

REVIEW

Metal - based Nanoparticle Siddha Formulations for the Management of Emerging Infectious Diseases (EIDs)

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ABSTRACT

Background: Emerging Infectious Diseases (EIDs) are infections are rapidly increasing in incidence or geographic range; includes previously unrecognized diseases such as AIDS, severe acute respiratory syndrome (SARS), ebola-haemorrhagic fever, nipah virus encephalitis, dengue fever and recent COVID-19 pandemic. Most pathogens involved in EID events are drug-resistant bacteria (54.3%), but virus constitute only 25.4% of EID events, in contrast to previous analyses which suggest that 37–44% of emerging pathogens are viruses and 10–30% bacteria. Metal-based nanoparticles accounts for their considerable interaction with bio molecules within the cell and on the cell surface. These unique properties make metal nanoparticles potential therapeutics for the treatment of infectious diseases

Method: In Siddha system of medicine, Ulogankal (metals) are eleven in numbers; they are Thangam (gold), Velli (silver), Sembu (copper), Naagam (zinc), Ehgu (steel), Irumbu (iron), Pithalai (brass), Thara (alloy of copper and lead), Karuvangam (lead) and Velvangam (tin). This review focuses about the antimicrobial, anti-viral, anti-bacterial and immunomodulatory activities of metal-based nanoparticles (NPs) which were already quoted in the Siddha system of medicine. **Result:** Metal nanoparticles have sufficient physico-chemical properties and surface charges. This review revealed that the metal-based medicines have considerable potential to manage and to provide prophylactic support to the EIDs due to immune enhancing, anti-viral, antibacterial, anti-microbial properties. **Conclusion:** Nanoparticles utilization is “double-edged sword” providing positive advantages for usefulness and negative impacts on health upon exposure. So, the manufacture authentications, Specific guidelines for metal drugs handling for clinical practice, Novel Drug Delivery System (NDDS), research rationales are essential for the metal based Siddha Medicines (Parpam, Chenduram and Chunnam) in this infection emerging period.

KEY WORDS: COVID-19, Infectious Diseases, Nano, Ulogam Particles.

INTRODUCTION

Emerging infectious diseases (EIDs) are infections that are rapidly increasing in incidence or geographic range, including such previously unrecognized diseases like AIDS, severe acute respiratory syndrome (SARS), ebola-haemorrhagic fever and nipah virus

encephalitis, dengue fever^[1] and recent COVID-19 pandemic^[2]. EIDs are significant burden on socio-economic, environmental and eco-logical factors^[3]. Infectious diseases account for 29 out of the 96 major causes of human morbidity and mortality listed by the World Health Organization^[4]. And also,

emergence of resistance among the most important bacterial pathogens is recognized as a major public health threat affecting humans worldwide^[5]. The Centres for Disease Control and Prevention conservatively estimates that at least 23,000 people die annually in the United States as a result of an infection with an antibiotic-resistant organism^[5]. Most pathogens involved in EID events are drug-resistant bacteria (54.3%). Virus constitute only 25.4% of EID events, in contrast to previous analyses which suggest that 37–44% of emerging pathogens are viruses and 10–30% are bacteria^[4,6].

Currently, the emergence of this COVID-19 has posed a situation that warrants urgent global attention. Though drugs are available in mainstream medicine for treating symptoms of COVID-19, currently there are no preventive medicine and exact treatment options. In view of this, complementary and alternative medicine (CAM) offers a plethora of interesting preventive possibilities in patients^[7].

Siddha system of medicine is one of the oldest traditional systems of medicine, which has been originated from India and is practiced mostly in the southern part of this country for treating various diseases including even chronic conditions^[8]. Pharmacopoeia of Siddha comprises of drugs derived not only from herbs but also from minerals, metals and animal products. Preparing medicines from metals and minerals is one of the unique features of Siddha system of medicine. These medicines were prepared in the form of *Parpam*, *Chendooram*, *Chunnam*, *Kattu*, *Kalangu* etc. This review article explore about the metallic nano particles (NPs) present in Siddha System of Medicine. Metal-based nanoparticles accounts for their considerable interaction with bio molecules within the cell and on the cell surface. Their high surface area promotes cell permeability. Metal nanoparticles have significant physico-

chemical properties and surface charges^[10]. These unique properties make metal nanoparticles potential therapeutics for the treatment of infectious diseases. And, using metal nanoparticles as prevention and management can induce more efficient immune responses against microbial infection. This short review will be focused on Siddha metal-based medicines as potential therapeutics against infectious diseases.

METHODOLOGY

Siddha system utilized the following metals in the form of nanoparticles for various kinds of diseases from the ancient period. In Siddha, *Ulogankal* (metals) are eleven in numbers, they are *Thangam* (gold), *Velli* (silver), *Sembu* (copper), *Naagam* (zinc), *Ehgu* (steel), *Irumbu* (iron), *Pithalai* (brass), *Thara* (alloy of copper and lead), *Karuvangam* (lead) and *Velvangam* (tin). All the metals are prepared as a *Parpam*, *Chenduram*, *Chunnam* format for using medicines^[11,12]. A nanoparticle property is based on its size, charge, hydrophobicity, hydrophilicity, and the steric effects^[10]. This review focuses about the anti-microbial, anti-viral, anti-bacterial and immunomodulatory activities of metal-based nanoparticles (NPs) which were already quoted in the Siddha system of medicine for the management of EIDs in pandemic situations.

RESULTS

Metal nanoparticles have sufficient physico-chemical properties and surface charges. It revealed that the Velli (Silver NP), Thangam (Gold NP), Velvangam (TIN NP), Ayam (Iron NP), Nagam (Zinc NP) metal-based medicines have considerable potential to manage and to provide prophylactic support to the EIDs due to immune enhancing, anti-viral, antibacterial, anti-microbial properties (Table 1).

DISCUSSION

Siddha medicines have many formulations with the combination of metals and minerals because of its minimal quantity to avail the high potency results. Saint Thirumoolar’s hypothesis about atomic theory has been reinstated as nanotechnology in this decade. Hence, *Parpam*, *Chenduram* and *Chunnam* of silver, gold, tin, iron, copper and zinc act as a Novel Drug Delivery System

(NDDS) and capable to produce better result on microorganisms with least side effects. By approaching in NDDS may increase the therapeutic value, bioavailability and act as smart drug^[44]. Since most of Siddha nano particle drug has been absorbed in the mucosal level. Nano particles improves the efficacy of drug delivery to the cells in cytoplasm and its absorption because of their size.

Table 1. Siddha metal based medicines with their therapeutic outcome

Metals Used in Siddha	Metal Nanoparticle	Therapeutic Outcome
<i>Velli</i> (Silver) <i>Parpam</i> , <i>Chenduram</i> , <i>Chunnam</i>	Silver-Based Nanoparticles	<ul style="list-style-type: none"> • Silver nanoparticles interact with bacteria and release silver ion resulting in deactivation of the cellular enzymes, hindered membrane permeability and cell death^[13] • Inhibition of CD4-dependent virion binding, fusion and infectivity^[14,15] • HSV-2 replication was inhibited^[16] • Effective against influenza viruses resulting in damage to their morphological structure. Inhibiting the host receptor binding sites of the virus^[17,18] • Silver nano particles were found to have inhibitory activity against human immunodeficiency virus (HIV), hepatitis B virus (HBV) and H1NI Influenza A virus^[19] • It can influence multiple manifestations of immune cell activity including cytokine production, proliferation, activation^[20]
	Silver nanoparticles prepared using plants extracts	<ul style="list-style-type: none"> • Stable nanoparticles prepared from using herbs like <i>Acalypha indica</i>, <i>Azhadirachta indica</i>, <i>Aloe vera</i> are reported to possess significant antibacterial activity^[21-24]
<i>Thangam</i> (gold) <i>Parpam</i> , <i>Chenduram</i> , <i>Chunnam</i>	Gold nanoparticles	<ul style="list-style-type: none"> • Effective as both virus entry inhibitors as well as virus neutralizing agent^[25] • Inhibited viral attachment and penetration into the cells thereby preventing infections^[26] • The nanoparticles inhibited HIV viral replication^[27,28] • The nanoparticles active against Gram-negative, Gram-positive uro-pathogens and multi-drug resistant pathogens^[29]
	Silver and gold Nanoparticles	<ul style="list-style-type: none"> • Metal nanoparticles synthesized by fungus <i>B. tetramera</i> could be used as an antimicrobial agents as well as cost effective and nontoxic

			immunomodulatory delivery vehicle ^[30]
Velvangam (tin) Parpam, Chenduram, Chunnam	Tin nanoparticles		<ul style="list-style-type: none"> • Trapped HSV-1 before entry into the host cell^[31,32] • Prevent and reduce the complications associated with HSV infection^[31]
Ayam (iron) Parpam, Chenduram, Chunnam	Iron-oxide nanoparticles		<ul style="list-style-type: none"> • Good antibacterial activity on <i>E. coli</i>, <i>P. vulgaris</i>, <i>Staphylococcus aureus</i>^[33-35] • Good synergistic antibacterial effects against <i>S. pneumonia</i>^[36]
Chembu (copper) Parpam, Chenduram, Chunnam	Copper oxide nanoparticles		<ul style="list-style-type: none"> • Good antibacterial activity of copper oxide nanoparticles against <i>E. coli</i>^[37,38] • Gram-positive (<i>B. subtilis</i> and <i>S. aureus</i>) and Gram-negative (<i>E. coli</i> and <i>P. aeruginosa</i>) bacteria^[39]
	Copper Iodide nano particles		<ul style="list-style-type: none"> • The high antiviral property of CuI nanoparticles was attributed to Cu⁺^[40]
Nagam (zinc) Parpam, Chenduram, Chunnam	Zinc oxide nanoparticles prepared from plants extract		<ul style="list-style-type: none"> • Enhanced antibacterial activity^[41] • The highest pro-inflammatory response was recorded after 4 to 6 hr exposure to ZnO NPs over a 24 h period^[42]
	Zinc oxide nanoparticles		<ul style="list-style-type: none"> • Good antibacterial activity against <i>Klebsiella pneumonia</i> that causes respiratory infection • Prevented viral entry and infection^[43] • Potential Immunomodulatory effect^[42]

Nanoparticles (NPs) exhibit antibacterial activity resulting from their ability to produce reactive oxygen species that damage the bacteria and their ability to bind to DNA or RNA, thereby hindering microbial replication processes^[45,46].

Metal-based NPs have been found to be effective against virus, resulting in decreased viral growth and replication. NPs interact with the CD4 membrane resulting in endocytosis. And the pH-dependent endosomal escape of the nanoparticles into the cell cytoplasm resulted in inhibition of viral protease^[47].

The metal nanoparticles provoke inflammatory cytokines and increase dendritic cell maturation, expression of co-stimulatory molecules and activation - proliferation of prime immature T-cell. CD trapped inside

fullerene cage nanoparticles has specific immunomodulatory effects on T-cells and macrophages, including polarization of the cytokine^[48].

Metal based Siddha formulations can be stored for a long period compared to the herbal based medicine. At the time of pandemic, large quantity of medicines is required to control the circumstances. If, we start using the metal-based medicine on pandemic time, the quantity of the medicine also would not fall short.

CONCLUSION

Nanotechnology in medicine is one of the most exciting industrial innovations of the 21st century. Many metal-based nanoparticles, such as nano-silver, nano-metallic oxides (zinc oxide, titanium dioxide, iron oxide and

quantum dots) are applied for many therapeutic uses. This review revealed that the metal-based medicines are considerably potent to manage and prophylactically support during EIDs with immune enhancing, anti-viral, anti-bacterial and anti-microbial properties. Nanoparticles utilization is “double-edged sword” providing positive advantages for usefulness and negative impacts on health upon exposure. This prudence was handled by in long centuries ago. So, the manufacture authentications, Specific guidelines for metal drugs handling for clinical practice, Novel Drug Delivery System (NDDS), research rationales are essential for the metal based Siddha Medicines (*Parpam*, *Chenduram* and *Chunnam*) in this infection emerging period.

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