Magnetic Hyperthermia for Isolation and Deactivation of Covid-19 or Similar Viruses; A Comprehensive Review.

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***ABSTRACT*--Recent Covid 19 pandemic has caused disruptions to both societies & economies around the globe. Despite the time passed since the outbreak, access to proper diagnostic or treatment methods are insufficient. This situation created an urgent need for novel approaches to combat the spread of covid or similar viruses. The authors of this article have undertaken an extensive examination of diverse research papers pertaining to the detection, isolation, and deactivation of covid 19 virus. The authors have determined that magnetic hyperthermia holds promise as potential technique to isolate and deactivate SARS Covid 2. This comprehensive review delves into the potential of magnetic hyperthermia, magnetic nanoparticles & expounds upon the principle of magnetic hyperthermia, the challenges of using it as treatment method as well as recent advances in this field. In summary this article highlights the potential of magnetic hyperthermia as a promising modality for isolation & deactivation of covid 19 or similar viruses.**

***Index Terms*— Curie Temperature, Covid 19, Heat Treatment, Hysteresis Loss, Ligand, Magnetic Field, Magnetic Hyperthermia, Magnetic Nanoparticle, SARC COV-2, Virus Deactivation.**

I. INTRODUCTION

In the month of December 2019, the world has come to know about COVID-19, and it appeared in the Hubei Province o f China. Across 216 countries/ areas/ territories, COVID-19 hasinfected 68,165,877 people with 1,557,385 confirmed deaths[1,2].

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America alone has 29,139,394 cases [3].As per the WHO [4], testing plays the important role in controlling the spreading of this virus. After so many days of its outbreak, proper diagnosis is still not sufficient worldwide. It can also be found in saliva, faces, and urine [5-8]. Forchildren, asymptomatic shedding spreads the viral infection mostly [9-10]. The pandemic was caused by an infectious agent called Severe Acute Respiratory Syndrome (SARC COVID 2). [5-8]. SARS-CoV-2 is the successor to SARS-CoV and MERS-Covid (Middle East respiratory syndrome coronavirus) and they belong to the Coronaviridae family [5-8]. Because of its corona-like structure under electron microscope EM, it was named Corona which is a Latin word means crown. Corona virus-induced ARDS is categorized through cytokine storm syndrome, and its a +ve feedback loop causing an increase of fluid extravasation and pulmonary inflammation leading to failure in respiratory system. ARDS, cardiac or respiratory failure, and sepsis because of secondary bacterial infection are the main reasons for death out of COVID-19 [8−11].SARS-CoV-2 is a positive ssRNA (sense single-stranded RNA) virus inside an envelope. Coronavirus genome is one of the largest RNA viruses that ranges from 26-32 kb lengthwise. There are 29903 nucleotide(nt) RNA genomes with four structural proteins in the infectious virion of around ~100 nm diameter. These proteins are Nucleocapsid(N), Envelope(E), Spike(S) and Membrane(M) [24]. Table I gives the molecular sizes of these proteins and corresponding copy numbers in a virion for them [5, 6, 12]. The RNA genome of SARC COVID 2 is bound by the nucleocapsid protein in a helical symmetry which forms a structure that looks like a string of breads. A lipid bilayer envelope the genome structure, this contains envelope membrane and spike protein.[13, 14]. In those hosting cells, the RNA genome of the virus gets replicated and 4 structural (E, M, S, N) and 25 nonstructural proteins' synthesis happens [15, 16].The enclosing of the genomic RNA having structural proteins will lead to generation of new viruses. Corona viruses reproduces the RNA genomes & sub genomic RNAs entirely from RNA templates. Contrasting to other RNA viruses undergoing replication that is likely to contain error ,Nsp14

ISSN NUMBER (ONLINE) – 2368-1209 & (PRINT) – 2691-5944

exonuclease is used by corona virus. It is the first detected proofreading enzyme that is encoded by an RNA virus. It also accommodates the large RNA genomes of coronaviruses [17]. The proofreading function indicates, corona viruses can transform frequently as compared to other RNA viruses.

TABLE 1
Molecular Sizes of SARS-COV 2 Proteins & their corresponding cop numbers in a Virion [22]

Protein	Molecular Size	Copy Numbers in a Virion
Envelope Protein (E)	75 aa: 8037 kDa (UniProtKB-P0DTC4)	20
Membrane Glycoprotein (M)	222 aa: 25.14 kDa (UniProtKB-P0DTC5)	2000
Nucleocapsid Phosphoproteins (N)	419 aa: 45.63 kDa (UniProtKB-P0DTC9)	1000
Spike Glycoprotein (S)	1273 aa: 141.18 kDa (UniProtKB-P0DTC2)	100

TABLE 2
Temporal trends of levels of COVID 19 RNA and antibodies for SARS-COVID 2 patients during the course of infection [23,24].

Target	Course of COVID-19 infection			
To be detected	Incubation	Early symptomatic	Symptomatic	Recovery
RNA	+	+	+	-
IgM	-/+	+	+	+=>-
IgG	-	-	+	+

Molecular diagnosis of SARS-CoV-2 virus mainly depends on detection of its RNA. [18-20]. For IgM and IgG, the seroconversion takes nearly 13 days [21]. RT-PCR, the Reverse transcription polymerase chain reaction facilitates detection of specific gene sequences encoding the nucleocapsid and RNA dependent RNA polymerase (RdRP), envelope, spike proteins of SARS-COVID 2. Even though RT-PCR testing is extensively applied and numerous alternate tests have been built, for quick, consistent, and broadly available molecular diagnosis. Many test kits have been developed to detect IgM and IgG antibodies in human serum. However, there are challenges of antibody testing as well as molecular diagnosis and it has captured the attention worldwide [18, 19].Table II talks about the challenges from collection of samples through detection. In addition, dynamic humoral response to COVID-19 exposure leads to challenges towards serological testing. Such diagnostic challenges are affecting the legitime.

II. LITERATURE SURVEY

Magnetic nanoparticles are small particles that are made-up of magnetic materials ex; iron oxide, nickel, cobalt, and their alloys. The dimensions of the particle ranges between 1 - 100 nm. Their unique magnetic properties can be engineered to be used in specific biomedical application. Magnetic nanoparticles possess magnetic properties which enable manipulation of these nanoparticles using magnetic field gradients. These magnetic nanoparticles interact with alternating magnetic fields, producing localized thermos-ablative effects, also known as hyperthermia [20]. Electric current and magnetic spin moment of elementary subatomic particles are two origins to which magnetism can be traced. The combination of these two sources of magnetism results in the complex magnetic properties of material such as iron, nickel and cobalt. In most cases, the arrangement of magnetic spin movement of individual subatomic particles cancels each other out and therefore produces no overall magnetization. Various materials exhibit different type of magnetism such as ferromagnetism and Para- magnetism. Para magnetism is observed in materials that contains unpaired electrons, resulting in the emergence of internally induced magnetic domain aligned with direction of application of magnetic field therefore paramagnetic material attracts to external magnetic-field gradients [21,22].

Ferromagnetism is observed in certain material that exhibit a permanent magnetic moment. This moment of magnets arises from alignment of individual atomic magnetic moment or spin within the material. These spins are coupled together in large groups known as magnetic domain. The size and shape of this domain depend upon composition, crystal structure and temperature. Magnetic materials are subject to Curie temperature, It is a temperature up to which a magnetic material can sustain its magnetic properties. Super para-magnetism is a property of ferromagnetic or ferrimagnetic single domain material. It arises when the diameter of magnetic material is between 3 to 50 nm.[23] There are many desirable properties of super paramagnetic nanoparticles which make it attractive candidate in a range of biomedical application. These properties are high magnetic susceptibility, coercivity, low remanence with a low risk of agglutination at room temperature[24].

ISSN NUMBER (ONLINE) – 2368-1209 & (PRINT) – 2691-5944

TABLE lll

Given properties of 6 different materials are generally used to create magnetic nanoparticles. Data for iron and iron oxide was taken from [25]; [26] for strontium ferrite; data for nickel from [27]; for chromium oxide value [28] and [29] for europium oxide.

Name of Material	Curie Temperature(k)	D_c (nm)	Types of Magnetism
Iron (Fe)	1043	~15	Ferromagnetism
γ-Iron (III) oxide (γ-Fe2O3)	948	<100	Super paramagnetic
Strontium Ferrite ($S_rFe_{12}O_{19}$)	~450	<100	Super paramagnetic
Nickel (Ni)	627	55	Ferromagnetic
Chromium (IV) oxide (CrO_2)	~390	<100	Ferromagnetism
Europium oxide (EuO)	69	<100	Para magnetism

The utilization of magnetic nanoparticles in the field of biology has gained significant attention because of its potential for cancer treatment and fight against infectious disease alongside enhancing tissue engineering procedures. In case of cancer, one distinctive biomedical anatomical characteristic of tumour cell that makes cancer cell more temperature sensitive than healthy cells. That property arises due to the lack of adequate perfusion which leads to condition of acidosis and hypoxia [30,31].

This unique property of cancer cells (temperature sensitive) can be exploited for therapeutic purpose by utilizing magnetic hyperthermia. In this process magnetic nanoparticles are coated with biocompatible compounds or ligand to specially target cancer cells. When these magnetic particles are exposed to external alternating magnetic fields, cycles of magnetic polarity change leads to the loss of thermal energy because of hysteresis loss, Neel or Brownian relaxation or due to the dynamic of viscous suspension there are frictional losses. The production of heat in multidomain ferromagnetic or ferrimagnetic material primarily offers because of hysteresis loss. The hysteresis loss is largely dependent upon the applied alternating magnetic field. The MNP domain structures, their size and nature have replayed impact on the hysteresis losses and as a result on their hyperthermia property [32].

Before proceeding for human trials as a clinical method forcancer treatment, initial experiments must be done on non-30 to 50nm. These nanoparticles are coated with polyethylene glycol (PEG) layer to prevent excess heat generation and dispersion. The particle of suspension was directly injected into cancerous tumour of mice. The mice were subsequently subjected to magnetic field 50.9 KA/m in a frequency of 114Hz for 6 minutes. The size of the nanoparticle changes between 50 to 80 nm. The temperature was maintained at 50° C by changing magnetic field from 30 to 50.9 KA/m. The temperature of tumour goes to 45°C after 6 minutes of application after the process. The tumour side exhibited black disc coloration and clear sign of necrosis within 3 days of treatment. After 14 days, scar tissues formation was observed on the tumour side, suggesting that the tumour was in the process of recovery [33].

III. MAGNETIC HYPERTHERMIA FOR COVID TREATMENT

Viral deactivation is necessary before the samples are handled and it reduces the risk of exposure to COVID-19 [34-35]. SARS viruses are temperature sensitive and can be destroyed around 56℃ in 30 minutes [36-39]. In this article, the authors have discussed the possibility of leveraging magnetic hyperthermia as an effective process of COVID-19 treatment and be an effective approach of COVID-19 deactivation [40]. Literature reports the results of comparison on antibody levels before and after heat deactivation. It describes the concentration changes of SARS-CoV-2 antibody prior to heating and post heating at 56℃ for around 30 minutes. Becauseof such heating, all the serum IgM (100%) has shown considerably lower levels, whereas 64.71% of the levels for IgG have reduced post heat deactivation.

In that process, the stability of SARS-CoV-2 has been determined at different temperatures. The virus has been put virus transport medium (VTM) with a concentration of ~6.8 log TCID50/mL and incubated up to fourteen days before tested for infectivity. SARS-CoV-2 virus remains highly stable around 4°C, nevertheless, heat sensitive. At 4°C on Day 14th, merely ~0.7-log unit of infectious titre is reduced. When the incubation human test subjects. An experimental approach involved the injection of iron oxide nano particles ranging in diameter from temperature is increased to 70°C, the virus gets deactivated in 5 minutes. Fig. 1 displays the variation of mean stability of SARS-CoV-2 over time (in minutes) at different incubation temperatures (in °C) [41] . Nonetheless, the influence of heating on COVID-19 still needs to be investigated.

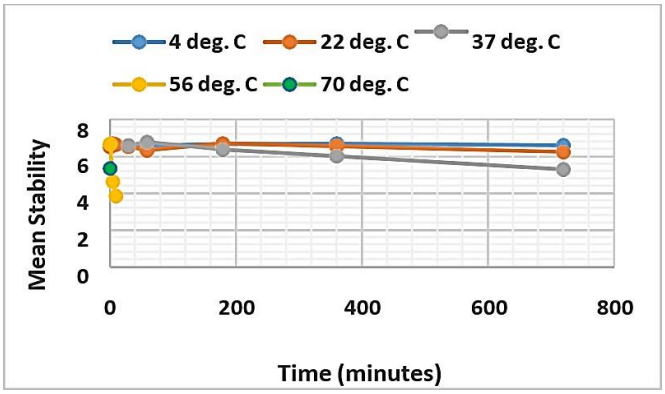

Fig. 1. Variation of mean stability of SARS-COV 2 over time (in minutes) at different incubation temperatures (in ^{o}C).

Since SARS-CoV-2 can be deactivated in 30 minutes at 56°C and in 5 minutes at 70°C , heat treatment can be used for COVID-19 treatment[42]. How heat treatment can be used inside the body cells of a COVID-19 patient is one of the challenges. Another challenge is the limit up to which the cell temperature can be increased without destroying uninfected normal cells. Magnetic hyperthermia or Magnetic fluid hyperthermia can solve the first challenge. It is one of the most encouraging techniques for gynecological cancer treatment without any side effects.

In their study of hyperthermia, Xu et al. used cobalt nanoparticles. However, instead of the alternating magnetic field, they heatedthe particles through ultrasonic sound at 350 kHz and they had reported that the outcome of the nanoparticles in vitro dependson nanoparticle concentration as well as exposure time[43]. In addition, magnetic hyperthermia will have more impact on the viability of cells in vitro as compared to heating signifying additional influence on viability of tumor cells. Hedayati et al. figured out the minimum tumor size for an effective magnetic hyperthermia. In their study, Asin et al. showed that an alternating magnetic field in vitro caused more cell death without rise of temperature because of damage of cells mechanically through actuating intracellular iron oxide nanoparticles[44-45].

Recently, Balanov et. al. has synthesized manganese-zinc ferrite nanoparticles for cancer treatment[46]. These particles can deactivate these viruses due to their magnetic property. In this method, when a body containing these particles is introduced to magnetic field It caused the heating of nanoparticles resulting in the deactivation of cancer cells. At Curie temperature orCurie point, the magnetic properties start disappearing.Therefore, in case of the nanoparticles, as soon as the Curie point is attained, a ferromagnetic material changes to a paramagnetic material and the effect of induced magnetic field starts reducing and the heating stops. When temperature falls below the Curie point, the nanoparticles become ferromagneticagain and they start showing magnetic properties. Magnetic field starts getting induced and heating resumes leading to increase in temperature. Thus, the temperature management is realized over a narrow range. The research group selected manganese-zinc ferrite nanoparticles for study purpose and it isrepresented by $Zn_xMn_{1-x}Fe_2O_4$, in which zinc and manganese are used in a certain proportion. These nanoparticles do not have toxic effect on human body. In addition, with the appropriate proportion of zinc and manganese, they achieved aCurie temperature over a range of 40°-60°C. Such temperaturerange will allow the deactivation of tumor cells over a period without causing harm to adjacent cells. This study is still confined to the laboratories and experiments on animals are yetto initiate.

The other challenge on the upper limit of the cell temperature can be addressed leveraging $Zn_xMn_{1-x}Fe_2O_4$ nanoparticles. To initiate the treatment in this approach, $Zn_xMn_{1-x}Fe_2O_4$ nanoparticles should be injected into a body which is exposed to magnetic field which will heat these nanoparticles. The cell temperature will start increasing. Temperature between 56^0 to 60^0 will result in deactivation of covid virus. in case of temperature 60^0+ nanoparticle will lose their magnetic property. This way, the temperature will start decreasing. When it goes below 60°C, their magnetic properties will be enabled and induction heating will start again. It will lead to further SARS-COV-2 virus deactivation. However, this approach of COVID-19 treatment is yet to be clinically accepted and it requires a lot of research work.

IV. CONCLUSIONS

It's obvious that covid 19 pandemic has brought unprecedented challenges to the world. However as highlighted in this article, magnetic hyperthermia may provide a potential solution, initially developed for cancer treatment, and still being used for cancer treatment for quite some time, magnetic hyperthermia has the ability to raise temperature of the targeted area for deactivation or viral particles and holds promise as a possible treatment option for covid 19. The authors have conducted extensive review of related articles and research works on the subject, examining principle of magnetic hyperthermia and magnetic nanoparticle and exploring the recent advances in the field. Even though there are visible challenges in using magnetic hyperthermia as a treatment method but with proper investment and exploration of this technology, magnetic hyperthermia can play an important role in fight against covid19 or similar viruses in the future,

V. ACKNOWLEDGMENT

I would like to express my heartful thanks to my co-authors for their support, expert guidance and valuable insight. Theirconstructive feedback played a pivotal role in shaping and enhancing this research article.

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ISSN NUMBER (ONLINE) – 2368-1209 & (PRINT) – 2691-5944

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