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A Review on Immune Boosting Effects and Pharmacological Action of Kamarasi Karpam

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Abstract:
The traditional Siddha medicine is one of the ancient practices that has emerged from South India especially Tamil Nadu. Recent global recognition of this traditional medicine has increased due to the present Corona Virus Disease-2019 pandemic and the need of Immunomodulators to tackle this situation. Siddha medicine research has a focus from 'Bedside to Bench' as there's an enormous source of time tested formulations that have been safely administered in clinical practice with minimal side effects when properly administered as per the indication. Among these formulations, Kaya karpam is considered an "Ambrosial medicine" used by Siddhars which was insisted to be followed to protect the body from demise and decomposing to increase life expectancy. Classical text indicates the rejuvenation of the entire body and enables to delay ageing by providing youthful vigour. However, Extensive researches are yet to be carried out in unveiling the scientific facts behind the traditional use of such age-old time tested formulations. This review work has been a preliminary literature analysis on one such Kaya Karpam formulation Kamarasi Karpam (KK) with special speculations on its Immunomodulatory action. In this review, each ingredient has been evaluated for their individual immune-modulating properties and a flow chart depicting its proposed Immunomodulatory action has been derived. The goal of this work is to re-instil hope on traditional medicines and to certify Siddha literature. Further extension of this work on preclinical and clinical studies with valid experimental proof would be necessary to substantiate the Immunomodulatory action of KK.

Key Word: *Kaya karpam, Tinospora cordifolia, Tribulus terrestris, Emblica officinalis, Siddha, Antioxidants.*

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I. Introduction

In Siddha system of medicine, *'Kaya Karpam'* always plays a significant role because of its Prophylactic and Therapeutic effects where *Kayam*- BODY; *Karpam*- STONE. This formulation was indicated in Siddha literature as the Concept of *Kaya Karpam* deals with the Prevention of NARAI (Whitening of hairs), THIRAI (Shrinkening of Skin), MOOPU (Ageing) and SAAKADU (Death).Siddha medicine has huge array of formulations for immune boosting activity. These old- age literary evidences conjoin with current scientific proofs which form a new pathway in boosting immunity and prevention of diseases. *Kaya Karpam* drugs have proven scientific evidences to prevent and manage the Non-communicable diseases like Diabetes mellitus, Obesity, Chronic deliberating diseases like cancer etc. [1]

In general, Immune therapies and chemotherapies are expensive and express a variable and unique spectrum of toxic effects. These well-known adverse effects include myelosuppression, alopecia, neuro-toxicity, and gastroenteritis.[2]Adverse side-effects and high cost of modern Immunotherapeutic drugs as well as conventional therapies (chemotherapy, immunotherapy, and surgery) has led the scientific community and the general public to gain more interest in herbal medicines for their safe, effective and multi-targeted action. Thus, ample proportion of the global drug market is represented by herbal medicine which promotes healthier living, acting as a balanced and moderate approach to cure. These cost-effective herbal medicines providing primary prevention/protection from disease like cancer can also be easily accessed by socioeconomically weaker domain of society. Therefore the escalating costs of modern drugs have led to the revival of interest in herbal medicines. Siddha system can fill such gaps thereby boosting immunity in a natural way. [3]

Oxidation reaction can cause damage or death to the cell. The term "antioxidant" refers to the substances that inhibits the oxidation and inhibits the production of free radicals thereby aids in the disease prevention.[4]Free radicals generated by cells during respiration and cell-mediated immune function is also generated through environmental pollutants, cigarette smoke, automobile exhaust, radiation, and pesticide. The

excess free radicals seek stability through electron pairing with biological macromolecules of healthy cells such as proteins, lipids, and DNA. The pairing of the free radicals with bio-molecules can eventually result in the induction of lipid peroxidation which leads to cancer, atherosclerosis, cardiovascular diseases, ageing, and inflammatory diseases. Prolonged oxidative stress can result in permanent damage to vital body organs, which could eventually lead to chronic disorders and premature aging. The antioxidants from natural sources are the only alternative to synthetic antioxidants in counteracting the free radicals associated disease. [5] Intake of antioxidant vitamins also act against free radicals by enhancing immune response. It plays a specific role as Immune booster and restricts pathological aspects of the cytokine mediated response. [6]

Many medicinal plant extracts have been used for the treatment and prevention of many diseases due to their antioxidant property and low cytotoxicity. Also they are the good source of radical scavengers. The usage of these medicinal plant extracts is vital in Indian traditional therapy like Siddha system of medicine. In Siddha system various herbal and herbomineral formulations are named as *Kaya Karpam* which focuses on delaying aging attributing to its antioxidant property. Hence there is a great need for the professionals as well as the public to be aware of *Kaya Karpam* formulations in Siddha texts.[7]The present literature review is about the scientific analysis of KK which consists of the ingredients, *Nerunjil vithai, Nellikai, Seendhil,* Ghee, Milk and Honey. Scientific analysis of the ingredients of KK indicated in the text *'KAYA KARPAM'* written by D.S.JANAGAKUMARI, has been the core of this review in specific to its Immunomodulatory and Anti-oxidative properties. [8]

II. Materials and Methods

Preparation of *KK:* KK a *Siddha Kaya karpam* medicine has been indicated in the text *"KAYA KARPAM"* and has the below ingredients tabulated in Table 1:

Table no 1: Ingredients of *KK*

S.No	Ingredients	Botanical Name	Parts used	Quantity
1.	Kamarasi (Nerunjil)	Tribulus terristris Linn.	Seeds	52.5 grams
2.	Nellikai	Emblica officinalis Gaertn.	Fruit	52.5 grams
3.	Seendhil	Tinospora cordifolia Miers.	Bark	52.5 grams

Procedure: The above tabulated shade dried drugs (Nellikai fruit without seeds and Seendhil bark without skin) are to be taken in equal ratio 1½ *palam* (52.5 grams each) and grinded. In order to obtain a fine powder, the mixture is to be filtered using a mesh cloth. This fine powder is to be stored in a container by adding cow's ghee ½ *palam* (17.5 gram) and honey ¾ *palam* (26 grams).
Dosage: 6-8 grams can be taken morning and evening with milk.
Indication: Immunity, Aphrodisiac, General tonic, Prevention of debility.
Diet Regimen: Milk, raw white rice, green gram can be taken. Tamarind, salt, meat, fish, buttermilk, garlic, asafoetida, mustard alcohol, smoking, narcotics should be avoided. Sexual abstinence is also advised. [8]

III. Scientific rationale on the Immune stimulating properties of Ingredients of *KK*

1. Tribulus terrestris (TT)

Tribulus terrestris belongs to family Zygophyllaceae, and it is a commonly used medicinal herb in India. It is also found in Mediterranean, China, southern USA, Mexico, Spain, and Bulgaria and desert climate regions around the world. [9]

This annual shrub contains various kinds of phytochemicals like flavanols, glycosides, alkaloids, saponins, nitrates, tannins due to which it possess antiurolithic, diuretic, aphrodisiac, antitumor, anticancer, immunomodulatory, hypolipidemic, antidiabetic, cardiotonic, antihypertensive, hepatoprotective, analgesic, anti-inflammatory, anthelmintic, antispasmodic, antimicrobial and larvicidal effects at different doses.[10]

1.1 Immunomodulatory activity

TT seeds contain β-carboline alkaloid called Harmine—a small molecule which promotes development of regulatory T-cells that effectively suppresses inflammation in vitro and in vivo. These studies highlight Harmine as a potential main compound to instruct the development of future small-molecule therapies for human autoimmune diseases. Furthermore, several targets have been reported for harmine. Dual specificity tyrosine-phosphorylation regulated kinase (DYRKs) is one of the potent targets of harmine. Inhibition of DYRKs promotes the differentiation of Treg cells that leads to decreased immune response by inhibiting the

production of T cells. Hence, these studies reveal Tregs as a potential target for restoring anti-tumor immunity, thereby improving the anti-tumor response and in auto immune therapies. [11] Harmine and ethanolic extract of TT has anti-inflammatory action. Ethanolic extract of *TT* is involved in the suppression of proinflammatory cytokines such as TNF-α and IL-4 in macrophage cell line. Thus they have beneficial effect on various inflammatory conditions. [9] Harmine also has osteomodulatory response with succedent effect on osteogenesis. These effects occur due to influence of harmine on macrophage polarization, a phenomenon that is tightly linked to the processes of resolving inflammation in immune mediated reactions. [12]

Qualitative analysis for phytochemicals revealed the presence of tannins, saponins, steroids and alkaloids in the aqueous extract of *TT* seeds. This extract contains a steroidal saponin Protodioscin, which increases the level of Dehydroepiandrosterone (DHEA) in the bloodstream. DHEA obtained from the conversion of Protodioscin, involves in the immune system improving the general sense of well-being. [13] DHEA is said to increase immunity by further suppressing expression of various proinflammatory cytokines. It also involves in the stimulation of IL-2 secretion from T cells, where Immunomodulation has beneficial results in adaptive immune response. [14]Ferulic acid (FA) also present in *TT* seeds shows improved lysozyme activity, enhanced phagacytosis, bactericidal and respiratory burst activities, which are considered as the indicator of strong innate immune function in Nile tilapia fish. The increase in lysozyme activity, serum total protein and albumin levels for IgM production indicates that FA might stimulate the innate immune response and Immunomodulatory effects.[15]Ferulic acid treatment inhibits an allergic Th2-response by decreasing the key features of pulmonary allergy, including lung and airway inflammation, eosinophil infiltration, mucus production and serum levels of Ovalbumin-specific IgE. These results are associated with lower levels of chemokines and cytokines (IL-4, IL-5, IL-13, TSLP, IL-25 and IL-33) in lung tissue homogenate. [16]

1.2 Antiangiogenic activity

Antiangiogenesis is the ability to prune tumor vessels and 'normalize' the remaining vasculature.[17]Tumor angiogenesis is believed to be induced due to increased production of angiogenic factors (such as TNF- α) and decreased production of angiogenic inhibitors (such as IFN-γ) by cancer cells, vascular endothelial cells and other stromal cells. Of stroma constituents, macrophages have an essential role in tumor angiogenesis and produce a number of growth stimulators and inhibitors. Thus macrophages are expected to influence every stage of angiogenesis.[18]Harmine, a potent angiogenic inhibitor can significantly decrease the proliferation of vascular endothelial cells and reduce expression of different pro-angiogenic factors such as vascular endothelial growth factor, Nitric oxide (NO) and pro-inflammatory cytokines. Nuclear factor-κB (NFκB) and other transcription factors like cAMP response element-binding (CREB) and Activating transcription factor 2 (ATF-2) involved in angiogenesis are also inhibited by harmine. Moreover, harmine decreases production of other factors by tumor cells, which play a significant role in angiogenesis. [19]

1.3 Hematinic property

A hematinic is a nutrient required for the formation of blood cells in the process of hematopoiesis.*TT* is considered to be rich in iron which is the essential for haemoglobin. A study shows that *TT* consumption increases the natural killer (NK) and NK-T cells in rats which could boost immunity and result a significant increase in hemoglobin level. This concludes that *TT* may have hematinic property. [20]90% of the total content of elements in *TT* is attributed by the macroelements Potassium and Calcium. Potassium is responsible for regulating osmotic pressure of body fluids, and for maintaining cardiac rhythm, and in constipation. Ca participates in the biochemical blood clotting process and to be responsible for proper nerve and muscle function. It is also necessary for the absorption of dietary vitamin B. [21]

1.4 Nutritive

TT products are commercially marketed under various names as Liver tonic, Nutritional supplement and Vitalizer.[22] Administration of *TT* extract decreases the overweight, blood pressure, serum cholesterol and some of the proteins involved in energy metabolism. Overnutrition leads to decreased expression of proteins related to acute phase reactants, immunity, hemostasis, transmembrane signaling and pheromone transmission, suggesting a decreased response to stress, low immunity and hemorrhagic tendency. *TT* increases these expression levels of proteins caused by Overnutrition. [23]*TT* seeds are diuretic with potassium sparing effects due to the presences of nitrates, tannins, essential oils, vitamins, fats and gums etc.[10]It increases libido in addition to prevent reluctance, infertility and menopausal disorders. It is considered that this herb provides nutritional support to uterus. [24]FA increases the growth hormone which improves nutritive and enzymatic digestibility further increasing the feed utilization. [15]

1.5 Antidepressant effect

Literature survey revealed *TT* seeds have CNS activity so its anxiolytic effects were explored. Methanolic seed extract of *TT* shows anxiolytic activity with improvement in locomotor activity. This effect is

probably due to presence of alkaloids like Ferulic acid and Harmine that contributes to the anxiolytic effect without affecting its locomotor activity. [10]

FA has anti-depressant activity as it significantly decreases the ACTH and corticosterone levels which may contribute to protecting the hippocampus neurons and improving depressive behaviour in male Prenatal Stressed offspring rats. [25] Monoamine oxidase (MAO) is an enzyme that catalyzes the oxidative deamination of tyramine, noradrenalin, dopamine, serotonin, and other biogenic amines to pharmacologically inactive acidic derivatives that regulate mood changes. Such alterations in MAO can cause mood disorders. [26]Harmine content of *TT* acts as MAO inhibitor, leading to higher levels of biogenic amines (dopamine) in the brain. Increased level of dopamine elevates the mood slowly providing a stronger and better feeling. [10]

Hypothalamic-pituitary-adrenal (HPA) axis, representing the interaction between the 'hypothalamus, pituitary gland and adrenal glands' plays an important role in stress response. Association between depressive disorders and neuroendocrine alterations shows that the hyperactivity of the HPA is involved in the pathogenesis of depression. Corticotropin-releasing factor (CRF), Adrenocorticotropic hormone (ACTH) and Cortisol (CORT) are the key mediators of the mammalian response to stress stimuli involving in the HPA axis dysfunction. Antidepressant treatment such as Tribulus Terrestris Saponins (TTS) can normalize the HPA axis hyperactivity in depressed patients by significantly attenuating the Chronic Mild Stress-induced serum CRF and CORT levels. In conclusion, TTS has potential antidepressant-like activity and may be a favourable alternative to currently available antidepressant drugs. [27]

1.6 Anticancer Property

TT extract has antitumor effect and exhibits weak cytotoxic effects in normal cells compared to cancer cells. Saponins isolated from *TT* were found to be less toxic for their cytostatic/cytotoxic activity on human fibroblasts. Aqueous extract of TT blocks proliferations in HepG2 cells (liver cancer cells) and also induce apoptosis through the inhibition of NF-κB signaling. Thus, *TT* has clinical therapeutic effects arresting the growth of liver cancer cells. [28] Alkaloids from *TT*, viz., trans-*N*-feruloyl-3-hydroxytyramine and *trans-N*-feruloyl-3-ethoxytyramine induce apoptosis in leukemic cancer cells. Terrestrosin-D, a steroidal saponin partly represents the anticancer effect of *TT* as it inhibits cancer cell growth through the induction of cell cycle arrest and apoptosis. [9] The methanol seed extracts as well as saponins from seeds of *TT* extracts may exert their anticancer activity in breast cells by triggering more than one apoptotic pathway. The seeds exert their anticancer effect by showing a significant increase in tumor suppressor protein indicating its activation in early apoptosis. Initiation of apoptosis activates the cellular endonucleases which cause the fragmentation and degradation of the DNA further resulting in cancer cell death. [29]

2. Emblica officinalis (EO)

Emblica officinalis belonging to the family Euphorbiaceae is widely distributed throughout India, Pakistan, Uzbekistan, Sri Lanka, South East Asia, China and Malaysia. It is one of the richest sources of vitamin-C, aminoacids and minerals. EO fruit extract has many bioactive compounds like ellagic acid, chebulinic acid, apigenin, gallic acid, quercetin, chebulagic acid, isostrictinin, corilagin, methyl gallate, luteolins and tannins like Emblicanin A, emblicanin B, phyllaemblicin B, punigluconin and pedunculagin.[30]It also has anti-inflammatory, antimicrobial, cytoprotective, anti-oxidant, anticancerous and immunomodulatory properties.[31]

2.1 Immunomodulatory property:

EO suppresses the proliferation of certain chemokines which resists the immune cells infilteration in damaged areas and induces the Immunoprotective cytokines to stimulate the repair process through its Immunomodulatory action. [32] Treatment of *EO* has shown augmenting cyto-protective activity, reduction in apoptosis and DNA fragmentation resulting in the suppression of free radical production.[33]

Gallic acid, a component present in *EO* increases the immune response of the host by inducing the proliferation of leucocytes and lymphocytes. [34]Presence of tannoid complexes like emblicanin-A (37%), emblicanin-B (33%), punigluconin (12%) and pedunculagin(14%) act as immunomodulators playing dual role of increasing or decreasing the immune cells which protect against oxidative stress and decreases lipid peroxidation. These complexes further increase the concentration of antioxidant enzymes. Any defect in the antioxidant system can damage nucleic acids, proteins and lipids. [35]

Ellagic acid is found to have significant anti-proliferative effect *invitro* model of cancer cells inducing apoptosis via mitochondrial pathway and without side effects on normal colon cells. It shows anti-inflammatory property by NF-κB repression causing downregulation of proinflammatory cytokines (iNOS, COX-2, TNF-α and IL-5). [36]Pedunculagin enhances IL-1b mRNA expressions and proinflammatory cytokines which activate the lymphocytes for murine dendritic cells. [37]

Luteolin blocks lipopolysaccharide (LPS)-induced IκB phosphorylation and IKK activity, and decreases IL-12 and TNF-α gene expression. This indicates that luteolin blocks LPS-induced NF-κB signalling

and proinflammatory gene expression in intestinal epithelial cells and dendritic cells preventing intestinal inflammation associated with dysregulated innate immune responses. [38]

Apigenin exerts immune-regulatory activity in an organ-specific manner by significantly modulating NF-κB activity in the lungs ameliorating the progression of asthma. It also normalize the expression of some colonic inflammatory markers e.g., TNF-α, transforming growth factor-β, IL-6 and intercellular adhesion molecule (co-stimulator of MHC II cells). Apigenin in combination with Quercetin and Luteolin has a protective effect on pancreatic beta-cells injured by cytokines during inflammation. Apigenin combined with Luteolin are strong inhibitors for murine and human T-cell responses specifically auto-reactive T cells. In sum, it seems that Apigenin can be considered as a modulator of immune system. [39]

2.2 Antiangiogenic activity:

Elevated ROS level induces VEGF activation resulting in the stimulation of angiogenesis and choroidal neovascularisation. Treatment of EO inhibits VEGF receptor activity and gene levels preventing VEGF-induced angiogenesis. [40]

EO is a naturally occurring plant extract that inhibits the growth of Ovarian Cancer cells *in vitro* and *in vivo*, through activation of autophagy and inhibition of angiogenesis. Anti-proliferative effect of Quercetin from *EO* was shown to suppress expression of genes associated with angiogenesis and inhibited HIF-1α (a protein associated with the angiogenesis) in OVCAR3 (ovarian carcinoma cell line 3) cells *in vitro*. *EO* significantly reduces the endothelial specific antigen-CD31 (an adhesive stress response protein). Finally within *in vivo* xenografts, microvessel density was significantly reduced. [41] Apigenin exhibits anti-tumor effects by decelerating growth and inducing apoptosis in HepG2 human hepatoma cells, decreasing the viability, adhesion, and migration of cancer cells and modulating angiogenesis and metastasis. [39]

2.3 Hematinic property:

EO Tonic has hematinic and lipolytic function useful in treatment of scurvy, jaundice, indigestion, and controls acidity and is a natural source of anti-aging. [30]Vitamin C deficiency leads to Anemia, or low red blood cell count which results in low immunity. *EO,* a natural cure for Anemia is rich in Vitamin-C, an essential ingredient that helps in the iron absorption. [42] The bioavailability of iron is influenced by the presence of factors such as organic acids and phytates in food that may enhance or reduce its absorption and utilization. With restricted diet, L-Ascorbic acid or vitamin C is considered to be a bioavailability iron enhancer. [43]

Administration of a Hydro-methanolic extract of *EO* in hepatotoxic mice is effective as an 'Iron chelator'. *EO* reduces the ferrous ion-mediated DNA breakdown, decrease the reductive release of ferritin iron and increase the levels of antioxidant enzyme. This results the decrease in liver iron, serum ferritin, lipid peroxidation, protein oxidation, collagen content and serum enzyme levels. These observations clearly indicate the usefulness of amla in reducing the iron load-induced liver damage. [44]

2.4 Nutritive property:

EO contains essential dietary nutrients like vitamin C, minerals and amino-acids.[45]Ellagitannin such as punigluconin and pedunculagin (ET) daily intake could perform potential health care functions and reduce the impact of certain chronic diseases due to modern lifestyle. Urolithins in urine produced during dietary Ellagitannin intake has potential homeopathic-like effect. Urolithin metabolism from Ellagitannin- rich food promotes the growth of human gut bacteria and these Ellagitannin gut microbiota-dervied metabolites have colon anticancer effect. [36]Treatment of EO shows suppression in low density lipoprotein cholesterol (LDL) and enhancement in high density lipoprotein cholesterol (HDL) levels. [48]Prophylactic administration of *EO* juice enriched with Emblicanin A and Emblicanin B reduces the iron-induced lipid peroxidation in the liver and serum levels of AST, ALT and (Lactate dehydrogenase) LDH in rats. *EO* is effective in normalising the elevated liver enzymes (AST, ALT, ALP and GGTP) following chronic intake of alcohol. Also, the levels of carbonyl content, lipid per-oxidation and nitric oxide are reduced, thus restoring the levels of SDH, NADH dehydrogenase, cytochrome C oxidase and cytochromes, thereby suggesting its usefulness in preventing alcohol-induced hepatic damage. [44]

2.5 Antidepressant effect:

Plants containing flavanoids, saponins and tannins possess activity against many CNS disorders. The aqueous extract of fruits of *EO* contains Tannins(30%), Gallic acid(13.4%), polyphenols, flavanoids and Vitamin C which causes behavioural variation indicating anxiolytic like and antidepressant activity.[47]

Gallic acid seems to have a dual mechanism of action by increasing not only serotonin but also catecholamine levels in the synaptic clefts of the central nervous system. Further, alpha adrenergic, serotonergic and dopaminergic receptors also seem to be involved in this antidepressant-like activity. [48]Chronic use of gallic acid has neurotropic action on the hypothalamus. It may induce the attenuation of oxidative stress produced

during depression by the polyphenols and tannic acid present in *EO*. Tannic acid has been shown to be a non selective inhibitor of MAO, thereby increasing the levels of monoaminergic neurotransmitters in the brain. [49] The methanolic extract of *EO* can inhibit Acetylcholine esterase enzyme which is primarily responsible for cholinergic dysfunction associated with Alzheimer Disease.[47]Chronic stress eventually influences glucose metabolic enzyme activities, which in turn alters Blood glucose level, such as hypoglycemia or hyperglycemia and causes depressive behaviour. Methyl gallate exerts an anti-depressant like effect attenuating hypoglycaemia by increasing Blood glucose level and also slightly inhibiting glucose elimination rate. This in turn attenuates Body weight loss and depressed behaviours under Repeated Restraint Stress. [50]

2.6 Anticancer property:

Gallic acid, ellagic acid, chebulinic acid, quercetin, ascorbic acid etc., identified in EO fruit has anti-proliferative activity by enhancing NK cell activity in various tumor cells. [30]

Methyl Gallate, a derivative of gallic acid has a significant anti-tumor effect by inhibiting tumor infiltration of $CD4^{+,}$ $CD25^{+}$ regulatory T cells, and by inhibiting focal adhesion formation and Protein kinase B (Akt) phosphorylation in glioma cells.[50] Ellagic acid is a powerful antioxidant that suppresses the mutation in genes and repairs chromosomal abnormalities.[30] Pyrogallol in *EO* has antitumoral effect by its cell cycle arrest which increases the Bax expression (an apoptoptic regulator). This causes reduction in mitochondrial membrane potential and triggers activation of caspases inducing 'cell death' via apoptotic death-receptor pathway. Gallic acid exhibits apoptosis on hepatocellular carcinoma cell line by supressing the multiplication of HeLa cells. [46]Tetra-isopalmitoyl ascorbic acid, a flavanoid present in the fruits of EO causes decrease in the production of intracellular peroxide after UVB(ultra violet type B) irradiation and ROS (reactive oxygen species) [51].

Ellagitannins such as Puniculagin, Pedunculagin, etc., along with Ellagic acid have high antioxidant effect by scavenging oxygen free radicals and further preventing inflammation and colon cancer. Ellagic acid downregulates DNA fragmentation by increasing caspase-3 enzymatic activity and reduce telomerase activity. Urolithin metabolism from Ellagitannin- rich food promotes the growth of human gut bacteria and these Ellagitannin gut microbiota-dervied metabolites have colon anticancer effect. β-glucuronidase, an enzyme released from lysosome of necrotic cells like solid tumours cleaves with the urolithin glucuronides and increase the concentration of bioactive urolithin aglycones which cause anti-inflammation and immune suppression in cardiovascular disease and cancer. [36]

3. *Tinospora cordifolia (TC)*

TC belonging to the family Menispermaceae is commonly called as *Seendhil* or *Amrita.* It is a deciduous climbing shrub widely distributed in tropical countries like India, Pakistan, Sri Lanka, Bangladesh, Myanmar, etc. It has immunomodulatory, anti-diabetic, anti-oxidant, anti-inflammatory, anti-pyretic, anti-spasmodic, hepato-protective, memory-boosting properties. [52]Anticomplement and Immuno-stimulating activities are found inTC-1 (clerodane furano diterpene glycoside), TC-2 (cordioside), TC-4 (syringin), TC-5 (cordifolioside A), TC, i5 (cordifolioside B) and TC-7 (cordiol) isolated from TC. [53]

3.1 Immunomodulatory activity

The aqueous extracts of TC enhance phagocytosis when treated *in vitro*. TC consists of compound called *α-D*-Glucan (RR1) shows unique immune stimulating properties by activating normal lymphocytes such as B cells, T cells and NK cells which is linked with killing tumor cells. Immune activation by RR1 elicits synthesis of IL-1β, IL-6 , IL-12 p70, IL-12 p40, IL-18 , IFN- γ, TNF-α in normal lymphocytes. RR1 also activates the complements in the alternate pathway which is one of the component of innate immune system.[1]Arabinogalactan (G1-4A) a polysaccharide from *TC* shows 100% protection against LPS induced mortality in mice and binds to the murine macrophages leading to their activation. It also reciprocally inhibits binding of LPS to macrophages. Thus G1-4A by modulation of cytokines and nitric oxide appeared to induce tolerance against endotoxic shock hence works on immunity and strengthens the immune system.[54]G1-4A activates the NF-KB through TLR4 - toll like receptor (a key to induce proinflammatory response) and can regulate gene expression, proinflammatory cytokine production and proliferation of B cells.[55]The RR-1 of TC activates human lymphocytes with downstream synthesis of the pro- and anti-inflammatory cytokines, *in vitro*. G1-4A (a polyclonal B cell mitogen) on binding to macrophages enhances immune response in mice by inducing secretion of IL-1, together with activation of macrophages. [56]

Choline present in TC with its increased concentration enhances the proliferative response of lymphocyte stimulation. It also conflict with the attenuated inflammatory response observed in choline-supplemented monocytes and neutrophils. By its potential role in immune cell responses, choline can either induce or attenuate responses of immune cells which may have an immunomodulatory role. [57]Components such as Cordioside, cordiofolioside A and cordiol (TC-7) activate macrophage with increasing incubation time. Syringin and cordiol shows inhibition against immune hemolysis inhibiting C3-convertase of the classical complement pathway resulting a significant increase in IgG antibodies *in-vitro*. [58] N-methyl-2-pyrrolidone and

11-hydroxymustakone, Magnoflorine and Tinocordiside extracted from stem of TC shows immunomodulatory effects by enhancing Reactive Oxygen Species (ROS) generation which augments the immune response. [59]

3.2 Antiangiogenic activity

Phyto-constituents like Berberine, Palmitine, Octosanol, Columbin acts on cells inhibiting angiogenesis on specific target. Inflammatory cell radicals and cytokines produce substances which cause direct DNA damage and exert tumour supportive effects such as angiogenesis stimulation, apoptosis deregulation, etc. These cytokine raise from the normal levels is pro-angiogenic and treatment with TC could decrease and inhibit angiogenesis. Thus TC regulates the levels of cytokines and growth factors in the blood. Studies say that the level of Antiangiogenic factors such as tissue inhibitor of metalloprotease-1 (TIMP-1) and IL-2 inhibits angiogenesis when treated with TC. Antiangiogenic activity of Berberine is mainly mediated through the inhibition of various proinflammatory cytokines and pro-angiogenic factors such as Hypoxia inducible factor (HIF), Vascular endothelial cell growth factor (VEGF), Cyclooxygenase 2 (COX-2), NO and NF-κB. [60]

Octosanol decreases the peritoneal lining angiogenesis in Ehrlich ascites tumor (EAT) bearing mice by inhibiting proliferation of endothelial cells and density of micro blood vessels. [61] Columbin treatment in Human umblical vein endothelial cells (HUVEC) shows reduced tubule formation and migration of endothelial cells which confirms the antiangiogenic potential of TC in tumor cells. It acts as a VEGFR2 inhibitor by forming a hydrogen bond with Asparagine's hexose rings oxygen by docking the two major VEGF receptors namely VEGFR 1 and 2. These observations confirm the anti angiogenic potential of columbin attributing to its competitive binding with VEGF receptors. [62]

3.3 Hematinic property

TC stimulates IL-1 and TNF-α production which are vital for the process of hematopoiesis.[63]Administration of TC extract causes significant reduction in eosinophil count and improved haemoglobin level in HIV patients.[64]Hepcidin is a regulatory protein of iron metabolism in human body. It inhibits iron transport by binding to the iron export channel ferroportin which is located in the basolateral plasma membrane of gut. In inflammatory anaemia, hepcidin is induced by pro-infammatory cytokines such asIL-1β, IL-6, and TNF-α8 that are produced by macrophages expressing TLRs in inflammatory conditions. A recent study reported that LPS induces hepcidin expression in hepatocytes through the TLR-4 expression via MyD88-dependent signaling pathway which plays a vital role in innate immune.TC administration to murine macrophage has shown a significant reduction in hepatic TLR-4 expression thereby inhibiting the hepcidin activation that increases iron absorption of gut *in vivo* whereas reduction in the expression of hepcidin, TNF-α, IL-1β, genes and also inhibited production of NO in vitro. This shows that TC extract has anti-inflammatory properties and also inhibits hepcidin expression in inflammatory anaemia. [65]

3.4 Nutritive

TC is a rich source of protein and micronutrients, such as iron, zinc, copper, calcium, phosphorus, and manganese.[66]"Guduchi-satva" is a starch obtained from stem of *TC* is said to be extremely nutritive which has fat (0.14 g/100 g), protein (0.64 g), dietary fibers (0.16 g/100g), energy contents (288.8 cal/100 g), Ca (70 mg/100 g) and Fe (9.7 mg/100 g). Thus *TC* helps in digestive ailments such as hyperacidity, colitis, worm infestations, loss of appetite, abdominal pain, excessive thirst, vomiting, and dyspepsia, fever, urinary diseases even liver disorders like hepatitis. [58]

TC acts as a hepatoprotective agent by reducing the levels of AST, ALT and ALP levels. It also acts on lipid metabolism by repressing serum triglycerides, cholesterol and high density lipoprotein in mice. Palmatine attenuated D-galactosamine /LPS induced hepatic failure acting as a potent hypolipidaemic factor. Magniflorine protects the high density lipoproteins (HDL) during oxidative stress. Treatment of TC regulates the rise in serum creatinine level averting renal dysfunction/injury. Antioxidants like SAG, TBARS and GSH levels are decreased in High Fat Diet fed animals which is normalized by TCP supplementation. It also suppresses the upregulation of hepatic HMGCoAR enzyme responsible for cholesterol synthesis in High Fat Diet rats. [67]

3.5 Antidepressant effect

TC is a unique herbal medicine which manages depression, Alzheimer's disease and attention deficit hyperactivity disorder further improving cognition and memory. [68]Nootropic drugs are a class of psychoactive drugs that selectively improve efficiency of higher telencephalic integrative activities. It has selective facilitatory effect on intellectual performance, learning and memory. The stem of TC has saponins and its N-butanolic fraction (TBF) possesses nootropic activity. TBF by virtue of its anti-cholinesterase may significantly enhance cholinergic neurotransmission in distinct brain regions that enhance learning and memory functions. [69]

Berberine possesses central nervous system activities, particularly the ability to inhibit monoamine oxidase-A, an enzyme involved in the degradation of norepinephrine and serotonin. [70]Berberine significantly

ameliorates anxiety-related behavior through activation of the serotonergic system in mice. It exerts antidepressant-like effects increasing brain biogenic amines, such as norepinephrine, serotonin, dopamine, and alleviates β-amyloid (Aβ)-induced spatial memory impairment, and inhibits pro-inflammatory cytokines expression, such as interleukin (IL)-1β. [71]Palmitine involves in the process of neurotransmission and cognition enhancement by its inhibitory activity against the acetylcholinesterase and butyrylcholinesterase enzymes present in the synaptic cleft. [72]

3.6 Anticancer Property

The term Amrita meaning 'rejuvenation of dead cells' is reputed to protect the celestial people from senescence and keep them eternally young. Here *TC* is referred to Amrita since it has been used for centuries for treating various ailments including cancer. TC extract arrests G0/G1-phase cell cycle in KB cell line (keratin-forming tumor cell line) to inhibit proliferation of oral squamous cells.[73]Anti-cancer effects has been induced by the Phyto-components of TC such as berberine, G1-4A, palmatine, newclerodane furano diptherine glycosidae, elligic acid, kaempferol, N-formylannonain, Magnoflorine, jatrorrhizine palmatine, 11-hydroxymustakone, cordifolioside A, tinocordiside, yangambin, anthraquinones, terpenoids, saponins and phenol, pyrrole-based small molecules, quercetin and rutin, clerodane-derived diterpenoids and hexane fractions via mitochondrial-mediated apoptosis, cytotoxic activity, mutagenic activity, reduction in tumor size, triggering reactive oxygen species, decreased gene expression of the cell cycle, effectively inhibiting cancer proliferation.[74]

Glutathione (GSH) plays a significant role in cancer, immunology and protects cell against ROS and free radicals. Superoxide dismutase (SOD) and catalase plays similar role like Glutathione (GSH). Oral administration of Palmatine, a phytocomponent of TC has shown improvement in the levels of anti-oxidant enzyme activity of GSH, SOD and catalase which can protect against environmental carcinogens that induce skin cancer. [75]

Berberine shows cell cycle inhibition, differentiation and epithelial–mesenchymal transition on HEP2 human laryngeal cancer cell lines. [74]It also shows inhibitory effects on the proliferation and reproduction of certain tumorigenic microorganisms and viruses, such as Heliobacter pylori and hepatitis B virus. Berberine inhibits azoxymethane (AOM)-induced aberrant crypt foci (ACF) formation and putative preneoplastic lesions of the colon in male F344 rats, which is because of its inhibition of COX-2 activity. [76]

4. Honey & Ghee:

The main antioxidants in honey are the phenols, such as Quercetin, Hesperetin, Chyrsin, and Melanoidins. Quercetin directly binds to and strongly inhibits cellular transcription factors' activities. The inhibition of the transcription factors surpasses the phosphorylation and activation process which avoids cellular effect of the free radicals.[77] Ghee contains medium chain fatty acids (MCFAs) which are absorbed directly by the liver and provide energy to burn other fats in the system and lose weight. Thus the MCFAs are renowned for anti-obesity properties. Ghee solely consists of butyric acid, a short chain fatty acid which is said to rope the production of killer T cells in gut therefore building a strong immune system. Ghee aids in the digestive process by stimulating the secretion of gastric acid. [78] Honey consumed along with ghee shows enrichment in antioxidants, browning and specific gravity without modifying the food utilization. [79]

Milk – Adjuvant:

Adjuvant is an additional therapeutic agent that improves the action of medicines. The most prominent reason for usage of adjuvant is to enhance or synergize the action of the core active components present in the formulation. [80]Cow's milk acts as a vehicle carrying the whole drug which boosts the immune system response. The α-Tocopherol, a most effective lipid soluble anti-oxidant, ascorbic acid, Vitamin E, carotenoids, casein and other proteins present in milk indicates anti-oxidant property for scavenging of Reactive Oxygen Species. [81] Cow's milk proteins namely BSA (Bovine Serum Albumin), ABBOS (17-Amino-Acid Bovine Serum Albumin Peptide), and β-LG (β- lactoglobulin) caused increased expression for INF-γ and IL4 mRNA in diabetic and healthy children. T-Helper lymphocytes have been divided into TH1 and TH2 lymphocytes based upon their different pattern of cytokine production. INF- γ, TNF and IL-2 produced by TH1 lymphocytes contribute to cell mediated immunity whereas humoral mediated immunity is related to TH2 lymphocytes producing cytokines like IL-4, 5, 10, 13. B-LG is able to cause a strong immune response including increased expression of INF-gamma and IL4 mRNA. [82]

Upon the evaluation of each ingredient's certain Immune modulating properties, the following flowchart has been depicted as Figure 1:

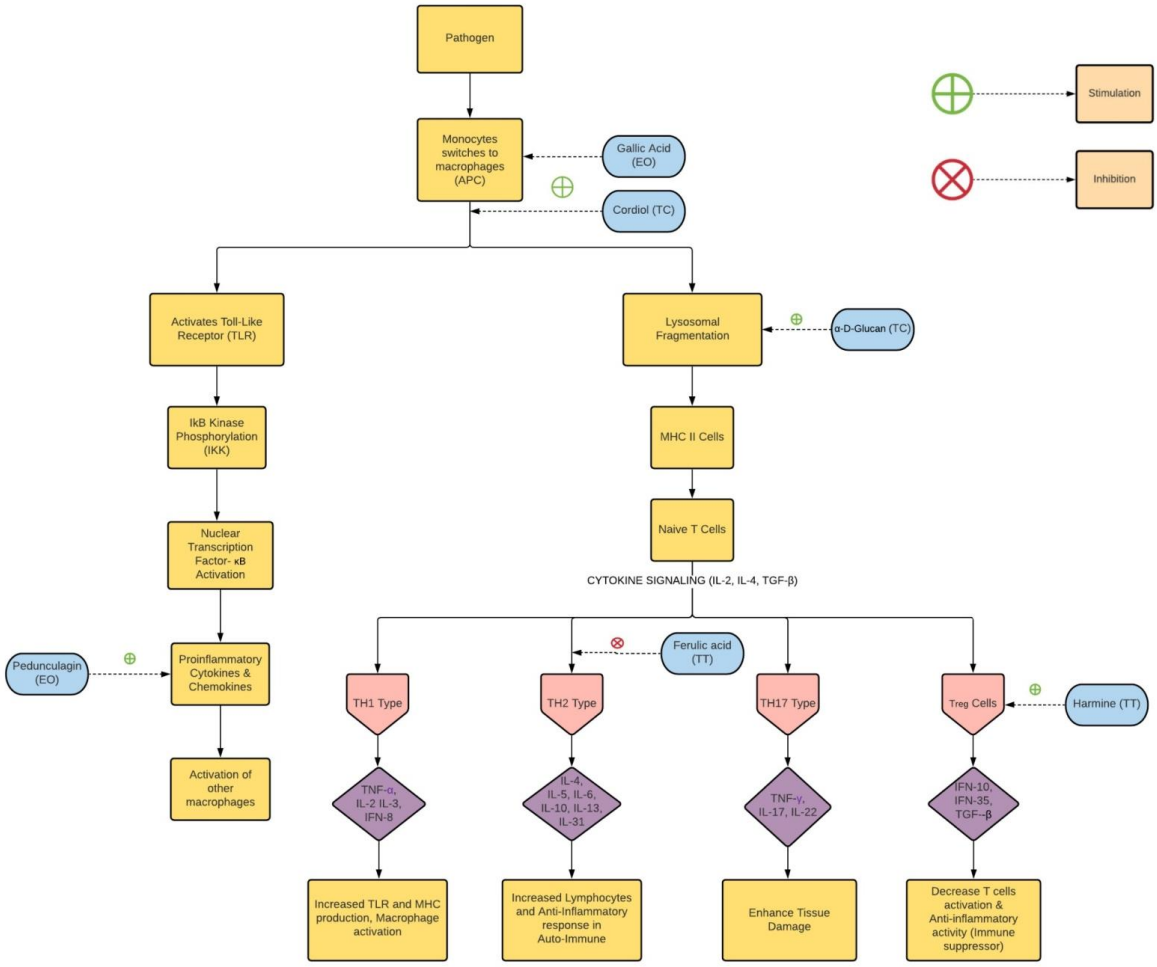


Figure 1: Proposed Immunomodulatory action of *KK* based on scientific analysis

Abbreviations:
TT: Tribulus terrestris, EO: Emblica officinalis, TC: *Tinospora cordifolia*, IFN: Interferon, IKK: IκB kinase, APC: Antigen Presenting Cells, TLR: Toll-Like Receptor, IL: Interleukin, NFκB: Nuclear Factor κB, MHC II: Major Histocompatibility 2 Cells, TNF: Tumour Necrosis FactorTH-1: T Helper-1, Treg cells: T regulatory cells, TGF: Transforming Growth Factor

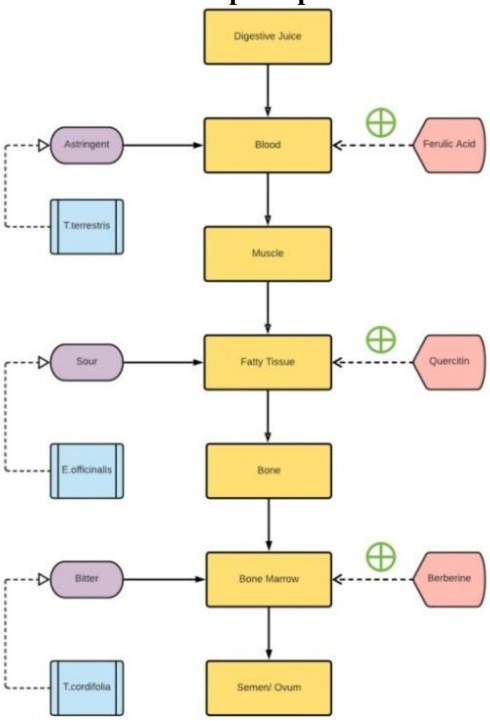
IV. Fundamental Theory of Siddha

Table No 2: Basics of Siddha

5 Elements	6 Taste	7 Body constituents
Earth Water Fire Air Ether	Sweet (*Inippu*) Sour (*Pulippu*) Salt (*Uppu*) Bitter (*Kaippu*) Pungent (*Karppu*) Astringent (*Thuvarpu*)	Digestive juice (*Saaram*) Blood (*Senneer*) Muscle (*Oonn*) Fatty acid (*Kozhuppu*) Bone (*Enbu*) Bone-marrow (*Moolai)* Semen\ovum (*Sukkilam/ Suronitham*)

According to Siddha physiology, the seven body constituents act as the essential building blocks and benefit the human health. Energy is provided within the body through the 6 tastes of the food intertwining with the cells. Initially, the food mixes with the digestive fluids on the first day. It associates with the blood on the second day. Gradually, it blends with muscle cells, fatty tissues, bones, bone marrow on third, fourth, fifth, sixth day respectively and finally fuse with Semen/ Ovum on the seventh day. Thus on eighth day, it gives out the needed solidity to the body. [83]

Figure 2: Action of Taste & active principles of KK in body constituents



Every disease comes from the origin of disturbance in the Tri-humour resulting in Tri-dosham. Based on the Tri-dosham ratio, it is identified whether the disease caused by single humour or combination of all the three humours. There are about 80 subtypes in *Vatham*, 40 in *Pitham* and 96 in *Kabam.*

Table No 3: Action of *Kamarasi Karpam* on Tri-Humour

S.No	Ingredients	Suvai	Gunam	Veeryam	Vibagam	Action on humours
1.	*Tribulus terristris (Nerunjil)*	Astringent , Sweet	Heavy to digest, unctuous	Seedham	Sweet	Sweet pacifies Vaadham Seedham pacifies Pitham Astringent pacifies Kabam
2.	*Emblica officinalis (Nelli)*	Sour, Astringent , Sweet	Heavy to digest and dry	Seedham	Sweet	Sour pacifies Vaadham Seedham pacifies Pitham Astringent pacifies Kabam
3.	*Tinospora cordifolia (Seendhil)*	Bitter	Heavy to digest and oily	Veppam	Pungent	Heavy & unctuous property pacifies Vaadham Bitter pacifies Pitham Pungent pacifies Kabam

Taking other drugs into consideration, increased *Vatham* is quietened by drugs having coolant and unctuous property (Ex: ghee); *Pitham* by *Seedha veeryam* (Ex: milk); *Kabam* by dry and *Veppa-veeryam* drugs (Ex: honey) thus treating the Tri-humour imbalance. [84]

Siddha Pathology:

It is understood that every medicine in Siddha given for *Vatham, Pitham* and *Kabam* diseases are composed of drugs based on its *Suvai*, *Veeryam* and other drugs added to it increase its medicinal efficacy.

In physiological condition, increased *Pitham* in the body is balanced through micturition. In pathological conditions, imbalance in the *Uyirthathukkal* (*Pitham*) causes impairment in kidney function. Provoked *Pitham* causes sedimentation of micronutrients which results in kidney stone formation ultimately leading to hydronephrosis. Here *Nerunjil* can be used due to its lithontripic and diuretic action. According to Siddha literature, tastes like astringent, sweet & bitter acts as a pacifier for *Pitham.* Astringent and sweet taste of *Nerunjil* makes it a Pitha-pacifier as its taste can dissolve the stones and its secondary sweet taste may remove them through urine. This can bring back the body's homeostasis by balancing the *Uyirthathukkal.* It is also used to treat *Pitham* diseases such as Oligospermia due to overheat, autoimmune disorders, loss of libido due to fear, nocturnal emission, leucorrhoea and Teratospermia.

Pitham is located in head and controls mind, intellect, intentions and the five sense organs. Provoked *Pitham* and decreased *Kabam* in head results in psychological disorders. Here *Nellikai* can be used to increase

Kabam due to its refrigerant action. Other than psychological disorders, it can also treat *Kabam* diseases, vertigo, sinusitis, vomiting, constipation & venereal diseases.

Among the seven body constituents, *Vatham* is present in bones; *Pitham* in blood and *Kabam* in rest of the places. Diabetes is said to affect all the seven constituents of the body. Here Seendhil can be used for its Alterative & Tonic properties helping to control the blood glucose level and nourishing these constituents. *Seendhil* prevents the seven constituents of the body from dryness and expert in detoxifying poisonous substances from the body. Cross section of fully grown *Seendhil* stem shows interspatial arrangement idealizing space aspect in five element theory. Space is present in the areas like hollow cavity of bones. *Seendhil* is composed of sour taste which is in turn is made of Air and Space. According to 5 element theory, *Pitha-Kabam* is a combination of Fire, Earth & Water. Since *Pitham* and *Kabam* both have viscous nature it increases the accumulation of Kabam in the body. The remaining 2 elements, Air and space combines to form bitter taste which is present in *Seendhil*. Therefore the 2 element combination Bitter must pacify the 3 element combination thereby treating *Pitha-Kabam* diseases.

Ghee is added along with these preparations as an adjuvant to avoid the heat increased by bitter in medication. *Vatham* is increased when sour is taken alone but *Vatham* is pacified when it is taken with ghee. *Vatham* and *Kabam* abnormalities in a diabetic individual are managed by suggesting ghee and milk as adjuvant.

Honey is mainly used along with drugs targeted to pacify *Kabam* in the body. It can work like 'specific receptor theory' targeting places where *Kabam* is increased and bringing it back to normal. *Veppam* and dry properties of Honey tranquillizes the Kabam in the body by removing its greasy and moisture-laden nature. It is also said to treat *Kabam* related disease like irritant cough, Rhinorrhoea, Asthma, Insomnia and improves digestion which involves *Pitham*. Hence Honey can acts as a carrier for drugs working on organ-specific diseases.

Milk acts as a main adjuvant in medicines used for treating increased *Pitham.* Dryness and *Veppam* are exhibited by *Pitham* under pathological conditions. This imbalance can be pacified by Milk exhibiting its unctuous, coolant and apathy properties. [85]

V. Conclusion

Principle of Siddha system of medicine illustrates the basic human physiology and functionality depending on the balanced state of Tri-humour. *Karpam* formulation is prescribed for management of such *Vatham, Pitham, Kabam* related diseases. Rejuvenating herbs explore the richness of *Kayakarpam* and develop Nutraceuticals. *Karpam* medicine mentioned in the above Siddha literature review could be used for prevention of ageing & stress, also maintain wellness, Immune enhancement and Neurotonic. On the other hand *karpam* also serves as curative medicine in treating various ailments. *Kamarasi karpam* can be used for Immunity, body strengthening and acts as prophylactic medicine for disease prevention. As *TC, TT, EO* have shown several Immunomodulatory properties separately, and when the whole drug is taken as *Kaya Karpam* for 40 days, a gradual immune response and an optimised immunity will be created against the pathogen which could be used in preventing the killer disease cancer.

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