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Botanical and phyto-pharmacological reports on *Stephania japhonica*

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ABSTRACT:

Medicinal plants play a key role in the human health. The use of plants, plant parts and their derived products is ancient. To date, a number of medicinal plants have gained attention of the medicinal scientists for their important phytoconstituents and in the treatment of various diseases. The plants of the genus *Stephania* (Family: Menispermaceae) are widely distributed, and are being used in the folk medicine for the treatment of various ailments, such as asthma, tuberculosis, fever, dysentery, hyperglycemia, malaria, and cancer. *Stephania japonica* belonging to this genus has been reported for many important phytochemicals and folk usages in the treatment of fever, diarrhea, dyspepsia, convulsions, skin diseases, cough, asthma, and urinary disorders. The scientific evidences suggest that, *S. japonica* has antioxidant, anti-inflammatory, antibacterial, antifungal, cytotoxic, anti-diabetic, anti-diarrheal, and analgesic activities. This review presents a current morphological and phyto-pharmacological scenario on this hopeful medicinal plant.

1. Introduction:

From the past, plant-based treatment of various diseases is an ongoing process. Interestingly, there is a great improvement in the use of medicinal plants in the modern era. It is due to the economy and abundant presence in nature (Islam et al., 2016). The genus *Stephania*, under the family Menispermaceae contains approximately 65 genera and 350 species, and is distributed in the warmer parts of the world (Semwal et al., 2010). Most of the family members of this genus are herbs or shrubs. The herbs under this are known as slender climbers; have been recognized as medicinal plants and are traditionally used in the treatment of asthma, tuberculosis, dysentery, hyperglycemia, cancer, fever, intestinal complaints, sleep disturbances and inflammation (Chopra et al., 1958; Gaur 1999; Kirtikar and Basu, 2004).

The plant *Stephania japonica* (*S. japonica*), a species of this genus (*Stephania*) has been reported to possess many medicinal properties. The juice of the whole plant is used in the treatment of convulsions, skin diseases, cough, asthma like symptoms and kidney disorders (Singh et al., 1975; Singh et al., 1978; Massiot et al., 1992; Adinolfi, 1994; Cowan, 1999). In Japan and Taiwan, a decoction of the plant is used as a drink to treat malaria (Sultana et al., 2012), while in Indonesia; the roots are used to treat stomachaches and convulsions (Gamble, 1958; Dey and Harborne, 1987; Seetharam et al., 2000). The leaves are bitter and roots are astringent and are used in fevers, diarrhea, dyspepsia and urinary disease (Seema, 2010). The leaf juice has antioxidant, analgesic and toxic effects (Hossain et al., 2010). Many plants under this genus are evident to contain large amounts of aristolochic acid, which can cause renal failure and even death. Generally, the aristolochic acid should not be taken with non-steroidal anti-inflammatory drugs (NSAIDs) due to the possibility of kidney damage or failure (Nunez, 2006).

The risk assessment for any medicaments, including natural origin or non-natural-based is crucial (Nishanthi et al., 2011). Unfortunately, the scientific reports on this traditionally used medicinal herb are not sufficient. Therefore, this text aims to sketch a current scenario on *S. japonica* to increase the attention of the medicinal scientists as well as traditional medicine practitioners.

2. Plant morphology

2.1 Macro characters of S. japonica

The plant *S. japonica* is a slender wiry climber; leaves are peltate thinly papyraceous, glabrous on both surfaces, broadly triangular, ovate- acuminate 3-12 cm long, apex acutely acuminate or obtuse, base rounded, and margin

entire. Flowers are small; male flowers are greenish-white (or) yellowish in color. Drupes are light yellow to orange-red, obovate, and glabrous (Senthamarai et al., 2012) (**Figure 1**).

2.2 Micro characters of S. japonica leaf (Nishanthi et al. 2012)

The leaf is distinctly dorsiventral and uniquely differentiated into adaxial and abaxial side. The adaxial part of the lamina consists of a less prominent, slightly thick part with a small vascular strand. This part represents the midrib. The midrib portion has 7-9 layers of fairly larger compacted cells. The innermost of the adaxial multilayered part comprises short, cylindrical bone shaped palisade layer. The abaxial part of the leaf consists of two or three layers of large thin walled compact cells. The two adaxial and abaxial zones are widely separated large air chambers which are partitioned from each other by thin vertical partition filaments (**Figure 2**).

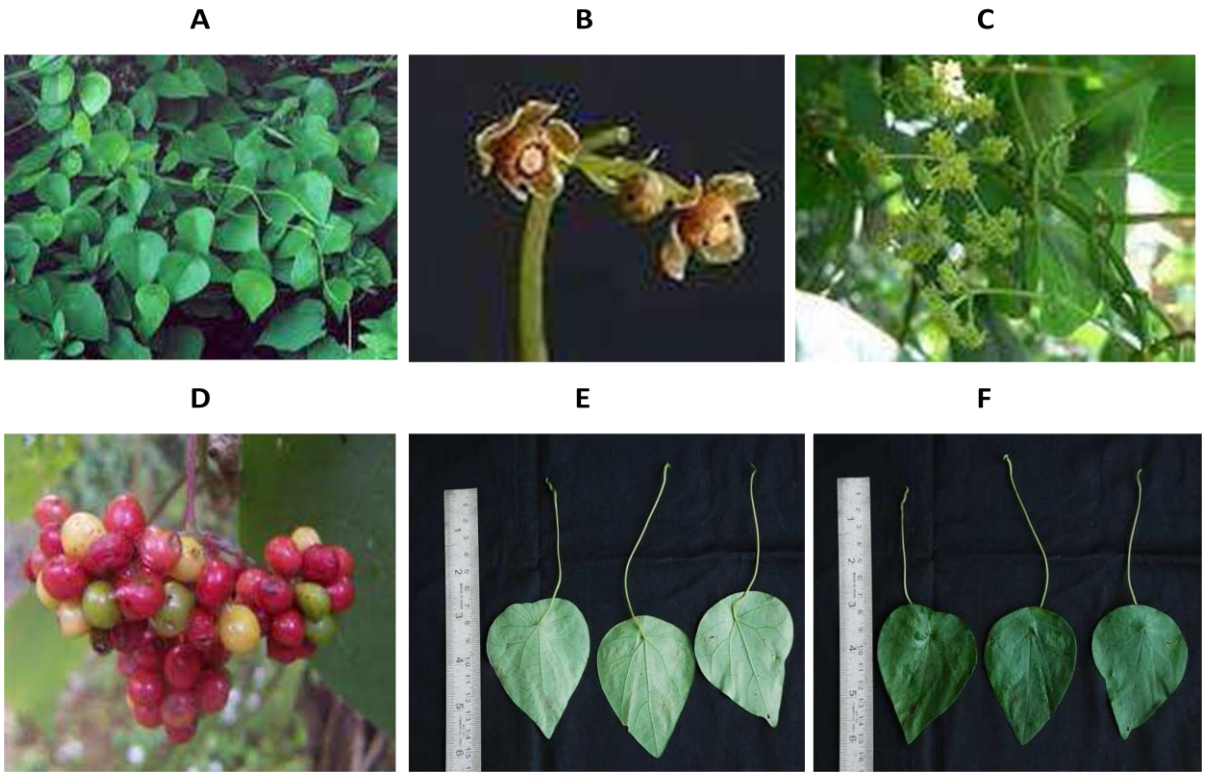

Figure 1. Macro-features of *S. japonica*. [A: plant, B: flowers, C: plant with flowers, D: fruits, E: leaves (dorsal view), and F: leaves (ventral view).]

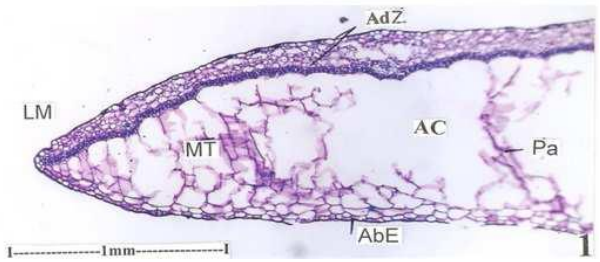

Figure 2. Photomicrographic view of the leaflet (lateral view) of *S. japonica*.

2.3 Lamina (Figure 3A):

Distinctly dorsiventral, about 500 µm long. The adaxial epidermis is tabular shaped and composed of horizontally extended narrow cells with plain surface. The adaxial epidermal layers consist of dilated

hemispherical thin walled papillate cells, which are 15 µm thick.

2.4 Midrib (cross-sectional view, Figure 3B):

Abaxially semi-cirhump. Its thickness is 1.5 mm and width is 1.2 mm. The epidermis of the midrib consists of small elliptical thick walled cells. Two or three layers of thick walled angular cells towards the periphery make the ground tissue and remaining portion includes compact thin walled parenchyma cells.

2.5 Vein terminations (Figure 3C):

Thin and glandular, present in most of the vein islets. The terminations are un-branched or branched once or twice.

2.6 Petiole (Figure 3D):

Circular in transactional outline. It is 1 mm thick, having a wide circular central canal formed by the lysis of the pith parenchyma. The epidermal layer is thin; the cells are spindle shaped with thicker outer tangential walls, inner to the epidermis with a wide paranely in atous ground tissue comprising 6 or 7 layers of angular, thick-walled compacted cells.

2.7 Epidermal trichomes (Figure 3E):

Unicellular, un-branched, non-glandular trichomes, heavily thick-walled with wide lumem. The surface of the trichome is smooth, thin, uniform in thickness, and gradually tapers at the tip. The trichome is 350 µm long and 25 µm thick at the base.

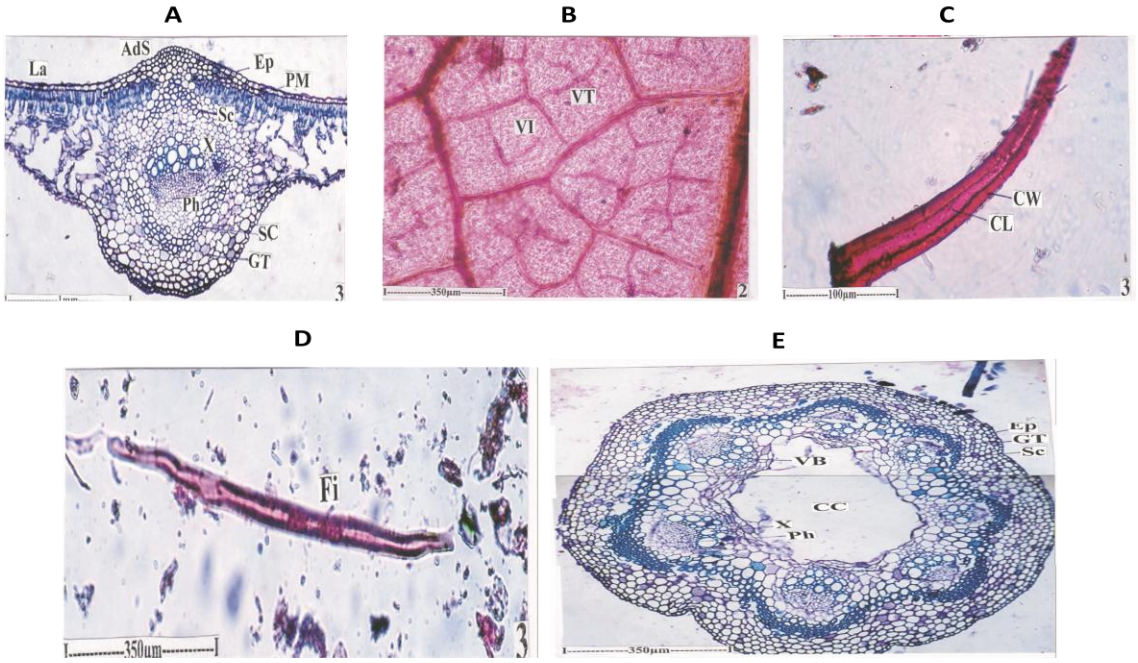

Figure 3. Microscopic observations of the *S. japonica* leaf. [A: midrib; B: venation pattern of the lamina leaf. enlarged vein islet and termination; C: epidermal non glandular trichome; D: afibre; and E: cross section of the petiole entire view]

3. Phytochemicals isolated from *S. japhonica*

Alkaloids are the main and common phytochemicals of the genus *Stephania*. Till date, more than 200 alkaloids have been isolated from this genus. Among them approximately 55 alkaloids are found in *S. japhonica*. Alkaloids are the main phytoconstituents found in S. japonica. However, the plant also contains flavonoids, lignans, steroids, terpenoids and coumarins (Semwala et al., 2010). Some of the isolated phytochemicals from *S. japonica* are: 2-dehydroepistephanine, oxostephabenine, oxostephanine, oxoepistephamiersine, oxostephasunoline, plastoquinone, protostephanaberrine, protostephanine, prometaphanine, 16-oxohasubonine, aknadicine, aknadine, bebeerines, 16-oxoprotometaphanine, aknadinine, cyclanoline, cycleanine, d-fangchinoline, stephabenine, lanuginosine, epistephanine, dehydroepistephanine, d-tetrandrine, hasubanonine and homoepistephanine (Inubushi and Ibuka, 1977; Matsui et al., 1973, 1975, 1982a,b, 1984; Kondo et al., 1983; Matsui and Watanabe, 1984; Taga et al., 1984; Yamamura and Matsui, 1985; Matsui and Yamamura, 1986; Duke, 1992; Hall and Chang, 1997). Some important phytochemicals isolated from *S. japonica* have been shown in **figure 4.**

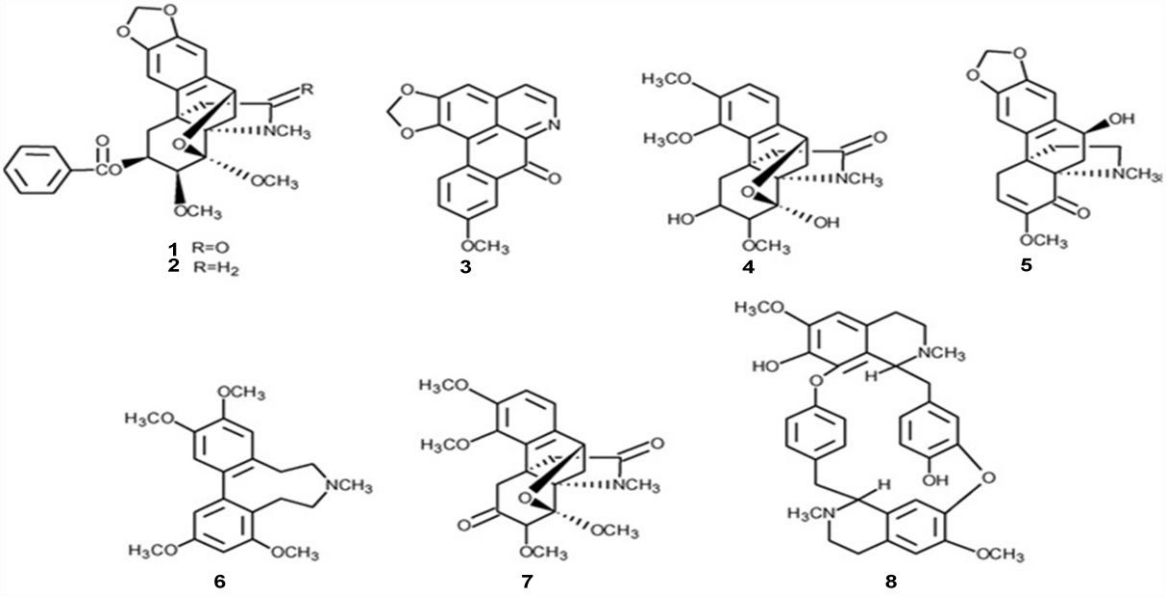

Figure 4. Structures of some phytochemicals found in *S. japonica*. [oxostephabenine (**1**), stephabenine (**2**), lanuginosine (**3**),oxostephasunoline (**4**),prostephanaberrine (**5**), protostephanine (**6**), oxoepistephamiersine(**7**), and bebeerine (**8**)]

4. Biological activities of *S. japhonica*

The plant *S. japonica* has been used in the folk or ethno-medicine in India, Bangladesh, Indonesia, Myanmar, China, Japan, and on. It is evident to contain four major alkaloids, namely dehydroroemerine, tetrahydropalmatine, xylopinine and cepharanthine (Semwala et al., 2010).

4.1 Antioxidant activity

Polyphenolic compounds like flavonoids, tannins, tannic acid, and phenolic acids are commonly found in *S. japonica*, that are thought to be linked to its multiple biological effects, including antioxidant activity (Moncada et al., 1991; Brown and Rice-Evans, 1998; Kahkonen et al., 1999; Rahman et al., 2011). The leaf extract of *S. japonica* was found to show a concentration-dependent (10 - 200 µg/mL) scavenger of 1,1-dipheny-2-picrylhydrazyl (DPPH) radicals (Rahman et al., 2011). Furthermore, the ethanolic extract of *S. japonica* has been reported to exhibit a strong radical scavenging capacity within a concentration range of 20 to 200 µg/mL (Ahmed et al., 2011; Uddin et al., 2014).

4.2 Anti-inflamamtory and gastro-protective effects

In a study, preliminary phytochemical test revealed that, the plant contains tannins, alkaloids and glycosides (Teh et al., 1990). Two alkaloids, namely tetrandrine and fangchinoline isolated in that study, were reported to exhibit an anti-inflammatory activity by decreasing leukotriene and prostaglandin in experimental animals (Teh et al., 1990). In another study, *S. japonica* was reported to possess saponins, tannins, triterpenes, alkaloids, flavonoids and glycosides. The pharmacological evidences observed in that study were anti-hyperglycemic and anti-hyperlipidemic activities (Sultana et al., 2012). Moreover, the plant is also evident to have reduced sugars (Uddin et al., 2014).

In a study, the *S. japonica* extract (2 g/kg and 1 g/kg) reduced the gastrointestinal motility in rats (Ahmed et al., 2011). These responses are orchestrated by highly modulatory interactions between the mediators of inflammation and inflammatory cells (Sacca et al., 1997), as the pathological states seem to be linked with an imbalance of cytokine network and to the excessive recruitment of leukocytes to the inflammatory sites (Feldmann et al., 1998; Young, 1998; Haddad, 2002).

4.3 Cytotoxic/anticancer activity

Two zwitterionic oxoaporphine alkaloids, Nmethylliriodendronine and 2-O,N-dimethylliriodendronine were found to show an anti-malarial and cytotoxic activity (Semwala et al., 2010). The other phytochemicals isolated from this plant such as liriodenine exerted a significant cytotoxic effect towards *Leishmania donovani*, while aloe-emodin acted against *Trypanosoma brucei* (Camacho et al., 2000).

The root extract of *S. japonica* showed significant *in vitro* activity together with *Cissampelos pareira* and *Cycleapeltata* (Hullatti and Sharada, 2010). An alkaloidal extract containing insotrilobine and trilobine of the vines of *S. japonica* showed multidrug resistance reversing

activity towards human breast cancer (MCF-7) cells (Semwala et al., 2010).

4.4 Analgesic activity

The methanol leaf extract of *S. japhonica* was found to show a dose-dependent analgesic activity, where *S. japonica* at 500 mg/kg (oral) exhibited almost a similar writhing reducing capacity in *Swiss* mice as the standard used, diclofenac sodium (25 mg/kg, intra-peritoneal) (Uddin et al., 2014). The analgesic activity of the leaf extract of *S. japonica* was also reported by Rahman et al (2011). Moreover, the ethyl acetate, chloroform, carbon tetra-chloride and petrolium ether fractions of the methanolic stem extract of the plant were also evident to show a dose-dependent analgesic activity in rodents (Bokshi et al., 2013). In a recent study, Moniruzzaman et al (2016) suggests that the methanol extract of *S. japonica* leaf did not produce any toxic effect to the *Swiss* mice up to 3000 mg/kg (oral gavage). The preliminary phytochemical screening report on the same study revealed the presence of alkaloids, glycosides, tannins, flavonoids, saponins and carbohydrates. The authors concluded a promising anti-nociceptive activity of the extract (50, 100 and 200 mg/kg; p.o.), possibly *via* opioid receptors and glutamatergic system involvement. *S. japonica* mediated analgesic activity was also seen by (Ahmed et al., 2011; Bokshi et al., 2013).

4.5 Hypoglycemic effect

Moreover, the ethanolic extract of *S. japonica* was found to exert an anti-hyperglycemic effect in diabetic mice, where a significant dose-dependent glucose lowering capacity was observed in comparison to the control groups (Sultana et al., 2012). In another study, the bisbenzylisoquinoline alkaloids isolated from this plant were found to exert a hyperglycemic effect in diabetic mice (Tsutsumi et al., 2003). In the latter case, the main bisbenzylisoquinoline alkaloid fangchinolin was reported to show a significant and dose-dependent (0.3 - 3.0 mg/kg) reducing capability of blood glucose level in the animals.

5. Conclusion

Together with the data, the scientific evidences found in the literature have been found to link with the ethno-pharmacological usages of *S. japonica*. It seems that this plant may be one of the potential sources of biologically important plant-derived natural products. However, toxic effects of the aristolochic acid, present in this plant are a major concern. Thus, more precautions are needed during folk usages of *S. japonica* in the treatment of diseases. Moreover, the scientific reports on this plant and its derived compounds are not sufficient. Therefore, more research is appreciated on this hopeful medicinal herb.

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Conflict of interest.
None declared.

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