

Repurposing Siddha Medicine *Amukkara Chooranam* as a Therapeutic Approach for the Management of COVID-19-A Review

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Abstract

COVID-19 is a global pandemic caused by SARS CoV-2. It is a dreadful disease due to its rapid spread and increase in mortality rate, now is of great global health concern. We are in an urgent need of vaccine/medicine to tackle COVID-19. Drug repurposing is the novel treatment option accelerating the drug discovery process through the identification of a novel clinical use for an already existing approved drug which minimize the costs, risks and save time when compared with invention of new drug. Siddha polyherbal medicine *Amukkara Chooranam* (AMKC) constitutes seven herbal ingredients being used in the treatment of various other diseases like Gastric ulcer, Peripheral neuritis, Gonorrhoea, Asthma and Tuberculosis. In this, *Withania somnifera*, *Zingiber officinale* have antiviral activity that inhibits M protease and Spike protein prevents the entry and growth of COVID-19. *Piper longum*, *Piper nigrum*, *Mesua ferrea*, *Syzigium aromaticum* binds with M protease [MPro] and ACE-2 receptors and *Elletaria cardamomum* binds with Nucleo caspid protein [N protein] thereby inhibiting the viral replication. The polyherbal synergism of AMKC enhances its efficacy over co morbid conditions also. From various research reports, ingredients of AMKC revealed anti-inflammatory, anti-viral, immuno enhancing properties can exhibit potential activities against COVID-19. This made reasonable grounds on drug repurposing of AMKC as a novel clinical use for COVID-19. In future, clinical trials to be conducted to induce drug discovery through drug repurposing initiatives. Hence this review is intended to repurpose and explore the comprehensive effects of polyherbal formulation AMKC as a therapeutic approach for the management of COVID-19.

Keywords: *Amukkara chooranam*, Polyherbal, Siddha medicine, COVID-19

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Introduction

COVID-19, a global pandemic is caused by SARS-CoV-2 virus. It is a dreadful disease worldwide due to its rapid spread and increase in mortality rate, now is of great global health concern.¹ SARS-COV (2002-2004), MERS-COV (2012) the antecedents of COVID-19, hit the world in the recent two decades. The outbreak of SARS-COV2 began in Wuhan, China, in December 2019.² COVID-19 entered a new phase- Adaptation to any kind of environment. It has a high rate of mutagenesis and changes in structure, which has created a barrier for both investigations and the therapeutic regimens. With the emerging battle against this deadly virus WHO on February 11, 2020 officially named this viral disease as COVID-19 and strategized to interrupt the human chain by isolating the patients in the early stages of infection to minimize the spread of infection.³ As of July 31, 2020, WHO reported the worldwide total number of confirmed cases were 17,064,064 and number of death cases 6, 68, 073. In India the total number of confirmed cases 16, 38, 870 and death cases 35,747.⁴

Siddha system of medicine is the ancient traditional medicine practiced in Tamil Nadu, south India, came into existence 5000 years ago.⁵ Indian traditional medical systems are considered as one of the oldest treatments in human history and it plays an important role in

encountering global healthcare needs.⁶ Nowadays traditional Indian medicines are used by millions of people worldwide proved its effects on flu like illnesses. A Siddha medicine is used effectively in the prevention and treatment of pox viruses since ancient times. Emerging and re-emerging infectious diseases continue to impose a constant threat on human population.⁷ Viral infection challenges survival of mankind on this planet.⁸ Herbal drugs are proven to be the powerful source of antiviral agents with some great advantages due to its extensive therapeutic potentials with limited side effects.⁹

In the last two decades, numerous in vitro and in vivo research studies done on herbal drugs. Polyherbal formulations are the combinations of multiple herbs mixed in a meticulous ratio that enhances therapeutic effects and decreases the toxicity due to the synergism of polyherbal the benefits not accessible to single herbal medicine.

Polyherbal formulations are effective in lower dose and safety in higher dose and are highly effective for lung diseases and other respiratory ailments.¹⁰

Globally still there is an urgent need of vaccine /medicine for COVID-19. Drug repurposing is the novel treatment option to accelerate the drug discovery process through the identification of a

novel clinical use for an already existing indications that minimize the costs, risks and time consuming associated with drug development programmes.^{11, 12}

Repurposing of herbal drugs is safe in treatment options.¹³ Siddha medicine *Amukkara chooranam* [AMKC] is the polyherbal formulation constitutes seven herbal ingredients and the therapeutic uses of AMKC includes gastric ulcer, splenic disorders, gonorrhoea, peripheral neuritis, tuberculosis.¹⁴ Several research studies proved herbal ingredients of AMKC possess anti-inflammatory, anti-viral, immune enhancing potentials that influences on COVID-19. The

Amukkara Chooranam

Amukkara chooranam a shastric Siddha medicine referred from Siddha literature, *Siddha Vaidya Thirattu* (SVT) paginated in 215. Amukkara chooranam [AMKC], Siddha polyherbal formulation contains the following seven ingredients Amukkara [*Withania somnifera*], Sukku [*Zingiber officinale*], Thippili [*Piper longum*], Milagu [*Piper nigrum*], Elam [*Elletaria cardamum*], Sirunagapoo [Mesua ferea], Kirambu [*Syzigium aromaticum*].¹⁴

The information of each herbal drug of Amukkara chooranam was collected from the Siddha literatures and also

approved drug for different herbal drugs of AMKC with its potential antiviral activity can reduce the symptoms of COVID-19 that can be effective in the management of COVID-19 yet to prove scientifically through clinical trials of AMKC on COVID-19 cases. Considering this in mind and also to accelerate the herbal drug discovery, consequently drug repurposing of AMKC may be applied for the management of COVID-19. Hence this review elucidated with the repurposing of polyherbal Siddha medicine *Amukkara chooranam* as a therapeutic approach for the management of COVID-19.

searched on the scientific databases like Pubmed, Science direct, and Springer for the recent research reports of the ingredients of Amukkara chooranam. Medicinal plants, anti-inflammatory, antiviral, immuno stimulants, potentials, traditional medicines, Drug repurposing, Repositioning, Reprofilng, molecular docking were the words used in searching through the scientific data bases. Research reports like anti-inflammatory, antiviral, immuno stimulants were searched for each herbal ingredient of Amukkara chooranam and data were collected.

Figure 1. Ingredients of Amukkara Chooranam ⁵²



1. Amukkara- *Withania somnifera*



5. Elam- *Elletaria cardamum*



2. Sukku- *Zingiber officinale*



6. Sirunagapoo-*Mesua ferea*



3. Thippili- *Piper longum*



7. Kirambu- *Syzigium aromaticum*



4. Milagu- *Piper nigrum*



Amukkara Chooranam (AMKC)

Table No 1. Ingredients of Amukkara chooranam¹⁴

S. No.	Ingredients of AMKC	Botanical Names	Part used	Measurements [Parts]	Indications of AMKC as in SVT
1.	<i>Amukkara</i>	<i>Withania somnifera</i>	Root	64	<i>Envagai kunmam</i>
2.	<i>Sukku</i>	<i>Zingiber officinale</i>	Rhizome	32	<i>Idapaattu earalnoi</i>
3.	<i>Thippili</i>	<i>Piper longum</i>	Fruit	16	<i>Kuthuvaivu, Vettai</i>
4.	<i>Milagu</i>	<i>Piper nigrum</i>	Seed	8	<i>Bramium,</i>
5.	<i>Elam</i>	<i>Elletaria cardamomum</i>	Seed	4	<i>Eraippu,</i>
6.	<i>Sirunagapoo</i>	<i>Mesua ferea</i>	Bark, Root, Flower	2	<i>Elaippu sayam</i>
7.	<i>Kirambu</i>	<i>Syzigium aromaticum</i>	Flower bud	1	

Method of Preparation of Amukkara Chooranam

In Siddha system of medicine, no medicinal preparation has been done without prior purification. By the process of purification, the undesirable toxic effects of raw drugs are lost and give better efficacy. After purification, the ingredients of AMKC is weighed and taken in the given measurements. Then each drug grinded separately and sieved made to a fine powder eventually mixed with all the

drugs. Finally, powdered sugar [128 parts] added to this fine powder to obtain *Amukkara chooranam*¹⁴. Preparation of chooranam is done by following the standard operative procedure of PLIM guidelines.

Shelf life of chooranam: 3months.

Dose of chooranam: 1 gm

Route of administration: Oral¹⁴

Table No 2. Siddha literary reports of the ingredients of *Amukkara chooranam*¹⁵

S. No.	Ingredients of AMKC	Suvai [Taste]	Pirivu [Bio-transformation]	Veeriyum [Potency]	Mahimai [Action]	Gunam [Indications]
1.	<i>Amukkara</i>	Bitter	Pungent	Hot	Alterative, Diuretic, Deobstruent	<i>Vatham, Kabam</i> diseases, nervous disorders
2.	<i>Sukku</i>	Pungent	Pungent	Hot	Stomachic Carminative	Cough, Asthma, Diarrhoea, Fever due to <i>kabam</i>
3.	<i>Thippili</i>	Sweet	Sweet	Cool	Stomachic Carminative	Head ache, cough, Fever, Throat infection, Lung disorders, <i>kabam</i> diseases, Asthma
4.	<i>Milagu</i>	Pungent, bitter	Pungent	Hot	Anti-vatha Anti dote Carminative	Fever, Cough, Throat infection, Phlegm due to <i>kabam</i> , Diarrhoea
5.	<i>Elam</i>	Pungent	Pungent	Hot	Stimulant Carminative	Cough, Throat diseases, Lung infection, Diarrhoea
6.	<i>Sirunagapoo</i>	Astringent	Pungent	Cool	Carminative	Cough
7.	<i>Kirambu</i>	Pungent	Pungent	Hot	Anti-spasmodic	Relieves the tiredness after pyrexia

Figure 2. Pharmacological activities of AMKC

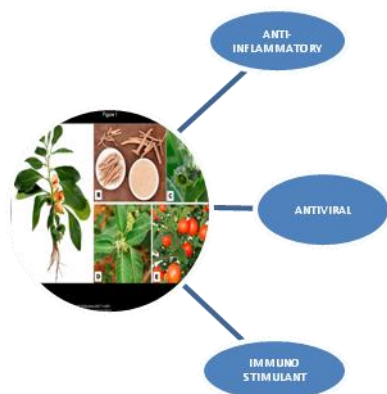


Figure 3. Structure of Noval Corona Virus⁵³

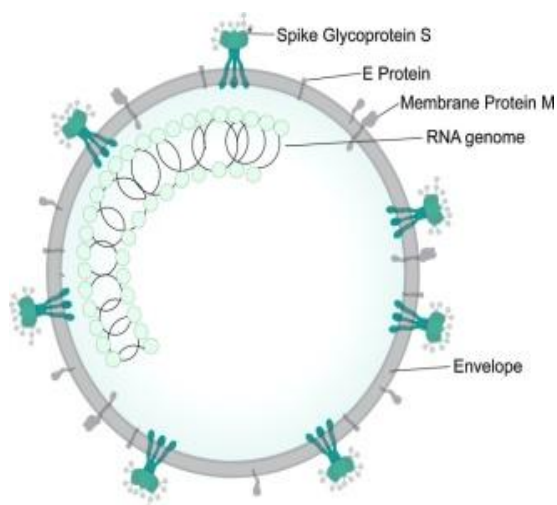


Table No 3. Research reports of *Amukkara chooranam* in the management of comorbidities

S. No.	Ingredients of AMKC	Pharmacological studies
1.	<i>Withania somnifera</i>	Cytotoxic, Cardioprotective . ⁴²
2.	<i>Zingiber officinale</i>	Anti hyperglycemic Antihyperlipidemic. ⁴³
3.	<i>Piper longum</i>	Antimicrobial, Anti asthmatic. ⁴⁴
4.	<i>Piper nigrum</i>	Antihyperlipidemic. . ³⁴
5.	<i>Elletaria cardamomum</i>	Cardio protective Anti hyperglycemic Antihyperlipidemic. ⁴⁵
6.	<i>Mesua ferea</i>	Cardio protective Anti hyperglycemic Chronic obstructive pulmonary disease. ³⁹
7.	<i>Syzygium aromaticum</i>	Anticancerous, Antihyperlipidemic, Anti hyperglycemic. ⁴⁰

Table No 4. Research reports of the ingredients of *Amukkara chooranam*¹⁶⁻⁴¹

S. No.	Botanical name and Phyto compounds of AMKC	Anti-inflammatory activity	Antiviral activity	Immuno enhancing activity
1.	<i>Withaniasomnifera</i> Withanolide Withanone Withaferin A	The pro inflammatory cytokines IL-6 decreased significantly. ¹⁶	binds the interface of ACE2- RBD complex ¹⁷ Significant interaction with M protease of sars-cov2. ¹⁸	Activates murine macrophages, phagocytosis, lysosomal enzyme activity, Immuno modulatory effect. ¹⁹ Enhances immuno modulatory effect. ²⁰
2.	<i>Zingiberofficinale</i> Gingerol 6- Gingerol Shagoal Quercetin	Enhances the effect in rheumatoid arthritis. ^{21,22}	Against HCV. ²³ Inhibiting effects on S protein and M protease of COVID-19. ²⁴	Effects on cell mediated immune response. ²⁵ Inhibits IL-6, IL-8 and ameliorates the infection. ²⁶
3.	<i>Piper longum</i> Piperine	Reduces pro inflammatory cytokines. ²⁸	Strong activity against HSV-1, Para influenza virus. ²⁹	Significant decrease in IL-6 IL-8, TNF- α . ³⁰
4.	<i>Piper nigrum</i> Piperine Piperamides	Effective in respiratory diseases. ³¹	Anti proliferative . ^{29,32}	Reduces pro inflammatory cytokines IL-1 β ,IL-6,TNF- α . ³³
5.	<i>Elletariacardamomum</i> 1, 8-cineole, α pinene, α terpineol	Improves inflammatory oxidative stress. ³⁴	Inhibits interaction with viral genomic RNA. ³⁵	Inhibits pro inflammatory cytokines IL-6 and TNF secretion. Attenuates inflammatory signalling pathways in lung alveolar macrophages. ³⁶

6.	<i>Mesuaferrea</i> Epicatechin Luteol Ellagic acid Gallic acid Kaempferol Myricetin Quercetin Rutin	Potent in acute and chronic conditions of inflammation. ³⁷ Enhances inflammatory arthritis. ³⁹	Potent ACE inhibitor. ³⁸	Elicit T cell stimulation and regulation of macrophages. ³⁹
7.	<i>Syzigiumaromaticum</i> Eugenol Carvacrol Quercetin Kaempferol Ellagic acid Ferulic acid	Effective in the treatment of arthritis. ⁴⁰ Potent anti-inflammatory. ⁴¹	Against HSV-1 and HSV-2. ⁴⁰	Prevents neutrophil / macrophages chemotaxis. Inhibits cytokine expressions in macrophages. ⁴⁰

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ACE2-RBD - Angiotensin converting enzyme 2-Receptor binding domain; HCV-Hepatitis C virus ; S protein- Spike protein; IL-Interleukin; TNF- Tumor necrotizing factor; HSV- Herpes simplex virus.

Discussion

The research reports of the herbal ingredients of AMKC possess anti-inflammatory, anti-viral, immuno enhancing properties in [Table 4]. *Withania somnifera*, *Zingiber officinale* inhibited M protease and S protein acting as antiviral entry and growth inhibitors of COVID-19. *Piper longum*, *Piper nigrum*, *Syzigium aromaticum* binds with M protease and ACE2 inhibitors. *Elletaria cardamum* binds with Nucleo caspid protein [N protein] thereby inhibits the viral replication. Inhibitory activity of *Elletaria cardamom* and *Mesua ferrea* on angiotensin converting enzymes blocks the viral entry. The presence of flavanoids, phenolic acids in the herbal drugs of AMKC inhibit the cysteine residue thereby damages the E [Envelope] protein structure and degrades the

transmission of corona virus. Research reports of AMKC showed significant immune enhancing activities. Amukkara chooranam also showed efficacy on comorbid diseases as in [Table 3].

In Siddha science, Health declined season termed as *Adana kaalam*⁴⁶. Usually in the *Adana kaalam* due to the decline in immune status, people are more prone for many diseases. The outburst of COVID-19 occurred in *Adana kaalam* season that influences easy and rapid spread of infection. The predominant symptoms like cough, throat infection, lung infection seen in COVID-19 cases due to the provoked *kabam*. In Siddha aspect, the treatment is based on neutralising the imbalance of three humours vatham, pitham, kabam. The hot potency [*veerium*] of *Amukkara*, *Sukku*, *Milagu*, *Elam*, *Kirambu* balance the provoked *kabam* and decrease the

accumulation of phlegm in the lungs. In AMKC all the herbals except *Thippili* tastes pungent, associated with the suppression of *kabam*. Medicinal plants from Siddha system of medicine are useful for treating respiratory diseases.³³ The pungent taste and hot potency of ingredients of *Amukkara chooranam* is favourable and pertinent for the management of COVID-19.

Polyherbal formulation of Siddha drug *Amukkara chooranam* exhibits pharmacokinetic and pharmacodynamic synergism.⁴⁷ The bioactive constituents with similar therapeutic activity targeted bio diverse mechanism of action. Due to this synergism of poly herbals expressed more effective in low dose and safety in high doses in numerous diseases.⁴⁸ Deaths are more common in COVID-19 due to the lesser immunity associated with comorbidities. Research reports of herbal drugs of *Amukkara chooranam* proved its therapeutic efficacy on comorbid diseases as in [Table 3].

Huge inflammation [cytokine storm] produced by the pro-inflammatory cytokines like IL-6, IL-8, TNF α observed in COVID-19⁵⁰. *Withania somnifera*, *piper longum*, *piper nigrum*, *Mesua ferrea* have enhanced effect in inhibiting the pro-inflammatory cytokines. All the herbal drugs of AMKC possess anti-inflammatory activity as in [Table 3]. The herbs in treating arthritis will have profound anti-inflammatory activity.

Zingiber officinale showed anti-inflammatory property in treating rheumatoid arthritis. Withanone from *Withania somnifera* may be the first choice to curb COVID-19. Molecules of *piper longum*, *Piper nigrum*, *Syzygium aromaticum* binds with ACE-2 and M protease enzymes acting as antiviral growth inhibitor and blocking the receptor binding domain [RBD] with Corona virus. *Elettaria cardamum* binds with nucleocapsid protein (N)Nucleocapsid protein inhibit viral replication. *Withania somnifera* and *Zingiber officinale* inhibits M protease and spike (S) protein. Molecules in *Elettaria cardamomum* and *Mesua ferrea* had inhibitory activity on angiotensin converting enzymes in [Table3]. E protein [Envelope protein] an additional protein present only in Corona virus contains cysteine residue.⁴⁹ Flavanoids, Phenolic acids in the herbal drugs of AMKC can inhibit the cysteine residue thereby damage the E protein structure and degrade the transmission of corona virus⁵¹. All the drugs of AMK chooranam possess immune enhancing property improving both the innate and adaptive immunity. [Table.4]. Moreover standardization of AMKC proved the presence of alkaloids, tannins, terpenes, steroid which are effective antiviral agents.⁵¹

Several research reports proved the herbal ingredients of AMKC possess anti-inflammatory, antiviral, immuno enhancing

properties. At this critical and pandemic situation all these data paved the way for repurposing of already existing drug *Amukkara chooranam* which targets over COVID-19. Hence Repurposing of Polyherbal formulation of Siddha medicine AMKC is the most innovative and effective treatment option for COVID-19. Therefore

AMKC may be a potential therapeutic approach for the management of COVID-19. In future, the utility of repurposing of existing Siddha medicine *Amukkara chooranam* can be accomplished with clinical trial studies to prove its therapeutic potential for the management of COVID 19.

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