3 REVIEW OF LITERATURE

In an attempt to retrieve previous studies on *Didymocarpus* Wallich ex Buch.-Ham., it was found that literature on the subject is meagre and fragmentary. About 50 papers on various areas of study of *Didymocarpus* Wallich ex Buch.-Ham. have been brought into the present review.

According to Fyson (1932), *Didymocarpus tomentosa* Wight is found in Nilgiris, Kotagiri, Biccapatti, Pulneys at 5,000 feet and above. It is common on the Kodaikanal Ghat path near Shenbaganur. The leaves are very like those of the English primrose but hairy.

*Didymocarpus pedicellata* R.Br. is a small herb with a reduced stem, bearing 2 – 3 pairs of opposite, roundy ovate, glabrous, glandular punctate leaves, 3 – 6 inches in diameter (Shah *et al.*, 1972; Kapoor & Kapoor, 1976)

Shah *et al.* (1972) studied the pharmacognostic details of the rhizome and leaves of *Didymocarpus pedicellatus* R.Br. which is commonly known as *pashanbhed*. According to these authors, the rhizome has many glandular trichome on the surface. The leaf is dorsiventral. The stomata are present on both the surface and are of anomocytic type. Both simple and glandular trichomes are seen. Calcium oxalate crystals of prism, cluster and rosette types are present throughout. Transverse section of the petiole is highly irregular in outline with two prominent winged projections.

According to Matthew (1981), *Didymocarpus tomentosus* Wight is seen in the hills above 900 m in crevices of rocks. Fresh growth is seen after summer. Flowers are bluish to purple with a peak during August to September. Fruits are seen from September onwards.
*Didymocarpus pedicellatus* R.Br., in a preliminary study, revealed the presence of flavonoids, saponins, sterols, terpenoids and glycosides; however alkaloids are absent (*Tewari et al., 1984*).

*Didymocarpus tomentosus* Wight is a scapigerous herb in hills and distributed in the hills of most of the districts of Tamil Nadu (*Henry et al., 1987*).

According to *Nayar et al. (1989)*, *Didymocarpus pedicellatus* R.Br. is found in Western Himalayas and used in medicine as a cure for stones in kidney and bladder.

*Mc Guffin et al., 2000* reported that *Didymocarpus pedicellata* R.Br. is native to Tropical Asia.

During the literature survey, it was found that *Didymocarpus pedicellatus* R.Br. was first reported from Buxa Duar by *Hilliard (2001)*. However *Mukherjee et al. (2008)* overlooked this report in their work.

*Agarwal (2003)* stated that *Didymocarpus pedicellata* R.Br. of Gesneriaceae grows on the Himalayas from Chamba to Kumaon. The leaves are aromatic with spicy odour and yield a red dye. The leaves are an indigenous medicine for kidney stones. The essential oil of the leaf is a medicine for swellings.

*Mabberley (2005)* stated that plants of Gesneriaceae have long narrow capsules split to form gutters down which raindrops carry away tiny seeds: *Didymocarpus platypus* C.B. Clarke produces 4 leaves a year, each lasting 22 months. The family includes 141 genera and 2900 species. The plants are usually herbs, sometimes epiphytic or shrubs or lianes, rarely trees.

Dry leaves of *Didymocarpus pedicellata* R.Br. possess a characteristic spicy odour and appear dusted with reddish colouring matter. (*Chopra et al., 1958*).
Tandon and Sharma (2009) have reviewed the articles on general information of five species of *Didymocarpus* Wallich ex Buch.-Ham., with special emphasis on pharmacognostic, pharmacological and biological studies on *Didymocarpus pedicellata* R.Br. It is mentioned in the review that the major bioactive phytoconstituents in *Didymocarpus* Wallich ex Buch.-Ham. are Didymocarpin A, Despedicellin, Methylpedicinin, Pedicinin, Pedicellin and Isodidymocarpin. It is felt that there is much scope for further comprehensive studies on various aspects of *Didymocarpus* Wallich ex Buch.-Ham. Pharmacognostical studies offer much reliable data for segregating the species of *Didymocarpus* Wallich ex Buch.-Ham. This part of study is given due accent in the present investigation.

The ether extract of the leaves of *Didymocarpus pedicellata* R.Br. was found to contain a new series of colouring matter viz., pedicin a coloured chalcone; isopedicin isolated as colourless prismatic needles; pedicinin crystallised as dark red flat needle and pedicellin isolated as colourless needles. (Siddiqui, 1937; Bahl & Seshadri, 1970).

The structure of the four compounds isolated from *Didymocarpus pedicellata* R.Br. were established as 5, 6- dihydroxy- 2, 3, 4 - trimethoxychalcone; 5- hydroxyl -2, 3, 4-trimethoxybenzylcoumaranone and 2, 3, 4, 5, 6 – pentamethoxychalcone, respectively (Sharma & Siddiqui, 1939).

A second isomer of pedicin, pseudo-isopedicin and a new colouring matter, pedicidin were also isolated from *Didymocarpus pedicellata* R.Br. (Warsi & Siddiqui, 1939a & b).

From the essential oil of the leaves terpenoidal constituents, didymocarpene, didymocarpol and didymocarpenol were isolated. The last two terpenoids were also
obtained from non-volatile fatty residue. Palmitic, stearic, behenic and lignoceric acids were also detected (Warsi & Siddiqui, 1939b).

Detailed studies carried out on pedicinin isolated from *Didymocarpus pedicellata* R.Br. led to the revision of the structure as 4, 5, 7- trihydroxy - 6 - methoxybenzylcoumaranone (Bose & Dutt, 1940; Salooja et al., 1947).

Visweswara Rao & Seshadri (1948) reported that pedicin is considered to be a para – dihydroxy chalkone and this constitution is confirmed by its synthesis from 2 – hydroxyl – 3 : 4 : 6 – trimethoxy chalkone using the method of nuclear oxidation with persulphate. The synthetic pedicin could be readily converted into pedicellin and pedicinin. Under the ordinary conditions of chalkone – flavonone conversion, it yields isopedicin which is therefore given the constitution of 6 – hydroxyl – 5 : 7 : 8 – trimethoxy flavonone. It is concluded that pedicinin and methylpedicinin have the hydroxyl – quinone – chalkone structure. Methylpedicinin which is an intermediate stage in the formation of pedicinin is now found to occur in the leaves of *Didymocarpus pedicellata* R.Br.

Seshadri (1965) and Rao et al. (1966) isolated dicarboxylic acid and pedicellic acid from the leaves of *Didymocarpus pedicellata* R.Br. The acid was characterized as α- methyl- α – tridecylsuccinc acid.

Rao et al. (1966) in their finding stated that pedicellic acid (C_{18}H_{34}C_{4}) obtained from the leaves of *Didymocarpus pedicellata* R.Br. is a dicarboxylic acid. Its UV and IR spectra indicate that it is a long chain aliphatic acid without unsaturation. The NMR spectrum of its dimethyl ester confirms the molecular formula and shows the presence of two different C-methyl groups and two identical carboxylic groups. Pedicellic acid
has been converted into the corresponding hydrocarbon called pedicellane. The constitution of the acid as \( \alpha \)-methyl-\( \alpha \)-tridecylsuccinic acid has been established.

**Bahl & Seshadri (1970)** reported that the yield of the total components like the proportion of individual ones, varied considerably but was usually about 30 percent of the weight of the dried leaves. Pedicin and pedicellin were major components, while pedicinin and methylpedicinin were obtained in smaller amounts. All these compounds were synthesized. The yield of pedicellic acid was about 1 percent of the air dried leaves in *Didymocarpus pedicellata* R.Br.

**Kapoor et al. (1971)** found that the root, stem, inflorescence and flowers of *Didymocarpus aromaticus* Wall. were devoid of saponins, alkaloids and flavonoids.

**Lowry (1972)** reported the occurrence of ‘normal’ 3- hydroxylated anthocyanins in 8 Malaysian species of the Gesneriaceae and this supports the important chemotaxonomic results for this family. New compounds found in *Didymocarpus* Wallich ex Buch.- Ham. are the 3 - arabinosylglucoside – 5 – glucosides of cyanidin and malidin, pigments which may have some systematic value.

The light petroleum ether extract of the root yielded three chalcones, besides \( \beta \)-sitosterol. All the three chalcones pedicin, pedicellin and pashanone, were isolated earlier from the leaves of *Didymocarpus pedicellata* R.Br. (Agarwal *et al.*, 1973).

**Bhaskar & Seshadri (1973)** reported that the petroleum ether extract of the leaves of *Didymocarpus pedicellata* R.Br. was found to contain, in addition to earlier isolated compounds, pedicin and pedicellin, pashanone and methylpedicin. The isolation of methylpedicin was reported from the plant source for the first time.

From the petroleum ether extract of *Didymocarpus aurantiaca* C.B. Clarke 2’- hydroxyl - 4’, 6’ – dimethoxy - 3’ - methylchalcone and 2’, 4’ - dihydroxy - 5’ - methyl -
6’-methoxycalcone, named aurentiacin A and aurentiacin B, respectively, were isolated. These were the first C-methylated chalcones to be found in nature (Aditya Chaudhury & Daskanungo, 1975; Aditya Chaudhury et al., 1976a).

Further studies with the petroleum ether extract of *Didymocarpus aurantiaca* C.B. Clarke yielded 2-pyrone derivatives 5, 6 – dehydrokawain and 7, 8 – epoxy – 5, 6 – dehydrokawain. The occurrence of 2-pyrone derivatives in *Didymocarpus* Wallich ex Buch.- Ham. was reported for the first time (Aditya Chaudhury et al., 1976b).

Murari et al. (1978) reported that the essential oil of *Didymocarpus pedicellata* R.Br. contains 70 percent humulene.

A flavanone, didymocarpin (7-hydroxy – 5, 6, 8-trimethoxyflavanone) as well as a new chalcone isodidymocarpin (2’, 4’-dihydroxy – 3’, 5’, 6’-trimethoxychalcone) were isolated from the leaves of *Didymocarpus pedicellata* R.Br. (Bose & Aditya Chaudhury, 1978a; b).

Bhattacharyya (1979) reported the presence of Isodidymocarpin from *Didymocarpus pedicellata* R.Br.

Bhattacharyya et al. (1979b) did further structural studies on isodidymocarpin.

In addition, another flavanone didymocarpin – A was isolated from the light petroleum extract of the leaves whose structure was established as 5, 8 – dihydroxy – 6, 7 – dimethoxyflavanone by its synthesis starting from pedicellin and pedicinin (Bhattacharyya et al., 1979b; 1980).

Garg et al. (1979) reported that the synthesized didymocarpin, however, did not match the natural one.

Mitra et al. (1980) reported that the petroleum ether extract of Didymocarpus oblonga Wall. yielded $7\beta$ - hydroxyl – (-) – 16 – kauren- 19 – oic acid.

Rathore et al. (1981) reported the isolation of $3'$ - hydroxyl – 2', 4', 5', 6' tetramethoxychalcone 5 – hydroxyl – 6, 7, 8 – trimethoxyflavanone and Isopedicin.

A chemical investigation of Didymocarpus pedicellata R.Br. has resulted in the isolation of 8 – hydroxyl – 5, 6, 7 – trimethoxy – flavanone, 2' - hydroxy - 4', 5', 6' - trimethoxychalcone 5, 6, 7, 8 - tetramethoxy flavanone, pedicellin, methylpedicin and beta – sitosterol. 8 – hydroxy – 5, 6, 7 – trimethoxy flavanone and 2' - hydroxy - 4', 5', 6' - trimethoxy chalcone flavanone and 2' hydroxy 4', 5', 6' - trimethoxy are hitherto new natural products while 5, 6, 7, 8 – tetramethoxy flavanone has been isolated from Didymocarpus pedicellata R.Br. for the first time. (Rathore et al., 1981)

The Benzene extract of Didymocarpus pedicellata R.Br. afforded a number of phenolic components including chalcones and flavanones. These were identified as $3'$ - hydroxy - 2', 4', 5', 6 – tetramethoxychalcone, 5 - hydroxy – 6, 7, 8 – trimethoxyflavanone and 6 – hydroxy – 5, 7, 8 -trimethoxyflavanone (isopedicin). (Rathore et al., 1981a)

The Benzene extract of Didymocarpus pedicellatus R.Br. afforded 8 – hydroxyl – 5, 6, 7 – trimethoxy flavanone 2' - hydroxyl - 2', 4', 5', 6 – trimethoxy chalcone, 4, 6, 7, 8 – tetramethoxy – flavanone, besides pedicellin, methylpedicin and $\beta$ – sitosterol. (Rathore et al., 1981b)
Amarendra Patra et al. (1982) reported carbon–13 signal assignment of 2’, 4’-dihydroxychalcone flemichapparin, pashanone, isodidymocarpin, pedicellin, pedicinin, methylpedicinin, didymocarpin–A and the corresponding quinoflavanone dehydrodidymocarpin–A.

The petroleum ether extract of Didymocarpus podocarpa C. B. Clarke yielded a compound identical to 7, 8–epoxy–5, 6–dehydralwain (Das et al., 1986) and aurenticin earlier isolated from D. aurantiaca C.B. Clarke (Haldar et al., 1989).

Guha and Bhattacharyya (1992) isolated a new flavone, pediflavone from the immature leaves of Didymocarpus pedicellata R.Br., identified as 5, 8–dihydroxy–7-methoxyflavone.

Sondhi and Agarwal (1995) estimated the percentage concentration of various mineral elements present in Didymocarpus podocarpa C. B. Clarke and found to be manganese (0.0124), cadmium (0.00013), magnesium (0.08610), zinc (0.00203), lead (0.00175), calcium (2.63000), iron (0.2822), nickel (0.00030), cobalt (0.00033), chromium (0.00033), sodium (0.0400), potassium (0.500), aluminium (0.1839), strontium (0.0035) and copper (-).

Gupta et al. (2008) reported that the aerial parts of Didymocarpus pedicellatus R.Br. yielded 31.4% (w/w) extract with ethanol. The percentage of pedicellin content was found to be 0.26 percent. Quantitative standards are also given as follows. Foreign matter: Not more than 2.0 percent. Ash: Not more than 13.0 percent. Acid–insoluble ash: Not more than 2.5 percent. Ethanol soluble extractive: Not less than 10.0 percent. Water soluble extractive: Not less than 10.0 percent.

Didymocarpus pedicellata R.Br. is only used as a household remedy in the areas in which it grows. It has a reputation in indigenous medicine as a cure for stones
in the kidney and bladder which it is believed are dissolved and passed out in urine (Chopra et al., 1958).

*Didymocarpus reptans* Jack is a creeping herb. Decoction of the leaves of this species is used for dysentery, colic and constipation (Uphof, 1959).

Bertolini and Greggia (1970) in their findings stated that an aqueous alcoholic extract of *Didymocarpus pedicellatus* R.Br. and pedicellin isolated from the plant produced a papaverine–like spasmolytic action on isolated ileum and uterus of the guinea pig and ascending colon of the rabbit. The extract inhibited the intestinal hypermotility produced by carbamoylcholine and prostigmine in cat and rat respectively.

Traditionally, *Didymocarpus pedicellata* R.Br. is used in the treatment of renal diseases, particularly kidney stones (Kapoor & Kapoor, 1976; Sharma et al., 1979; Methela et al., 1980; Jain, 1991; Samant & Palni, 2000).

Singh et al. (1978a), in their *in vitro* study, state that the essential oils of some of the constituents of *Origanum vulgare, Carum anethifolium, Didymocarpus pedicellatus* R.Br. and *Cymbopogon pendulus* were screened for antimicrobial activity in their original form and 1 : 1 combination against a number of bacteria and fungi viz., *Esch. coli, Staph. aureus, Salm. typhi, Salm. paratyphi, Salm. enteritidis, Salm. schottmuelleri, Sh. boydii, Proteus sp., Pasteurella multocida, Klebsiella sp., Ps. aeruginosa, Strept. sp., Salm.typhimurium, Bac. subtilis, Corynebacterium equi, Candida albicans, Trichophyton mentogrophytes, Aspergillus flavus, A. parasiticus, A. tamrri, A. ochraceous, Microporum gypsum, Penicillium expansum, Sporotrichum schenckii* and *Epidermophyton cresense. Didymocarpus pedicellatus* R.Br. was found to be the least active. However, *Didymocarpus pedicellatus* R.Br. oil
in 1:1 combination with other oils was found to be more active than the individual oil against the organisms.

Singh et al. (1978b) found that the essential oil of *Didymocarpus pedicellatus* R.Br. was quite effective in their *in vitro* against *Staph. aureus*, *Salm. typhii* and *Salm. boydii*. The oil also had good antifungal activity against *Aspergillus tamarii*, *A. ochraceous* and *A. flavus*.

Chatterji et al. (1979) reported that didymocarpin, isodidymocarpin and pedicellin isolated from *Didymocarpus pedicellatus* R.Br. showed potent larvicidal activity against jute semilooper last instar larvae.

Biswas et al. (1981) reported that the chalcones and flavanones viz., methylpedicin, isomethylpedicin, pedicinin, pedicellin, isodidymocarpin, didymocarpin – A, and despedicellin isolated from the leaves showed some degree of antibacterial activity against *Xanth campestris*. Amongst them pedicellin, didymocarpin and pedicinin were found to be good inhibitors at concentrations as low as 100 ppm. The compounds also showed strong antifungal activity against the plant fungi viz., *Rhizopus artocarpii*, *R oryzae sativae*. *Fusarium oxysporum* ssp. *ciceri*. However, less activity was noted against *Sclerotium rolfsii* and *Thanatephorus cucumeris*.

An Ayurvedic compound preparation (Cystone – *Didymocarpus pedicellata* R.Br. is a constituent) comprising nearly 15 plants and mineral products was found to contain water soluble substances which inhibited the initial precipitation of calcium and phosphate ions in the form of a mineral phase bound to the organic matrix and the subsequent growth of the preformed mineral phase. The aqueous extract of the
compound could stimulate the demineralization of the matrix–bound mineral phase (Jethi et al., 1983).

According to Ambasta (1986), Didymocarpus pedicellata R.Br. is lithontriptic. The leaves yield an essential oil. A number of crystalline colouring matters, including pedicin which is toxic to fish, have been isolated from the leaves.

Six teaspoons of Corallodiscus lanuginosus are taken twice daily to treat coughs and colds. Two teaspoons of plant juice are taken 4 times daily to treat flu. It was reported that whole plant extract of Corallodiscus lanuginosus is a potential antibiotic and potential antiviral agent. Didymocarpus primulifolius D.Don. is a potential antiviral agent. The two plants show no zone of inhibition against Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhimurium, Serratiam arcescens, Saccharomyces cervisiae and Aspergillus fumigatus. Corallodiscus lanuginosus is active only when exposed to UV light and its activity is enhanced against Mycobacter phlei. Didymocarpus primulifolius D.Don is active against Bacillus subtilis, Mycobacter phlei, Microsporum gypseum and Trichophyton mentagrophytes (Taylor et al., 1995).

Angels Bonet et al. (1999) reported that Ramonda myconi of Gesneriaceae is used as a folk medicine. The leaf and flower infusion of the plant is administered orally and it is a good anticatarrhal.

Mahadev Rao et al. (1999) reported that the composition of cystone has 65 mg of Didymocarpus pedicellata R.Br. flower. The effect of cystone, a polyherbal ayurvedic preparation, on the nephrotoxicity and antitumor activity of cisplatin is studied in C57BL/6J mice bearing B16Fi melanoma. Intraperitoneal administration of cisplatin 6 mg/kg, resulted in significant reduction of body weight, elevation of blood
urea nitrogen (BUN) and serum creatinine levels on day 5. Cystone was found to protect tumor-bearing mice from cisplatin–induced nephrotoxicity, when given intraperitoneal administration one hour before cisplatin. At 1000 mg/kg, it showed 46, 57 and 66% protection on body weight, BUN and serum creatinine levels, respectively. Treatment of cisplatin alone to tumor bearing mice resulted in significant antitumor activity as measured by tumor appearance, tumor volume and tumor weight. Pre-treatment with cystone (1000 mg/kg) did not reduce the antitumor activity of cisplatin. These results suggested that cystone protects against cisplatin – induced nephrotoxicity without interfering with its antitumor activity. The present study has many clinical implications in cisplatin chemotherapy.

Davis & Jonathan (2003) reported that the use of three herbal / nutritional products over a period of two months normalized blood urea nitrogen (BUN), serum creatinine and creatinine clearance in case of early functional kidney impairment. One among the three is the Ayurvedic Herbal formula consisting of 100 mg of *Didymocarpus pedicellata* R.Br.

Ethanolic extracts of the aerial parts of *Didymocarpus pedicellata* R.Br. demonstrated significant antioxidant and protective activity against ferric nitriloacetate induced renal oxidative stress, nephrotoxicity and tumor promotion response. Further, the extract significantly gave protection against ferric nitriloacetate mediated damage to lipid and DNA. The nephroprotective activity of the plant is attributed to polyphenolic compounds. The study further supported ancient use of plant in the treatment of kidney diseases (Gurpreet Kaura et al., 2007).

An ethanobotanical survey was carried out among the ethnic groups of Badagas in the Western Ghats of India. Traditional uses of 178 plant species spread over 78 families are described. One among them is *Didymocarpus tomentosa* Wight
The leaves of the plant are applied externally to cure skin allergy (Sathyavathi and Janardhanan, 2007).

Sudarshan Churna is a very potent Ayurvedic preparation which is used traditionally as an antimalarial and antipyretic formulation. Heart wood of *Didymocarpus pedicellata* R.Br. is one of the ingredients of sudarshan churna (Sushil Bhargava et al., 2008).

The outcome of 50 clinical studies indicated that cystone is useful in the management of urolithiasis as revealed by the clearance of calculi, symptomatic relief, increased urine volume and reduction in the stone forming constituents in urine with negligible adverse effects. Cystone is efficacious in management of urolithiasis especially when the site of urinary stone is ureter. Cystone treatment revealed a significant reduction in 24 hour urinary excretion of oxalate, uric acid, calcium, magnesium and phosphorus with a significant increase in urine volume. Cystone has a safety profile which has *Didymocarpus pedicellata* R.Br. as one of the constituents (Dilip Karamakar et al., 2010).

Pashanabheda is an Ayurvedic drug used in the treatment of urinary calculi, dysuria, polyuria, fever, piles, dysentery and uterine disorders. *Didymocarpus pedicellata* R.Br. is used as Pashanabheda in North India (Narayanaswami & Ali, 1967, Mukherjee et al., 1984). However Madhavan et al. (2010) claimed that the authentic source of Pashanabheda is *Nothosaerva brachiata*.

Paul and Ajita Sarkar (2010) have given a brief account of chemical composition of *Didymocarpus pedicellatus* R.Br. The plant contains polyterpenes (didymocarpol; didicarpenol), flavonoids (didymocarpin, isopedicin, pedicellin, pediflavone) and decarboxylic acid (Pedicellic acid). Pedicellic acid is the active
principle for anticancer activity. The essential oil, didymocarpene is said to possess antimicrobial activity. The authors also reported that the tribal community use this plant as home remedy for anal and blood cancer.