# International Journal of Biological Chemistry

ISSN 1819-155X

Academic Journals Inc.

www.academicjournals.com

International Journal of Biological Chemistry 9 (6): 318-331, 2015
ISSN 1819-155X / DOI: 10.3923/ijbc.2015.318.331


# A Review of the Medicinal Plants of Genus *Orthosiphon* (*Lamiaceae*)

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## ABSTRACT

In the genus *Orthosiphon* (*Lamiaceae*), *Orthosiphon aristatus*, *Orthosiphon pallidus*, *Orthosiphon thymiflorus*, *Orthosiphon stamineus* are widely used in traditional medicine to prevent different diseases such as diabetes, kidney stone, edema, rheumatism, hepatitis, hypertensive and jaundice. A different variety of phytoconstituents has been isolated from the *Orthosiphon* species which include monoterpenes, diterpenes, triterpenes, saponins, organic acid and flavonoids compound. Antidiabetic, anti-inflammatory, antioxidant, hepatoprotective, analgesic and nephroprotective activities have been reported in the plant extract and phytoconstituents. Hence, the purpose of this review is to provide a comprehensive report about the *Orthosiphon* genus based on its toxicity in order to identify its therapeutic potential and future prospects for betterment of research.

**Key words:** *Orthosiphon*, phytochemistry, pharmacological activities, toxicity studies

## INTRODUCTION

The genus *Orthosiphon* was coined from two Latin words, iorthos and siphon. The words referred to straight while siphon meant tube like or cylindrical. These two words actually referred to the straight tube like flowers that were produced by the *Orthosiphon* species and this was considered as one of the main characteristics of the Labiatae or Lamiaceae family (Keng and Siong, 2006).

The genus *Orthosiphon* benth in tribe ocimeae comprises 40 species and was recorded from the old world: in tropical and subtropical Asia including Southern Africa and Madagascar. The species usually occurs in grassland, woodland or forest margins (Sadashiva *et al*., 2013).

Some of these species are important medicinal plants that are used in herbolism and thought to have medicinal properties. Up to date, the genus provided a large number of chemical compounds of which some indicated dynamic pharmacological activity (Sundarammal *et al*., 2012).

*Orthosiphon aristatus* has long history of medicinal use in Indonesia, Malaysia, Southeast Asia, this plant was initially recorded as a treatment for diabetes, kidney stone and hypertension (Matsubara *et al*., 1999; Ohashi *et al*., 2000; Masuda *et al*., 1992; Shibuya, 1999). *Orthosiphon pallidus* is herbaceous shrub native to South East Asia and India has been used to treat urinary lithiasis, edema, fever, influenza, rheumatism, hepatitis and jaundice (Kiruthika and Meenakshi, 2011). *Orthosiphon thymiflorus* used in India to treat cytotoxic, diabetic,

anti-inflammatory and hypertensive (Sundarammal *et al*., 2012; Sini *et al*., 2012; Kavimani *et al*., 1997). *Orthosiphon stamineus* is used to treat diabetes, hypertension, oedema, epilepsy, fever, influenza and jaundice (Arafat *et al*., 2008; Akowuah *et al*., 2005; Ho *et al*., 2010; Awale *et al*., 2003a). The traditional indigenous uses and pharmacology of ethnobotanic herbs provides basic knowledge for further development of medicinal plants and a useful approach for drug discovery (Heinrich and Gibbons, 2001).

The genus *Orthosiphon* comprises an impressive number of species some of which have been used in traditional medicine. Hence the purpose of this review is to provide a comprehensive report about the genus based on its toxicity in order to identify its therapeutic potential and future prospects for betterment of research. This will be possible through analysis of collected data related to botany, local and traditional uses, pharmacology and toxicology of *Orthosiphon* species.

## BOTANICAL DESCRIPTION

*Orthosiphon* plants are herbaceous shrubs which grow to a height of 1.5 m. *Orthosiphon* is a popular garden plant with whitish flower having unique identification and bluish filaments resembling a cast's whiskers. *Orthosiphon pallidus* Royle ex Benth, *O. aristatus, O. thymiflorus* and *O. stamineus* are commonly used in traditional medicines.

The morphology characteristics of *O. pallidus* are as follows: perennial herb with a woody root stock not aromatic. Stems are diffusely branched ascending erect 10-35 cm, slender, quadrangular, velvety or almost hairless. Leaves are ovate, 1-3.5×1.2, palegreen, slightly fleshy, nearly entire to saw-toothed, gland-dotted, stalked, velvety to almost hairless. Flower stalks are 2 mm in flower and up to 6 mm in fruit, velvety in lower part, upper lobe ovate-circular.

*Orthosiphon aristatus* is slender, smooth or hairy undershrub 30-60 cm high. Leaves in distant pair, narrowed in to the stalk ovate, 5-10 cm long, pointed at bath ends, coarsely toothed margins. The flowers are borne with extreme lax racemes. The calyxes of flowers have naked throat and bell shape with two slender lower teeth. Corolla is purple-white in color with 2.5 cm long and smooth. Nutlets are oblong and compressed.

*Orthosiphon thymiflorus* straggling, somewhat shrubby perennial herb up to 1.5 m tall not or hardly aromatic. Stems several ascending to erect to 4-angled, normally well branched, retrorsely pubescent along the angles and sometimes with dense hairs. Leaves are usually oval or elliptic with 1.4-4.5 cm long but larger in well shaded plants, glandular punctuate and hairless/pubescent mostly along the veins beneath, margin scalloped or toothed, petiole up to 25 mm long.

*Orthosiphon stamineus* is a perennial herb. It attains 0.3-1.5 m high and 4 angle stem. Leaves are simple, opposite, ovate, oblong lanceolate, elliptic orrhamboid, which have 2-4 cm wide and 4-7 cm long. The flowers are white, blue or violet.

## TRADITIONAL USES OF SELECTED SPECIES

The plants of genus *Orthosiphon* have been used by the various parts of Asia and Africa. Traditional uses of selected *Orthosiphon* species (Table 1) point to their importance especially in the treatment of diabetes, kidney stone, influenza, hepatitis and jaundice.

In order to cover all published botanical names, a list of synonyms based on the relevant taxonomic literature is provided (Table 2). The list encompasses representatives of the genus that have ethanomedicinal relevance according to the present comprehensive literature review.

Table 1: Traditional uses, pharmacological and biological activities of selected *Orthosiphon* species

| Species | Region | Plant part | Traditional uses | Pharmacological activity | Active extract | Reference |
|---|---|---|---|---|---|---|
| *Orthosiphon aristatus* | Indonesia and Malaysia | Dried leaves and tops of stem | Used in hypertension and diabetes | Antibacterial activity | Aqueous extract | Chen *et al*. (1989) |
| | Indonesia and Malaysia | Leaves | Used as a diuretics | Diuretic effects | Aqueous extract | Chen *et al*. (1999) |
| | Indonesia | Dried leaves | Used in hypertension Used in diabetes | Antihypertensive | Water decoction | Matsubara *et al*. (1999), Ohashi *et al*. (2000), Masuda *et al*. (1992) and Shibuya *et al*. (1999) |
| | Southeast Asia and Australia | Dried leaves | Treatment of renal inflammation used in Kidney stone | Antioxidant and anti-inflammatory | Methanol, ethanol and water extract | Di *et al*. (2013) and Hsu *et al*. (2010) |
| | Southeast Asia and Australia | Dried leaves | Used in dysuria | Antioxidant and anti-inflammatory | Hexane extract | Di *et al*. (2013) and Hsu *et al*. (2010) |
| *Orthosiphon pallidus* | Africa and South-East Asia | Aerial part | Used to treat urinary lithiasis, edema, influenza, rheumatism, hepatitis and jaundice | Anticancer (51.74% cytotoxicity) | Absolute alcohol | Ashokan and Muthuraman (2011) |
| | Baluchistan, Arabia, India (Kashmir, Punjab, West Bihar and Southwards to Travancore) | Whole plant (coarse powder) | Treatment of neurasthenia, general tonic and aphrodisiac | Lower the blood pressure and inhibition of heart of pithed frog | Absolute alcohol and Basu and Singh | Basu and Sing (1956) (1956) |
| *Orthosiphon thymiflorus* | Aliyar foot hills of valparal, Coimbatore, Tamilnadu | Fresh leaves | Antioxidant | Antioxidant, cytotoxic and vasodialative | Hydrodistilation, Clevenger and apparatus | Sundarammal *et al*. (2012) |
| | Attapady palakkad and Kerala | Powdered plant material | Anticancer | Cytotoxic activity, anti diabetic, antihepatotoxic, antibacterial and hypertensive | Imbbibition, meceration and percolation in chloroform | Sini *et al*. (2012) |
| | Tirunelveli and Tamilnadu | Whole plant | Aquaretic | Diuretic activity and anti-inflammetory | Meceration in boiling water | Kavimani *et al*. (1997) |
| | Maruthamalal hills Coimbatore and Tamilnadu | Dried leaves | Larvacidal | Larvacidal activity | Hexane, chloroform, ethyl acetate, acetone and methanol | Kovendan *et al*. (2012) |
| *Orthosiphon stamineus* | Malaysia, Indonesia and Japan | Leaf part (fresh) | Treating stone diseases and gout, Java tea and decocted leaves as diuretics | Bladder inflammation, food preservative, inhibitory effect in growth of calcium crystal, diabetes, hypertension, rheumatism, tonsillitis, menstrual disorder, urinary lithiasis, biliary litiasis, epilepsy, oedema, eruptive fever, hepatitis, jaundice, influenza, gonorrhoea, syphilills, renal calculus, gallstone, diuretics, inhibitory activity of nitric oxide and body detoxification | Methanol, Chloroform, Ethyl acetate and Acetone | Awale *et al*. (2003a, b), Hossain and Ismail (2013), Akowuah *et al*. (2005), Ho *et al*. (2010), Arafat *et al*. (2008), Akowuah *et al*. (2005) and Hossain and Ismail (2013) |
| | Myanmar | Leaf part (dried) | Antidiabetics to treat urinary tract and renal diseases | Diabetes, urinary tract and renal diseases | Methanol | Awale *et al*. (2003a, b, 2004) and Han *et al*. (2008) |
| | China, Indonesia and Veitnam | Arial part | | Urinary lithiasis, edema, eruptive fever, influenza, hepatitis and jaundice | Methanol | Awale *et al*. (2003b, 2004) and Paton *et al*. (2004) |

Table 2: Representatives of genus *Orthosiphon* used in traditional medicine and their synonyms

| *Orthosiphon* species | Synonyms |
|---|---|
| *Orthosiphon adenocaulis* | *Orthosiphon adornatus*, *Orthosiphon affinis* Benth, *Orthosiphon adscendence* and *Orthosiphon albiflorus* |
| *Orthosiphon allenii* | *Orthosiphon amabilis*, *Orthosiphon ambiguous* Bolus and *Orthosiphon angolensis* |
| *Orthosiphon aristatus* var. *aristatus* | *Orthosiphon asperus*, *Orthosiphon atacorensis*, *Orthosiphon australis* and *Orthosiphon bartsioides* |
| *Orthosiphon biflorus* | *Orthosiphon bodinieri*, *Orthosiphon bolusii*, *Orthosiphon bracteatus*, *Orthosiphon brevicaulis*, *Orthosiphon buchananii* and *Orthosiphon bracteotus* |
| *Orthosiphon bullosus* | *Orthosiphon buryi*, *Orthosiphon calaminthoides*, *Orthosiphon cameronii*, *Orthosiphon canescens and Orthosiphon capitatus* |
| *Orthosiphon cladotrichos* | *Orthosiphon cleistocalyx*, *Orthosiphon colouratus*, *Orthosiphon comosus* Wight and *Orthosiphon comosus* Baker |
| *Orthosiphon cuanzae* | *Orthosiphon debilis*, *Orthosiphon decipiens*, *Orthosiphon degasparisianum* and *Orthosiphon diffuses* |
| *Orthosiphon discolor* | *Orthosiphon dissitifolius*, *Orthosiphon ehrenbergii*, *Orthosiphon ellenbecki* and *Orthosiphon elliottii* |
| *Orthosiphon ellipticus* | *Orthosiphon emirnensis* and *Orthosiphon engleri* Perkins |
| *Orthosiphon ferruginous* | *Orthosiphon foliosus* |
| *Orthosiphon fruticosus* | *Orthosiphon gerrardii*, *Orthosiphon glabratus* Benth, *Orthosiphon* glabratus var. *Palviflorus (Benth)* and *Orthosiphon glabrascene* |
| *Orthosiphon glandulosus* | *Orthosiphon glutinosus Chiov*., *Orthosiphon gofensis S. Moore* and *Orthosiphon grandiflorus* Bold. |
| *Orthosiphon hanningtonii* | *Orthosiphon helenae* Buscal, *Orthosiphon* heterochrous Briq, *Orthosiphon heterophyllus* Gurke, *Orthosiphon hildebrandtii* Vatke, *Orthosiphon* hildebrandtii Baker, *Orthosiphon* hispidus Benth., *Orthosiphon hockii*, *Orthosiphon holubii* and *Orthosiphon homblei* |
| *Orthosiphon humbertii* | *Orthosiphon humilis*, *Orthosiphon incisus* and *Orthosiphon inconcinnus* |
| *Orthosiphon incurvus* | *Orthosiphon inodorus*, *Orthosiphon iodocalyx* Briq, *Orthosiphon* johnstonii Baker, *Orthosiphon kelleri Briq*, *Orthosiphon kirkii* Baker and *Orthosiphon labiatuss* |
| *Orthosiphon lanatus Doan* | *Orthosiphon lanceolatus* Gurke, *Orthosiphon* lanceolatus, *Orthosiphon latidens*, *Orthosiphon laurentii*, *Orthosiphon liebrechtsiauum*, *Orthosiphon linraris* Benth, *Orthosiphon* longipes Baker, *Orthosiphon* macranthus, *Orthosiphon macrocheilus*, *Orthosiphon macrophyllus*, *Orthosiphon mairei*, *Orthosiphon malosanus* Baker, *Orthosiphon* marmoritis, *Orthosiphon marquesii* Briq., *Orthosiphon* menthifolius Briq and *Orthosiphon massinensis* |
| *Orthosiphon miserabilis* | *Orthosiphon molis* Baker, *Orthosiphon* mombasicus, *Orthosiphon mossianus*, *Orthosiphon muddii*, *Orthosiphon natalensis* and *Orthosiphon neglectus* |
| *Orthosiphon nigripunctatus* | *Orthosiphon nyasicus*, *Orthosiphon obbiadensis*, *Orthosiphon oblongifolius*, *Orthosiphon obscurus* and *Orthosiphon omatus* |
| *Orthosiphon parvifolius* | *Orthosiphon pascuensis*, *Orthosiphon persimilis*, *Orthosiphon petiolaris*, *Orthosiphon petrensis*, *Orthosiphon physocalycinus* and *Orthosiphon pretoriae* |
| *Orthosiphon pseudoaristatus* | *Orthosiphon pseudomatus*, *Orthosiphon pseudorubicundus*, *Orthosiphon pseudoserratus*, *Orthosiphon rabaiensis*, *Orthosiphon reflexus*, *Orthosiphon rehmannii*, *Orthosiphon retinervis* and *Orthosiphon rhodesianus* |
| *Orthosiphon robustus* | *Orthosiphon rogersii* and *Orthosiphon roseus* |
| *Orthosiphon rubicundus Benth* | *Orthosiphon rubicundus* var. canescene |
| *Orthosiphon rubicundus* var. *hainanensis* | *Orthosiphon rubicundus* var. *hohenackeri*, *Orthosiphon rubicundus* var. *macrocarpus,* *Orthosiphon rubicundus* var. *mollissimus* and *Orthosiphon rubicundus* var. rigidus |
| *Orthosiphon rubicundus* var. *rubicundus* | *Orthosiphon rufinervis* and *Orthosiphon salagensis* |
| *Orthosiphon sarmentotus* | *Orthosiphon scabridus* |
| *Orthosiphon schimperi* | *Orthosiphon schinzianus*, *Orthosiphon secundiflorus*, *Orthosiphon serratus*, *Orthosiphon shirensis*, *Orthosiphon silvicola*, *Orthosiphon sinensis*, *Orthosiphon somalensis*, *Orthosiphon spicatus Baker*, *Orthosiphon spicatus* Benth, *Orthosiphon* spiralis, *Orthosiphon stamineus*, *Orthosiphon stenophyllus*, *Orthosiphon stuhlmannii*, *Orthosiphon subvelutinus*, *Orthosiphon suffrutescene*, *Orthosiphon tagawae* *Orthosiphon tenuiflorus*, *Orthosiphon tenuifrons*, *Orthosiphon teucriifolius*, *Orthosiphon teucriifolius* var. *galpinianus*, *Orthosiphon teucriifolius* var. *teucriifolius* and *Orthosiphon thorncroftii* |
| *Orthosiphon thymiflorus* | *Orthosiphon thymiflorus* var. *viscosus*, *Orthosiphon tomentosus* Benth, *Orthosiphon* tomentosus De wild, *Orthosiphon tomentosus* var. *glabratus*, *Orthosiphon tomentotus* var. *parviflorus*, *Orthosiphon tomentosus* var. *rubiginosus*, *Orthosiphon tomentotus* var viscosus, *Orthosiphon* transvaalensis and *Orthosiphon tristis* Benth |
| *Orthosiphon truncates* | *Orthosiphon tuberosus*, *Orthosiphon tubiformis*, *Orthosiphon tubulascene*, *Orthosiphon unyikensis* *Orthosiphon usambarensis*, *Orthosiphon varians* and *Orthosiphon velteri* |
| *Orthosiphon vernalis* | *Orthosiphon viatorum* and *Orthosiphon villosus* |
| *Orthosiphon violaceus* | *Orthosiphon virgatus*, *Orthosiphon viscosus* and *Orthosiphon welkefieldii* |
| *Orthosiphon wattii* | *Orthosiphon welwitschii*, *Orthosiphon wilmsii gurke*, *Orthosiphon wilmsii* var. *komghensis*, *Orthosiphon wilmsii* var. *wilomsii*, *Orthosiphon woodii* and *Orthosiphon xylorrhizus* |

**PHYTOCHEMISTRY**

These plants generally reported to contain monoterpenes, diterpenes, triterpenes, saponins, flavonoids, organic acids and etc. Considering the similarity of the chemical constituents of plants in the same genus. We summarized the phytochemical studies of five investigated plants, including *O. stamineus*, *O. ariatatus*, *O. pallidus*, *O. thymiflorus* and *O. diffuses*. This summary allows an understanding of the general and phytochemical constituents that has been discovered. It should also aid in further utilization of the plant resources in this genus. Selected chemical structure identified in *Orthosiphon* plants are depicted in Fig. 1.

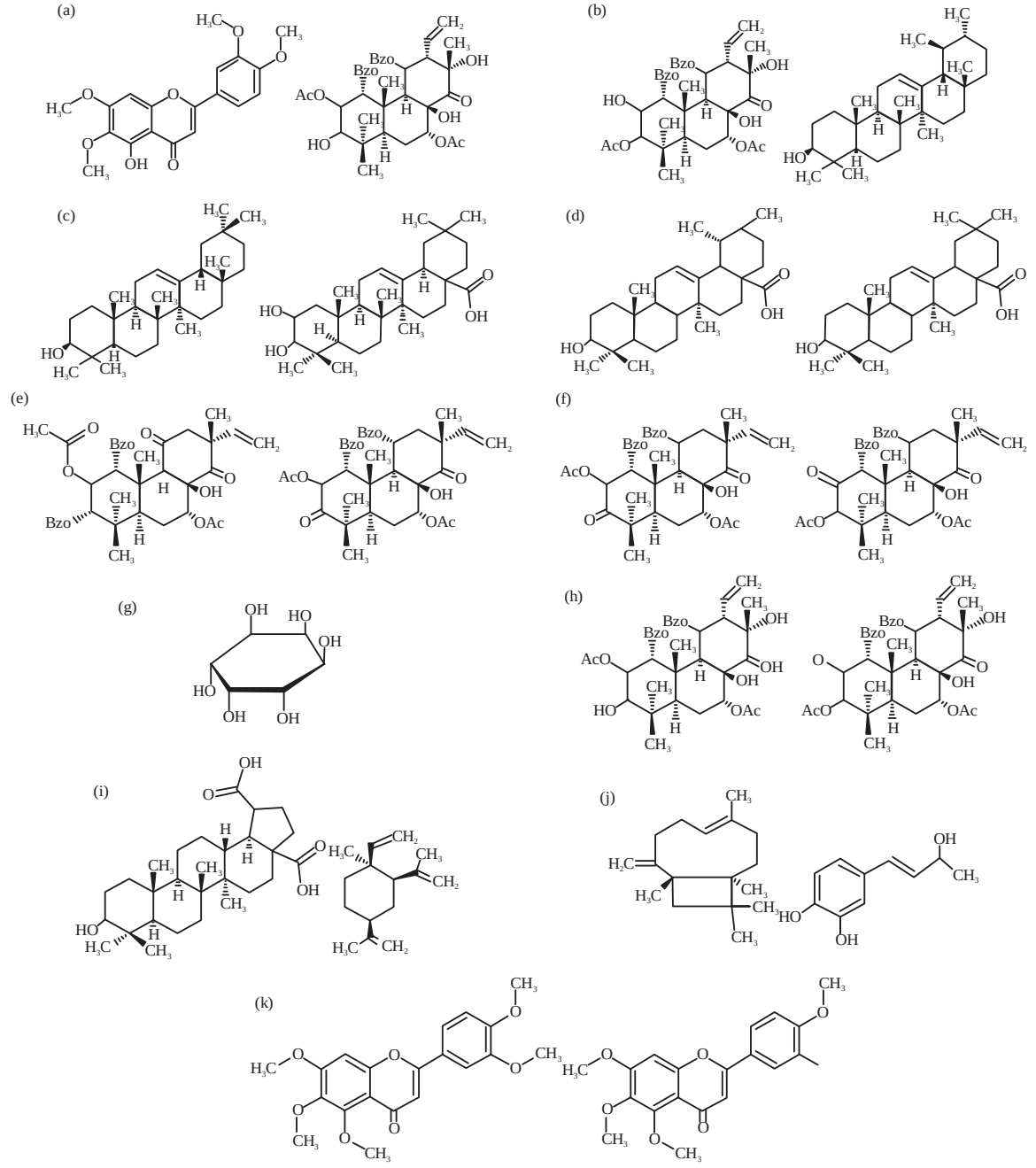


Fig. 1: Continue

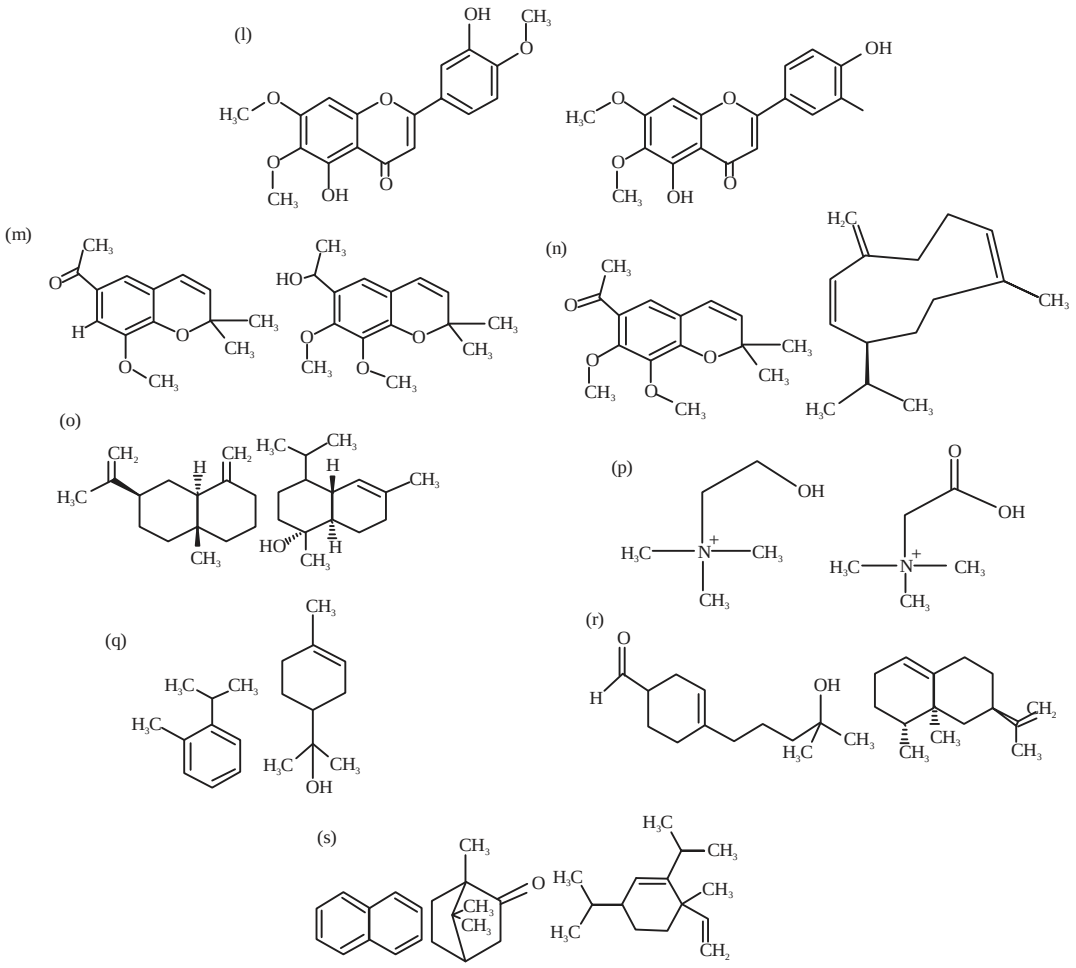

Fig. 1(a-s): Chemical Structures of typical and bioactive constituents isolated from *Orthosiphon* species, (a) 3'-hydroxy-5, 6, 7, 4'-tetramethoxyflavoneNeoorthosiphol A, (b) Neoorthosiphol Bα-amyrin, (c) β-amyrinMaslinic acid, (d) Urosolic Acid Oleanolicv Acid, (e) *Orthosiphon*one A *Orthosiphon*one B, (f) Orthosiphol A Orthosiphol B, (g) Myo-inositol, (h) Neoorthosiphol A Neoorthosiphol B, (i) Betulinic acid β-Elemene, (j) β-Caryophyllene Caffeic acid, (k) Sinensetin Tetra-methyl scutellarein, (l) Eupatorin Cirsimaritin, (m) Acetovanillochromene Orthochromene A, (n) Methylripario Chromene Agermacrene-D, (o) β-Selinen α-Cadinol, (p) Choline Betaine, (q) O-cyamenea-terpineol, (r) LyrolValencene and (s) Nephthalin Camphor α-elemene

Moreover, previous research have detected 116 chemical compound have been isolated from the *O. stamineus*. They were 3-hdroxy 5, 6, 7, 4 tetramethoxy flavones, 2-O-deacetyl *Orthosiphol* J, 4' hydroxyl-5,6,7-trimethoxy flavone, α-cadinol, α-humulene, β-bourbonene, β-caryophyllene, β-elemene, β-pinene, aurantiamide acetate, caffeic acid depside A-C, cismaritin, eugenol, eupatorin, ladanein, methylripario chromene A, neoorthosiphol A-B, neo*Orthosiphon* A, norstaminol A-C, *Othosiphol* A-Z, *Orthosiphon* A-D, pillion, quercetin, rosamarinic acid salvigenin, secoorthosiphol A-C, siphonol A-E, staminol A-D, ursolic acid, betulinic acid, vomifoliol beta amyrin, α-amyrin, maslinic acid, oleanolicy acid and other minor constituents (Adnyana *et al*., 2013; Ameer *et al*., 2012; Guerin *et al*., 1989).

In the case of *O. aristatus*, the major constituents were sequiterpenes including β-elemene, β-caryophyllene, orthochromene A, acetovanillochromene, sinensetin, tetramethyl scutellarein, eupatorin, neo*Orthosiphon*s A and B, *Orthosiphones* A and B with some minor constituents (Shibuya *et al*., 1999; Schut and Zwaving, 1986; Bombardelli, 1972; Lyckander and Malterud, 1992).

In the case of *O. pallidus* is rich in gemacrene D, β-selinene, α-cadinol, choline, betainine, *Orthosiphonone* A and B, *Orthosiphol* A and B with some minor other constituents (Basu and Sing, 1956; Basu and Singh, 1956).

Moreover *O. thymiflorus* and diffuses leaves were identified 33 and 25 compound. Most of the compounds are terpenoids. *Orthosiphon thymiflorus* content camphor, o-cymene, α-terpineal, nephthaline, lyrol, α-elemene and valencene etc.

Other major compound of *Orthosiphon diffuses* were t-caryophyllene, octocosane, n-eicosane, limonene, β-ocimene and kauran-18-al and minor compounds were farnesol, calarene, octanol, β-selive, β-bisebolene, α- terpinolene and methylioso stearate etc. (Sadashiva *et al*., 2013).

## PHARMACOLOGICAL PROPERTIES

**Anti-inflammatory activity:** Mostly 60-75% of the medicinal species of *Orthosiphon* reported in Table 1 have been traditionally used for treatment of inflammation and diseases like arthritis, bronchitis and rheumatoid. The pharmacological activity of the species of genus *Orthosiphon* provides primarily *in vivo* information for anti-inflammatory effects.

In different studies on *O. stamineus* methanolic extract on various amount model suggested that oral administration of methanolic extract of *O. stamineus* exerted significant anti-inflammatory activity from 250-1000 mg $kg^{-1}$ of dose (Ameer *et al*., 2012).

The activity of chloroform extract was studied on various models like anti-peritoneal capillary permeability, carrageenan-induced rat paw edema along with *in vitro* radical scavenging activity. It was found that oral administration of chloroform extract at 500-1000 mg $kg^{-1}$ reduced edema and no dye leakage to the peritoneal cavity (Yam *et al*., 2010).

Masuda *et al*. (1992) investigated that isolation of *Orthosiphol* A and B showed strong inhibitory activity against the inflammation induced by a tumor promoter on the ears gene targated mice (Masuda *et al*., 1992).

**Antioxidant activity:** Several *Orthosiphon* species traditionally used for expectorant and rheumatism indicated antioxidant activity. In different studies of *O. stamineus* for different extract (50% hydroalcoholic, distilled water, 50-70% hydroacetone and chloroform extract) was investigated that for free radical scavenging activity using different model like DPPH, superoxides and xanthin oxidase that *O. stamineus* extract showed potential antioxidant activity. The highest activity was found in hydroacetone extract. Other study found that all the extract had potential antioxidants comparable to that of some standard antioxidants BHA and quercetin (Adnyana *et al*., 2013).

**Hepatoprotective activity:** Yam *et al*. (2009) reported that pretreatment with methanolic extract of *O. stamineus* to hepatoprotective activity in $CCL_{4.}$ induced liver damage in rats. It was investigated that hepatoprotective effects caused by antioxidants properties (Yam *et al*., 2007).

Another study Maheswari *et al*. (2008) investigated that methanol extract of *O. stamineus* showed hepatoprotective activity on paracetamol-induced rats. Further, they proposed that there quality of medicinal plant due to ability to prevent the depletion of the tissue GSH (Maheswari *et al*., 2008).

**Anticancer activity:** Stampoulis *et al*. (1999) proposed cytotoxic activity of methanolic extract of *O. stamineus* against liver methanolic clon 26-LS carcinoma cells. The isolated compound stamina lactones A and B and norstaminal a showed mild cytotoxic activity against high malignant live metal stalic clone carcinoma cells (Stampoulis *et al*., 1999). Another study Awale *et al*. (2003a) investigated the possible cytotoxic activity a compound isolated from japans *O. stamineus* against highly malignant liver metastatices murine colon 26-LS carcinoma and human HT-1080 fibrosarcoma cell line (Adnyana *et al*., 2013).

**Antihypertensive activity:** The antihypertensive activity of aqueous extract of leaves and active constituent isolated from *O. stamineus* benth was examined. Methylripariochromene A (from aqueous extract of leaves), *Orthochromene* A, *Orthosiphonone* A and B and neoorthosiphol A and B (from $CHcl_3$ fraction of leaves), tetramethylscutell are in posses diuretic action. These constituents led to decrease in blood pressure and cardiac output. Subcutaneous administration of aqueous decoction of leaves led to decrease in systolic blood pressure conscious SHRSP. Does dependent decrease in urinary volume was observed ofter oral administration of isolated constituents of *Orthosiphon stamineus benth* urinary excretion of electrolytes was increased 2-3 times. These results confirmed that flavonoids and isopimarane-type compounds contributes significant antihypertensive activity (Adnyana *et al*., 213; Ameer *et al*., 2012).

Koay and Amir (2012) investigated antihypertensive activity of *O. stamineus* benth in combination with folic acid, coenzyme-Q, policosanol which indicated effective control of high blood pressure in patients with metabolic syndrome (Koay and Amir, 2012).

**Gastro protective activity:** Methanolic extract of leaves of *O. stamineus* benth posses significant effects for treatment gastric ailments. Fifty percentage of methanolic extract led to decrease in ulcer index, gastric mucosa mucosal damage, lipid peroxidation with an increase in mucus secretion.

The antiulcerogenic activity was investigated in male Sprague Dawley rats against ethanol-induced ulcers. The traces of histological changes, mucosal secretion, Ulcer index and lipid.

Peroxidation level was estimated using both *in vitro* and *ex vivo* models. The results showed significant does dependent gastro protective responces (125-1000 mg $kg^{-1}$) (Yam *et al*., 2009).

**Antisebum activity:** Sebum is an oily waxy matter secreted by exocrine sebaceous gland. Antisebum activity is observed in plants with phenolic and flavonoidal, terpennidal contents. *O. stamineus* benth exhibit prominent antisebum activity. The leaf extracts of *O. stamineus* decrese the activity of enzyme 5 α-reductase. The enzyme triggers the secretion of sebum. The extract of *O. stamineus* inhibits the synthesis of squaline (30 carbon natural orgaic compound) importent sebum constituents and help in skin glow there by reducing the oily appearance. Two percentage of leaf extract of *O. stamineus* reduces the oily appearance of skin and significantly reduces the pore size leading to improved skin complexion (Vogelgesang *et al*., 2011).

**Hyperlipidemic acivity:** The aqueous extract of *O. stamineus* benth showed significant hyperlipidemic activity in diabetic rats. Mariam *et al*. (1996) investigated the oral admnistration of aqueous extract of *O. stamineus* benth on lipid profile in normal and Streptozotocic induced diabetic male wistar rats (Mariam *et al*., 1996).

**Nephroprotective activity:** Adnyana *et al*. (2013) investigated the potential of hydroalcoholic *O. stamneus*. The study revealed that the plant posses nephroprotective activity significantly at a dose of 50 mg $kg^{-1}$. When compared to standard drug hydrochlorothiazide (10 mg $kg^{-1}$). Similarly when the methanolic extract of the plant was investigated gentamycin-induced nephrotic model, A does dependent nephroprotective effect was observed (100-200 mg $kg^{-1}$) with a steep decrease in decreased serum creatinine and blood urea level (Adnyana *et al*., 2013).

**Antipyretic activity:** Antipyretic study of *O. stamineus* hydrochloric extract executed a profound effect from a dose range of 50-1000 mg $kg^{-1}$ b.wt. The yeast induced pyrexia model was employed to investigate the effect. Similarly the effect was observed in 50% methanolic extract of *O. stamineus* in yeast-induced pyrexia in Sprague Dawley rats was investigated. The study showed that oral administration of the extract in the range from 450-1000 mg $kg^{-1}$ led to no reduction in body temperature, but a significant alleviation of the pyrexia induced by yeasts was observed (Yam *et al*., 2008).

**Antiangiogenic activity:** Plant *O. stamineus* possess significant anti-angiogenic activity. Ethanolic extract of *O. stamineus* showed retarding effect on the colorectal tumor and human umbical vein endothetical cell formation. Ethanolic extract of the plant at a concentration of (211±0.26 pg $mL^{-1}$) inhibited VEGF *in vitro* and *in vivo* (53-54) (Sahib *et al*., 2009; Goodwin, 2007).

**Antibacterial activity:** The studies on *O. stamineus* extract showed antibacterial activity on serotypes c and d of Streptococcus mutans (MIC = 7.8-23.4 mg $mL^{-1}$). The potency decreased about one-half for type d but no change was found in type c, with the presence of 5% sucrose (Chen *et al*., 1989). *Orthosiphon stamineus* methanolic extract at concentration of 50% inhibited *Bacillus subtilis*, *Bacillus cereus*, *Litseria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli*, *Vibri parahaemolyticus*, *Salmonella enteritidis*, *Salmonella typhimurium* and *Klebsiella pneumoniae*. This antibacterial activities of *O. stamineus* may be due to the high concentration of rosmarinic acid (Hossain *et al*., 2008).

Whole *O. stamineus plant* (powdered) methanolic extract demonstrated inhibitory activity against vibrio parahaemolyticus *in vitro*. The inhibition showed with *O. stamineus* extracts was comparable to the inhibition seen with that of 5% lactic acid; this may be likely due to high concentration of rosmarinic acid found in the *O. stamineus* extracts (Ho *et al*., 2010).

**Antidiabetic activity:** In oral glucose tolerance test, the water extract at doses of 0.2-1.0 g $kg^{-1}$ significantly decreased plasma glucose concentration in dose-dependent manner for both normal and diabetic rats. At a dose of 1.0 g $kg^{-1}$ showed similar effect with glibenclamide (5 mg $kg^{-1}$). In diabetic rats, after they were given the extract orally (0.5 g $kg^{-1}$) for 14 days, plasma glucose concentrations were reduced significantly. In addition, plasma triglyceride concentration was also lower in the extract-treated diabetic rats than that of untreated group. Furthermore, plasma HDL-cholesterol concentration was significantly increased in diabetic rats treated with the extract. In perfused rat pancreas, 100 μg $mL^{-1}$ extract potentiated the glucose-induced insulin secretion (Sriplang *et al*., 2007).

Antidiabetic effects of the chloroform, methanol, petroleum ether and water extracts of *Orthosiphon stamineus* was studied. Chloroform extract at a dose of 1 g $kg^{-1}$ b.wt., significantly

reduced blood glucose level. Further, this extract was fractionated and finally one subfraction showed similar antidiabetic effect with metformin (Mohamed *et al*., 2011a).

**Diuretic activity:** Diuretic activity of *O. stamineus* hydroalcohol extract from aerial parts was reported. At a dose of 50 mg $kg^{-1}$, this extract showed similar effectivity with hydrochlorothiazide at a dose of 10 mg $kg^{-1}$ (Beaux *et al*., 1999).

Other studies reported that a water extract and tincture of leaves enhanced ion excretion of rats which were not due to the potassium content of the starting material (Englert and Harnischfeger, 1992).

Arafat *et al*. (2008) studied the diuretic and hypouricemic activity of different *O. stamineus* methanol extracts by Sprague, Dawley rats model. A single dose infusion (2 g $kg^{-1}$) of methanol and methanol: Water (1:1) extracts possesses significant diuretic action, where the effect was quantitatively similar to the control, hydrochlorothiazide. Repeated dose of 0.5 g $kg^{-1}$ of methanol: water (1:1) extracts showed an increase in diuresis from the third day of treatment. Oral administration of 0.5, 1.0 and 2.0 g $kg^{-1}$ of methanol: water (1:1) extracts significantly reduced serum urate level of hyperuricemic rats at hour 6, whereby the decrease in the uric acid level was also observed for the standard, allopurinol at hour 6 (Arafat *et al*., 2008).

Adam *et al*. (2009) investigated the diuretic effects of *Orthosiphon stamineus* aqueous extract. Orally at doses of 5 and 10 mg $kg^{-1}$ to Sprague, Dawley rats and was compare with furosemide or hydrochlorothiazide at 10 mg $kg^{-1}$. Urine pH, urine volume, urine density and urine electrolytes were determined every hour for 4 h. Blood was assayed for albumin, glucose, Blood Urea Nitrogen (BUN) and creatinine. *Orthosiphon stamineus* extract exhibited dose-dependent diuretic activity. However, $Na^+$ and $Cl^-$excretion was not markedly elevated but urinary excretion of $K^+$ was significantly increased. *Orthosiphon stamineus* extracts increased the serum BUN, creatinine and blood glucose level slightly (Adam *et al*., 2009).

The diuretic, saluretic and uricosuric actions of 50 and 70% ethanol extracts of *O. stamineus* (700 mg $kg^{-1}$) in rats revealed that the diuretic effect of the 50% ethanolic extract was higher than that of the 70% ethanolic extract or furosemide. It was characterized by higher absolute excretion of sodium and lower potassium wasting. Furthermore, the same 50% ethanol extract showed a relatively higher uricosuric effect. As the hydrophilicity of the extract increases, its diuretic and uricosuric effects also increase. This may be attributed to the abundance of polyphenols (Olah *et al*., 2003).

## TOXICITY STUDY

The only toxicity literature and reports on members of the *Orthosiphon* genus were concerning *O. stamineus*. Different studies proved that the possible acute toxicity effects of orally administered *Orthosiphon stamineus* plant extract in rats. Acute toxicity was evaluated by $LD_{50}$ method. No toxicity was found at a dose of 2 g $kg^{-1}$ (Padilla *et al*., 1996).

Another study Mohamed *et al*. (2011b) proved that standardized 50% ethanol plant extract at a dose 5 g $kg^{-1}$ given orally to Sprague Dawley rats did not show an changes in macroscopic and microscopic. These results were proved that subchronic toxicity. Different concentration of plant extract (1250-5000 mg $kg^{-1}$) on male and female Sprague Dawley rats for 4 weeks, showed no significant changes with control group. The parameters were hematological, organ weight, biochemical value, macroscopic and microscopic observation of the heart, brain, liver, kidney, spleen, tests, uterus and stomach (Mohamed *et al*., 2011a).

Recently Muhammad *et al*. (2011) investigated genotoxicity of *O. stamineus* using salmonellal microsome mutation and mouse bone marrow micronucleus assays method. The results were concluded that use of *Orthosiphon* stamineus in traditional medicine poses no genotoxic risk (Muhammad *et al*., 2011).

## SUMMARY AND CONCLUSION

In the present review, summarized to congregate traditional use of medicinal plants in the genus *Orthosiphon* and research on its phytochemical, pharmacological and toxicological information on *O. aristatus*, *O. pallidus*, *O. thymiflorus* and *O. stamineus*, medicinal herbs used in the India and all over the world.

Survey of literature data provided a practical base for further scientific research on this genus. In another equally very important to understand if the pharmacological studies on this genus are available to validate their traditional uses. Preliminary report in experimental studies says that it is significantly effective in diseases related to gastrointestinal, lungs and liver. Hence the purpose of this review is to provide comprehensive report about the genus based on its toxicity in order to identify its therapeutic potential and further prospects for betterment of research and provides basic knowledge for development of medicinal plants and useful approach for drug discovery.

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