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 both 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 or rhomboid, 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 and 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) |
| *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 (1956) | Basu and Singh (1956)                        |
| *Orthosiphon thymiflorus* | Ailsyar foot hills of valparal, Coimbatore, Tamilnadu | Fresh leaves              | Antioxidant                                           | Antioxidant, cytotoxic and vasodilative                          | Hydrodistillation, Clevenger and apparatus | Sundarammal et al. (2012)                   |
|                        | Attapady palakkad and Kerala  | Powdered plant material   | Anticancer                                            | Cytotoxic activity, anti diabetic, antihepatotoxic, antibacterial and hypertensive | Imbibition, meceration and percolation in chloroform | Sini *et al.* (2012)                        |
|                        | Tirunelveli and Tamilnadu      | Whole plant               | Aquaretic                                             | Diuretic activity and anti-inflammolary                           | Meceration in boiling water          | Kavimani *et al.* (1997)                    |
|                        | Maruthamal 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, tusslitis, menstrual disorder, urinary lithiasis, biliary lithiasis, epilepsy, oedema, eruptive fever, hepatitis, jaundice, influenza, gonorrhoea, syphilis, 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 Vietnam  | 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 amabiis, Orthosiphon ambiguous Bolus and Orthosiphon angolensis |
| Orthosiphon aristatus var. aristatus        | Orthosiphon asperus, Orthosiphon atacorensis, Orthosiphon australis and Orthosiphon bartsoides |
| Orthosiphon biflorus                       | Orthosiphon bodiniieri, Orthosiphon bolusii, Orthosiphon braceatus, Orthosiphon brevicaulis, Orthosiphon buchananii and Orthosiphon braceatus |
| Orthosiphon bullosus                       | Orthosiphon buryi, Orthosiphon calaminthoides, Orthosiphon cameronii, Orthosiphon canescens and Orthosiphon capitus |
| Orthosiphon cladotrichos                    | Orthosiphon cleistocaulys, Orthosiphon colouratus, Orthosiphon comosus Wight and Orthosiphon comosus Baker |
| Orthosiphon cuanzae                        | Orthosiphon debilis, Orthosiphon decipiens, Orthosiphon degasperianus and Orthosiphon diffuses |
| Orthosiphon discolor                       | Orthosiphon dissifolius, Orthosiphon ehrenbergii, Orthosiphon ellenbecki and Orthosiphon eliottii |
| Orthosiphon ellipticus                     | Orthosiphon emirnensis and Orthosiphon engleri Perkins                  |
| Orthosiphon ferruginos                     | Orthosiphon foliaceus                                                    |
| Orthosiphon fraticosus                     | Orthosiphon gerrardii, Orthosiphon glabrateus Benth, Orthosiphon glabrateus var. Palviflorus (Benth) and Orthosiphon glabraceae |
| Orthosiphon glandulosus                    | Orthosiphon glutinuosus Chiov., Orthosiphon gosensis S. Moore and Orthosiphon grandiflorus Bold. |
| Orthosiphon hanningtonii                   | Orthosiphon helenae Buscal, Orthosiphon heterochrous Briq, Orthosiphon heterophyllus Gurke, Orthosiphon hildebrandtii Vatke, Orthosiphon hildebrandtii Baker, Orthosiphon hispisus Benth., Orthosiphon hookii, Orthosiphon holubii and Orthosiphon hombele |
| Orthosiphon humbertii                      | Orthosiphon humilis, Orthosiphon incisus and Orthosiphon inconcinnus      |
| Orthosiphon incurvus                       | Orthosiphon inodoras, Orthosiphon iodoxyc Briq, Orthosiphon johnstonii Baker, Orthosiphon kelleri Briq, Orthosiphon kirki Baker and Orthosiphon labiatus |
| Orthosiphon lanatus Doan                   | Orthosiphon lanceolatus Gurke, Orthosiphon lanceolatus, Orthosiphon latidens, Orthosiphon laurantii, Orthosiphon liebrechtiaurom, Orthosiphon linearis Benth, Orthosiphon longipes Baker, Orthosiphon macranthus, Orthosiphon macrocheilus, Orthosiphon macrophyllus, Orthosiphon macrileus, Orthosiphon malosanus Baker, Orthosiphon marmoritis, Orthosiphon marquesi Briq., Orthosiphon menthofilius Briq and Orthosiphon massinensis |
| Orthosiphon miserabilis                    | Orthosiphon molis Baker, Orthosiphon mombacius, Orthosiphon mossianus, Orthosiphon muddii, Orthosiphon natatalis and Orthosiphon neglectus |
| Orthosiphon nigripunctatus                 | Orthosiphon nyacicus, Orthosiphon obbiadiensis, Orthosiphon oblongifolius, Orthosiphon obscurus and Orthosiphon omatus |
| Orthosiphon parvifolius                    | Orthosiphon pascuenas, Orthosiphon persimilis, Orthosiphon petiolaris, Orthosiphon petrensis, Orthosiphon physocalycinus and Orthosiphon pretoriae |
| Orthosiphon pseudoaristatus                | Orthosiphon pseudomatus, Orthosiphon pseudorubicundus, Orthosiphon pseudoserratus, Orthosiphon rabaenensis, Orthosiphon reflexus, Orthosiphon rehmannii, Orthosiphon retinervis and Orthosiphon rhodosianus |
| 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. macaropus, Orthosiphon rubicundus var. macrurans, Orthosiphon rubicundus var. mollissimus and Orthosiphon rubicundus var. rigidus |
| Orthosiphon rubicundus var. rubicundus     | Orthosiphon rubinervis and Orthosiphon salagensis                        |
| Orthosiphon sarmentotus                    | Orthosiphon scabridus                                                    |
| Orthosiphon schimperi                      | Orthosiphon schizianius, 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 subelutatus, Orthosiphon suffrutescens, Orthosiphon tagauae Orthosiphon tenuiflorus, Orthosiphon tenuifrons, Orthosiphon teucrilifolius, Orthosiphon teucriformis var. galpinianus, Orthosiphon teucrilifolius var. teucrilifolius and Orthosiphon thorncroftii |
| Orthosiphon thymiflorus                    | Orthosiphon thymiflorus var. viscosus, Orthosiphon tomentosus Benth, Orthosiphon tomentosus De wild, Orthosiphon tomentosus var. glabrateus, Orthosiphon tomentosus var. parciflorus, Orthosiphon tomentosus var. rubiginosus, Orthosiphon tomentosus var viscosus, Orthosiphon transvaalensis and Orthosiphon tristis Benth |
| Orthosiphon truncates                      | Orthosiphon tuberosus, Orthosiphon tubiformis, Orthosiphon tubulascene, Orthosiphon unyikensis Orthosiphon usambarensis, Orthosiphon varians and Orthosiphon veltleri |
| Orthosiphon vernalis                       | Orthosiphon viatoum and Orthosiphon villosus Orthosiphon viator and Orthosiphon villosus Orthosiphon violinus Orthosiphon violaeus |
| Orthosiphon waltii                         | Orthosiphon virgatus, Orthosiphon viscosus and Orthosiphon wellefeldii Orthosiphon welaentsehii, Orthosiphon wilmseii gurke, Orthosiphon wilmseii var. komhensis, Orthosiphon wilmseii var. wilomseii, Orthosiphon woodii and Orthosiphon xylorhizus |
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’-tetramethoxyflavone Neoorthosiphol A, (b) Neoorthosiphol Ba-amyrin, (c) β-amyrin Maslinic acid, (d) Urosolic Acid Oleanolic Acid, (e) *Orthosiphonone A* Orthosiphonone B, (f) Orthosiphol A Orthosiphol B, (g) Myo-inositol, (h) Neoorthosiphol A Neorthosiphol 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-cyamene-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, Orthosiphol A-D, pillion, quercetin, rosamarinic acid salvigenin, secocorthosiphol A-C, siphonol A-E, staminol A-D, ursolic acid, betulinic acid, vomifoliol beta amyrin, α-amyрин, maslinic acid, oleanolic acid and other minor constituents (Adnyana *et al*., 2013; Ameer *et al*., 2012; Guerin *et al*., 1989).
In the case of \textit{O. aristatus}, the major constituents were sesquiterpenes including \(\beta\)-elemene, \(\beta\)-caryophyllene, orthochromene A, acetovanillochromene, sinensetin, tetramethyl scutellarein, eupatorin, neo\textit{Orthosiphon}s A and B, \textit{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 \textit{O. pallidus} is rich in gemacrene D, \(\beta\)-selinene, \(\alpha\)-cadinol, choline, betaine, \textit{Orthosipholone} A and B, \textit{Orthosiphol} A and B with some minor other constituents (Basu and Sing, 1956; Basu and Singh, 1956).

Moreover \textit{O. thymiflorus} and diffuses leaves were identified 33 and 25 compound. Most of the compounds are terpenoids. \textit{Orthosiphon thymiflorus} content camphor, o-cymene, \(\alpha\)-terpineal, nephthaline, lyrol, \(\alpha\)-elemene and valencene etc.

Other major compound of \textit{Orthosiphon diffuses} were t-caryophyllene, octocosane, n-eicosane, limonene, \(\beta\)-ocimene and kauran-18-al and minor compounds were farnesol, calarene, octanol, \(\beta\)-selive, \(\beta\)-bisebolene, \(\alpha\)-terpinolene and methylisostearate etc. (Sadashiva et al., 2013).

**PHARMACOLOGICAL PROPERTIES**

**Anti-inflammatory activity:** Mostly 60-75\% of the medicinal species of \textit{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 \textit{Orthosiphon} provides primarily \textit{in vivo} information for anti-inflammatory effects.

In different studies on \textit{O. stamineus} methanolic extract on various amount model suggested that oral administration of methanolic extract of \textit{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 \textit{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 \textit{Orthosiphol} A and B showed strong inhibitory activity against the inflammation induced by a tumor promoter on the ears gene targeted mice (Masuda et al., 1992).

**Antioxidant activity:** Several \textit{Orthosiphon} species traditionally used for expectorant and rheumatism indicated antioxidant activity. In different studies of \textit{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 \textit{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 \textit{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 \textit{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 static 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 CHCl3 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 after 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 contribute 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 responses (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, terpenoidal contents. O. stamineus benth exhibit prominent antisebum activity. The leaf extracts of O. stamineus decrease 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 organic compound) important 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 activity: The aqueous extract of O. stamineus benth showed significant hyperlipidemic activity in diabetic rats. Mariam et al. (1996) investigated the oral administration 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. stamineus. The study revealed that the plant possesses 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 umbilical 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, Listeria monocytogenes, Staphylococcus aureus, Escherichia coli, Vibrio 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 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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