

“KAPASURAKUDINEER”- A REVIEW OF ITS BROADSPECTRUM BIOACTIVITY

¹Dr.M.Nithiyasoundari ,²Dr.M.Arputha Bibiana and ³Arun Balaji,

^{1,2}New Prince Shri Bhavani Arts and Science College,Chennai, Tamil Nadu, India.

³New Prince Shri Bhavani College of Engineering and Technology, Chennai, India.

Corresponding Author E mail: nithiyasoundari83@gmail.com

ABSTRACT

Herbal immunomodulator is a substance which stimulates the compounds of immune system. A number of Indian medicinal plants have been reported in Siddha medicine to possess immunostimulatory effects and thus can act as efficient and potential source of drug for treatment of various diseases. The use of plant product for treatment of various human diseases has been mentioned in Indian medicines like Siddha and Ayurveda. Some of these plant products are believed to enhance the natural resistance of body against infection. Among these Siddha formulated medicine is one of the oldest medical systems in India. Siddha medicine become popular nowadays, it is used to treat various outbreaks of communicable diseases. One of the well known poly herbal decoction of Siddha medicine is “Kapa sura kudineer”. This review describes role of plant derived immunostimulants in various medicine and also discusses about the biological screening methods for various plant based drugs that reveals the mechanism involved in immune response.

Key Words:

Kapa sura kudineer, Bioactive compounds, Herbal medicine

INTRODUCTION

World Health Organization define Traditional herbal medicines as naturally occurring, plant-derived substances with minimal or no industrial processing that have been used to treat illness within local or regional healing practices (Tilburt JC,2008). The use of plants for healing purposes predates human history and forms the origin of much modern medicine. Clinical, pharmacological, and chemical studies of these traditional medicines, which were derived predominantly from plants, were the basis of most early medicines such as aspirin (willow bark), digitoxin (from foxglove), morphine (from the opium poppy), quinine (from cinchona bark), and pilocarpine (Jaborandi) (Butler MS,2004). Recently WHO classified herbal medicines into four different classes according to their origin, evolution and its current use.

- ❖ Indigenous herbal medicines
- ❖ Herbal medicines in systems
- ❖ Modified herbal medicines

- ❖ Imported products with a herbal medicine base(WHO,2004).

The clinical use of plants described in Indian Vedas for curing different diseases. In the present context, the traditional system of medicine is widely accepted and practiced by people worldwide. At this stage, India has a unique position in the world where a number of recognized Traditional system of medicine i.e, Ayurveda, Siddha, Unani, Homeopathy, Yoga and Naturopathy (Kumar N,2015). Medicinal plants have been recognized as potential drug candidates because they possess drug like properties (Bernhoft A,2010).

Nowadays, the majority of studies still rely on their traditional medicine for its daily health care needs. This review encompasses the available source on the various biological compounds of “Kapa Sura Kudineer”, as well as its clinical studies.

***Zingiber officinale* (Ingee)**

Ginger has been known and used practically worldwide and in all medicines. It has been cultivated for thousands of years in China and India, reaching the West for at least 2000 years. The name of this genus, Zingiber, derives from a Sanskrit word meaning “horn-shaped” in reference to the protrusions on the surface of the rhizome. Ginger has several names, including gengibre, ajengibre, and jengibre dulce (Brazil, Argentina, and Spain), ginger (United States and England), and gingembre (France) (Corrêa Junior C,1994 and Morgan R,1994).

The antimicrobial activity of ginger oil can be attributed to its constituent monoterpenes and sesquiterpenes, as they are capable of altering the permeability and fluidity of the plasma membrane of microorganisms. The lipophilic character of its hydrocarbon skeleton and the hydrophilic character of some of its functional groups confer this property (López EIC,2017). *Z. officinale* essential oil contains considerable amounts of phenolic compounds (eugenol, shogaols, zingerone, gingerdiols, gingerols, etc.), which may be responsible for the observed effects, and has different chemotypes in which the efficiency can be attributed to the major compounds, although the possibility of a synergistic action of all constituents is not ruled out either (Singh G,2005).

Ginger act as an analgesic and helpful for muscle soreness, arthritis, chest pain, stomach pain, low back pain, and menstrual pain. Ginger is a well-known medicinal plant to treat cough, respiratory tract infections, bronchitis. Fresh and dilute juice of ginger is very useful in skin burns treatment. Active components of ginger are utilized as a laxative and antacid medication. As per Ayurveda system, Ginger is well known for the treatment of a variety of cancers including skin, oral, breast, liver, gastric, pancreatic, colon, renal, prostate, brain, ovarian and cervical cancer. Ginger has antioxidant, anti-inflammatory and anti-mutagenic properties (Srinivasan K,2014).

***Piper nigrum*(Kurumilagu)**

Piper nigrum L. is a flowering vine in the family of piperaceae, therefore an important medicinal plant is used in traditional medicine in Asia and Pacific islands especially in Indian medicine(Srinivas VP,2006).Pharmacological and clinical studies have revealed that piperine has CNS depressant, antipyretic, analgesic, antiinflammatory (Ratner et al., 1991), antioxidant, and hepatoprotective activities(Al-Marzoqi AH,2015 and Hussein AO,2016).Chromatogram GC-MS analysis of the methanol extract of *P. nigrum* showed the presence of fifty five major peaks and the components corresponding to the peaks were determined.

The major compounds found in this essential oil are sabinene, α -pinene and β -pinene, β -caryophyllene, phellandrene, limonene, linalool, citral and others. Among other compounds, antioxidants such as beta carotene, lauric, myristic and palmitic acids, as well as piperine, are found in pepper (Meghwal, M.,2012). The pungent taste of pepper and its many pharmacological properties are attributed to piperine (piperoylpiperidine, C₁₇H₁₉NO₃), one of its major alkaloids. Investigations on piperine bioactivities have reported the very high spectrum of physiological effects, including antihypertensive, antiaggregant, antioxidant, antitumor, antispasmodic, antiasthmatic, antidepressant, anxiolytic, and many others (Damanhour, Z.A,2015). Bezerra *et al.*, (2008) reported that the incubation of tumor cell lines with 5-fluorouracil (5-FU) in the presence of piperine produced an increase in growth inhibition, observed by lower IC₅₀ values for 5-FU. At the same time, leucopenia induced by treatment with 5-FU was reduced by the combined use with piperine, showing improved immunocompetence hampered by 5-FU. In the study of Bernardo *et al.*, (2015), which evaluated the effect of piperine to B cell functioning and on the humoral immune response to T-un/dependent antigens, it was found that, in vitro, it inhibits proliferative response induced by lipopolysaccharide (LPS) and immunoglobulin α -IgM antibody. Also, piperine resulted in inhibition of IgM antibody secretion and reduced expression of cluster of differentiation CD86 (Bernardo *et al.*,(2015).

Piperine inhibits PKC α and ERK phosphorylation and reduces NF- κ B and AP-1 activation, leading to down-regulation of MMP-9 expression in human fibrosarcoma HT-1080 cells. In B16F10 melanoma cells, piperine (2.5, 5 and 10 μ g/mL) inhibited activation of transcription factors NF- κ B, c-Fos, cAMP response element-binding protein (CREB), activated transcription factor (ATF-2) and consequently downregulated inflammatory and growth regulatory genes IL-1 β , IL-6, TNF- α , and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Pradeep, C.R,2004). In ultraviolet-B-irradiated mouse melanoma cells (B16F10), piperine promotes cell death through the elevation of intracellular ROS formation, calcium homeostasis imbalance, and loss of mitochondrial membrane potential. Synthetic piperine–amino acid ester conjugates exhibit cytotoxic activities against IMR-32, MCF-7, PC-3, DU-145, Colo-205, and Hep-2 cancer human cell lines (Rao, 2012).

***Syzygium aromaticum* (Karambu)**

Spices as clove, oregano, mint, thyme and cinnamon, have been employed for centuries as food preservatives and as medicinal plants mainly due to its antioxidant and antimicrobial activities. Nowadays, many reports confirm the antibacterial, antifungal, antiviral and anticarcinogenic properties of spice plants. Clove in particular has attracted the attention due to the potent antioxidant and antimicrobial activities standing out among the other spices (Shan B, 2005).

The antioxidant activity of aqueous extracts of clove has been tested by different in vitro methods as 2,2-diphenyl-1-picrylhydrazyl (DPPH); 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), oxygen radical absorbance capacity, ferric reducing antioxidant power, xanthine oxidase and 2-deoxyguanosine (Dudonné S, 2009).

The antiviral activity of eugenin, a compound isolated from *S. aromaticum* and from *Geum japonicum*, was tested against herpes virus strains being effective at 5 µg/ml, and it was deduced that one of the major targets of eugenin is the viral DNA synthesis by the inhibition of the viral DNA polymerase (Kurokawa M, 1998). In another study, the eugenol suppressed the growth of the malign melanoma WM1205Lu of both anchorage-dependent and anchorage-independent growth, decreases size of tumors and inhibits melanoma invasion and metastasis by the inhibition of the two transition factors of the E2F family (Ghosh R, 2005).

***Tragia involucrata* (Senthatti)**

T. involucrata is a shrub, widely distributed in the Indian subcontinent and grows in dry land weed. It is found to have enormous medicinal properties and have been used by the Malaiyali tribes of Western Ghats of India. The preliminary phytochemical screening results revealed the presence of alkaloids, carbohydrates, protein, tannins, flavonoids, sterols and saponins in the different extracts of *T. involucrata* (Dash *et al.*, 2000). Several colorless phytochemicals have been isolated and characterized from *T. involucrata* such as vinyl hexylether, shellsol, 2,4-dimethyl hexane, 2-methylnanone, and 2,6-dimethyl heptane. In addition, five other different compounds, namely; TIR-01, TIR-02, TIR-03, TIR-04 and TIR-05 have been identified in the ethyl acetate extract of *T. involucrata* (Panda *et al.*, 2012).

T. involucrata leaf has been traditionally used to treat inflammation, wounds, eczema, scabies and skin infections. It has also been found to be effective in treating pain and bronchitis (Kirtikar and Basu, 1987). The *T. involucrata* root has been traditionally used for the treatment of high fever. It reduces the elevated body temperature to normal by its diaphoretic action. Besides, the antimicrobial activity of *T. involucrata* root/leaf extracts have been reported against *P. vulgaris*, *E. coli*, (Gram-negative bacteria) and *S. aureus* (Gram-positive bacteria) with disc diffusion techniques (Gopalakrishnan *et al.*, 2006, Sathish *et al.*, 2013).

In another study, hexane and ethyl acetate extracts of aerial parts of the *T. involucrata* was reported for anticancer activity. This study revealed the optimum anticancer activity of these

extracts on Ehrlich's Ascites Carcinoma (EAC) model and demonstrated the involvement of antioxidant property of *T. involucrata* in the anticancer activity (Jayaprasad et al., 2012).

Anacyclus pyrethrum (Akirakaram)

Anacyclus pyrethrum DC roots and leaf have important role in the traditional Ayurvedic and Unani system of holistic health and herbal medicine of the East. Especially the root of *Anacyclus pyrethrum* is reported to have good medicinal values in traditional system of medicine (Kishor and Lalitha, 2012). It contains essential oils and an alkaloid pellitorine that is intensely pungent constituent with a mixture of isobutyl amide. Traditionally, plant is used as antibacterial, anti-inflammatory and tonic to the nervous system (Tyagi et al., 2011).

Various studies reported a number of chemical constituents in *A. pyrethrum*. The phytochemical screening of roots, leaves and flowers revealed presence of alkaloids, reducing compounds and catechic tannins. Further, plant contains other chemicals such as gallic tannins, triterpenes, sterols, mucilage, coumarins, saccharids and holosids (Hanane E,2014). Plant root also exhibit mollusidal and anti-inflammatory activity (Annalakshmi R,2012), analgesic, anti-rheumatic, carminative, antiviral, anti-catarh, improve digestion, emmenagogue, febrifuge, vermifuge and nervine activity(Usmani A,2016).

Plant extracts also exhibit free radical scavenging or antioxidant activity against the stable radical DPPH as tested by using a UV-visible spectrophotometer (Kameshwaran M,2017). 5-diphenyltetrazolium bromide (MTT) and flow cytometry assay of plant extract induce apoptosis in colorectal cancer cells by increasing the caspase 3 mRNA expressions, decreasing Bcl-2, Vimentin and MMP1, along with arresting cell cycle in G1 stage (Mohammadi A,2017).

Barleria cristata (Cem-Mulli)

Whole plant of *B. cristata* L. is traditionally used as medicine in inflammation, wounds, burns, gingivitis, nocturnal ejaculation and diabetes. It is also recommended in cough, skin infections, anaemia and tuberculosis (Quattrocchi U,2012). The phytochemical studies with *B. cristata* led to the isolation and identification of biologically active compounds such as 4-hydroxy-transcinnamate derivatives, polysaccharides, triterpenes especially oleanolic acid and glycosides (Chowdhury N,2014).

The studies also revealed the presences of secondary metabolites such as steroids, triterpenes, alkaloids, phenols, flavonoids, saponins, tannins, proteins and amino acids in the ethanolic extract of leaves of *B. cristata*. Among the large number of phytoconstituents, phenolic compounds, flavonoids, phenylethanoid and iridoidal glycosides are the major phytoconstituents (El-Mawla A,2005 and V,2012).

Treatment of viral diseases is great challenge for the peoples even today because of different reasons like easily adaptations of virus, emergence of resistant viral pathogens,

development of new viral strains, high cost and side effects of medicine, and host resistance to antiviral drugs (Chiang LC,2002 and Peera C, 2012). Antibiotics are ineffective against viral infections because viral envelope and set of replicating machinery are completely different than that of bacteria. The common treatment for viral diseases includes antiviral drugs that do not destroy their target pathogen; instead, they inhibit their development, shorten infection and help prevent complications (Wang X, 2014). Present review reported plant extracts likely to be promising candidates in the race of developing third generation anti-influenza drugs, thus challenging the neuraminidase drug-resistant viruses in an effort to protect human health and the global economy (Rajasekaran D *et al.*,2013).

***Terminalia chebula* (Kadukkai)**

T. chebula has many medicinal properties and was commonly termed as ‘King of Medicine’ in Tibet. The entire plant retains great medicinal significance and has been conventionally employed for the management of various diseases of humans. Certain rural folks utilized this plant in the management of sore throat, high cough, asthma, ulcers, gout, heart burn, vomiting, diarrhea, dysentery, bleeding piles, and bladder diseases (Saleem A, 2002; Kim HG,2006 & Lee HS, 2007). *T. chebula* has been also employed as co-ingredient in Ayurvedic formula named ‘Triphala’. In Indian system of medicine (ISM) it is widely mentioned as Rasayana drug. Three plants, such as *Embllica officinalis*, *T. chebula*, *T. bellerica* are used in preparation of triphala and utilized in ratio of 1:1:1, according to Ayurvedic Formulations of India (AFI) (GOI, 2001). This formulation is useful as detoxifying agent of colon, purgative in chronic constipation, to help in digestion and as a body rejuvenator.

The plant has been proved to exhibit many medicinal and pharmacological activities, for instance antidiabetic, antimicrobial, antioxidant, anti-mutagenic, anti-proliferative, anti-inflammatory, cardioprotective and wound healing (Rathinamoorthy R, 2014). Gautam *et al.*, 2013 showed curative effect of *T. chebula* extract on acetic acid-induced experimental colitis and indicated the presence of active principles with proven antioxidants, anti-inflammatory, immunomodulatory, and free radical scavenging and healing properties in the extract. In present review, recent advances in medicinal properties of *T. chebula* are discussed. The main phytoconstituents found in *T. chebula* are tannins, phenolic compounds and some miscellaneous constituents, which are responsible for the therapeutic activity of this herb. Williamson *et al.*, 2002 showed that tannins isolated from *T. chebula* are of pyrogallol category and other components contain phenolics such as ellagic acid, chebulinic acid, anthraquinones, and polyphenols including galloylglucose, corilagin, terflavin A, punicalagin and triterpene maslinic acid. A team of investigators established 14 constituents of hydrolysable tannins (chebulagic acid, gallic acid, punicalagin, neochebulinic acid, corilagin, chebulanin, ellagic acid, 1,6-dio-galloyl-D-glucose, chebulinic acid, 3,4,6-trio-galloyl-D-glucose, 1,2,3,4,6-penta-O-galloyl-βD-glucose, terchebulin, and casuarinin) from the fruits of *T. chebula* (Juang LJ, 2004).

Ethanol extract of *T. chebula* fruit induced cell apoptosis and inhibited cell division in numerous malignant cell lines with mouse (S115) breast cancer cell line and human (MCF-7), human osteosarcoma cell line (HOS-1), prostate cancer cell (PC-3) and a noncancerous immortalized prostate cell line (PNT1A) in a dose response manner and established that the extract from *T. chebula* fruit harbors ingredients with hopeful anti-carcinogenic action (Reddy DB, 2009). Wani *et al.*, (2016) reported anticancer activity of commercially available homeopathic preparations of *T. chebula* against breast cancer and revealed their nanoparticulate nature.

***Adhatoda vasica*(Adathodai)**

Adhatoda vasica is a perennial plant, well known for its efficacy in the Ayurveda system of medicine, with several medicinal properties (Manjunath 1948; Maurya & Singh 2010; Kaur *et al.* 2012). The leaves of *A. vasica* have been found to contain several alkaloids including vasicinone, vasicinol, adhatodine and peganine, as well as steroids and flavonoids such as astragalol, kaempferol, apigenin and quercetin (Maurya & Singh, 2010). Moreover, *A. vasica* possesses several biological activities including anti-inflammatory, antispasmodic, antibleeding, antidiabetic and antijaundice effects (Maurya & Singh, 2010). A qualitative phytochemical screening of ELEAV to detect the presence of essential phytoconstituents, such as alkaloids, tannins, saponins, flavonoids, anthraquinone glycoside, steroids, terpenes, glycosides, proteins, amino acids, reducing sugars and phenol (Edeoga *et al.*, 2005; Patra *et al.*, 2009).

As a cell signalling molecule, nitric oxide has been associated with a variety of physiological processes in the human body. It transmits signals from vascular endothelial cells to vascular smooth muscle cells, resulting in vasodilatation (Aliev *et al.*, 2009). It plays an important role in vital physiological functions in the respiratory, immune, neuromuscular and other systems. This molecule also regulates the release of neurotransmitters, and is involved in neuronal excitability, learning and memory processes, as well as inflammatory bowel syndrome, sepsis, septic shock, cephalalgia, dementia, multiple sclerosis and stroke (Aliev *et al.*, 2009). In addition, it has been shown that nitric oxide modulates neurotoxin-induced cellular damage and is involved in neuronal cell death in Parkinson's disease and other neurodegenerative disorders such as Alzheimer's disease (Aliev *et al.*, 2009).

Plants contain thousands of secondary metabolites that have a broad range of bioactivities. Hence, it is interesting to test antiviral properties of plant extracts that are active against infectious diseases. For the plants we selected, we did not find any prior reports on activity against yellow fever, chikungunya, or enterovirus. Nonetheless, from a member of the same genus (*Kalanchoe gracilis*), compounds such as ferulic acid, quercetin, and kaempferol have already been isolated, which exhibited antiviral effects against enterovirus 71 (EV71) and coxsackievirus A16 (CVA16). Another study conducted by Ojha *et al.*, (2015) isolated (using bioassay-guided purification) luteolin, which was active against herpes simplex virus type 2 (HSV-2).

***Anisochilus carnosus*(Karpooravalli)**

A. carnosus (L.f.) wall, an annual herbaceous plant which is a member of the family Lamiaceae, breeds on high elevation amid small rocks. Distribution in India is mainly seen in Karnataka, Maharashtra, Rajasthan, and Tamil Nadu and practiced traditionally in tribal communities for the treatment of ulcer, stomach ache, cough, and eczema (Thillaivanan et al., 2015). This plant's phytochemical study has revealed it to be rich in active compounds such as saponins, tannins, flavonoids (apigenin and luteolin), phytosterols, triterpenoids, and essential oil components (carvacrol, β -selinene, camphor, α -cis-bergamotene, and caryophyllene). Two new diterpenes, 4-epi-triptobenzene L and 12-O-deacetyl-6-O-acetyl-19-acetyloxycoleon Q, as well as eight known diterpenes isolated from the aerial parts of *Anisochilus* sp (Ratsami et al., 2010).

The *A. carnosus* with potent phyto-constituents were identified to be active against 32 clinical strains of *Helicobacter pylori* with MIC of 500 μ g/ml. The anti-*H. pylori* activity is irrespective of the virulence genotypes harbored by strains observed by checking cagPAI-positive and cagPAI-negative strains. It is noteworthy to be considered as a potential antimicrobial agent for the eradication of *H. pylori* especially due to the development of increasing drug resistance by *H. pylori* strains (Vignesh et al., 2017). The organic solvent extracts of *A. carnosus*, with an MIC of 0.33 ± 0.14 mg/dl and a 72 % antibacterial activity against the 50 clinical isolates tested including most of the emerging drug resistant MRSA, VISA and VRSA isolates is being developed as a promising and novel therapeutic candidate (Priya et al., 2020).

The ethanolic extract of the whole plant of *Anisochilus carnosus* (Lamiaceae) was evaluated for hepatoprotective activity in wistar rats with liver damage induced by paracetamol. The extract of an oral dose of (200 mg/kg, bw and 400 mg/kg, bw p.o.) exhibited a significant protective effect against paracetamol induced hepatotoxicity by lowering the serum levels of aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), total serum bilirubin, and malondialdehyde equivalent, an index of lipid peroxidation of the liver. The activity of the ethanolic extract of *Anisochilus carnosus* whole plant was comparable to the standard drug, silymarin (100 mg/kg, p.o.). *Anisochilus carnosus* possesses significant hepatoprotective effect on paracetamol -induced hepatotoxicity in mice (Rajeev et al., 2016). *A. carnosus* possess potent antimicrobial activity, antiulcer, and anticancer activity.

***Sassurealappa*(Kostam)**

Sassurealappa is a perennial herb, globally distributed across Himalayan region. It is used since ancient days for its medicinal property without adverse effects. The active constituents of *S. lappa* are mainly anthraquinones, alkaloids, flavonoids and terpenoids. They are noted mainly for its anti inflammatory properties (Gokhalae et al., 2002).

The ethanolic extracts of *S.lappa* were found to cure acute and chronic inflammation induced in mice and rats. The compound costunalide was identified to possess anti-inflammatory activity. They were also confirmed to have efficient hepatoprotective activity tested from Hep A2 cell line analysis. The compound dehydrocostus lactone were examined and concluded to have the inhibiting activity against many cytotoxic T lymphocytes (Taniguchi et al., 1995).

The effective property of *S.lappa* lies in the control of diabetes resulting from obesity (Kang et al., 2004). Hypolipidaemic effect was also studied in aqueous extracts of *S.lappa* (Uphadhyay et al., 1996).

The high potentiality towards many drug resistant bacteria were identified and proved it could be used for gastritis, skin infections, hepatitis, diarrhea and some oral cavity diseases. They showed resistance against many fungal pathogens (Rao et al., 2007). The antiviral property was also proved against human hepatoma Hep3B cells (Chen et al., 1994).

***Tinospora cordifolia* (Seenthil)**

Tinospora cordifolia is a deciduous climbing shrub described as “the one who protects the body against diseases” belonging to family Menispermaceae known as Amrita (Guduchi). It is widely used by tribal’s for the treatment of many diseases including gastrointestinal disorder. The biological and chemical significance of this plant is mainly because of the leaves, barks and roots contain various bioactive compounds such as alkaloids, glycosides, lactones, steroids, polysaccharides and aliphatic compounds having various medicinal importance viz., immunomodulatory or immunostimulatory, antitumor, cognition, anti-inflammatory, anti-neoplastic, antihyperglycemia, antihyperlipidemia, antioxidant, antituberculosis, gastrointestinal and hepatoprotection, anti-osteoporotic, anti-angiogenic, anti-malarial, anti-allergic and side effects prevention of the cancer chemotherapy (Dwivedi and Enespa 2016).

Alcoholic extract of *T. cordifolia* has been reported to be cytotoxic in a transplantable mouse tumor. Administration of the polysaccharide fraction from *Tinospora cordifolia* was found to be very effective in reducing the metastatic potential of melanoma cells, inhibition in the metastases formation in the lungs of syngeneic mice, when the drug was administered simultaneously with tumour challenge (Jagetia and Rao 2006).

An Ayurvedic compound formulation Transina (TR) containing *T. cordifolia* and other drugs was studied for hyperglycaemia and superoxide dismutase (SOD) activity of pancreatic islet cells. The result indicates that the earlier reported antihyperglycaemia activity of streptozotocin (STZ) being the consequence of decrease in islet SOD activity leading to the accumulation of degenerative oxidative free radicals in islet beta cells (Bhattacharya et al., 1997).

T. cordifolia was found to be more effective than acetylsalicylic acid in acute inflammation (Jana *et al.*, 1999). The aqueous stem extract of *T. cordifolia* has been antagonize the various autocoids in the pathophysiology of clinical joint inflammation.

The alcoholic and aqueous extracts of *T. cordifolia* have been tested successfully for immuno-modulatory activity. Pretreatment with *T. cordifolia* reduced mortality in mice injected with *E. coli* intraperitoneally. This was associated with significantly improved bacterial clearance as well as improved phagocytic and intracellular bactericidal capacities of neutrophils in the *T. cordifolia* treated group (Desai *et al.*, 2002).

George *et al.*, reported the methanolic, ethanolic, and water extracts of *T. cordifolia* for their antioxidant activity, in which the stemic ethanol extract increased the erythrocytes membrane lipid peroxide, catalase activity and decrease the superoxide dismutase, glutathione peroxidase in alloxan-induced diabetic rats. The leaves extract of methanol, partitioned in water with ethyl acetate and butanol at 250 mg/ml, and showed their antioxidant activity, extracts of methanol phosphomolybdenum and metal chelating activity were high followed by ethyl acetate, butanol, and water extract (Priyanka *et al.*, 2019).

The *Tinospora cordifolia* extract have been used to possess desirable bioactivities including fungicidal activities (Soliman and Badeaa, 2000), bactericidal (Dorman and Deans, 2000; Aher and Wahi, 2010).

***Clerodendrum serratum* (Siruthekku)**

Clerodendrum serratum is a shrub which is not much branched with stems. The root of the plant is attributed with various activities like anti-inflammatory, digestive and carminative and many more. It is used to treat the conditions like inflammations, anorexia, cough, asthma, hiccough, tubercular glands, skin diseases etc. Various minerals like Na, Mg, Al, Ca etc. saponins, terpenoids, D-mannitol are the phytoconstituents present in the plant (Poornima *et al.*, 2015).

The hepatoprotective activity of constituent ursolic acid extracted from roots of *Clerodendrum serratum* is significant as similar to the standard drug and showed more significant hepatoprotective activity than crude extract (S.M Vidya *et al.* 2005). The methanolic extract of the roots of *Clerodendrum serratum* exhibits anticancer activity at the dose of 100 and 200 mg/kg body weight (Zalke *et al.* 2010).

Both root and stem have shown the anti-inflammatory effect, but root showed significant activity in comparison with Dexamethasone (Bhangre *et al.*, 2012). In yet another study, the methanolic extracts of aerial and root parts of *Clerodendrum serratum* Linn. was carried out to study the anti-rheumatic properties based on the effects on carrageenan induced paw oedema in rats. The results showed that the roots possess significant while the aerial parts exhibited

moderate anti-inflammatory activity. Thus, from the study it is evident that the roots of *Clerodendrum serratum* L. possesses potent anti-rheumatic properties (Shareef I et al. 2013).

The 80 percent ethanolic extract of the leaves at 25 mg/ml showed inhibition of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus subtilis*. It exhibited antifungal activity against *Curvularia tuberculata*, the causal fungus of die-back disease and *Pestalotiopsis mangiferae*, the causal organism of leaf spot disease (Gupta et al., 2008).

***Andrographis paniculata* (Nilavembu)**

Andrographis paniculata (Burm. f.) Nees (Acanthaceae) (*A. paniculata*), is a medicinal herb with an extremely bitter taste used to treat liver disorders, bowel complaints of children, colic pain, common cold and upper respiratory tract infection. The herb contains diterpenoids, flavonoids and polyphenols as the major bioactive components. Active compounds extracted with ethanol or methanol from the whole plant, leaf and stem include over 20 diterpenoids and over ten flavonoids have been reported from *A. paniculata* (Wen-Wan Chao 2010).

Andrographolide exhibits multiple pharmacological properties and is a potential chemotherapeutic agent (Cheung et al., 2001). Andrographolide contains an α -alkylidene γ -butyrolactone moiety and three hydroxyls at C-3, C-19 and C-14 responsible for the cytotoxic activities of andrographolide against many cancer cell lines.

Andrographolide inhibits nitric oxide (NO) production and the expression and stability of inducible synthase (iNOS) protein in lipopolysaccharide (LPS)-stimulated RAW264.7 (RAW) cells (Chiou et al., 2000). Andrographolide inhibits oxygen radical production in neutrophils, inhibits macrophage migration, NF- κ B activity as well as TNF- α and IL-12 production (Qin et al., 2006). These anti-inflammatory activities of andrographolide may be a result of its interference with protein kinase C dependent pathway, extracellular signal-regulated kinase1/2 (ERK1/2) or PI3K/Akt signalling pathway.

Andrographolide and its analogues exert direct anti-cancer activities on cancer cells by cell-cycle arrest at G0/G1 phase through induction of cell-cycle inhibitory protein and decreased expression of cyclin-dependent kinase (Rajagopal et al., 2003).

Rajagopal et al. and Kumar et al. have reported the immunostimulatory activity of andrographolide *in vitro* in PHA-stimulated human peripheral blood lymphocytes (HPBLs) by increased proliferation of lymphocytes and production of IL-2. *In vivo* immune responses, such as an antibody response to a thymus-dependent antigen and delayed-type hypersensitivity, were considerably lessened in mice treated with andrographolide.

In vitro antibacterial activity of the crude powder of *A. paniculata* has been reported against *Salmonella*, *Shigella*, *E. coli*, gram A streptococci, and *Staphylococcus aureus*, even at a

concentration of 25 mg/mL. Singha et al. found significant antibacterial activity in an aqueous extract with andrographolide.

The virucidal activity of andrographolide has been reported against herpes simplex virus 1 (HSV-1) without having any significant cytotoxicity (Thanasekaran et al., 2013). At a concentration of 0.05mg/mL of a chloroform extract of *A.paniculata*, the plant completely inhibits malarial parasitic growth within 24 h of incubation; and the same inhibition has been noted within 48 h with methanol extract concentration of 2.5mg/mL.

Among these plants is *A. paniculata* which exhibits a neutralizing activity against the human immunodeficiency virus (HIV). Andrographolide was investigated for antiviral activity against herpes simplex virus (HSV), HIV (Calabrese et al., 2000), flaviviruses, and pestiviruses (King Spalding 2006). Lin et al. demonstrated that 25 µg/mL of ethanolic extract of *A.paniculata* and 5 µg/mL of andrographolide effectively inhibit the expression of Epstein-Barr virus (EBV) lytic proteins, Rta, Zta, and EA-D, during the viral lytic cycle in P3HR1 cells. A recent study has demonstrated that *A. paniculata* has the most antiviral inhibitory effects among six medicinal plants tested against DENV1-infected Vero E6 cells.

***Cissampelos pareira* (Vattathirupiver)**

The plant *Cissampelos pareira* is a sub-erect or climbing herb, belongs to the family Menispermaceae. It is commonly known as Bhatindupat in Punjab and laghupatha or ambastha in Indian traditional medicine. There are around 30 plant species summarized under this botanical name “*Cissampelos pareira*”, found in all over the world. Only one species is found in tropical and subtropical parts of India. Its aerial parts contain number of secondary plant metabolites like alkaloids, flavonoids, tannins, volatile oils and glycosides. The root of this plant has a rich history, being used by resident peoples of South America, for centuries to treat many women’s ailments i.e. menstrual cramps, to stop uterine hemorrhages after childbirth, prevents threatened miscarriage, ease childbirth and postpartum, because of its intense relaxant effect on smooth muscle (Kamal shah et al., 2017).

C. pareira extract and its polyherbal formulation in combination with *Pongamia pinnata* (L.) Pierre and *Vitex negundo* L., exhibited *in vitro* anti-inflammatory activity at a dose of 600 mg/kg on carrageenan-induced hind paw oedema by 0.16 mL, respectively (Batista-Lima, 2001). Moreira et al., in 2003 determined that the hydroalcoholic extract of *Cissampelos sympodialis* leaves showed an immunomodulatory effect on B-lymphocyte function. It has been reported that the methanolic root extract of *C. pareira* at a dose of 200-800 mg/kg has an immunomodulatory activity in mice.

The hydroalcoholic leaf extract of *C. pareira* at a dose of 200 and 400 mg/kg, (p.o.) has been evaluated to exhibit antidiabetic activity on streptozotocin-induced diabetic rats. It

significantly reduced fasting blood glucose and improved the body weight of rats compared to glibenclamide (5 mg/kg).

Surendran et al., in 2011 reported that hydroalcoholic root extract of *C. pareira* exhibit significant hepatoprotective effect against CCl₄-induced hepatotoxicity in rats at doses of 100, 200 and 400 mg/kg. The levels for anti-oxidant Superoxide Dismutase (SOD) enzymes were enhanced at doses of 200 and 400 mg/kg. At the same doses, it has shown to decrease cholesterol levels and increased triglyceride levels when compared to silymarin.

The ethanolic root extract of *C. pareira* (containing polyphenols) exhibited anti-oxidant activity in the 2, 2-Diphenyl-1-Picrylhydrazyl (DPPH) assay at doses ranging between 50 and 300µg/kg *in vitro*. He also reported that the extract exhibited effective protective effects in an acute oxidative tissue injury on benzo(a)pyrene induced gastric toxicity in mice at a dose of 100 mg/kg. The alkaloidal fraction from *C.pareira* roots showed strong anti-oxidant activity by scavenging the superoxide ion, stable free radical DPPH and by inhibiting lipid peroxidation in rat liver homogenate induced by iron/ADP/ascorbate complex (Hussain et al., 2010).

Kumar et al., in 2006 reported that an extract from the whole plant of *C. pareira* showed antifungal activity against *Saccharomyces cerevisiae* and *Aspergillus nigervia* complete inhibition at concentrations of 1000 mg/mL in comparison to the positive controls amphotericin B at a concentration of 3 mg/mL. Moreover, Dichloromethane extracts from aerial parts of *Cissampelos mucronata* showed activity against bacteria including *Salmonella typhi*, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus faecalis* and *Vibrio cholera*.

Cipa extract shows virucidal effect in a time and dose-dependent manner in the type-1 assay format. This extract exhibited statistically significant protection against dengue virus infection using the AG129 mouse model. A preliminary evaluation of Cipa extract exhibited no adverse effects on RBC viability and platelet counts. The effect of *C. pariera* extract on virus titers confirmed a >1 log reduction compared to untreated virus, that suggests its potent efficacy in altering the course of major dengue disease to a more favorable outcome (Sood et al., 2015).

***Cyperus rotundus* (Koraikilangu)**

The nut-grass (*Cyperus rotundus*) is a slender, erect, perennial sedge which spreads by means of a fibrous root system. It is slender, underground, known as rhizomes, are initially white, fleshy and covered with scaly, modified leaves, but become brown and woody with age. On reaching the surface, a rhizome may swell into a small, rounded structure called a (basal bulb), from which shoots, roots and further rhizomes arise. Phytochemical surveys revealed that the plant contained flavonoids, tannins, glycosides, fluorochromes, monoterpenes, sesquiterpenes, sitosterol, alkaloids saponins, terpenoids, essential oils, starch, carbohydrates, protein and amino acids (Sharma et al., 2011 & Shivapalan et al., 2013)

Cyperus rotundus contained many secondary metabolites such as sesquiterpenes (with diverse skeletons such as patchoulane, rotundane, eudesmane, guaiane, cadinane and caryophyllene types), quinones, flavonoids (visnagin, khellin, ammiol, isorhamnetin, and triclin), saponins, alkaloids, phenolic acids (salicylic acid, protocatechuic acid, caffeic acid and *p* coumaric acid), coumarins and steroids (steroidal glycoside, sitosterol - (6'-hentriacontanoyl)- β -D-galactopyranoside) (Huang et al., 1999).

Cyperus rotundus rhizomes petroleum ether, chloroform, ethanol and water extracts were evaluated against six important pathogenic microbes (*Staphylococcus epidermidis*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Aspergillus niger* and *Candida*). The antibacterial and antifungal activities were performed by both agar well diffusion and serial dilution methods. The ethanolic extract exhibited highest activity against the tested bacteria. However all extracts were ineffective against fungal strains. The inhibitory effect is very similar and comparable with that of standard drug (Sharma et al., 2011).

The alcoholic extract (70% alcohol) possessed anti-inflammatory activity against carrageenan induced oedema and against formaldehyde induced arthritis in albino rats (Sundaram et al., 2008). The anti-inflammatory activity of crude extract of *Cyperus rotundus* was studied in rats at a dose of (300mg/kg and 500mg/kg). Inflammation was produced by carrageenan in rats and compare with saline and aspirin treated groups. Plant extract exhibited significant anti inflammatory effect (Ahmad et al., 2014). The Anti- inflammatory, anti- arthritic and analgesic of *Cyperus rotundus* essential oils were evaluated using anti- inflammatory (carrageenan induced), antiarthritic (formaldehyde induced) and analgesic (formalin induced writhing) in rats. The results showed dose dependent activity, indicated by reduction in paw edema in anti-inflammatory and antiarthritic activity. When compared with the control, treatment with *Cyperus rotundus* significantly ($p < 0.01$) reduced the paw edema from 2nd hr after carrageenan injection. Pretreatment with *Cyperus rotundus* at doses of 250 and 500 mg/kg showed a dose dependent effect. The assessment of anti- arthritic activity on the 10th day showed that, treatment with *Cyperus rotundus* (500 mg/kg) significantly reduced ($p < 0.01$) the swelling in the injected (left) hind paw as compared to Diclofenac sodium treated group.

Antioxidant activity of *Cyperus rotundus* rhizomes extract (CRRE) was evaluated in a series of *in vitro* assay. CRRE exhibited scavenging effect in concentration dependent manner on superoxide anion radicals, hydroxyl radicals, nitric oxide radical, hydrogen peroxide, in addition to property of metal chelating and reducing power. The lipid peroxidation effect of the extract was also studied by thiobarbituric acid-reactive substances (TBARS) using young and aged rat brain mitochondria. The extract prevented mitochondrial lipid peroxidation induced by FeSO₄ ascorbate in concentration dependent manner (Nagulendran et al., 2007).

Age associated increase in serum glucose was observed in aged rats compared to young rats. Administration of CRRE to aged rats prevented the age associated changes in glucose level (Oh GS et al., 2013). The hexane fraction of *Cyperus rotundus* might be a novel therapeutic

remedy for fatty liver disease through the selective inhibition of the lipogenic pathway (Purachikody et al., 2006)

CONCLUSION

This review paper describes the detailed study of the therapeutic effects of the components of Kapa sura kudineer. The decoction prepared from the combined herbal powder of it exerts a wide spread bioactivity against various human diseases and disorders. The controlled and combined effect of the herbal extracts exhibit a major restorative mechanism in the human body. The combined phyto-constituents in the decoction was found to be useful as anti-inflammatory, anti-cancer, hepatoprotective, antibacterial, antiviral, analgesics and antipyretics. Hence it enhances the immune system along with the recovering of the ailments.

Each of the plant was explained to have diversified effects on various diseases and disorders. The combinatory property of fifteen medicinal plants in equal proportion in the formulated product helps to evade out of the sufferings quickly without any side effects. The recurrence of the infection will also be prevented with immune boosting effects of the formulate. The above data would be helpful in further study of the plant research and development in field of medicine and therapeutic significance.

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