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Current status of research on the medicinal plant American skullcap (*Scutellaria lateriflora)*: A review

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ABSTRACT

Scutellaria lateriflora is commonly known as American skullcap. For over 200 years this plant has been traditionally used to treat insomnia, anxiety, and to promote a healthy menstrual cycle. Phytochemical analysis of this plant has revealed the presence of flavonoids, volatile oils, iridoids, diterpenoids, waxes, and tannins. American skullcap is found as natural supplements in the commercial herbal health industry and available in the form of tea, capsules, extracts, and tinctures. Plant can be used singly or in combination with multiple herbs. Recent studies indicating presence of melatonin (phytomelatonin) in skullcaps may strengthen its claim on anxiolytic property and lead to popular tea formulations. As the demand for American skullcap in increasing, it is important to revisit the plant to understand its production, natural landraces available, agronomy, breeding strategies, biotechnological modifications, and biomedical potential. In this review we will investigate, the history and current uses of this plant as well as discuss its botany, distribution, methods used to eliminate the presence of adulterants now found in the current herbal products market, phytochemical constituents, and future prospects of this plant in the horticulture and herbal products industry.

INTRODUCTION

The genus *Scutellaria* is a member of the mint family (Lamiaceae) that has been valued for its phytochemicals and their bioactivity (Joshee et al., 2002; Shang et al., 2010; Irvin et al., 2019). *Scutellaria* species include herbaceous annuals and perennials that grow best in partial shade / full sunlight, and well-drained soil with limited nutrients (Similien et al., 2012; Shiwakotiet al., 2016). There are many *Scutellaria* species located across the globe, mostly in the northern hemisphere. North America and Irano-Turanian regions exhibit highest diversity of *Scutellaria* species (Salimov et al., 2021). A thorough scrutiny of literature reports over 295 phytochemicals, including essential oils, isolated from 35 *Scutellaria* species (Shang et al., 2010) and systematic research identified a germplasm base of about 400 species (Paton, 1990). Skullcaps have been used in many traditional medicinal systems and biomedical studies to treat epilepsy, insomnia, hysteria, anxiety, delirium tremens, bronchitis, hepatitis, jaundice, diarrhea, dysentery, thrombosis, hypertension, tumors and withdrawal from barbiturates and tranquilizers (Moerman, 1998; Parajuli et al., 2009; Zhao et al., 2016; Setzer, 2018; Irvin et al., 2019; Sherman et al., 2021a). Native Americans have used *S. lateriflora*, *S. elliptica* and *S. incana* as strong emmenagogue, to promote a healthy menstrual cycle, expel afterbirth, and to stimulate the reproductive system post-partum in addition to treat fever, chills, diarrhea, sore throats, eye pain, kidneys, nerves, heart conditions and insomnia (Moerman, 1998; Wills and Stewart, 2004). The chemical constituents of the *Scutellaria* genus include flavonoids, volatile oils, iridoids, diterpenoids, waxes, and tannins (Wren, 1998; Wills and Stewart, 2004).

Growing medicinal plants provide farmers an avenue to diversify their crops and generate additional income. More consumers are becoming

interested in buying locally grown or locally sourced products assisting herbal products market to flourish. The herbal products market is projected to reach around USD 86.74 Billion by 2022 (Markets and Markets, 2016). There is continuing demand for high-quality herbal products and estimates of American Herbal Products Association (AHPA) suggest that 3000 plant species are being traded at any point of time (Mudge et al., 2016). In the context of Southeastern United States, American skullcap (*Scutellaria lateriflora*), black cohosh (*Actaea racemose* L.), bloodroot (*Sanguinaria canadensis* L.), California poppy (*Eschscholzia californica*), ginseng (*Panax quinquifolius* L.), goldenseal (*Hydrastis canadensis*), purple coneflower (*Echinacea purpurea* (L.) Monech), and valerian (*Valeriana officinalis*) have been suggested as suitable herbs to grow for commercial gains (Davis, 2012). Worldwide investigations keep enriching skullcap literature as two new species were reported from Burma and Thailand (Paton et al., 2016) and four *Scutellaria* species (*S. barbata*, *S. discolor*, *S. orientalis*, and *S. prostrata*) were recorded from the Himalayan region for their phytochemical profile and medicinal applications (Dahal et al., 2021). *Scutellaria barbata* has been used to treat several health issues associated with inflammation, stress, and anxiety. Clinical studies have used *S. barbata* extracts in the treatment of breast and prostate cancer (Rugo et al., 2007; Perez et al., 2010). Many of the traditional uses of this plant, especially in relation to treating stress, insomnia, headaches, and the menstrual health of women, are still practiced (Duke, 1997; Irvine et al., 2019). In this review, we will discuss American skullcap, its botany, phytochemistry, and its role as a medicinal plant throughout history and future prospects.

Scutellaria lateriflora. *Scutellaria lateriflora* L. is commonly referred to as American skullcap. It is one of the most traded skullcaps as herbal supplement and tea. Native Americans have employed this plant to treat anxiety, insomnia, help treat breast pain and expel afterbirth (Moerman, 1998). American skullcap has been used for over 200 years as a mild sedative or relaxant (Foster and Duke, 2000). The plant was first named as *Cassida* (Tournefort, 1716) but was later changed to *Scutellaria* (Latin word *scutella* meaning 'little dish'), in reference to the lid of the calyx (Upton, 2009). The first mention of American skullcap in medical literature was a curative and prophylactic one in canine rabies. These claims were disproven but explains the common name 'mad dog skullcap'. Cherokee Native Americans utilized American skullcap as an infusion or decoction to treat breast pain, expel afterbirth and promote menstruation (Moerman 1998, 2009). The Iroquois used *S. lateriflora* roots in a concoction to prevent smallpox and treat throat ailments (Upton, 2009).

Currently, American skullcap is one of the most commonly cultivated skullcap species along with *S. baicalensis* and *S. barbata*. The aerial parts of *S. lateriflora* are harvested and used for the herbal products market in the form of extracts, tinctures, capsules, and granules in addition to tea. *Scutellaria baicalensis* (Chinese skullcap) is harvested for its roots containing wogonin and used in numerous formulations in Traditional Chinese medicine (TCM). American skullcap has been associated erroneously with hepato-toxicity in the past due to the adulteration with germander (*Teucrium canadensis* and *Teucrium chamaedrys*). Germander, which is also known as pink skullcap, is morphologically similar to American skullcap and can be misidentified easily (Gafner and Blumenthal, 2016). Adulteration of herbal products is an issue that is often caused by misidentification introduced by the form in which it is sold or poor preparation by personnel responsible for processing or formulating herbs (Fennel et al., 2004). Study of micromorphological traits can provide a tool for identifying adulterated herbal samples with other species from the same genus or some distantly related plants (Soundappan et al., 2018; Shahin et al., 2019; Song et al., 2020).

Distribution and Botany. *Scutellaria lateriflora* is a facultative wetland plant that grows naturally in moist wooded areas (Foster and Duke, 2000; USDA, 2020). Riparian habitats that include stream banks, marshes, and wet meadows are natural habitat for *Scutellaria lateriflora*. American skullcap grows throughout most of North America ranging from Canada to Florida and westward to British Columbia, Oregon, and New Mexico (USDA, 2020).

Scutellaria lateriflora is an upright herbaceous perennial plant (Gill, 1980). The stems are quadrangular, and glabrous to sparsely hairy. The leaves are simple, opposite and ovate, crenate to

serrate, and can reach < 11 cm long and 1.5-5.5 cm wide (Upton, 2009). Inflorescences are slender, spreading, and arranged in racemes that are mostly axillary. Flowers are perfect, bilabiate, pedicellate, 1-3 mm; calyx bilabiate 1.5-3.0 mm, and corolla is blue, 6-8 mm in length. The upper lip is smaller than the lower, the lower lip has three lobes. The ovary is superior with four lobes. Four stamens are present that are fused with corolla lobes (Upton, 2009). The gynobase (seed base) supports four ovules that form the future nutlets (achenes). These parts and the base of the calyx constitute the ovary.

Cultivation and propagation. American skullcap can be propagated from seed, cuttings, and root division. The plant grows in full sun but prefers partial shade (Similien et al., 2012). Seeds sown in late fall germinate the following spring. Seeds can also be sown in the spring and germinate within one to two weeks (Upton, 2009; Upton and Dayu, 2012). Most *Scutellaria* species grow poorly in rich organic soils and should not be over-fertilized. Considering the demand and medicinal importance, a general guideline of the production of American skullcap was reported by Wills and Stuart (2004) for Australian conditions. This followed many studies in different parts of the US to establish guidelines for field production of American skullcap; Greenfield and Davis (2004) in North Carolina and Janke et al. (2005) for small farmers in Kansas. In the south-eastern USA, Similien et al. (2012) demonstrated that application of a combination of nutrients were helpful in enhancing yield, and Shiwakoti et al. (2016) tested the role of individual nutrients to study flavonoid content of *S. lateriflora*. Application of 400 kg/N ha^{-1} was best for shoot dry weight with higher baicalein concentration and overall yield of baicalein and chrysin. Phosphorus application at 300 kg/P ha^{-1} resulted in a linear response for shoot dry weight, yield of scutellarein, baicalein, baicalin, and higher chrysin and baicalein concentrations. An application 200 kg/K ha^{-1} of potassium produced the highest shoot dry weight. Applying potassium had no effect on scutellarein, baicalin, baicalin, and chrysin concentration or yield.

The systematic research on the investigation of *Scutellaria* germplasm is initiated and protocols for multiplication of commercially important species and preservation of rare germplasm to assist conservation is optimized. A few successful micropropagation studies on *S. lateriflora* have been reported (Tascan, 2007; Tascan et al., 2010; Kawka et al., 2017, 2020). A summary of past micropropagation efforts on *S. lateriflora* are summarized in Table 1. Major focus on the micropropagation / sterile culture of *S. lateriflora* has been for developing an *in vitro* multiplication system and to study secondary metabolite synthesis (Tascan, 2007; Tascan et al., 2010; Kawka et al., 2017, 2020). A comparative micropropagation study including three skullcaps (*S. lateriflora, S. costaricana,* and *S. baicalensis*), using semi-solid agar, liquid stationary, liquid agitated, and liquid culture with floating paper raft systems were analyzed for fresh weight, dry weight, percent dry weight, multiplication ratio, role of sucrose, media constituents and water uptake (Tascan, 2007). Semi-solid agar medium produced the highest multiplication ratio, whereas dry weight yield was highest in liquid agitated followed by agar, and liquid stationary system with fiber paper. Tascan et al., 2010 reported the biomass production of *S. lateriflora* employing micropropagation in semi-solid and liquid culture system (Liquid Lab Bioreactor system) (Figure 1 A, B). *In vitro* produced plants were acclimatized using a standardized protocol and eventually transferred to the greenhouse (Figure 1 C, D). These plants grew well, attained full vegetative growth and flowered (Figure 1 D, E). Culture conditions played an important role in the generation of higher biomass and quality plants. Plants with highest quality (on the basis of physical look and multiplication) were produced in semi-solid agar and liquid cultures with fiber support. The multiplication ratio was 8 shoots per explant for semi solid agar and 6 shoots per explant using liquid stationary with fiber support after 8 weeks in culture (Tascan et al., 2010). An issue that adversely affects plant quality and biomass recovery is generation of hyperhydric plants that was prominent in liquid agitated system and were rather rare in liquid stationary system with fiber support and semi-solid agar medium (Tascan et al., 2010). Biomass production was highest in liquid agitated system using MS medium supplemented with 1.0 mg L^{-1} BAP and 1.0 mg L^{-1} NAA. In comparison to semi-solid agar based medium, liquid agitated cultures produced 5-10 folds higher biomass on dry weight basis (Kawka et al., 2020). Though sucrose is the most widely used sugar in plant tissue culture, a variety of carbon sources (reducing and non-

reducing) are used to suit various species at specific stages of development (Yaseen et al., 2013; Vaidya et al., 2016). *In vitro* multiplication of *S. ocmulgee* has been optimized using transverse thin cell layer explants testing Murashige and Skoog (MS) (1962) and Gamborg's B5 (B5) (Gamborg et al., 1968) media incorporating various concentrations of phytohormones and carbon source as sucrose or maltose. High number of adventitious shoot induction was optimized producing an average of 52 and 59 shoots from stem and leaf explant, respectively (Vaidya et al, 2016). In summary *S. lateriflora* does best on semi-solid agar culture conditions or liquid conditions with additional fiber support. The fiber support seems to play an important role in reducing hyperhydricity thus producing a higher quality product suitable for acclimatizing into field or greenhouse conditions (Tascan et al., 2007; 2010).

Phytochemistry. Several studies have been conducted screening of the chemical composition of *S. lateriflora* tissues resulting in the identification of anxiolytic and antioxidant compounds (Awad et al., 2003; Bergeron et al., 2005; Sarris, 2007; Zhang et al., 2009; Brock et al., 2010; Lohani, 2014; Vaidya et al., 2013). The most prominent flavonoids found in American skullcap are wogonin, baicalin, and lateriflorin (Nishikawa et al., 1999; Gafner et al., 2000). Bioactive compounds extracted from *S. lateriflora* include: baicalin, baicalein, wogonin, melatonin, serotonin, viscidulin III-2'-O-glc, Chyrin-6-C-ara-glc, *trans*-verbascoside, viscidulin, *trans*-martynoside, oroxylin A-7-O-glc, wogonoside, chitin, oroxylin A, and scutellarin (Nishikawa et al., 1999; Cole et al., 2008; Zhang et al., 2009). The chromatographs of three *S. lateriflora* extracts obtained with distilled water, 50% EtOH, and 95 % EtOH, when compared, revealed the presence of baicalin whereas baicalein partitioned to the ethanolic extracts (Awad et al., 2003). Other compounds like gluatmine, β-alanine, taurine, and GABA were detected in 95 % EtOH extracts (Awad et al., 2003). While studying anticonvulsant properties of American skullcap, 10 flavonoids and two phenylethanoid glycosides were isolated (Zhang et al., 2009). Comparative phytochemical screening of five *Scutellaria* species in various plant parts, including *S. lateriflora*, revealed that liquid chromatography coupled with diode array detector method (LC-DAD) and Liquid Chromatography with tandem mass spectrometry (LC-MS/MS) both are robust analytical methods (Nurul Islam et al., 2011). In this study scutellarin and baicalin were detected in *Scutellaria lateriflora* leaf tissue, and acteocide and scutellarin were present in stem tissues. Baicalin, baicalein, wogonin, and oroxylin A were detected in the roots of *S. lateriflora* (Nural Islam et al., 2011).

Essential oils from *Scutellaria lateriflora* L. plants growing wild in northern Iran were investigated (Yaghmai, 1988). The oil contained sesquiterpenes as the major group of compounds that were represented by τ-cadinene, calamenene, β-elemene, α-cubebene, and α-humulene as the major components. A total of 73 volatile compounds were detected in the oil with non-terpenoid constituents being in lower concentrations. A recent study comparing essential oil profile of four *Scutellaria* species grown in Alabama, USA, revealed the presence of eight dominant terpenoids (Lawson et al., 2021). Essential oils perform various important functions for the plants and are produced in special structures called trichomes (Figure 1 F). Secretory trichomes are peltate or capitate type and primarily help plants with antifeedant compounds to repel insects and in tiding over adverse weather conditions (Sherman et al., 2021b).

In vitro culture systems provide opportunity to study production of desired and novel chemicals under controlled conditions by varying nutritional regimen, phytohormones, elicitor molecules, precursor molecules and their biotransformation and reproducibility with scaled up operations. A comparative study of *in vitro* grown cultures and soil grown plants of *Scutellaria lateriflora*, and *S. baicalensis* revealed that the antioxidant capacity of *in vitro* cultures was significantly higher than their soil grown counterparts (Dziurka et al., 2021). It is suggested that this is due to the variability in the outdoor growing conditions in comparison to the controlled *in vitro* environment. Further, controlled and /or semi-controlled environment production eliminates climate, soil, and nutritional variation and thus becoming a major force in the production of chemicals, medicinal plants, and vegetable crops. *In vitro* micropropagation of *S. lateriflora* carried out on MS medium with different combinations of phytohormones (BAP and NAA) under different light conditions (monochromatic, white, blue, UVA,

and no light) revealed that blue light specifically stimulated the production of secondary metabolites (Kawka et al., 2017). It was under these conditions that the highest amounts of flavonoids and flavonoid glucuronidides, baicalin, wogonoside, and verbascoside were detected (Kawka et al., 2017). Semi-solid Linsmaier-Skoog (1965) culture medium supplemented with 1.0 mg L^{-1} BAP and 1.0 mg L^{-1} NAA was the best treatment for the production of flavonoids, phenolic acids and their precursors, and phenylethanoid glycosides (Kawka et al., 2020). The effect of light on the production of bioactive compounds has been reported in *S. lateriflora*, *S. galericulata*, and *S. racemosa* (Forsyth et al., 2020). It was found that melatonin, serotonin, abscisic acid (ABA), indole acetic acid (IAA), and jasmonic acid was detected in all three species grown under white, red, blue, and green light conditions using daylight fluorescent or LED lights. Supplementation of the media with melatonin had no effect on the production of melatonin under blue, white, or red light conditions. Data from this study indicates that relative amounts of melatonin correlate with the plant's exposure to specific light spectra (Forsyth et al., 2020). Plant growth regulators like melatonin and serotonin play important roles mediating different aspects of metabolism, plant growth, and development (Erland et al., 2015).

Studies conducted using carbon dioxide (CO_2) enrichment on a medicinal plant *Hypericum* (St. John's wort) in a closed culture system provided ample evidence that in general, all the growth parameters and bioactive compounds hypericin and pseudohypericin levels were significantly higher (Zobayed and Saxena, 2004). Another study with CO_2 enrichment on *S. lateriflora* and *S. barbata* indicated increased growth rate and reduced time to bloom in controlled environment (Stutte et al., 2007). But these responses are species specific and vary a great deal suggesting no clear chemical or biosynthetic explanation. Stutte et al. (2008) used CO_2 enrichment to enhance growth and flavonoid content of *S. barbata* and *S. lateriflora* and found *S. lateriflora* was more responsive to CO_2 enrichment when compared to *S. barbata* for biomass and flavonoid contents. All four flavonoids that were marked, increased in response to CO_2 enrichment. Baicalin concentration increased up to 4.7 - fold at 3000 $\mu mol \cdot mol^{-1}$ concentration of CO_2. Flavonoids baicalein, wogonin, and chrysin increased in a similar fashion (Stutte et al., 2008).

Genetic transformation and production of bioactive compounds. Metabolic engineering is a promising way to direct preferred or enhanced production of bioactive compounds by supplementation of precursors, and the overexpression of regulatory genes or transcription factors targeting desired biosynthetic pathways. This approach requires the understanding of the regulation of the secondary metabolite pathways involved on the levels of products, enzymes and genes, including aspects as transport and compartmentation and can be facilitated by various genetic transformation strategies. A summary of genetic transformation work of *S. lateriflora* is detailed in Table 2.

Agrobacterium rhizogenes induced hairy root cultures can be useful in the bioproduction of secondary metabolites (Giri and Narasu, 2000; Georgiev et al., 2007; Marsh et al., 2014; Fang et al., 2020) and have been successfully used for *S. lateriflora* (Marsh et al., 2014). Hairy root cultures induced by *Agrobacterium rhizogenes* are important because they can serve as a platform for production of bioactive compounds especially since they exhibit growth rates comparable to cell suspension cultures (Giri and Narasu, 2000; Georgiev et al., 2007; Marsh et al., 2014). It has been reported that hairy root cultures are capable of reproducing the biosynthetic capacity of the entire plant (Ono and Tian, 2011). Transgenic hairy root cultures of *S. lateriflora* exhibited potential for the production of bioactive secondary metabolites in response to elicitors (Wilczanska-Barska et al., 2012; Marsh et al., 2014). Hairy roots of *S. lateriflora* were established for elicitation studies using internode explants (Marsh et al., 2014). After six weeks in culture, the plants were treated with various concentrations of β - cyclodextrin (β-CD) and β-CD combined with methyl jasmonate for 24 h in either light or dark conditions. After 24 h of elicitor treatment seven phenolic compounds (flavones scutellarein, baicalein, wogonin, and their respective glucuronides; scutellarin, baicalin, and wogonoside) were detected (Marsh et al., 2014).

Commercial Production and economics. Skullcap is commercially available in the form of liquid extracts, capsules, tablets, tea, and dried

powder. Tinctures of skullcap use ethanol: water (40-60 % ethanol) solvent that typically extracts about 70 % flavonoids (Wills and Stewart, 2004). In the U.S., many commercial companies sell dry herb for tea. An earlier study predicted the demand for skullcap in the world markets to grow at an annual rate of 20–30% (Greenfeild and Davis, 2004). The dry powder form of the herb *Scutellaria lateriflora* is sold in the market at $121.41/kg that may be adulterated with germander and other species of *Scutellaria* (Gafner and Blumenthal, 2016; Upton, 2009). Reports of hepatotoxicity was linked to the ingestion of skullcap products in the past. On a closer investigation it was found that the adulterant was germander (*Teucrium canadense*, *T. chamaedrys*) which has morphology similar to skullcaps (Upton, 2009; Upton et al., 2011; Gafner and Blumenthal, 2016). Analytical methods like thin-layer chromatography with ultra-violet or diode array detection, and liquid chromatography/mass spectrometry, flow injection Mass spectrometry fingerprinting approach and an ultra-high performance liquid chromatography high resolution MS method have been used to distinguish raw plant material of *S. lateriflora* and *T. canadensis* and *T. chamaedrys* (Sun and Chen, 2011). These methods are highly expensive, time consuming, and not readily available, hence impractical for day-to-day use. Microscopy produces quick cost-effective results to obtain a better understanding of plant structure and identity and purity of dried herbs and spices (Upton et al., 2011; Osman et al., 2019). Traditional medicine involves the use of plant parts in crude form, either fresh or dried. Quantitative microscopy can assist in scoring micromorphological features like vein-islet number, vein termination number, stomatal number, stomatal index, trichomes, and palisade ratio for identification of crude biomass. Light and scanning electron microscopy was used to study palisade ratio, vein islet and termination number, trichome morphology, and cuticle, whereas fluorescent microscopy- based detection was used to study presence of secondary metabolites on the leaves and flowers of *S. lateriflora* (Sherman et al., 2021b). Microscopic protocols may serve as a quick method to distinguish plant material from an adulterant. No differences were found between greenhouse grown research material and commercial tea sample (vendor) in terms of palisade ratio and vein islet number though data for the number of vein termination points varied. This may be due to degradation of the plant material during processing (Jayeloa, 2009).

Biomedical studies. Biomedical studies show that *S. lateriflora* and other *Scutellaria* extracts exhibit anti-tumor properties due to the presence of flavonoids wogonin, baicalein, and baicalin (Parajuli et al., 2009; Patel et al., 2013). The whole extract, as well as the isolated phytochemicals present in *S. lateriflora*, showed strong anti-cancer activity against cancer cell lines U87-MG and U251 (Human malignant glioma), MDA-MB231 (malignant breast cancer) and PC3 (human prostate cancer) (Parajuli et al., 2009). Baicalin, a flavonoid isolated from the *S. lateriflora,* has been shown to suppress migration and invasion of an aggressive breast cancer cell line, MDA-MB-231 without any effect on cancer cell viability. Baicalin also inhibited expression of markers for epithelial to mesenchymal transition (EMT), a phenomenon associated with metastatic events. In addition, *in vivo* study in xenograft mouse model illustrated that baicalin inhibits breast cancer metastasis to the lungs and liver (Zhou et al. 2017).

The anxiolytic properties of American skullcap are attributed to γ-aminobutyric acid (Bergeron et al., 2005). Anti-anxiety effects of *Scutellaria lateriflora* has been studied in both humans and animals. A double blind study in humans to study the anxiolytic effects of American skullcap suggested that the group receiving skullcap capsules rated reduction in anxiety parameters when compared to the placebo and that the antianxiety effects was dose-dependent (Wolfson and Hoffman, 2003). In summary, *S. lateriflora* extract were found to have protective effects which suppress apoptosis and by increasing anti-oxidative capacity of neurons therefore, provide novel insights into the molecular mechanisms underlying the neuroprotective activity of *S. lateriflora* compounds using PC12 (pheochromocytoma) and H19-7 (hippocampal) cells from mice (Lohani, 2014). Beneficial effects of *S. lateriflora* tea for prevention and therapy of protein misfolding diseases were attributed to anti-aggregatory and potential anti-oxidative effects of baicalein and baicalin. It was concluded that herbal components of *S. lateriflora* are a promising remedy in prion diseases and related ailments (Eiden et al., 2012).

There is considerable interest in the sedative and calming properties of *Scutellaria* species after the

discovery of melatonin (phytomelatonin) though it was first reported in edible plants (Hattori et al., 1995). Melatonin production has been reported in approximately 300 plant species including *S. lateriflora, S. galericulata,* and *S. racemosa* (Hattori et al., 1995; Murch et al., 2000; Forsyth et al., 2020). Melatonin plays an important role in shoot organogenesis promoting new shoot development and help maintain existing tissues (Erland et al., 2015). Regulation of flowering time has been reported as an activity of melatonin in the short-day plant *Chenopodium rubrum*. Application of melatonin at specific time points, before darkness or in the first half of the dark period, resulted in a significant decrease in flowering (Kolar et al., 2003). Exogenous application of melatonin has been reported to increase seed growth and germination in soybean (*Glycine max*), cucumber (*Cucumis sativus*), corn (*Zea mays*), mung bean (*Vigna radiata*), red cabbage (*Brassica oleracea rubrum*) and purple tansy (*Phacelia tanacetifolia*) (Posmyk et al., 2008, 2009; Tiryaki and Keles, 2012; Byeon et al., 2013; Zhang et al., 2014; Wei et al., 2015).

Future prospects. *Scutellaria lateriflora* has been used in herbal formulations in many plant - based medical systems and the demand for plant - based remedies have witnessed an upswing in recent years. This provides an opportunity to grow skullcaps for additional income with limited land resources. Many of the *Scutellaria* spp. are good in attracting pollinators thus important component for the surrounding ecosystem. The demand for increased quality control should be addressed using all available methods. Microscopy is not always useful as the sole method of identification but this technique can be used in association with other analytical methods such as mass spectroscopy, or chromatographic profiling (Lin et al., 2009; Sun and Chen, 2011). Depending on the taxonomist and system followed, there are a reported 360-400 *Scutellaria* species. Micromorphological features can be of great help to assign correct taxonomic position when used with other tools. Micropropagation has a lot of potential to scale up pathogen free biomass production of valuable medicinal plants such as *S. lateriflora*. It is important to study *in vitro* physiology and biochemistry of the plant to assist future large-scale production. There is potential to go further with genetic transformation of this plant which could eliminate susceptibility to pathogens such as powdery mildew disease further improving plant quality and reduce or eliminate the need for fungicides and other chemical disease control.

CONCLUSIONS

Scutellaria lateriflora is an important medicinal plant which has been used for centuries by Native Americans. There are few reports available on the bioactive compounds and essential oil profile of this plant. Biomedical studies have shown promise with anxiolytic properties of *S. lateriflora* compounds that promises a market for value-added products. Micropropagation and genetic transformation /gene editing studies have great potential to help scale up biomass production and *in vitro* production of desired bioactive compounds. More studies are required to understand geographical regions and soil types where it can be grown as a commercial crop. Collection of various landraces and ecotypes will help broaden the germplasm base (gene pool) for breeding strategies to develop lines with higher bioactive compounds, resistance against biotic and abiotic factors, higher biomass recovery at harvesting.

Figure 1. *Scutellaria lateriflora* micropropagation and reproductive biology. A. Adventitious shoot bud induction in semi-solid medium, B. Shoot elongation and rooting in the 'Liquid Lab Bioreactor', C. Successful acclimatization of micropropagated plants and transfer to the pots, D. Micropropagated plants flowering in the greenhouse, E. Close-up of flower, F. Anther sac with trichomes and glands (Joshee et al., 2010).

Table 1. Role of different *in vitro* culture systems on shoot induction, biomass production, hyperhydricity and accumulation of bioactive compounds in *Scutellaria lateriflora.*

Media	System	Cytokinin (µM)	Auxin (µM)	Experiment type	Explant	Type of Light	Shoot count	Reference
MS	Liquid agitated	BAP 5.0	NAA 0.025	Shoot induction/ biomass	Nodes	White	2	Tascan et al., 2007
MS	Liquid stationary	BAP 5.0	NAA 0.025	Shoot induction/ biomass	Nodes	White	3.4	
MS	Agar	BAP 5.0	NAA 0.025	Shoot induction/ biomass	Nodes	White	7.3	
MS	Floating paper	BAP 5.0	NAA 0.025	Shoot induction / biomass	Nodes	White	5.5	
MS	Floating paper 20	BAP 5.0	NAA 0.025	Shoot induction/ biomass	Nodes	White	7.2	Tascan et al., 2010
MS	Liquid	BAP 5.0	NAA 0.025	Shoot induction/ biomass	Nodes	White	4.2	
MS	Agar	BAP 5.0	NAA 0.025	Shoot induction/ biomass	Nodes	White	8.5	
MS	Floating paper 30	BAP 5.0	NAA 0.025	Shoot induction/ biomass	Nodes	White	6.2	
MSV	Agar	-	IBA 2.54	Bioactive compound synthesis	Internode	White		Marsh et al, 2014
MS	Liquid	BAP 4.4	NAA 5.2	Biomass	Nodes	Blue		Kawka et al., 2017
MS	Liquid	BAP 13.3	NAA 5.2	Biomass	Nodes	Red		
MS	Liquid	BAP 8.8	NAA 10.4	Biomass	Nodes	UVA		
MS	Liquid	BAP 8.8	NAA 10.4	Biomass	Nodes	No light		
MS	Liquid	BAP 13.3	NAA 10.4	Biomass	Nodes	White		
MS	Liquid agitated	BAP 4.4	NAA 5.2	Biomass	Microshoots	White		Kawka et al., 2020
LS	Agar	BAP 4.4	NAA 2.6	Total flavonoids	Microshoots	White		
MSO	Agar	-	-	Indoleamines	Seedlings	White		Forsyth et al., 2020
MSO	Agar	-	-	Indoleamines	Seedlings	Blue		
MSO	Agar	-	-	Indoleamines	Seedlings	Red		
MSO	Agar	-	-	Indoleamines	Seedlings	Green		
MS	Agar	BAP 4.4	NAA 2.6	Biomass/ antioxidant capacity	Microshoots	White		Dziurka et al., 2021

*Linsmaier and Skoog (1965; LS), Culture medium containing MS salts and B5 vitamins (MSO).

Table 2. Genetic transformation studies on *Scutellaria lateriflora*.

Media	**System**	**Plant growth regulator (µM)**	**Elicitator (µM)**	**Antibiotics (mg L^{-1})**	**Experiment type**	**Explant**	**Light / Dark**	**Reference**
MS	Semi-solid and liquid	4.92 IBA	Methyl jasmonate 100	-	Hairy Root cultures	Stem	Darkness	Wu et al., 2009
MS	Semi-solid and liquid	-	Acetosyringone	Cefotaxime 250, Kanamycin 50	Hairy root cultures	Leaf	-	Yang et al., 2012
MSV	Semi-solid and Liquid	2.46 IBA	Methyl-β-cyclodextrin 15	Cefotaxime 600	Hairy root cultures	Internode	Light	Marsh et al., 2014

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