



Betel Leaf: A Source of Ingredients having Potential to Combat Influenza

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Received: April 25, 2018; Published: May 30, 2018

Ayurveda is one of the oldest medical systems that originated in India and promotes the use of herbal compounds for the treatment of various ailments. Several literatures on Ayurveda mentions the use of piper betel leaves (Vedic name: sapsira) for the treatment of diseases like bad breath, boils and abscesses, conjunctivitis, constipation, headache, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea, swelling of gum, rheumatism, cuts and injuries. The plant is cultivated in most of South and Southeast Asia and valued both as a mild stimulant and for its medicinal properties. The phytochemical investigation of betel leaves has shown the presence of alkaloids, amino acids, carbohydrate, tannins and steroidal components in them apart from the vitamins, minerals and essential oils [1,2]. In past decade, several validation studies have been performed with betel leaf extracts to show its efficacy against various gram positive and gram negative bacterial strains [3-5], fungal strains [6] and parasites [7]. The books like Charak Samhita mentions that apart from the above-mentioned antimicrobial activities, the betel leaf extracts can also cure flu like symptoms which may be caused by respiratory viruses like influenza, respiratory syncytial viruses, human metapneumoviruses etc. Among the respiratory viruses, influenza viruses are the leading cause of morbidity and mortality among the diverse age groups and are RNA viruses which show frequent changes in their genome, hence posing a great challenge to the development of therapeutics. Many antiviral drugs have been developed and commercialized against these viruses but as a result of mutations in viral genome, there has been increasing trend in the generation of antiviral drug resistant strains which needs to be addressed. Two classes of influenza virus specific antivirals i.e. M2 ion channel inhibitors (rimantadine and amantadine) and neuraminidase inhibitors (oseltamivir and zanamivir) are available but generation of drug resistant strains have rendered these drugs ineffective in many countries. Though error prone replication of viral genome is an important cause for resistance development which is selected under antiviral drug pressure but enhanced free radical generation during the influenza virus infection has also been shown to induce mutation in viral genome [8]. In addition to the genome alteration, free radicals cause oxidative tissue injury and immune modulation which was demonstrated by Akaike et al. who showed that the pathogenicity of the virus involves excessive biosynthesis of nitric oxide (NO) via production of IFN γ during the viral infection and that the neutrophils and macrophages are responsible for the production of O $_2^-$ in the alveolar spaces of infected mice model. The reaction of NO and O $_2^-$ leads to the generation of peroxy nitrite which is a much stronger oxidant than either of the reactants [9]. Betel

leaf has the ingredients with anti-oxidant properties which may minimize the disease severity caused due to generation of free radicals during influenza A virus infections. The antioxidant activity of betel leaf extracts is due to the presence of phenolic compound, hydroxy-chavicol, which is a proven preservative for vegetable oils [10]. It has been shown that the chevibetol and allylpyrocatechol are the two components of betel leaf extracts which are also responsible for the antioxidant activities and hence, for their therapeutic potential [11]. Apart from the antioxidant activity, the betel leaf extracts can also affect the immunological parameters in host organism. Alam, et al. showed that oral intake of betel leaf extract had anti-edematous effect on carrageenan-induced paw edema in rats. It was hypothesized that inhibition of synthesis of cyclooxygenase enzyme and inhibition of enzymes involved in production of chemical mediators of inflammatory activity are caused by the components of betel leaf extracts [12]. The inflammatory reactions induced in the influenza A virus infected hosts are largely associated with pathogenicity of influenza and hence, anti-inflammatory property of betel leaf ingredients may also be significant in reducing the disease severity.

To summarize, the antioxidant and anti-inflammatory activity of betel leaf extracts have the capacity to combat influenza like illness. Further, if commercially available influenza specific antivirals are tested in combination with betel leaf ingredients, they may show a synergistic activity and the effective dose of antivirals may be reduced thus minimizing the drug pressure and development of resistant viral strains in treated individuals.

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Volume 1 Issue 6 June 2018

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