

REVIEW

Potential Pharmacological Basis of Zinc Based Siddha Formulations for Handling COVID like Illness - An Overview

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ABSTRACT

Introduction: In the wake of dreadful pandemics affecting the global population, there is much focus on traditional medical systems. Siddha medicine advocates the use of plain herbal therapy, mineral therapy or its combination in managing diseases of epidemic nature. Zinc based Siddha formulations are widely gaining popularity in Medical practices due to its multidimensional applicability in numerous disease conditions. In Siddha system, there is still limited knowledge on its usage in communicable diseases. This study was aimed at critically appraising various scientific literatures concerned with the pharmacological aspects of zinc in terms of its immunomodulatory, antioxidant and antiviral properties so that rationality of its use in managing COVID-19 like epidemic illness can be substantiated. **Results:** There is much evidence in the scientific field that proves the choice of zinc formulations for treating various infections particularly of viral origin. Traditionally, zinc metal has been promoted in Siddha medicine as a wonder element to treat sexually transmitted diseases associated with immune compromised status. *Naga Parpam* (NP), the zinc based nano dosage form in Siddha medicine is acclaimed for its indicative role in treating respiratory affections with or without infectious background. The main compound of NP, zinc oxide (ZnO) exists in nano range, decides the therapeutic outcome of the drug owing to its fine biocompatibility and targeted action in cellular levels without resulting in any toxicity. The mechanism which the zinc ions act in response to any pathogenic assaults of viral origin includes direct competitive inhibition of important cellular target receptors of the virion, stimulation of local host immune responses and many other systematic cellular responses like oxidant radical scavenging. **Conclusion:** The review justifies the motive of introducing zinc based Siddha formulations like NP as one of the front-line choices for preventing COVID-19 like epidemics for further validation through preventive clinical trials.

KEYWORDS: Antioxidant, Anti-viral, COVID-19 like illness, Immunomodulator, NP, Siddha medicine, Zinc oxide.

1. INTRODUCTION

The compounds and elements, which we are using now in common medical practices were documented and revealed in traditional medical systems long before our knowledge and

understanding. Knowingly or unknowingly, from ancient period itself zinc was considered as one of the leading choices in the field of Siddha medical customs and practices^[1]. The potential of this metallic drug is unexplored largely as its

popularity and clinical applications are focused only to treat few medical conditions. Its unparalleled medical opportunities as a choice in communicable diseases or epidemics is still not put in practical considerations. Appreciative Siddha traditional logic supported with the modern pharmacological considerations should be the initial step of multidisciplinary research from bench to bedside aspects. In this regard, this paper reviews the pharmacological background of zinc element and zinc ions on the perspective of its antioxidant, immunomodulatory and antiviral properties. This article may embolden the usage of popular zinc-based Siddha formulation *Naga Parpam* (NP) as one of the top priorities for managing COVID-19 like illness.

1.1 Zinc in biological system

Zinc is a nutritionally important nontoxic trace element, which plays a crucial part in the overall balance of the bodily processes^[2]. It forms an integral part of about 10% of human proteins and numerous enzyme system that are important for regulating cellular processes and signalling pathways^[3]. It is documented as the second most abundant element in the body and as one of the safest mineral to be used for human health. In the advisable body limits, it is neither cytotoxic, mutagenic nor teratogenic^[4,5].

This mineral is vital for the structure and function of nearly 2800 macromolecules. About 300 zinc dependent enzymes are identified which has specific physiological functions in the body, which highlights its significance in critical cellular functions like liver metabolism, free radical scavenging, nucleic acid metabolism, formation of extracellular matrix etc. Zinc ion plays a key role in cell proliferation, cell differentiation and programmed cell death (apoptosis). It's proven that zinc has involvement in DNA synthesis, reproductive function, vision, taste perception and cognitive functions^[6].

Zinc in the human biological system exist in a stable form (Ionic state +2). This accounts its advantage over other metals like copper or iron,

as many of the detrimental redox reactions that generate free radicals and ROS (reactive oxygen species) does not happen due to the presence of metal ion within the system^[7].

The zinc element in its ionic state is present in each organ system, which proves its wide part in cellular physiology and other bodily mechanisms. Even mild to moderate deficiency results in numerous health complications. Deficiency of zinc within the body is primarily manifested as features of diminished immune response and oxidative damages resulting in increased susceptibility of the subject to catch up any kinds of infections attack. Further, it signifies the incidence of neurological deficits, delay in wound healing and regeneration of healthy tissues, growth failure, reproductive issues etc^[8].

The current recommended dietary allowances of zinc for an adult male is 11 mg/day and for females, it is 8 mg/day. Nevertheless, it is mostly dependent on the age, the oxidative stress and pathological conditions of the subject of concern. This highlights the importance of oral zinc supplementations. Zinc based formulations are also widely used in modern medicine^[8,9].

1.2 Evidence based zinc pharmacology

Zinc element has multitude of properties, but in this study important aspects in relation to infectious pathology is focussed.

1.2.1 Effects of zinc on immunoresistance

The immune system particularly of cell-mediated immunity is governed by two major groups of cells, lymphoid cells and cells of mononuclear phagocytic system. Lymphoid cell group that includes B and T lymphocytes play a dominant part in the host immunity against any threat of infectious pathogens. The T cells in circulation comprise 70-80 % of lymphocytes and have three subtypes: Helper T (T_H Cells or CD4+), suppressor or Cytotoxic T Cells (CD8+) and regulatory T cells. Each has its own specific immune action in the body. T cells play a key role in the direct cytotoxic activity against viruses,

tumor cells and simultaneously limits the immune response against self-antigens. Its subtypes, T_{H1} , T_{H2} , and T_{H17} , which are activated by immunomodulating proteins called interleukins (IL), perform in delayed hypersensitivity reaction, activity of macrophages, synthesis of IgG and in defence against parasitic infestations, bacterial and fungal infections. An imbalance in T_{H1} and T_{H2} is particularly observed with advanced ageing, which make the elderly subjects more susceptible to infections^[9].

Zinc affects multiple facets of the immune system from skin barrier to the gene regulation within the lymphocytes. Zinc has marked role in the conservation of immune resistance particularly of the elderly. Its supplementations have been validated for its property in maintaining the balance of T cells, thereby reducing the risk of infections particular to the geriatric population^[10,11]. In a randomized, double-blind, placebo-controlled study involving 53 nursing home elderly (aged ≥ 65 y), zinc supplementation was beneficial and were found to improve T cell proliferation^[12].

Zinc improves the host immunity through the activation of a thymic hormone called thymulin, which is very important for the maturation and differentiation of T cells, production of cytokines and for the activity of natural killer cells. It has been discovered that the decline of thymulin level is associated with ageing process, that hampers the persons overall immunity. This is managed through zinc supplementations^[13,14].

Maintaining zinc level in the body is a high priority for the activation of polymorphonuclear cells (PMNs), macrophages and natural killer (NK) cells, which are deliberated as the first cells of innate immunity against any pathogenic assaults. Reduction in PMN chemotaxis and phagocytosis are reflected in zinc deficiencies^[9].

It has been reported that, administration of Zinc supplementations has benefitted in minor and severe infections of common cold and cough and in conditions of diseases like Acrodermatitis

enteropathica, sickle cell anaemia, were the incidence of occurrence of infections are higher^[13]. Zinc is accountable for sustaining membrane barrier structure and function particularly in the epidermal layer and linings of Gastrointestinal and pulmonary tracts. Its deficiency weakens the integrity of the stratum and eases the entry of active pathogens or any other noxious elements into the system^[10].

One of the studies in animal model concludes the finding of improvement of survival rate of infected animals administered with Zinc supplementations. The Immunomodulatory effects of hormones like melatonin, thyroid hormones and growth hormone is inclusive with the level of zinc reserve in the body^[14].

1.2.2 Effects of zinc as an anti-oxidant prevention of free radicals

Superoxide dismutase (CuZn-SOD) is an important enzyme responsible for the catalyses of the free radical superoxide to H^2O^2 , which is then changed into harmless by-products within the system. SOD is a zinc dependent enzyme and adequate concentration of serum zinc concentration maintains its basic structural integrity and functions. This powerful antioxidant enzyme of the primary immune defense system is impaired in times of zinc deficits resulting in extreme oxidative stress and irreversible cell injury. Therefore, zinc supplements are considered as an important candidate of anti-oxidant therapies^[15].

It has also been reported that with increasing age, there will be impairment or decline in the level of zinc dependent enzymes like nucleoside phosphorylase and thymidine kinase, which makes the cell membrane weak and vulnerable to ROS injury resulting in cellular death. Zinc has a notable part in preventing apoptosis and low zinc bioavailability that is common in ageing and infections results in the accelerated rate of apoptosis^[6,13,16].

1.2.3 Induction of metallothionines

Zinc element has a leading role in preventing apoptosis and DNA damage caused by oxidative stress especially through induction of metallothionines. Metallothionine is a powerful metal ion binding protein, which has notable role in controlling intracellular redox potential, activated oxygen detoxification etc. In times of chronic zinc deficiency there is impairment in its activity. Thus, the cells become viable for easy oxidative stress injury^[17].

1.2.4 Stabilization of sulfhydryl-containing proteins

Sulfhydryl-containing proteins are much needed for the integrity of gastro duodenal cells and for defence against any chemically induced injuries that is prone to happen in various tissues or organs. It is highly reactive to oxidation processes that result in its damage and inactivity^[18]. Zinc dependent enzymes like d-aminolevulinate dehydratase prevents the oxidation of the proteins there by stabilizing its constant defensive function^[18].

1.3 Role of zinc in Infections

1.3.1 Common cold

Common cold is the recurrent illness affecting the general population, mainly triggered by the infectious viral pathogens of various serotypes. Rhinovirus (30% to 50%), corona viruses (10% to 15%), respiratory syncytial virus, para influenza viruses and adenoviruses (5%) hold the leading part of origin of infections in the respiratory tract^[19]. There is numerous evidences to validate the efficacy of zinc in the above mentioned viral respiratory illnesses as it not only holds direct antiviral actions as in the case of influenza, but also vital for producing both innate and acquired antiviral responses^[19,20].

1.3.2 Anti-Rhinovirus activity of Zinc

1.3.2.1 Effect of zinc at capillary epithelium

Zinc ions have exceptional role in the control of respiratory infections. Much credit of its

action goes to its astringency especially in the region of cell membrane. Because of astringent property, it modifies the capillary epithelium resulting in the prevention of trans capillary movement of plasma proteins decreasing local inflammation, edema, exudation, and mucus secretion during the time of infections^[21].

1.3.2.2 Effect of zinc at cellular receptor level

Intercellular adhesion molecule-1 (ICAM-1) is an important cellular receptor located in the nasal epithelium, which plays a great role in inflammatory processes and T-cell-mediated host defence system. Rhinoviruses have much affinity on the receptor site where it's binding triggers a cascade of mechanisms resulting in viral penetration and replication. One of the leading assumptions of zinc as an anti-viral is through the competitive inhibition of ICAM-1 of the nasal epithelium. Attaching of the ICAM-1 receptor sites by the zinc ions effectively foils the binding of rhinovirus with it and its entry and replication processes. Zinc ions also directly inhibits the virus by binding with it. It also found to disrupt the binding of leukocyte function-associated antigen (LFA-1) to ICAM-1, thus suppressing the chain of inflammatory processes associated with respiratory infections. These reports substantiate the effect of zinc ions in controlling viral replications, associated proinflammatory phase and shortening the duration of symptoms. This satisfies the much-needed effects from zinc based oral medicines and supplements given during common cold^[21,22].

1.3.2.3 Anti-respiratory syncytial virus (RSV) activity of zinc

RSV is the one among the important cause of acute respiratory tract infection (ARI) in infancy and early childhood. It is the most common source of community acquired pneumonia (interstitial pneumonitis). This particular respiratory epidemic is more prevalent in malnourished and in children of immunocompromised status living in developing countries. The infections mainly affect

the upper respiratory tract with symptoms of common cold^[19]. Many of the *in vitro* studies of zinc on RSV concluded its inhibition in a concentration dependent manner. It was reported that zinc ions modify the ability of the cell to support viral replication, binds with the virions preventing its coupling with cells. In addition to that it blocks the enzyme protease in RSV, that is chiefly responsible for the breakdown of virus polypeptide essential to produce individual functional proteins^[19,22,23]. One of the cochrane study that involved children aged between 2 to 59 months (Sample 5193) evaluated the efficacy of zinc supplementation for the prevention of pneumonia testified positive outcome in terms of reduction in its incidence (13%) and prevalence (41%)^[24].

1.3.2.4 Zinc and severe acute respiratory syndrome (SARS) corona virus Infections

Severe acute respiratory syndrome (SARS) corona virus is a positive strand, enveloped RNA virus causes zoonotic infection characterized by respiratory, gastrointestinal and neurological diseases. Out of so many supplements that produce outcome in the control of the disease, zinc is considered the foremost accepted one. Zinc compounds were found to be the leading potent inhibitor of SARS COVID-19. One of the *In vitro* studies revealed a strong inhibitory effect of zinc ions on the RNA synthesizing activity of isolated SARS- CoV replication and transcription Complex (RTC). Another study of zinc in SARS- CoV (Vero-E6) cells shown its inhibition of RdRp template binding and elongation^[25,26]. Zinc supplements not only have a direct effect on COVID-19 like illness but also controls its key features like diarrhea and respiratory infections^[27].

1.3.2.5 Zinc and HIV infections

Insufficiencies of anti-oxidants with increase in the free radicals are directly related with diminution of T cell mediated immunity (CMI) and multifold increase in HIV expression. Similarly,

zinc deficiency may worsen the disordered CMI, resulting in increased HIV replication^[28].

HIV subjects with particular zinc induced lymphoproliferative responses (LPR) will have probability to have lower CD4 lymphocyte counts and serum zinc levels. Some of the studies reported the progression of the HIV stage, lower CD4 levels and mortality rate are linked with lower serum zinc concentration. The infection (bacterial origin) susceptibility is high under this condition. Also, it was found that AIDS subjects would clinically present the symptoms identical to that of zinc deficiency like immune deficits, gastrointestinal complications like diarrhea, skin lesions, hypogonadism, male subfertility, anosmia, anorexia etc^[28-30].

1.4 Zinc based Siddha drugs

1.4.1 Logic of use

Siddha medical system highpoints within itself the splendour of healing part derived from almost all natural sources. Even though the vast materia medica of Siddha medicine primarily uses herbal resources, much number of mineral resources are also put into practice in the armamentarium of pharmacopoeia. It is the ethics and the fundamental basis that enables a Siddha physician to select the right fitting ingredient from the nature for a particular disease of concern. The physician may select a single plant product to treat a simple illness and may switch on to higher inorganic groups of drugs for treating chronic or life-threatening diseases. The inorganic elements that they have chosen for drug preparations include various salts, alkalis, minerals and metals from natural resources^[31].

The inorganic pharmaceutical preparations comprise of so many elite classes of medicines under nano dosage forms appreciated for its easy palatability, smaller dosage, higher efficacy and potency. The medicines categorized under *parpam*, *chenduram* that are the calcined oxides of mineral substances and *pathangam* which are the mineral sublimates are the best examples of nano dosage forms^[31-33].

One of the striking leads of mineral or metallic based formulations is because of its sharp and targeted action in the body in micro dose levels. The minimal dosage maximizes the therapeutic outcome and expected target of delivery is achieved through various vehicles used along with it. This makes metallic medicines more reliable for managing critical medical conditions^[34].

1.4.2 Zinc and zinc formulations in Siddha medicine

The element zinc (*Nagam*) is considered as a superior native metal in Siddha medicine. Its various forms are used in alchemy and in medicines. It has the documented property as follows;

*"Mēkañ kiḷarpēti veṭṭai yaḷalai taṇikkum
Vēkañ kirāṇi vilakkuñ kāṇ pōkāp
Pariyamūaipuṇṇai ppayittiyattai ppōkkum
Ariya tuttanāka mitu
"Collimuṭiyā tuttanākam poṭiyāy
Mella tturattum viyātikaḷai - nalla
Uraṇuṭaimai yuṇṭākkum uṇṭavaraiyeṇru
Kirumi maṇaimaṇmaki maikē!"*

Siddha medicine advocates the use of zinc as a medicine that is having the property to cure *Megham* (genitourinary diseases), *Vettai* (sexually transmitted diseases), *Krani* (dysentery), *Mulai pun* (hemorrhoidal ulcers and fistula), *azhal* (hyperthermia) and *Paithyam* (psychiatric ailments). The selective indications of the metal zinc could be purely interpreted for its astringent, styptic, antiulcer or wound healing, demulcent and anti-viral actions in general. The quote "*Melley thuraththum vyathikale*" from its material property denotes that its actions are best achieved through long term usages and "*Uranudaimai undakkum undavarai*" literally means the metal is capable to improve one's vitality, strength and immunity (tonic and immunomodulator)^[32,33].

The crude metal ore is not used directly in internal medicines. It is used after stringent detoxification methods followed by repeated processing with herbal metal oxidisers, followed by subjecting to extreme heat through a traditional process called *Putam* (calcination)^[34,35]. The final product should pass all the traditional testing parameters before introducing as an oral dosage. The ultra-fine white calx product called *Naga parpam* and red calx product called *Naga chenduram* are the commonest formulations distinguished in the classical Siddha literatures. Different preparatory methods of zinc calx are available, with diverse adjuvants, and therapeutic benefits. Most of the zinc calx formulations are indicated for phlegmatic respiratory affections with infectious origin (tuberculosis or cough) or without infectious origin^[32]. The drug is given at doses of 100 to 200 mg with specific adjuvants like ghee, or honey that permits its faster absorption and assimilation in to the cells for a marked target activity^[32,33].

X-ray fluorescence spectrometry studies of *Naga parpam* (NP) revealed the presence of ZnO (zinc oxide - 65.59%), iron (2.27 %) and other trace elements. ZnO is considered as the most active form of the element zinc that is non-toxic and biocompatible. Moreover, there are enough evidences that support its antioxidant and antimicrobial properties. One study reported its non-toxicity in animals at minimal therapeutic dose levels. The nano size of the zinc oxide enables large surface area for its absorption, besides the bioavailability is increased largely than other dosage forms. The particle size of the drug materials in NP ranged from 24 to 32 nm in one XRD study, along with its chemically stable nature mark it as the safest and potent drug to act specifically at cellular level without any toxicity^[34-36].

1.4.3 Rationality of use of NP as an alternative to zinc based formulations

In the traditional approach, the metal zinc or its formulations are considered as powerful

candidates against infections of sexual transmission and respiratory system^[32]. Its multiple benefits in improving blood picture, immunity, controlling inflammations make it as an ideal choice for treating COVID-19 like viral respiratory illnesses^[6]. Zinc is the basic trace element used in Siddha materia medica and modern medicine for its exquisite therapeutic potential. Zinc oxide is the major form of NP and there are substantial evidences to prove its efficacy in antiviral treatments.

One of the prominent leads of Siddha medicine over allopathic medical practice is its holistic approach on treating a medical condition by considering so many factors of drug administration. This not only includes age and sex, but also the body nature (*Dekam*), stage of the disease (*Noi vanmai*), climate or seasons (*Kalam*), nature of the pulse (*Nadi*), body strength (*Udal vanmai*), digestive capacity (*Jadaragni*), pshychomental qualities (*Gunam*) etc^[37-39]. The food interactions, adjuvant therapies are other key factors of concern for NP drug^[39]. Siddha literature evidences advices restrictions in diet that may hamper zinc drug absorption, assimilation, metabolism and bioavailability. This include acidic

diets (sour food articles, meat products), certain fruits, vegetables, seeds and cereals^[33]. These are strictly avoided during the drug period. The regimen also supports the subject to quickly recover from the illness.

The adjuvants selected are dependent on how much extent the NP is soluble on it. The medium chosen for this decides the bioavailability of the drug^[40]. Depending on the above, the adjuvants may vary with NP. The most common adjuvants for NP include ghee or honey which enhances better absorption and metabolism of the drug as compared with others^[39,40]. Considering the efficacy over existing zinc supplementations, the nano dosage form of NP may yield better response, when administered as per the medical reference of the literature in terms of therapeutic dosage, adjuvant, diet regimen, timings and coarse. Therefore, the practitioners of Siddha medicine may consider using NP as an equal alternative to zinc formulations used in allopathic medicine for treating immuno-compromised states associated with infections, particularly respiratory viral infections or other illnesses due to zinc deficiency or that could be managed by it.

Table 1. Zinc based Siddha formulation and its role in SARS COVID-19 prevention and zinc deficiency states

Clinical picture of SARS-COVID-19	Clinical picture of zinc deficiency	Therapeutic properties and traditional claim of Nagam (Zinc) / NP mentioned in the classical Siddha literatures with its valid pharmacological interpretations
Respiratory tract infections^[27]	Susceptibility to frequent respiratory tract infections resulting in trans capillary movement of plasma proteins, local edema, exudation and mucus secretion at pulmonary capillary epithelium ^[19,20]	<ul style="list-style-type: none"> – NP is beneficial for cough, phlegmatic respiratory ailments with or without infections^[30]. – Thuvarppi (astringency and styptic)^[32]. – Tightens and maintains the integrity of the epithelium, constricts pores^[37]. – Reduces glandular secretions^[37]. <p><i>Pharmacological Interpretation</i> Because of astringent property, it modifies the capillary epithelium resulting in the prevention of trans capillary movement of plasma proteins decreasing local</p>

Fever	Fever due to secondary infections	inflammation, edema, exudation, and mucus secretion ^[19,20] .
Diarrhoea^[27]	Diarrhoea is a leading feature of acrodermatitis enteropathica due to zinc deficiency ^[13] .	Capable of controlling hyperpyrexia ^[32] . Nagam is beneficial for diarrhea and dysentery ^[32] .
High risk group	Immuno compromised states	Uramundakki: Nagam / NP is Capable of improving vitality, health and immunity ^[32] .
Immuno compromised states^[26,27]	featured by occurrence of opportunistic infections ^[26-28] .	<i>Pharmacological Interpretation</i> Zinc can be used as an alterative, rejuvenative, tonic and immunomodulating drug ^[10-15] .

CONCLUSION

Zinc mineral stands in an exceptional role in developing immunity, preventing oxidative stress and protecting against viral assaults. The review focussed only few concerns in relation to its priority in preventing COVID-19 like viral illness. Zinc based formulations in Siddha medicine could be a leading candidate if interpreted in a scientific background as mentioned in this review.

Its effects on long term administration is better valued than short drug period, this will bring us to a conclusion of its selection as a preventive and promotive medicine. We can correlate the activity of zinc and the features of its deficit states directly linked to numerous pathological conditions manifested as symptoms of respiratory tract and gastrointestinal system. The symptom relativity is better controlled with zinc supplementations from Siddha medicine. Apart from its therapeutic role in phlegmatic respiratory diseases, zinc based mineral formulations from Siddha medicine may be used as immunomodulating supplement's along with other therapies for better clinical outcome. Further clinical trials are appreciated on the side to validate its efficacy for acclaiming its scientific recognition

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