across the globe

AN OUTLINE OF PHYTO-CONSTITUENTS

Phytochemicals and their derivative compounds are becoming more widely recognised as effective treatments for a wide range of illnesses. Some are actively participating in various therapies such as Syracusans A-C, a chemical marker of H. syriacus, was being revealed as an anti-oxidant and enzyme inhibitory agents, among other things. Chemiosmosis A, C & D are anti-oxidant agents, whereas nonanoic acid possess antifungal property. In addition to the phytochemicals indicated in Table 1, the present review found numerous other compounds.

Table 1: Major Chemical Groups & Compounds of *H. syriacus*

S. No.	Phyto-constituents	Chemical Formula	IUPAC Name	Class of Compounds	Structure	Properties	References
1.	Linoleic acid	$C_{18}H_{32}O_2$	(9*Z*,12*Z*)-octadeca-9,12-dienoic acid	Fatty acid		Anti-aging	13
2.	Palmitic acid	$C_{16}H_{32}O_2$	-	Fatty acid		Anti-aging	13
3.	Isovitexin	$C_{21}H_{20}O_{10}$	5,7-dihydroxy-2-(4-hydroxyphenyl)-6-[(2*S*,3*R*,4*R*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one	Flavones		Enzyme inhibitory	14
4.	Syracusan A	$C_{13}H_{12}O_4$	2,7-dihydroxy-8-methoxy-6-methylnaphthalene-1-carbaldehyde	-		Enzyme inhibitory	14
5.	Hydroquinone	$C_6H_6O_2$	benzene-1,4-diol	Depigmenting agent		Neuroprotective	15
6.	Naringenin acid	$C_9H_8O_3$	(E)-3-(4-hydroxyphenyl)prop-2-enoic acid	Flavanone		Neuroprotective	15
7.	p-hydroxybenzaldehyde	$C_7H_6O_2$	2-hydroxybenzaldehyde	Aldehyde		Neuroprotective	15
8.	Vanillic acid	$C_8H_8O_4$	4-hydroxy-3-methoxybenzoic acid	Dihydroxybenzoic acid derivative		Neuroprotective	15
9.	Fumaric acid	$C_{10}H_{10}O_4$	(*E*)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid	Hydroxycinnamic acid		Neuroprotective	15
10.	Triterpenoids	$C_{29}H_{44}O_5$	(4*aS*,6*aS*,6*aS*,6*bR*,9*S*,10*S*,11*S*,12*aR*,14*bS*)-9,10,11-trihydroxy-2,2,6*a*,6*b*,9,12*a*-hexamethyl l-1,3,4,5,6,6*a*,7,10,11,12,13,14*b*-dodecahydropicene-4*a*-carboxylic acid	Tetracyclic and pentacyclic compounds		Anti-cancer	16
11.	Botulin	$C_{30}H_{50}O_2$	(1*R*,3*aS*,5*aR*,5*bR*,7*aR*,9*S*,11*aR*,11*bR*,13*aR*,13*bR*)-3*a*-(hydroxymethyl)-5*a*,5*b*,8,8,11*a*-pentamethyl-1-prop-1-en-2-yl-1,2,3,4,5,6,7,7*a*,9,10,11,11*b*,12,13,13*a*,13*b*-hexadecahydrocyclopenta[a]chrysen-9-ol	Terpenoid		Anti-cancer	16
12.	Nonanoic acid	$C_9H_{18}O_2$	-	Fatty acid		Anti-fungal	17
13.	Syracusan B	$C_{14}H_{14}O_5$	2-hydroxy-6-(hydroxymethyl)-7,8-dimethoxynaphthalene-1-carbaldehyde	-		Anti-oxidant	18
14.	Syracusan C	$C_{13}H_{10}O_4$	5-hydroxy-11-methoxy-10-methyl-2-oxatricyclo[6.3.1.0^{4,12}]dodeca-1(11),4,6,8(12),9-pentaen-3-one	-		Anti-oxidant	18
15.	Chemiosmosis A	$C_{20}H_{18}O_8$	(2*R*,3*R*)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-5-methoxy-2,3-dihydropyrano[3,2-h][1,4]benzodioxin-9-one	-		Anti-oxidant	19

16.	Chemiosmosis C	$C_{21}H_{20}O_9$	(2*R*,3*R*)-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(hydroxymethyl)-5-methoxy-2,3-dihydropyrano[3,2-h][1,4]benzodioxin-9-one	-		Anti-oxidant	19
17.	Chemiosmosis D	$C_{21}H_{20}O_9$	(2*S*,3*S*)-2-(4-hydroxy-3,5-dimethoxyphenyl)-3-(hydroxymethyl)-5-methoxy-2,3-dihydropyrano[3,2-h][1,4]benzodioxin-9-one	-		Anti-oxidant	19

Source: PubChem

Ethnomedicinal Usages of *Hibiscus Syriacus* L.

The medicinal herbs have considerable importance to be used as food material as well as, for the treatment of many diseases. They provide minerals, proteins and enzymes, which act as various structural and functional components in our body. On the basis of ethnomedicinal, pharmacological and phytochemical information available, this study evaluates the efficacy of *H. syriacus* in the treatment of a variety of disorders and risk factors. Different parts of the plant are being used in Indian and other traditional medicine systems for the treatment of various diseases such as abdominal pain, ascariasis, colitis, diarrhea, dysentery, dyspepsia, gastro-intestinal dysfunctions etc. [11,20-26]. in Figure 3. Henceforth, the species plays an important role in traditional medicinal systems mentioned in Figure 4.

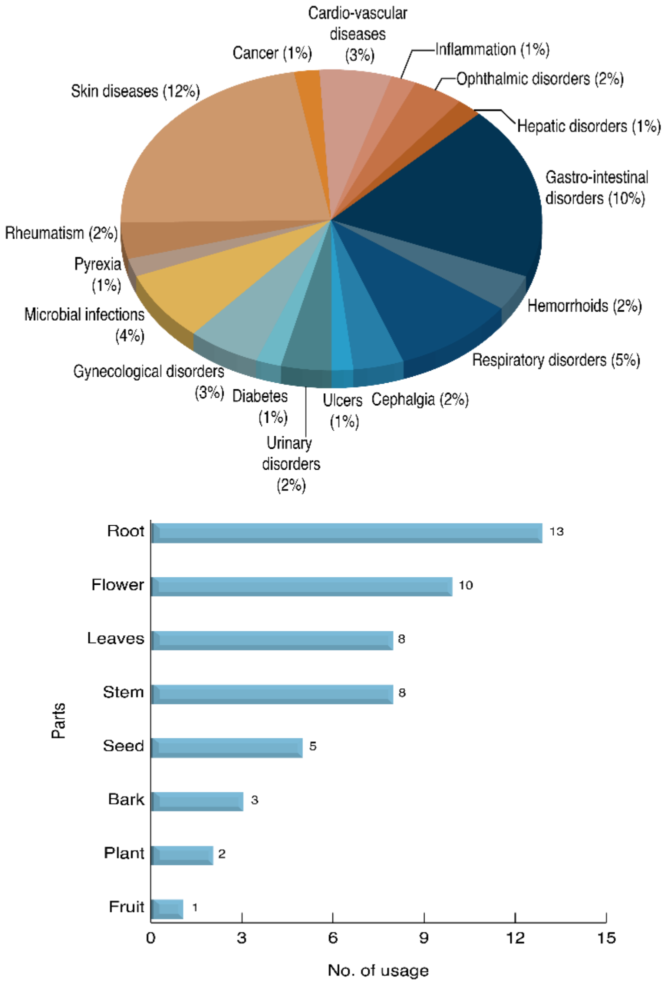


Figure 3: a & b- Different Parts of *Hibiscus syriacus* L. Used Globally for Various Medicinal Purposes

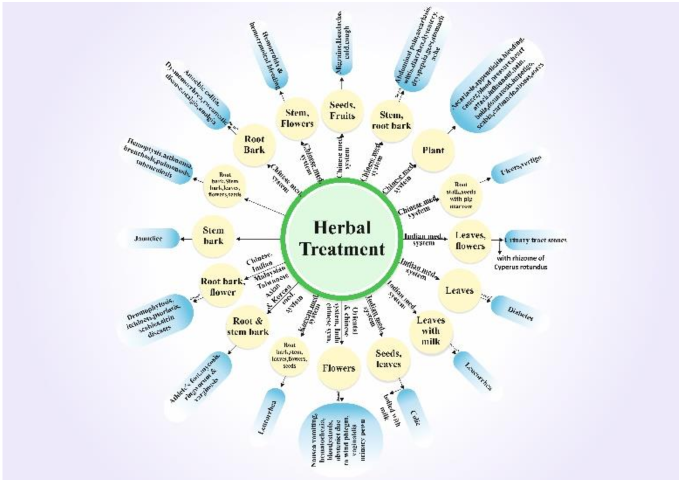


Figure 4: Various Medicinal Importance of *H. syriacus* L

Scientific Evidences

The active phytochemicals and secondary metabolites found in *H. syriacus* plant extracts and isolated compounds include linolenic acid, palmitic acid, hydroxyhibiscone A, hibiscuses D, Syracusans A, pentacyclic triterpene esters, triterpenoid, nonanoic acid, anthocyanins, and others, which are responsible for its pharmacological effects and related properties like anti-aging, anti-cancer, anti-depressant, anti-fungal, anti-melanogenic, anti-oxidant, cytoprotective, etc., mentioned in Table 2.

Mechanistic insight of various pharmacological properties of *Hibiscus syriacus* l.

Hibiscus syriacus L. contains anthocyanin, which has anti-melanogenic, cytoprotective, anti-inflammatory, enzyme inhibitory, and other biological activities. Anthocyanin reduces MITF and tyrosinase in α-MSH-treated B16F10 cells while, increasing melanin pigmentation in Zebrafish larvae. Furthermore, anthocyanin improves the viability of HaCaT keratinocytes in the presence of H_2O_2. In BV2 microglia cells, anthocyanin inhibits the LPS/ATP-mediated NLRP3 inflammasome, NF-κb and ER stress-induced Ca^{2+} buildup, mitochondrial ROS generation, and IL-1β and IL-18 release. The action of mushroom tyrosinase was significantly reduced by anthocyanin (*in vitro*). A minor reduction in mitochondrial impact was detected at higher concentrations (over 200 µg/ml) of anthocyanin, however this did not result in an increase in the population of dead cells, cell viability, or total cell counts. In B16F10 cells, melanin synthesis was reduced both extracellularly and intracellularly. Figure 5 depicts a diagram-based mechanistic perspective of anthocyanin from *H. syriacus* L. numerous pharmacological actions.

Table 2: Pharmacological Evidences of Different Solvents & Isolated Compounds from *H. syriacus* L.

S. No.	Parts/Extract/ Isolated Compounds	Dose/Routes of Administration	Pharmacological Activity/Model/ Method	*Interpretations*	References
1.	Root & stem bark/ Aqueous, linoleic acid (LA) & palmitic acid (PA)	HSL 250µg/ml); LA(0.25 µg/ml) & PA (0.25&2.5 µg/ml)/p.o.	Anti-aging /mice/ *in vitro* & *in vivo*	HSL↑ type I procollagen expression, ↓matrix metalloproteinase-1 (MMP-1), mitogen-activated protein kinases (MAPKs), protein-1 (AP-1) expression and intracellular ROS ;↓ mRNA level of MMP-1 , ROS production & ↑ mRNA level of type I procollagen	13
2.	Root bark/ hydroxyhibiscone A, hibiscone D		Anti-aging /*in vitro*/Human neutrophil elastase (HNE) assay	IC50 (5.2 & 4.6 µM)	27
3.	Flower & leaves/ Petroleum ether (PEE), chloroform (CE), ethyl acetate (EAE), n-butanol (BE) and water (WE)	500 µg/ml	Anti-cancer/MCF-7, BALL-1, Huh-7 and HeLa/ *in vitro*/MTT assay	PEE: IC50 (32.16->250 µg/ml); CE (34.32-219.40 µg/ml)	28
4.	Root bark/syriacusins A		Anti-cancer/ ACC62 (melanoma), MCF7 (breast), NCI-H23 (lung), ACHN (renal), PC-3 (prostate), SW620 (colon) & SF539 (central nervous system) human tumor cell lines/*in vitro*.	ED50: ACHN (1.46 µg/ml); SF539 (1.53 µg/ml), SW620 (1.56 µg/ml) & UACC62 (1.73 µg/ml)	18
5.	Root bark/pentacyclic triterpene esters (1,2)		Anti-cancer / UACC62 (melanoma), MCF7 (breast), NCI-H23 (lung), ACHN (renal), UO-31 (renal), PC-3 (prostate), SW620 (colon), HCT15 (colon) and SF539/ *in vitro*	ED50: 1-ACHN (1.2 µg/ml), PC-3 (1.6 µg/ml), SW620 (1.1 µg/ml), HCT15 (0.8 µg/ml), SF539 (1.4 µg/ml), 2- SW620 (1 µg/ml) & HCT15 (1.3µg/ml) cell lines	29
6.	Root bark/triterpenoid		Anti-cancer/Human lung adenocarcinoma cell line A549 / MTT assay	12-IC50 (4.3 µM)	15
7.	Root bark/triterpenoid betulin (K02) and its derivatives (K03, K04, and K06)		Anti-cancer/breast cancer cell lines MDA-MB-231 and HBL100 / MTT assay	Induced apoptosis	16
8.	Root bark/ Ethanol	HSR (100 & 200 mg/kg); (200 and 400mg/kg)	Anti-depressant/ mice/in vivo/sucrose preference test (SPT), forced swimming test (FST) and tail suspension test (TST)	SPT↑ sucrose; FST and TST ↓immobility time;↓corticosterone;↑serotonin	30
9.	Root/Nonanoic acid		Anti-fungal/trichophyton mentagrophytes /*in vitro*/agar diffusion assay	Inhibition zone (16 mm)	17
10.	Anthocyanins	25, 100 & 400 µg/ml	Anti-melanogenic/α-MSH-treated B16F10 cells, invitro and Zebrafish larvae, invivo.	↓Microphthalmia-associated transcription factor (MITF) and tyrosinase &↑melanin pigmentation	31
11.	Stem & root bark/Aqueous	250 µg/ml	Anti-oxidant /*in vitro*/DPPH, ABTS assay	Inhibition (10.7 & 56.2%)	13
12.	Root bark/Naphtha lenes (Syracusans A-C)		Anti-oxidant /rat liver microsomes/lipid peroxidation assay	IC50 (0.54, 5.90 & 1.02 µg/ml)	18
13.	Root bark/Pentacyclic triterpene esters		Anti-oxidant /rat liver microsomes/lipid peroxidation assay	IC50 (2.3 & 1.1 µg/ml)	29
14.	Stem & root/ Hydroalcholic		Anti-oxidant/*in vitro*/DPPH	IC50 (1.4 & 2.6 mg/ml) & (3.8 & 6.5 mg/ml)	32
15.	Root bark/ coumarin(V,III)		Anti-oxidant /rat liver microsomes/lipid peroxidation assay	IC50 V(0.7µg/ml) ,III (1.4 µg/ml).	19

16.	Petals/Anthocyanin	100, 200 & 400 μg/ml	Cytoprotective/ HaCaT keratinocytes(H2O2 induced oxidative stress)*in vitro*	↑Viability HaCaT keratinocytes	18
17.	Root bark/Coumarins(I,II)		Enzyme inhibitory /Monoamine oxidase/*in vitro*	IC50 I(44.5μg/ml), II(19.4μg/ml).	19
18.	Leaves/ Compounds (I-XV)		Enzyme inhibitory/α-glucosidase /*in vitro*	IC50 VII (39.03 mg/l), IX(32.12 mg/l)	33
19.	Anthocyanins		Enzyme inhibitory/ Tyrosinase/*in vitro*	↓mushroom tyrosinase effect *in vitro*	31
20.	Root bark/ Ethanol	10,50, 100 μg/ml	Neuroprotective/SK-N-SH human neuroblastoma (Corticosterone treated)/*in vitro*	↑ Cell viability,↑ ATP levels , ↑MMP.↓ROS levels, ↓caspase -3/7, ↓mRNA expression levels of IL-1β, IL-6, IL-8, and TNF-α	30
21.	Flower/ Polyphenols(I-V)		Neuroprotective/SH-SY5Y cells (H2O2 induced oxidative stress & LPS-induced neuro-inflammation)/*in vitro*	↓ROS, MDA;↑SOD, GSHPx , CAT;↓ TNF-α, IL-1β and IL-6 &↓ LPS-induced cellular damage, ↑ Mrna levels of Spy, BDNF , NGF	34
22.	Leaves/ Ethanol		Wound healing/human HaCaT keratinocytes, human dermal fibroblasts (HDF)/*in vitro*	↑G1 cells, cell migration &↑pro-collagen type I , ↑fibronectin ,↑wound contraction	35
23.	Anthocyanin		Cytotoxicity/B16F10 cells /*in vitro*/ MTT assay	At higher concentrations (over 200 μg/ml) slightly ↓ mitochondrial activity Did not increase population of dead cells, sustained cell viability and total cell numbers ↓ extracellular and intracellular melanin production in B16F10 cells	31
24.	Stem & root bark/ Aqueous	10, 100 & 250 μg/ml	Cytotoxicity/UVB-irradiated normal human dermal fibroblasts (NHDFs)/*in vitro*/ MTT assay	Viability of cells treated with UVB radiation (144 mJ/cm^2) alone was about 80%, compared to that in non-irradiated cells. Not cytotoxic effect at tested concentrations	13
25.	Leaves/ Ethanol		Cytotoxicity/HaCaT keratinocytes , human dermal fibroblasts (HDF)/ *in vitro*/MTT assay	Slightly or very less cytotoxic	35
26.	Petals/Anthocyanin	100-1000 μg/ml	Anti-inflammatory/ NLRP3 inflammasome in BV2 microglia cells	↓NLRP3 inflammasome in BV2 microglia cells, NF- κ B- and ER stress-induced Ca^{2+} accumulation and mitochondrial ROS production	36

CONCLUSION

Findings suggested that *H. syriacus* possess significant biological potential. The review deals with the detailed information associated with ethnomedicinal & phytopharmacological properties of the plant which suggests its protective role in many diseases. Its various ethnomedical uses vary from country to country, and some important medical uses such as eczema, scabies, and dysentery are almost common. *H. syriacus*, as an herbal medicine, has attracted researchers for decades due to its therapeutic properties. More importantly, there is no research to prove its adverse effects or toxicity. Thus, information regarding phytochemical and phytopharmacological activities appears to be very useful and may led to development of novel therapeutic agents for diseases which can be explored further for commercial purposes. However, there are many features, which need to be focused like well-controlled clinical trials using large sample size (test group) for evaluating the efficacy and toxicity; and the molecular mechanism associated with the biological study of plant. The current evidence is mainly limited to the correlation between the identified plant chemical constituents and the mode of action of any pharmacological activity. However, study into the mechanism of action should pave the way for the development of new medications with superior pharmacological qualities. This may be accomplished by molecular model studies including the interaction of H. syriacus bioactive phytochemicals with their respective molecular targets, and the extract can be further studied in the future as a source of valuable phytochemicals in the pharmaceutical business.

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Conflict of Interest

None declared.

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