



THE RATIONALE AND POTENCY OF KABASURAKUDINEER – A SIDDHA FORMULATED MEDICINE TO PREVENT AND CONTROL SARS-CoV-2.

Renuka Radhakrishnan	Department of Biochemistry, V.V.Vanniaperumal College for Women, Virudhunagar, Tamilnadu, India.
Suguna Rajendran*	Department of Biotechnology, The Madurai College, Madurai, India. *Corresponding Author
Jeya Jeyamani	Department of Microbiology, V.V.Vanniaperumal College for Women, Virudhunagar, Tamilnadu, India.
Sankar Anand	Siddha Medical Officer and Co-Ordinator, of Covid Siddha Care centre Almaa Siddha Hospital, Tirumangalam, Madurai, Tamilnadu, India.

ABSTRACT Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of the recent global pandemic COVID-19 with increased mortality rate. It was described as a public health emergency of global concern by the World Health Organization. The corona virus is more prone to mutation. Genome analysis has proved that many mutations have occurred in SARS-CoV-2 and variants of the virus have evolved globally. Siddha medicines have proved to be the effective way in curing the corona virus infection by treating with Kabasurakudineer formulation. The objective of this review is to trace the rationale behind the efficacy of Kabasurakudineer formulation in treating, controlling and preventing SARS-CoV-2.

KEYWORDS : SARS-CoV-2, COVID-19, Kabasurakudineer, quercetin, coumarin, flavonoids.

INTRODUCTION

In the past few decades, the emergence of new infectious diseases has created improved medical concepts, that has eventually advancements in scientific findings and lifestyle of public health; and also has affected political responses at all international, national and regional levels, and it has created a serious economic impact; and affected the angst and belief of the public to a greater extend¹. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) provisionally named 2019-nCoV is the causative agent of the recent global pandemic COVID-19 with increasing mortality rate. It is described as a public health emergency of global concern by the World Health Organization (WHO)². Specific mutations and unique combinations of SARS-CoV-2 mutations are correlated with severity of the disease. Since the first case identified various strategies were followed to prevent the spread of this SARS-CoV-2. Many drugs such as antiviral, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or statins together with monoclonal antibodies, immunomodulators, non-steroidal anti-inflammatory agents (NSAIDs) and corticosteroids, were given to high-risk patients who were diagnosed with mild to moderate illness. Siddha system of medicine, practiced in Tamil Nadu, South India maintains a distinctive identity of its own by considering humans as a universal entity and implies that any change in the environment will have an influence on human existence and living. According to the Siddha system of medicine, the spices and condiments, namely ginger, garlic, turmeric, pepper, cumin seeds etc present in the South Indian food are itself considered as the medicine and proper intake of food could provide immunity. Number of immunomodulatory herbs has been reported in Siddha as preventive drugs. Siddha system of medicine emphasizes the usage of botanical medications for many severe respiratory diseases. The drugs used in Siddha are the formulation of herbs and medicinal plants³. The Siddha treatment strategy has always been an effective method in par with allopathic medicines, that has even proved during this pandemic COVID-19. This article aims to study the therapeutic property based on photo chemicals present in kabasurakudineer formulation that prevents the control of COVID-19 virus and hence responsible for the remedy and prevention of COVID-19.

Types Of Corona Virus And Its Variants

The Coronaviridae family of viruses are enveloped, single stranded positive-sense RNA viruses grouped into four genera (alpha corona virus, beta corona virus, gamma corona virus, and delta corona virus) that primarily infect birds and mammals including humans and bats. The seven corona viruses known to infect humans fall within the genera alpha and beta corona virus, whereas gamma and delta corona viruses primarily infect birds. During the recent decades, three highly pathogenic corona viruses have emerged into the human population

from wildlife that has caused severe respiratory illness: severe acute respiratory syndrome corona virus (SARS-CoV) in 2002, Middle East respiratory syndrome corona virus (MERS-CoV) in 2011, and most recently, severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) in 2019⁴.

WHO has reported that the first human cases of COVID-19, the disease caused by the novel corona virus, in Wuhan City, China, in December 2019⁵. In India the first case of COVID-19 infection was reported in Kerala, on January 27, 2020⁶. Four Corona virus strains identified in India are responsible for most of Covid-19 cases and several others that are locally concentrated and region-specific variants. The Covid-19 virus variants are commonly referred by the name of the country where they were first discovered. Like any other RNA viruses; SARS-CoV-2 is more prone to mutation. With genome analysis many mutations have been detected globally. Most of these genetic variations may provide a better adaptability, by enhancing transmissibility to greater extent or decreasing the susceptibility to natural immunity or medical treatments. Through natural selection, variants with an adaptive advantage will over time tend to displace existing strains⁷. Alpha variant also known as B.1.1.7, was first identified in United Kingdom in September, 2020⁸, Beta Variant B.1.351, was first detected in South Africa in May 2020, Gamma Variant B.1.1.28 was first identified in Brazil in November 2020⁹. Delta variant, also known as B.1.617.2, belongs to a viral lineage first identified in India during the ferocious second wave of COVID-19 infections in April and May 2021. Delta variant were found to be 60% more transmissible than the Alpha variant⁹.

Covid-19 Virus Mutations In India

Apart from the Covid-19 India variants, many several mutations of the Corona virus have been observed. As the virus spreads, it mutates and replicates, the mutations may be the reason behind the dangerous second Covid wave in India¹⁰. In the beginning the Covid-19 outbreak (reportedly from China's Wuhan) was a single strain outbreak, but as it gets transmitted from people to people and across countries it got mutated to get itself evolved into a more virulent strain that can evade the human immune system. The analysis of the genome sequences of the SARS-CoV-2 in Indian SARS-CoV-2 sequences, has revealed E484Q and L452R mutation (commonly known as a double mutant) in the spike protein of SARS-CoV-2, which is considered to have higher transmission rates. The Double Mutant Corona virus Strain — or simply, a combination of more than two Covid-19 variants — was found in samples in Punjab, Delhi and Maharashtra. Classified as the “B.1.617 variant”, and it contains mutations from two separate corona virus variants — L452R and E484Q, and has been found in 20% samples in the state of Maharashtra¹¹. The variants and mutants were

responsible for the greater pathogenicity of the virus .As the people are not immune to such virus the severity was greater and has caused greater mortality during the first and second wave in India.

Treatments For Covid-19 In Tamilnadu, South India.

As per the ICMR recommendations the allopathic treatments were followed in TamilNadu both during the first wave and second wave. But during the second wave in India, the Tamilnadu state included Siddha medicines to treat Covid 19 in addition to the allopathic treatments. Siddha medicines were comprehended in Covid Care Centres for patients who tested positive for Covid 19 with mild symptoms. The medicines given for the treatment at the Siddha centre included Kabasurakudineer, together with other herbal foods, herbal steaming, breathing exercise and mental health support ¹². The Siddha, the oldest Tamilian treatment has proved to be successful in various Siddha Covid care centre across the state. During the second wave of pandemic Covid 19 between the month of May and June 2021, one of the Covid Siddha Care centre at The American College was a Tamil Nadu Government and Private joint venture, which was maintained by The Madurai City Corporation, Tamil Nadu Chamber of Commerce and Almaa Siddha Hospital. Covid Siddha Care centre at The American College had treated 262 inpatients. Of which 171 were male and 91 female. From the data available, of 260 patients admitted to the Siddha care centre 220 were with symptoms of Corona infection and 42 were admitted asymptomatic .Those asymptomatic patients got admitted as they were tested positive by RT-PCR molecular diagnostics test.

Table 1: Details Of Patients With Co Morbidities At Covid Siddha care Centre At The American College, Madurai, Tamil Nadu State, South India.

Co morbidities in patients	Number of patients
High blood pressure or Hypertension	34
Diabetes Mellitus	62
Both hypertension and Diabetes Mellitus	23
Asthma	9

(Source: From Covid Siddha Care centre, The American College –Madurai, Tamil Nadu state, South India during the second wave pandemic Covid 19 between the month of May and June 2021)

All in-patients in the Siddha Covid care centre were treated with Siddha medicines such as Kabasurakudineer (A Siddha formulation containing 15 herbal plant parts as given in Table 2) and AdathodaManapagu(*Adhathoda zeylanica* in sugar syrup formulation) which were quoted in the classical Siddha ancient literatures, and approved by Drug and Cosmetic Act, The Siddha Formulary of India, Part I, published by Department of Health and Family Welfare, Government of India¹².The formulation was recommended twice a day after food . After the treatment, the patients were discharged in 5 to 18 days based on the severity of the infection. On discharge the patients were advised to continue the kabasurakudineer and Adhathoda Manapagu (Syrup) for a fortnight to recuperate and to prevent reinfection.

Table 2: Composition Of Kabasurakudineer And The Phytochemical Components Present The Siddha Formulation To Treat SARS CoV2 .(percentage Of Each Plant Parts In The Formulation Is 6.66%)

S. No	Botanical Name	Parts	Phytochemical components present
1	<i>Zingibe officinale L</i>	Dried rhizome	Gingerols, shogaols, paradolszingerone, quercetin, , gingerenone-A, 6-dehydrogingerdione ¹³
2	<i>Piper longum L.</i>	Fruit	Piperine, pipartinesamin, pipasterol, pipelonguminin, steroids glycosides ¹⁴ .
3	<i>Syzygium aromaticum (L.)</i>	Flower bud	Monoterpenes, sesquiterpenes, hydrocarbon, phenolic compounds, eugenol, eugenyl acetate, and β-caryophyllene, quercetin and kaempferol , phenolic acids ¹⁵

4	<i>Tragia involucrate L.</i>	Root	Isoquinoline, auronones (sulpheretin), flavanones (naringin), chalcones (butein), quercetin, kaempferol myricetin ¹⁶
5	<i>Anacyclus pyrethrum (L.)</i>	Root	Alkaloids, catechic tannins, gallic tannins, triterpenes, sterols, coumarins ¹⁷
6	<i>Hygrophilaauriculata</i>	Root	Apigenin, lupeol, botulin, , acacetin, proanthocyanins, phenolic acid ¹⁸
7	<i>Terminalia chebula</i>	Pericarp	Rutin, Quercetin, Luteolin, Pelargonidin , β-Sitosterol ¹⁹
8	<i>Adhathoda zeylanica</i>	Leaves	Vasicine, vasicinone, vasicol, vasicinol, vasicinoline, peganine , adhatonine, kaempferol, quercetin ²⁰
9	<i>Coleus aromaticus</i>	Leaves	Rosmarinic acid , caffeic acid, rutin, gallic acid, quercetin , p-coumaric acid ²¹
10	<i>Saussurea lappa</i>	Tubers	Luteolin-7-O-β-D-glucoside, apigenin-7-O-β-D-glucoside, RutinKaempfero ²²
11	<i>Tinospora cordifolia</i>	Stem	11- hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, cordifolioside A, magnoflorine, tinocordiside, isoquinoline alkaloid , tinosporin, palmatine, isocolumbin, , tetrahydropalmatine, magnoflorine ²³
12	<i>Andrographis paniculata</i>	Whole plant	Deoxyandrographolide, neoandrographolide, 14-deoxy11,12-didehydroandrographide , isoandrographolide ²⁴
13	<i>Clerodendron serratum</i>	Root	Hispidulin , cleroflavone , apigenin, 7-hydroxy flavanones, scutellarein serratagenic acid, pectolinarigenin , acteoside, indolizino, verbascosidebetulin, oleanolic acid, clerodermic acid, betulinic acid, friedelin ,monomelittoside ²⁵
14	<i>Sida acuta</i>	Root	Vasicine, ephedrine , cryptolepine, saponosides, scopoletin, coumarins, evofolin-A, and B, loliolid and 4-ketopinoresinol ²⁶
15	<i>Cyperus rotundus</i>	Rhizome	Cucurbitacin B, E, isocucurbitacin, 23,24- dihydroisocucurbitacin B, E, lycopene ²⁷

Bioactive Components That Are The Potential Drug Candidates For Treating Corona Virus

Flavonoids include a large number of secondary metabolites synthesized in the plant cells to defend against pathogens and insects. Flavonoids possess a potent virucidal activity to a moderate range. But later quercetin was found effective in reducing the infectivity and intracellular replication of Para influenza virus type 3 (Pf-3), Herpes Simplex Virus type 1 (HSV-I), polio-virus type 1, and Respiratory Syncytial Virus (RSV)²⁸. Plant metabolites such as Quercetin, luteolin, coumarins, hesperidins, eriodictyol, naringin, epigallocatechingallate are identified as potential inhibitors of S-protein of SARS-CoV and ACE-2 host receptors^{29,30}.

Quercetin (3,3',4',5,7-pentahydroxyflavone) is one of the most important compounds in the group of flavonoids and it is a carbohydrate-free flavonoid that is most abundant in vegetables and fruits. Quercetin is mainly known for its neuroprotective effects due to its antioxidant capacity and free radical scavenging ability. Quercetin can also pass through the blood brain barrier. Quercetin, while acting as an antioxidant and anti-inflammatory factor, also prevent the cells

from apoptosis by inhibiting the apoptotic process³¹. Quercetin has been identified to inhibit recombinant human ACE 2 receptors. The IC 50 value of quercetin is 4.48µm. Quercetin inhibits the interaction between ACE host receptor and the envelope spike glycoprotein of SARS-CoV 2³². For a solution of quercetin to be active, at least three times the inhibition constant is required reasonably at the site of interaction, i.e. $\geq 25 \mu\text{M}$ ($\geq 7.6 \mu\text{g/ml}$). A single dose of 10 ml of nasal spray would therefore be required to contain ~ 76 µg of quercetin. The nasal spray of quercetin is transported and diffuses into lungs and blood. US, FDA has recommended oral Quercetin as safe.[33] Molecular docking study has revealed that Quercetin interacts with ACE 2 receptor by forming a salt bridge. Blocking of the hot spots on ACE 2 prevents the viral attachment to the cells and thereby preventing the entry into the host cells. Similarly hesperidin, naringin and EGCG have also been identified to interact with ACE 2 receptor by various molecular docking platforms²⁹.

Coumarins are a naturally occurring benzopyrene compound that is stable, soluble, low molecular weight compound without any adverse side effects and toxicity. The properties of coumarins make them a potential drug candidate against many viral and bacterial diseases³⁴. *In silico* studies have predicted that Coumarin is potential inhibitors against the Protease, NSP10/NSP16-Methyltransferase, Phosphatase and Endo ribonuclease of SARS CoV-2. Coumarins interact with ACE 2 through various hydrogen bonding and hydrophobic interactions and competitively inhibits the attachment of the S protein to the ACE 2 receptor³⁵. By docking analysis it has been found that C terminal of S1 domain and S2 domain of the spike protein are important for binding with Kaempferol, curcumin, pterostilbene, fisetin, quercetin, isorhamnetin, genistein, luteolin, resveratrol and apigenin, interacts with the S2 domain of spike protein³⁶.

DISCUSSION

Flavonoids with its pleiotropic effect are emerging as a promising and powerful candidate drug molecule of natural compounds with potential antiviral capacity. Flavonoids such as quercetin, baicalin, luteolin, hesperidins, gallicocatechingallate, and epigallocatechingallate are identified by Molecular docking study and invitro studies, to inhibit key proteins involved in corona virus infective cycle, such as PLpro, 3CLpro, NTPase/helicase. And it has been reported by various studies that these do not cause any systemic toxicity. Hence flavonoids and their derivative may represent the lead molecules that need to be tested in future clinical trials as drug against corona virus infections²⁸. Kabasurakudineer formulation that was followed to treat and prevent the SARS-CoV infection during both the waves in Siddha medicine has effectively controlled the severity of the infection. This is clear from the data, that all the 262 patients who underwent the treatment at The American College –Covid Siddha Care centre, Madurai, Tamil Nadu state, South India got recovered from Covid-19 after the Siddha treatment.

The plant parts that are formulated in SIDDHA medicine as Kabasurakudineer to treat SARS CoV 2 mostly contains the flavonoids like quercetin, kaempferol, apigenin, coumarins etc.. The plant parts present in the kabasurakudineer such as *Zingiber officinale* L.¹³, *Syzygiumaromaticum*L.¹⁵, *Tragia involucrate* L.¹⁶, *Terminaliachebula*¹⁹, *Adhathoda zeylanica*²⁰ *Coleus aromaticus*²¹ contains the bioactive compound Quercetin . Quercetin present in the formulation being an anti-oxidant can prevent the activation of inflammasomes and prevent exacerbation of infection³¹. Quercetin is a best flavonoid that blocks ACE2 R thereby preventing interaction between virus and its target cell³². Luteolin and quercetin, has been found to possess the capacity to block the entry of SARS-CoV into host cells²⁸. The Quercetin present in the kabasurakudineer formulation hence prevent the entry and attachment of virus to the human target cell . The flavonoid coumarins are present in the plant part *Anacyclus pyrethrum* (L.)¹⁷. The flavonoid such as coumarin forms a ligand with both viral protease and methyl transferase and inhibits the attachment of the Corona virus to the host cell. It also interacts with ACE 2 Receptor and inhibits the attachment of corona virus to the host cell³⁵. Kaempferol present in the Kabasurakudineer formulation interacts with the S2 domain of spike protein and prevents the attachment of the virus to human receptor³⁶.

Flavonoids are generally soluble in water and hence it can be extracted by boiling in aqueous solution. Lipinski's rule of five has indicated that flavonoids have a good permeability across the membrane³⁷. The flavonoids present in the kabasurakudineer formulation can easily be extracted by boiling in water and upon oral intake of

kabasurakudineer in a decoction form makes the availability of flavonoids to the cells as the flavonoid gets easily absorbed , passes through the membrane and effectively controls the SARS CoV 2 attachment and replication .

CONCLUSION

Through this review we conclude that though Siddha medicines are formulated based on the historical literatures of the past, the efficacy of the formulation is rationale with no observable side effects. The plant parts included in the Kabasurakudineer has the bioactive component flavonoids such as quercetin, coumarin and kaempferol could have efficiently prevent the attachment of the virus to the human ACE-2 receptor and hence Kabasurakudineer is more efficient in controlling and preventing Corona Virus. As there are less of evidence and unknown mode of action, these Siddha medicine deserves the attention for more scientific works to meet the challenges and to combat the unexpected infectious diseases outbreak in the future.

Conflict Of Interest

The authors have declared that there is no conflict of interest.

Abbreviation:

SARS-CoV-2 -Severe Acute Respiratory Syndrome Coronavirus-2.

ACE-2 -Acetyl choline esterase -2.

ICMR-The Indian Council of Medical Research.

NSP – Non Structural protein.

IC 50 - Half-maximal inhibitory concentration.

RT-PCR-Reverse transcriptase –Polymerase Chain Reaction.

Funding Source

None

Acknowledgement

The authors gratefully acknowledge the support from the Siddha Covid Care Center, The American College, Madurai Corporation, Tamilnadu, India and Almaa Siddha Hospital, Thirumangalam, Tamilnadu, South India.

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