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Exploring the potential of *Centella asiatica* and *Bacopa monnieri* in immunodeficiency disorders in women: Two herbs as Holy Grail

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ABSTRACT

Immunodeficiency disorders are serious and debilitating illness that affect multitude of women. While research is still shedding light on genetic as well as hormonal and environmental risk factors that contribute to the causes of these autoimmune diseases in general population, they still remain among the most poorly understood and poorly recognized forms of infirmities. Many adaptogens exert immunomodulatory properties and some herbal plants are the promising candidates to treat immunodeficiency disorders. The review focuses on the role of oxidative stress in the pathogenesis of immunodeficiency and autoimmune disorders and the protective efficacy of herbal plants, namely Centella asiatica and Bacopa monnieri against these diseases.

***Keywords*:** Immunodeficiency disorders, oxidative stress, *Centella asiatica*, *Bacopa monnieri*.

INTRODUCTION

There are some 6-8 major immune diseases that in particularly disable women at a ratio of 8/9:1 over men (Voskuhl, 2011; Mariani, 2004). These are lupus, chronic fatigue, fibromyalgia, Sjogrens syndrome among others. These are very complex and comprehensive disabling diseases and the third most common category of disease in the United States (NIH report, 2002; Rose, 2002; Rose, 1997). An important unifying theme in autoimmune diseases is a high prevalence in women and it is estimated that 6.7 million or 78.8% of the persons with immunodeficiency disorders are women (Jacobson *et al*., 1997; Whitacre, 2001). The reasons for the high prevalence in women are unknown, but circumstantial evidence links autoimmune diseases with preceding infections. In several instances, such as rheumatoid arthritis, multiple sclerosis, and myocarditis, it was noted that such disorders have high prevalence in women because of higher levels of antibodies and initiate larger inflammatory responses than men when their immune systems are triggered. This possibly increases the risk of autoimmunity increasing susceptibility of various autoimmune diseases leading to morbidity and mortality. Hormones are thought to play a role because some autoimmune illnesses occur more frequently after menopause and others suddenly improve during pregnancy with flare-ups occurring after delivery or even get worse during pregnancy (Levy *et al*., 2013; Fairweather and Rose, 2004). To help women live longer healthier lives, a better understanding of these diseases is needed, as well as providing early diagnosis and treatments. Most of the allopathic treatment available today are cytotoxic and exerts a variety of side effects. This has given rise to stimulus to research for locating natural resources as alternatives showing immunomodulatory activity (Patil *et al*., 1998; Patil *et al*., 2008). Triterpenoid saponins are either triterpene or steroid glycosides, widely distributed in plant and animal kingdom and include a large number of biologically active compounds. They have been reported to exert immunomodulatory activity since long (Plohmann et al., 1997; Mali *et al*., 2006; Campbell and Peerbaye, 1992; Lacaille-Dubois, 1999). Two of the reputed herbal plants *Centella asiatica* (CA) and *Bacopa monnieri* (BM) have been used in the treatment of numerous diseases for thousands of years and continues to draw worldwide attention for its roles in the treatment of both mild and chronic diseases. These two important herbal plants were found to contain triterpenoid saponins as their major active constituents. CA and BM are adaptogens which have broad therapeutic activities that encourage the body to adapt better to stress as indicated in autoimmune conditions. The present article focuses

on exploring the protective efficacy of both these herbal plants in treating immunodeficiency disorders in women based on their immunomodulatory, antioxidant and related activities deliberating on the role of oxidative stress in the pathogenesis of immunodeficiency and autoimmune disorders.

Immunodeficiency disorders

The term 'immunity' traditionally refers to the resistance obtained by host toward injury caused by microorganisms and their products. The mechanisms of immunity are involved in the protection of the body against infectious agent but they can also damage host organism called as autoimmunity (Ananthanarayanan and Jayaram, 2008). The causes of autoimmunity are commonly multifactorial, involving a combination of genetic, environmental, hormonal and immune factors. Key factors involve abnormal cytokine biology and activation of auto- or self-reactive CD4 positive T cells. Environmental factors that trigger these immune processes include reproductive hormones, mechanical injury, chemicals (such as cigarette smoke) and, most significantly, viral and bacterial infections (Janeway *et al*., 2001; Belkaid and Hand, 2014). Susceptibility to these diseases are influenced in large part by genetics, particularly MHC-related genes, but they may also be influenced by environmental agents (Pollard *et al*., 2010). The natural regulation of the autoimmune process is known to involve antigen-specific regulatory cells as well as antiinflammatory cytokines such as IL-10 and TGF-beta (Benjamine *et al*., 2016). The antigen-specific immune therapy, targeted at a specific immune response, rather than general therapies targeted at the whole immune system, remains a critical goal for the treatment of these chronic debilitating diseases (Rosenblum *et al*., 2012). Moreover, familial studies suggest a clear association between genetics and autoimmune diseases, particularly those with an organ-specific pathology (Castiblanco *et al*., 2013; Cruz-Tapias *et al.*, 2013). TCR-ax gene polymorphisms have also been associated with disease susceptibility (Smith and Germolec, 1999). For some time, the basic immune response between men and women has been known to differ, with women producing a more vigorous immune response and increased antibody production (Whitacre, 2001; Da Silva, 1995). Estrogens and androgens have been found to directly influence whether a Th1- or Th2-type immune response develops by interacting with hormone receptors on immune cells (Da Silva, 1995). Many animal models of autoimmune disease have shown a similar sex bias, with a higher incidence of disease in women. Sex hormones, such as estrogen, testosterone, and progesterone were indicated to mediate most of the sex-biased differences in the immune response (Klein, 2000). Apart from sex hormone receptors found on immune cells, cytokine receptors (e.g., IL-1R, IL-18R) have also been discovered on hormone-producing tissues, which suggest bidirectional regulation of the immune response. Moreover pro-inflammatory cytokines such as TNF-α and IL-1β stimulate the release of glucocorticoids from the hypothalamus-pituitary-adrenal axis, which regulates the inflammatory process, along with androgens and estrogens (Bijlsma *et al*., 1999). The precise interaction between hormones and the innate immune response after infection is poorly understood. However, previous study has shown that hormones like testosterone may exert anti-inflammatory effects by reducing macrophage TNF-α expression while the effects of estrogen on macrophage CRP expression may depend upon the extracellular lipid environment (Corcoran *et al*., 2010). Also the elevated immune response in women may even further amplify the adjuvant effect of infection, thereby increasing the possibility that chronic, autoimmune disease will subsequently develop in women. With the increase in the number of autoimmune cases in recent years, the possible role of infections in exacerbating disease, particularly in women, is of rising concern.

Herbs as Holy Grail

Recently, the interest in the use of herbal products and the focus on plant research has grown dramatically in the western world as well as developed countries including antioxidants and immunomodulators among natural plants (Yuan *et al*., 2016; Ekor, 2013; Kumar *et al*., 2020; Pal and Ghosh, 2019). As autoimmune conditions are characterized by chronic inflammation and

improper regulation of immune responses, management of therapy focuses on restricting or removing factors that contribute to inflammation and immune triggers to prevent the damage to supporting organs and tissues as a result of these conditions.

Centella asiatica (CA)

Centella asiatica (L.) Urban (CA), commonly known as Gotu Kola, is a plant belonging to the family *Umbelliferae* (*Apiaceae*) (Bown, 1995; Gohil *et al*., 2010). It is native to the Southeast Asian countries as well as South Africa and Madagascar. The major bioactive constituents of CA are asiaticoside (AS), madecassoside, and their respective aglycons (asiatic acid and madecassic acid) are collectively known as the centellosides or triterpene saponosides (Randriamampionona *et al*., 2007; James and Dubery, 2009; Pan *et al*., 2007). Several flavonoids have been reported in CA including quercetin, rutin, and others (Matsuda *et al*., 2001; Subban *et al*., 2008). It is also one of the main herbs for revitalizing the nerves and brain cells and in treating emotional disorders, such as depression and anxiety (Bradwejn *et al*., 2000), apart from other diseases. The plant has been used in traditional medicine mainly for wound healing purposes. In addition, the plant is also known to prevent infection and inhibit scar formation on the affected body parts. A number of important pharmacological properties of CA have been demonstrated, such as antiulcer (Cheng and Koo, 2000; Cheng *et al*., 2004), cytotoxic and antitumor (Lee *et al*., 2002; Bunpo et al., 2004), antiviral (Yoosook *et al*., 2000), antibacterial (Zaidan *et al*., 2005), antioxidant (Jayashree *et al*., 2003; Bajpai *et al*., 2005) and anti-inflammatory activities (George *et al*., 2009). Neuroprotective effects have been demonstrated in several models including protection of cholinergic neurons from the toxic effects of aluminum and prevention of the cognitive deficits that occur following treatment with streptozotocin (Veerendra Kumar and Gupta, 2003). In addition, CA has been shown to decrease protein carbonyl production in the brains of aged rats to accelerate nerve regeneration to attenuate the neurobehavioral and neurochemical effects of stroke (Subathra et al.,2005; Soumyanath et al.,2005; Tabassum *et al*., 2013) and to protect against oxidative neurotoxicity (Haleagrahara and Ponnusamy, 2010).

Bacopa monnieri (BM)

Bacopa monnieri (BM), from a family Scrophulariaceae, a small creeping herb with numerous branches, small oblong leaves, and light purple or small and white flowers, with four or five petals is a well-known memory booster (Gohil and Patel, 2010). Referred as Herpestis monniera or water hyssop, it is locally known as brahmi or Jalanimba. BM is one of the herbs primarily used in the traditional system of Ayurvedic medicine to improve intelligence and memory (Uabundit *et al*., 2010). In ancient literature, the name Brahmi was also used to refer to another plant species, *Centella asiatica* Linn. known as an Indian pennywort (Brinkhaus and Lindner, 2000). However, these plants are distinctly different. (Refer, figure 1. The herb plant- *Centella asiatica* and figure 2. The herb plant- *Bacopa monnieri*). The vernacular name "mandukaparni" as assigned to *centella asiatica*, often confused with BM, in fact refers to the critical study of the comparative phytochemistry, pharmacology and therapeutic properties of these two botanicals also support the view that they are dissimilar. Both the plants are referred to as Brahmi, but BM contains mixtures of bacosides as main constituents (Chatterji *et al*., 1965) and CA contains asiaticosides as active constituents (Singh and Rastogi, 1996). The ancient text in Sushruta Samhita defined the properties of BM as belongs to 'tikta rasa' (bitter), while CA belongs to 'kasaya rasa' (astringent) (Kumar and Chauhan, 2006). The plant has been recommended in formulations for the management of a range of mental conditions including anxiety, poor cognition and lack of concentration, as a diuretic and a tonic for the nervous system and heart (Mukheijee, and Dey, 1996; Malhotra and Das, 1959). The compounds responsible for the pharmacological effects of BM include alkaloids, saponins, and sterols. The major chemical entity shown to be responsible for pharmacological effects of BM, is bacoside A, which usually co-occurs with bacoside B. Specific uses include the treatment of asthma, insanity and epilepsy (Chatterji *et al*., 1965; Chopra, 1958). It

has been utilized extensively as a nootropic, digestive aid, and to improve learning, memory and respiratory function (Chatterji *et al*., 1965; Kirtikar and Basu, 1918). The entire plant is used medicinally (Satyavati *et al*., 1976). BME or bacosides have shown an antioxidant activity (Kapoor *et al*., 2009; Singh *et al*., 2006; Bafna and Balaraman, 2005; Rohini *et al*., 2004; Sumathy, and Subramanian, 2001; Sumathy *et al*., 2001; Tripathi *et al*., 1996; Pawar *et al*.,2001; Bhattacharya *et al*., 2000; Bhakuni *et al*, 1969) and anti-stress effects (Singh *et al*., 1996). A previous study suggests an involvement of the GABA-ergic system in the mediation of these central nervous system effects of BM (Singh *et al*., 1996; Singh and Singh, 1980).

DISCUSSION

Both CA and BM showed similar type of activities despite being taxonomically totally different at family level. Also, the total phenolic and flavonoid contents also revealed a significant similarity in the two plants. The previous study has compared the equipotent power of BM and CA with evidence very good *in vitro* free-radical scavenging properties of both the plants (Mukherjee *et al*., 2011). CA has been reported in various animal models of autoimmune diseases apart from models of wound healing, diabetic complications, liver diseases, anxiety, and cognition (Gohil *et al*., 2010; Das, 2011; Incandela *et al*., 2001; Paocharoen, 2010). Earlier findings indicated that an *aqueous* extract of CA is effective in preventing the cognitive deficits, as well as the oxidative stress, caused by intracerebroventricular injection of streptozotocin in rats (Veerendra Kumar and Gupta, 2003). Subsequent studies in neuroblastoma cells expressing Aβ identified the ERK/RSK signaling pathway to be involved in a possible molecular mechanism for memory enhancing property of CA extracts (CAE). CAE was found to selectively decrease hippocampal Aβ levels in mice models (Dhanasekaran *et al*., 2009). One study demonstrated the influence of CAE on cell-mediated and humoral immune responses and found that it significantly increased proliferation and the production of IL-2 and TNF-alpha in human peripheral blood mononuclear cells (PBMCs). In contrast, an ethanol extract of CA inhibited human PBMC mitogenesis and the production of IL-2 and TNF-alpha. This study revealed immunomodulating activity of CA with regard to both non-specific cellular and humoral immune responses (Punturee *et al*., 2005). One study explored the anti-inflammation and anti-oxidative effects of CAE in lipopolysaccharide (LPS)-stimulated BV2 microglia cells. And it was found that CA dose-dependently inhibited the production of nitric oxide, tumor necrosis factor-α, and reactive oxygen species that were induced by LPS. These results indicated that CA, at non-toxic concentrations, exerts its anti-inflammatory and anti-oxidative effects by inhibiting NF-kB activation and the PI3K/AKT and ERK1/2 signaling pathways in LPS-stimulated BV2 cells (Mairuae *et al.*, 2019).

Preclinical research has shown that the BM extracts (BME) modulate the expression of certain enzymes involved in generation and scavenging of reactive oxygen species in the brain (Govindarajan *et al*., 2005). It was suggested that the adaptogenic properties of the herb would be beneficial in the management of stress related conditions as BM showed the potential to be effective in stress (Chowdhuri *et al*., 2002). In this study, BME was not only found to induce the constitutive expression of heat-shock protein (HSP 70) but also induce the CYP 450 enzymes in all regions of brain. An increase in the activity of CYP 450 dependent enzymes 7-*pentoxyresorufin-odealkkylase* (PROD) and 7- *ethoxyresorufin-o-deethylase* (EROD) was observed in all the brain regions after exposure to stress alone and with both doses of BME. Therefore, it was suggested that the BM primed the brain for stress by stockpiling these useful enzymes even before stressful conditions and that our susceptibility to stress could be lowered by using this medicinal herb. The level of SOD was also increased in brain in the groups pre-treated with BME. The data indicated that BME has a potential to modulate the activities of HSP 70, CYP 450 and SOD and thereby possibly allowing the brain to be prepared to act under adverse condition like stress. Researchers concluded that BM helps in coping with combined hypoxic, hypothermic and immobilization stress that could lead to onslaught of "free radicals"(Rohini *et al*., 2004).This indicated

Fig. 1: The herbal plant- Centella asiatica (Source: Wikipedia).

Fig. 2: The herbal plant- *Bacopa monnieri* (Source: Wikipedia).

that BME exhibits remarkable antioxidant properties, expressed by its capacity to scavenge superoxide anion and hydroxyl radical, and to reduce H2O2-induced cytotoxicity and DNA damage in human fibroblast cells (Rai *et al*., 2003; Tripathi *et al*., 1996; Seiss, 1993). BME has shown neuroprotective effect against aluminium induced oxidative stress in the hippocampus of rat brain (Jyoti and Sharma, 2006). An aqueous extract of BM was shown to reduce nicotine-induced lipid peroxidation (LPO) and conferred geno protection in Swiss mice (Vijayan and Helen, 2007). The protective role of bacoside A was reported against chronic cigarette smoking induced oxidative damage in rat brain (Anbarasi *et al*., 2006) and that against aluminum induced toxicity in medulla oblongata of albino rat revealing the distinctive antioxidant activity (Madhvi and Mahitha, 2013). Another study evaluated the effect of BM on transient intracarotid artery (ICA) occlusion induced ischemia by testing the neurobehavioral and biochemical parameters on treated and control rats (Saraf and Sudesh, 2010). It also decreased nitrite, nitrate and lipid peroxidation and significantly improved catalase activity. These findings further confirmed the neuroprotective and antioxidant activities of BM on ischemia induced brain injury. This antioxidant activity of BM is also able to explain, at least in part, the reported antistress, cognition-facilitating and anti-aging effects produced pre-clinically and clinically (Aloe and Alleve, 2002; Singh *et al*., 1996) and may justify further investigation of its other beneficial biological properties such as immune disorders. One study reported that BME reduces amyloid levels in PSAPP mice and can be used in the therapy of Alzheimer's disease (Holcomb *et al*., 2006). Further evidence was provided by one randomized, double-blind, placebo-controlled trial that BM has potential for safely enhancing cognitive performance in the aging (Calabrese *et al*., 2008). In one study, BM alone enhanced NO production in the spleen suggesting that both BM and deprenyl can protect the central and peripheral neuronal systems through their unique effects on the antioxidant enzyme activities and intracellular signaling pathways (Priyanka *et al*., 2013). BM was used in numerous Ayurvedic formulations with other components like honey to build and strengthen immunity and improving overall health (Gupta *et al*., 2019, Kumar and Ojha, 2017). A total of 12 miRNAs as identified from BM pertaining to 11 miRNA families and gene ontology analysis of 68 human target genes exhibited significance in various biological processes. These human target genes were found to be associated with signaling pathways like NF-kB and MAPK with TRAF2, CBX1, IL1B, ITGA4 and ITGB1BP1 as the top

five hub nodes. This provides initial insights about the potential of miRNA-mediated cross-kingdom regulation and unravels the essential target genes of human with implications in numerous human diseases including cancer or immune diseases (Gadhavi *et al*., 2019).

CONCLUSION

The causes of various autoimmune diseases have been associated with over production and accumulation of free radicals due to its undisclosed genesis (Srivastava *et al*., 2017). In an oxidative stress, reactive oxygen species generally provoke the series of oxidation at cellular level. The buildup of free radicals in turn triggers various inflammatory cells causing release of various inflammatory interleukins, cytokines, chemokines, and tumor necrosis factors which mediate signal transduction and transcription pathways as nuclear factor- kappa B (NF-κB), signal transducer and other activators. The imbalance could only be offset by supplementing natural defensive antioxidant enzymes such as SOD and catalase. This provides a platform for understanding importance of CA and BM plants as antioxidants and its potential therapeutic applications in treatment of various autoimmune disorders. The efficacy of both these plants known as brahmi in different formulations is believed to be equipotent in regard to their medicinal values. However, the same has to be validated by more preclinical and clinical experimental studies which can throw light on the exact mechanism of action of these plants to explore their potential further in autoimmune disorders. Also, clinical studies are required, to corroborate the existing preclinical results to indicate that BM and CA modulate many effects that may underline their ability as effective immunodeficiency agents. Often, women are found to not report their illness to their health care providers due to many socio-economic reasons. As the use of complementary and alternative therapies is generating momentum, the effective utilization of these herbal plants in many autoimmune disorders can prove out to be efficient and cost effective way of providing therapy to many autoimmune or immunodeficiency disorders in women. But precautions regarding safety especially for herbal products have to be exercised with care. Some women have multiple concerns in using prescription drugs, especially if they are breastfeeding their infants. With the availability of information from multiple sources, irrespective of accuracy, women may use these therapies inappropriately. Although both, CA and BM are important herbal plants due to its remarkable pharmacological effects, some precautions and safety need to be employed in terms of recommended doses and herbal drug interactions (Gohil and Patel, 2007). The interactions of CA and BM with other conventional drugs and herbs are reported in the studies (Gohil *et al*., 2012a, Gohil *et al*., 2012b; Newall *et al*., 1996; Dutta and Basu, 1968). Pregnant and breast-feeding women are suggested to be doubly conscious of using CA and BM in case of pregnancy, lactation and menopause by avoiding their simultaneous use with drugs or using the optimum dose and time lag required in ingestion between the two, as desired, in consultation with the physicians. Also, large multi-centric clinical trials to confirm bio safety profile of CA and BM are needed to explore its additional and serious side effects. Comparative studies between CA and BM and similar allopathic medicines are essential to evaluate the efficacy and safety profile of the erstwhile therapies.

ABBREVIATIONS

CA: *Centella asiatica*; BM: *Bacopa monniei*; CD4: cluster of differentiation 4; IL1: Interleukin 10; TCR:T-cell receptor; TNF: Tumor necrosis factor; GABA: Gamma aminobutyric acid; CAE: Centella asiatica extracts; BME: Bacopa monierra extracts; PBMCS: Peripheral blood mononuclear cells; LPS: Lipopolysaccharides; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; P13/AKT: Phosphatidylinositol 3-kinase/ Protein kinase B; ERK1/2: Extracellular signal-regulated protein kinases 1 and 2; PROD: 7-pentoxyresorufin-odealkkylase; EROD: 7-ethoxyresorufin-o-deethylase; SOD: Superoxide dismutase; HSP 70: Heat shock protein 70; CYP

450: Cytochromes P450; LPO: Lipid peroxidation; ICA: intracarotid artery; PSAPP: NO: Nitric oxide; MAPK: Mitogen-activated protein kinase; TRAF2: TNF receptor-associated factor 2; CBX1: Chromobox protein homolog 1; IL1B: Interleukin 1 beta; ITGA4: Integrin Subunit Alpha 4; ITGB1BP1: Integrin beta-1-binding protein 1.

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