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Review Article

Suggestions for re-purposing of Siddha Herbal formulations to COVID-19 positive patients with comorbidity - A review

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Abstract

SARS-CoV-2 causes COVID-19, a disease that has killed millions of people around the world. Comorbidities are non-communicable diseases that account for roughly two- thirds of all deaths worldwide. COVID-19 mortality risk rises with age, particularly in males over 60 and in those with chronic diseases such diabetes, cancer, and cardiovascular disease. The key variables for COVID-19 vulnerability have been identified as advanced age and underlying illnesses. There is currently no new drug available to combat this fatal illness. Siddha is a traditional system of medicine which has many Herbal formulations with antiviral activity and anti-inflammatory activity. The pharmacological actions of Siddha Herbal formulations which was already in practice for the above-mentioned comorbidities were reviewed by searching key words botanical names and pharmacological actions against COVID -19 and botanical names in Google Scholar and PubMed databases. Here, we explore the scientific evidences of Siddha Herbal formulations which has antiviral, anti-inflammatory, anti-oxidant, anti-platelet, and immune-modulator actions for re-purposing them in the management of Covid-19 with comorbidity.

Keywords: Antiviral, Comorbidity, COVID-19, Herbal Formulations, Personalization, Traditional medicines, Siddha

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Introduction

Corona virus disease 2019 (COVID-19) is a pandemic infectious disease caused by the severe acute respiratory syndrome corona-virus 2, which is a positive-sense RNA virus (SARS- CoV- 2). (1) It is a mild to severe respiratory sickness that spread mostly by infected people's respiratory droplets and aerosols, as well as contaminated objects or surfaces (2) According to the WHO, this pandemic infectious disease claimed the lives of nearly 95 percent of people over the age of 60. According to reports, 8 out of 10 deaths occur among people who have at least one comorbidity, such as cardiovascular disease, hypertension, or diabetes, but also a variety of other chronic underlying diseases. (3). A higher number of comorbidities has been linked in worsening of COVID-19 disease severity and poor prognosis. (4). According to the Siddha system *Vali (Vatham), Azhal (Pitham),* and *Aiyam (Kabam)* are the three biological humours responsible for an individual's overall health and well-being. Diet, physical activity, and environment will affect these three humours, resulting in disease. Increased *Aiyam* is characterized by a loss of appetite, excessive salivation, decreased activity, paleness, cough, and dyspnea. Elevated *Aiyam* will cause respiratory problems. (5) Fever, fatigue, dry cough, myalgia, and dyspnea were the most prevalent symptoms of Covid 19. (6) According to Siddha pathology, the primary cause of these symptoms is increase in *Aiyam* humour. Siddha Experts have coined the equivalent word for COVID-19 as *Aiya Suram/Kaba Suram* based on these symptoms and pathology. (7) Siddha is a holistic system of medicine with several basic medicine formulations such as *Kudineer, Karkam, Choornam,* and others. (8) Many Siddha Herbal preparations that have been proven to have potent antiviral, anti-platelet, immune- modulator, antipyretic, and anti-inflammatory properties which are used for the treatment of diabetic mellitus, hypertension, COPD, and chronic liver illnesses. Treating covid 19 patients with comorbidities by using Siddha herbal formulations which has pharmacological actions which act against COVID-19 may reduce the mortality rate. The scientific evidences which strengthen Siddha herbal formulations to repurpose against COVID-19 with comorbidities has been reviewed in this article.

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Materials and Methods

This article is a compilation of different Siddha herbal formulations for COVID-19 patients with concomitant illnesses. The selected comorbidities were Diabetes mellitus, Hypertension, COPD and in addition to Geriatric population with Comorbid conditions as these comorbidities and geriatric age was the main cause for increase in Mortality rate in people infected with COVID-19. The pharmacological actions of Siddha Herbal formulations which was already in practice for comorbidities were reviewed by searching key words such as botanical names and pharmacological actions against COVID -19 in Google Scholar and PubMed databases. Anti-viral activity, Antioxidant activity, Immunomodulator activity, Hypoglycemic activity, antihypertensive, Antiatherogenic, antispasmodic, anti-inflammatory and Antipyretic activity, Anti-hyperlipidemic, Immunostimulant, Expectorant, Thrombolytic, Anti-platelet activity are the key words used to search in Google Scholar and PubMed databases. Since it is a review article to evaluate these treatment regimens against patients with COVID-19 with comorbidities further case studies, case series and RCTs are essential. And also these treatment regimens can be applicable to Mild and Moderate COVID-19 patients and not for Severe COVID-19 patients.

Siddha humoral concepts for mortality in Covid-19 Positive with Co-morbid conditions Increased *Kabam* humour is mostly responsible for diabetes and COPD. (9) Systemic vascular resistance and vasculature stiffness play a major influence in geriatric hypertension patients (10). *Vatham* and *kabam* will grow in aged people, creating vascular stiffness, according to Siddha pathophysiology. (11) Even while increased pitha humour is the primary cause of hypertension, as chronicity grows owing to age, the increased pitham will modify the other two humors, favoring the preponderance of *kabam*. (12)

Pitham increases the early pathological change in hepatic disorders. (13) The other two humours vatham and *kabam* will grow in chronic liver illnesses such as cirrhosis of the liver, causing reduced hepatocyte (liver) function, increased intrahepatic resistance, and even contributing to the development of hepatocellular cancer. (14)

Based on the trihumoural hypothesis, the Siddha system has a unique way of comprehending ailments. A hundred years of human life is split into three periods, according to the Siddha scripture *Sathaga Naadi*. Each phase has a duration of 33 years and 4 months. *Kabam* is the initial phase (up to the age of 33 years and 4 months), *Pitham* is the middle phase, and *Vatham* is the last phase (after the age of 66years 8 months). As a result, the geriatric population has been classified as *Vatha kaalam* (Predominant *vatham* humour). (15) The geriatric population with Covid-19 has increased *kabam* within the prominent zone of *vatham*.

"*Vathathil kabam meeril maranam*" is a core Siddha concept, states that as kabam increases in vaatha kaalam which may lead to the end stage (*Maranam*-death).

Sathaga Naadi has clearly quoted this as.

"*Kabathil Vatham pirantaalum, Vaathamaiyam pinal kondaalum kuriyaaga marunthu palavitham seithaalum koondavidam vittuuyirkadakkunthaanae*".(16) If these Geriatric patients with the above-mentioned comorbidities are infected with Covid-19, their Kabam levels will continue to rise, leading to severe end- stage diseases.

According to Siddha pathology, the primary cause of the symptoms in COVID-19 is an increase in *Aiyam* humour. According to the Siddha Literature Pungent (*Kaarppu*), Bitter (*Kaippu*), and Astringent (*Thuvarppu*) will pacify the increased *Aiya* humour. The increased *Azhal* humour will be soothed by sweet (*Inippu*), bitter (*Kaippu*), and astringent (*Thuvarppu*) flavours. The increased *Vali* Humor will be soothed by sweet (*Inippu*), sour (*Kaarppu*), and salt (*Uppu*). We may be able to treat Covid-19 or minimize mortality in Covid-19 with comorbidities by calming *Aiya* humour. (17)

Table 1: Siddha Pharmacodynamics for Siddha Regimen based on Taste and Trihumoural theory

S.no	Indications for Covid-19 with Comorbidity	Dominant Humour in comorbid conditions	Siddha Formulations	Predominant Taste of Siddha formulation	Actions of taste on Trihumor
1	Diabetes mellitus	*Aiyam and Azhal*	*Thetran Vidhai Kudineer*	*Thuvarpu*	Pacify the elevated Aiya humour Pacify the elevated Azhal humour
			Seendhil Chooranam	*Kaippu*	Pacify the elevated Aiya humour Pacify the elevated Azhal humour
2	Hypertension	*Azhal and Aiyam*	*Aadathodai Kudineer*	*Kaarppu*	Pacify the elevated Aiya humour
			Venthaamarai Chooranam	*Inippu and Kaarppu*	Pacify the elevated Vali humour Pacify the elevated Aiya humour
3	Chronic Obstructive Pulmonary Diseases	*Aiyam and Vali*	*Kaba Sura Kudineer*	*Kaippu and Kaarppu*	Pacify the elevated Aiya humor Pacify elevated Vali humor
			Adhimadhura Chooranam	*Kaarppu and Inippu*	Pacify the elevated Aiya humour Pacify elevated Vali humor
4	Geriatric population with comorbidities	*Vali and Aiyam*	*Nilavembu Kudineer*	*Kaippu*	Pacify the elevated Aiya humour Pacify the elevated Azhal humour
			Amukkara Chooranam	*Kaippu*	Pacify the elevated Aiya humour Pacify the elevated Azhal humour
			Thiripala Chooranam	*Thuvarppu*	Pacify the elevated Aiya humour Pacify the elevated Azhal humour

Table: 2 Pharmacological actions of Siddha Herbal Formulations for the Management of Covid-19 with Diabetes Mellitus

Siddha Management Regimen for Covid-19 with Diabetes mellitus			
Siddha Formulations	**Ingredients**	**Parts Used- Taste**	**Proven Pharmacological actions**
1.*Thetran Vidhai Kudineer* (TVK)	*Limonia acidissima* Linn.	Resin	L.acidissima improve the glucose tolerance (18)
	Terminalia chebula (Gaertn.)	Fruit-Thuvarpu	Inhibitory effects on HSV-1, CMV viral entry (18) Cardio-protective property (18) Immunomodulatory action (19)
	Strychonus potatorum Linn.	Seed-Thuvarpu	Anti–HIV1 effects (19) Antioxidant property (20)
	Cassia auriculata Linn	Seed-Thuvarpu	Stimulate Beta-cells to release more insulin (21
2.*Seendhil Chooranam* (SC)	*Tinospora cordifolia* (Thunb,)Miers.	Stem - Kaippu	Antioxidant properties. Increases the IgG antibody. (22) Regenerates of β-cells of Langerhans, increases glycolysis. (23) Enhance insulin sensitivity, improves insulin signaling and hepatic metabolism during insulin resistance. Lowers cholesterol level (24) Stimulate NK cells, B cells, and T cells and various immune-stimulatory cytokines (25)

According to Siddha system of medicine Increased Kabam is responsible for Diabetes mellitus as well as COVID-19. Thetran Vidhai Kudineer and Seendhil Choornam were indicated for Neerizhivu in Gunapaadam Mooligai and Siddha vaithiya thirattu respectively (26) (27). The presence of a persistent pro-inflammatory state is a universal symptom of ageing. Chronic inflammation is currently recognized to be a risk factor for several age-related illnesses, including hypertension, diabetes, atherosclerosis, and cancer (28). Due to oxidative stress and low-grade chronic inflammation, diabetes and hypertension patients are already at risk of developing atherosclerosis (29). The excessive inflammation seen in some COVID-19 patients, particularly those who develop severe sickness, is one of the disease's hallmarks. (30) Systemic pro-inflammatory cytokine responses, directly contribute to plaque rupture through local inflammation, as well as induction of pro-coagulant factors and haemodynamic changes that predispose to ischemia and thrombosis. Which is followed by Hypoxia, septic shock, and multi- organ failure. (31). In a pre-clinical study, when compared to diabetic control group, TVK and metformin reduced blood glucose, lipid profile, creatinine level, SGOT, and SGPT levels in male Wistar rats, however TVK treatment raised body weight, HDL levels, TNF-alpha levels, and insulin levels. In the fructose and STZ generated diabetes model, the researchers discovered that TVK has anti-hyperlipidemic activity in addition to anti-diabetic activity (32). SC significantly minimizes the fasting blood glucose levels in steptozotocin (STZ)- induced diabetic rats while lowering the elevated urea levels in diabetic rats (33). Syringin in and T.cordifolia is said to inhibit immune hemolysis, which is one of the cause of death (34).

As mentioned in Table 2. Antiviral, immune-modulatory, antioxidant, cardioprotective, anti- hemolytic, and hypoglycemic effects of TVK and SC may reduce the mortality in Covid-19 patients with diabetes mellitus.

Table: 3 Pharmacological actions of Siddha Herbal Formulations for the Management of Covid-19 with Hypertension

Siddha Management Regimen for Covid-19 with Hypertension			
Siddha Formulations	Ingredients	Part used-Taste	Pharmacological actions
3.*Adathodai Kudineer* (AK)	*Justicia adhatoda* Linn.	Leaf- Kaippu	InhibitACE functioning, produce vasodilation, Anti-atherogenic and antioxidant activity (35),(36)
	Glycyrrhiza glabra L.	Root- Inippu	Inhibits replication, adsorption and penetration of SARS-associated coronavirus.(37) Has antitussive and expectorant activity. (38)
	Abies webbiana Lindl.	Leaf- Kaarpu	Spasmolytic activity.(39)
	Piper longum Linn.	Dry Fruit-Kaarpu	Inhibit ACE activity. Has Anti-oxidant activity.(40)
4. *Venthaamarai chooranam* (VTC)	*Nelumbo nucifera* Gaertn.	Petals- Inippu, Thuvarpu	Suppress the pro-inflammatory cytokines, oxidative stressors and cytokines. (41)(42),(43)
	Elettaria cardomum L.Maton	Fruit- Kaarpu	Decrease the secretion of IL-1β, TNF-α, and IL8 (44)
	Zingiber officinale Roscoe.	Dry Fruit- Kaarpu	Suppresses prostaglandin synthesis, Inflammatory responses, cytokines, chemokines, enzyme cyclooxygenase-2 (45)
	Glycyrrhiza glabra L.	Root- Inippu	Already mentioned in Adathodai kudineer (38) (39)
	Cuminum cyminum Stein.	Seed- Kaarpu, Inippu	Suppression of inflammatory cytokines.(46)
	Piper longum Linn.	Dry Fruit-Kaarpu	Mentioned in adathodai kudineer (41)

Aadathodai Kudineer, a classical Siddha Formulation described in Siddha manuscript Gunapadam Mooligai Vaguppu is used for treating Iya Erumal, Kozhai Kattu, and Kabasuram.(47) Adhatodine, Anisotine, Tinosporide, Apigenin, Vasicoline, Berberine, Diosgenin, Lupeol and Vasicinone present in the herbs of this formulation Aadathodai Kudineer revels significant binding against the target protein thereby these compounds may exerts promising inhibition against ACE-2 receptor. (48). The binding energy of specific chemical components in the ethanolic extract of AK against SARS-CoV-2 Spike Protein (PDB ID 6LU7) and the SARS- CoV-2 Spike Protein – ACE 2 receptor complex was investigated (6LZG). The binding energy for the compounds Alpha-Copaene, Gamma-Muurolene, and Selina-3,7 (11)–Diene towards the protein targets 6LZG is -10.9 Kcal/mol, -8.0 Kcal/mol, -7.8 Kcal/mol, and for the compounds Alpha-Copaene, Cubebol, and Aromadendrene towards the target 6LU7 is -8.2 Kcal/mol, -6.6 Kcal/ These findings reveal that Adathodai Kudineer (AK), a Siddha formulation, may have substantial antiviral effect against the SARS-CoV-2 Virus, which causes COVID19 disease. (49)

In AK, A.vasica's antihypertensive effect was likely due to suppression of ACE, act on the vascular endothelium to promote the release of EDRF, resulting in vasodilation. (50) By suppressing ACE, hospitalisation and mortality rate in Covid-19 patients with Hypertension as comorbidity will reduce (51) Glycyrrhizic acid in G.glabra inhibits cyclooxygenase activity and prostaglandin E2 production, and hence indirectly inhibits platelet aggregation which is the major cause of mortality in Covid-19 (52). A.webbiana prevents the aggregation of human platelets caused by ADP and epinephrine (40)

The major ingredient in Venthamarai Chooranam is Venthamarai-Nelumbo nucifera. In Siddha literature, it is mostly used to cure Kurudhi azhal noi (hypertension) (53). It was discovered that VTC interacts with renin-angiotensin components and endothelial activities, and so produces its antihypertensive effect in rats with renal hypertension. (54) VTC's cardioprotective effect was demonstrated in a cell line model employing H9C2 cardio myoblasts, indicating that the herbal formulation possessed significant cardioprotective properties. (55)

From the above references we may propose AK and VC which has Anti-viral, Anti-oxidant, Anti-inflammatory, Anti-atherogenic, Anti-platelet and vasodilator activity may reduce the mortality in Covid-19 patients with diabetes mellitus.

Table 4: Pharmacological actions of Siddha Herbal Formulations for the Management of Covid-19 with COPD (Chronic Obstructive Pulmonary Disorder)

Siddha Management Regimen for Covid-19 with COPD			
Siddha Formulations	**Ingredients**	**Part used-Taste**	**Pharmacological actions**
5.*Kaba Sura Kudineer* (KSK)	*Zingiber oficinale* Roscoe.	Rhizome- Kaarpu	Mentioned in venthamarai chooranam (46)
	Piper longum L.	Fruit- Kaarpu	Mentioned in Adathodai kudineer. (41)
	Syzygium aromaticum (L.)L.M Perry	Fruit- Kaarpu	Antioxidant activity attributed to the strong hydrogen donating ability, metal chelating ability and scavenging of free radicals, hydrogen peroxide and superoxide. (56)
	Tragia involucrata L.	Root- Kaippu	Has anti-inflammatory and analgesic activities mediated by inhibition of prostaglandins sensitized pain receptors at inflammatory site. Has hepato-protective activity. It also improve glucose Tolerance (57)
	Anacyclus pyrethrum (L.)Lag	Root- Kaarpu	The phenolic compounds in A. pyrethrum are known to act as antioxidants by their ability to donate hydrogen or electrons and also, they are stable radical Intermediates. (58)
	Hygrophilla auriculata (Schum.) Heine Lam.	Root- Inippu, Sirukaippu	Hepatoprotective by normalizing the elevated levels of the hepatic enzymes. Protective may be due to its anti-lipid peroxidative and free radical scavenging properties (59).
	Terminalia chebula (Gaertn.)	Fruit-Thuvarpu	Mentioned in Thetran vidhai kudineer (18) (19)
	Justicia adhatoda Linn.	Leaves- Kaippu	Mentioned in Adathodai kudineer (36)(37).
	Plectranthus amboinicus (Lour.) Spreng	Leaves- Kaarpu	Has anti-inflammatory activity by preventing tissue protein denaturation. it also has an expectorant, hypoglycemic and has antihyper lipidemic activity. (60)
	Costus speciosus (J.Koing)Sm	Root- Kaippu	Has anti-oxidant activity by its strongest DPPH radical scavenging activity. (61)
	Tinospora cordifolia (Thumb.)Miers,	Stem- Kaippu	Already mentioned in seendhil chooranam (22)(23)(24)(25)

	Clerodendron serratum (L).Moon	Root- Kaippu, Thuvarpu	Antinociceptive, anti-inflammatory and Antipyretic effect indicated a likelihood of intervention with prostaglandin synthesis (62)
	Andrographis paniculata (Burm.f.)Nees	Leaves- Thuvarpu Kaippu	Has Immuno-stimulant activity. (63)
	Sida acuta (Burm f.)	Root- Kaippu	Has analgesic and anti-inflammatory activity (64)
	Cyperus rotundus L.	Root tuber- Thuvarpu	Antioxidant property, Natural immune modulator. (65)
6.Adhimadhura Chooranam (AMC)	*Glycyrrhiza glabra* L.	Root - Inippu	Already mentioned in Adathodai kudineer (38) (39)
	Foeniculum vulgare Mill.	Seed- Kaarpu	Antioxidant action (66)
	Plumbago zeylanica Linn.	Root- Kaarpu	Antioxidant action (67)

KSK is a herbal decoction recommended by the Ministry of Ayush, Government of India, in Siddha Vaidhiya Thirattu for Aiya Suram (68). It has received global honour during the Covid-19 pandemics. Through suppression of cyclooxygenase-1 and cyclooxygenase-2, Z.officinale,T.involucrata S.lappa and C.serratum in KSK has the action to suppress cytokines production and thereby will suppress cytokine storm which is the major cause of death in Covid-19 patients. T.cordifolia(22) , A.vasica (36), S.aromaticum (56), and A. pyrethrum (58) in KSK and F.vulgare (66) in Adhimadhura Chooranam have antioxidant activity and thereby reduce the inflammation caused by cytokine cascade. KSK suppresses COVID-19 by acting on the major protease, according to a molecular study aiming at identifying compounds from natural products of KSK (3CLpro). (69). KSK has immunomodulatory and thrombolytic activity which is studied in vitro immunomodulatory models of phagocytosis of Candida albicans assay and nitro blue tetrazolium. KSK is giving better results compared with the controls (pooled serum, lipopolysaccharide, and streptokinase). The KSK at the concentrations of 12.5, 25, 50, and 100 µg/ml showed % immune-stimulations of 12.40 %, 20.81 %, 33.53 %, 43.20 % and for NBT showed 19.00 %, 25.50 %, 64.00 %, 71.00 % respectively. Similarly, the thrombolytic activity showed 50 and 100 µg/ml concentration showed 43.83 %, 71.83 % clot lysis respectively; and the control value for the streptokinase showed 83.78 %. (70). KSK boosts immunity and works as an immunomodulator. Magnoflorine, 5-Hydroxy-7, 8- dimethoxyflavanone, Tinosponone, Cirsimaritin, Chrysoeriol, 6-Methoxygenkwanin, Vasicinone, Quercetin, and Luteolin are phytoconstituents with the highest affinity for SARS COVID-2 spike protein. Anti-inflammatory, anti-oxidant, and anti-pyretic properties are all found in KSK. (71). Antinociceptive, anti-inflammatory, and antipyretic hypoglycemic and hypolipidemic actions of some herbs in KSK are depicted in Table.4

Adhimadhuram has the ability to emaciate phlegm and soothe elevated Pitha humour. In Gunapaadam Mooligai-I, it is also used to prevent sickness (72). AMC also has antiviral anti-inflammatory antioxidant antitussive and expectorant activity as depicted in table 4.

Table 5: Siddha Management Regimen for geriatric population with Covid-19

Siddha Formulations	Ingredients	Part used-taste	Pharmacological actions
7. *Nila Vembu Kudineer* (NVK)	*Andrographis paniculata* (Burn.f.)	Whole Plant-Kaippu	Immuno-stimulant activity(63)
	Chrysopogon zizanioides Linn.	Root-Inippu	Suppress the inflammatory responses and cell apoptosis (73)
	Plectranthus vettiveroids (K.C Jacob) N.PSingh & B.D Sharma	Root- Kaippu	Anti-inflammatory action .(74)
	Santalum album L.	Stem- Kaippu Thuvarpu	Anti-inflammatory and antipyretic activity.(75)
	Trichosanthes cucumerina L.	Whole Plant- Kaippu	Has anti-inflammatory, hepatoprotective anti-diabetic activity and antioxidant activity.(76)
	Cyperus rotundus L.	Root tuber-Thuvarpu	Antioxidant potential , anti-diabetic and anti-inflammatory activity.(77)
	Zingiber officinale Roscoe.	Rhizome- Kaarpu	Already mentioned in venthamarai chooranam (46)
	Piper nigrum L.	Dry Fruit- Kaippu, Kaarpu	Antioxidant, Anti-inflammatory activity.(78)
	Mollugo cerviana L.	Whole Plant- Kaippu	Anti-inflammatory activity (79)
8. *Thiripala Chooranam* (TPC)	*Terminalia chebula* Retz.	Dry fruit- Thuvarpu	Mentioned in *Thetran vidhai kudineer* (18) (19)
	Phyllanthus emblica Gaertn.	Dry fruit- Thuvarpu, Inippu	Inhibit Superoxide radicals (80). Enhances immunity and has phagocytic function. (81)
	Terminalia bellerica Gaertn	Dry fruit- Thuvarpu	Anti-HIV-1.(82)

9. *Amukkara Chooranam* (AMC)	*Withania somnifera* L.	Root- Kaippu	Antiretroviral activity.(83) It has pancreatic islet free radical scavenging activity(84) Immune-modulatory action(85)

In Siddha Literature NVK is indicated for fever (86). NVK reduces the release of inflammatory mediators in the first and second phases of the inflammatory response. Neoandrographolide, found in *Andrographis paniculata*, has anti-inflammatory properties.(87) NVK inhibits cyclooxygenase and lowers PGE2 levels in the hypothalamus, which is a common mechanism of action for antipyretics. NVK inhibits the ACE2 enzyme receptor, which is where the Novel Corona Virus enters humans. (88) *A.paniculata* contains diterpenes, andrographolide, and polysaccharides that boost the immune response by activating complements, lymphocytes, and macrophages. Interferon production is stimulated by flavonoids in NVK, resulting in immunomodulation. Alkaloids, glycosides, tannins, and phenols are secondary metabolites in NVK that have immunomodulatory properties. (89) NVK possesses anti-diabetic properties. (90)

Thiripala Chooranam is a *Kayakarpam* that enhances health and prevents ailments. (91) Individual Triphala medicines contain anti-diabetic glycosides, alkaloids, terpenoids, flavonoids, and carotenoids. Antiviral, cardioprotective and Immunomodulatory property of *T.chebula* was already briefed in Table 2. Which may help to reduce mortality in Covid-19. E. officinalis protects pancreatic alpha cells from oxidative stress and improves their function, with the added benefit of modifying lipid profile. Hepatotoxicity is prevented by reducing liver injury. (92)

Amukkara Chooranam is said to be able to heal diseases caused by elevated *Vali* and *Aiya* humour as mentioned in Siddha literature (93). Antiretroviral, anti-Oxidant and anti- inflammatory activities of *Amukkara chooranam* were briefed in Table 5.

From the above-mentioned references, it is evident that the pharmacological actions of Siddha regimens for Diabetes mellitus, Hypertension, COPD and Geriatric population can be repurposed to reduce the mortality in COVID-19 patients with comorbidity which should be established by randomized controlled clinical trials.

Conclusion

Immune dysregulation caused by cytokine storm is the leading cause of death in Covid -19. The deleterious effects of immunological dysregulation are further influenced by oxidative stress and increasing inflammatory changes related to age and comorbid diseases, which increases mortality in covid-19 patients with comorbidity. The antiviral, anti-inflammatory, anti-oxidant, immune-modulatory, and anti-atherosclerotic activities of the selected Siddha formulations have been demonstrated with scientific backing through this exhaustive review. As a result, these formulations may help Covid 19 patients with comorbidity live longer.

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