Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 **VOL 11, ISSUE 03, 2020**

Role of Metallic Nanoparticles in Cardiovascular Disease

M. Kavitha[1]*, Narmada Vallakeerthi[2], P. Ramesh[3,4], and P. Muralidhar Reddy[3*]

[1]Department of Chemistry, University College for Women, Osmania University, Hyderabad, Telangana, India.

[2]Department of Pharmacy, University College of Technology, Osmania University, Hyderabad, Telangana, India

[3]Department of Chemistry, Osmania University, Tarnaka, Hyderabad, Telangana, India.

[4]Department of Chemistry, S.R&B.G.N.R. Government College (A), Khammam 507 002, India.

[*1,3] Corresponding authors: kavithamannem@gmail.com, pmdreddy@gmail.com

ABSTRACT

The key role played by metallic nanoparticles in atherosclerosis is summarized in this review. Nanotechnology includes nanoparticles and nanostructured materials/devices, for the treatment and diagnostics of cardiovascular disorders. An atherosclerotic plaque is created when lipids and fibrous materials build up in the walls of the major arteries as a result of the inflammatory process known as atherosclerosis. According to reports, magnetically attracted metallic nanoparticles locate and stop inflammatory processes in atherosclerotic plaques. This review focuses on the nano-delivery system and its importance for therapy and diagnosis of subclinical atherosclerosis.

Keywords: Atherosclerosis, Metallic nanoparticle, Inflammatory pathway.

BACKGROUND

Non-communicable illnesses, which usually include cardiovascular disease (CVD), are a major cause of death worldwide. India has significantly higher death rate than the global average of 235. One of the largest global CVD is seen in India. According to predictions, there would be 4.77 million CVD deaths in India annually by 2025, up from 2.26 million in 1990. Globally, it has been seen that more than million attributable to CVDs in 2019, while more than thirty percent of all fatalities includes secondary complications of CVD. Heart attack and stroke deaths accounted for 85% of these fatalities [1]. There are numerous distinct conditions included within CVD. Some of these can manifest simultaneously or give rise to additional disorders or diseases that affect the group. As seen in figure 1, diseases and disorders that affect the heart are described.

ISSN: 0975-3583, 0976-2833 **VOL 11, ISSUE 03, 2020**

The arteries, veins, or capillaries throughout the body, as well as those near the heart, are affected by vascular illnesses. Stress is known to make cardiovascular disorders more prone to etiology and development. Basic research shows that the few therapies such as diet modification, Transcendental Meditation practice, and good exercise reduces sympathetic tone and stress reactivity acutely and over time. Fruits can help with CVD prevention or after-injury heart and vascular shape and function rehabilitation. The involved pathways included preventing ischemia/reperfusion injury, controlling lipid metabolism, altering blood pressure, suppressing platelet activity, minimizing thrombosis, lowering oxidative stress, and reducing inflammation. Numerous antioxidants, including CoQ10, beta carotene, lycopene, quercetin, resveratrol, vitamin C, and vitamin E, have demonstrated both therapeutic and preventative advantages in a variety of CVD types. However, the use of several antioxidants as therapeutic agents is constrained by their weak biological characteristics and inconsistent pharmacokinetics [2]. Because of passive and active targeting to the heart tissues, enhanced target specificity, and sensitivity, the application of nanoparticles and nanocarriers in the field of cardiology has attracted great attention. According to reports, nanotechnology can be used to successfully treat more than 50% of CVDs. Targeted medications can be delivered by nanoparticles through blood and tissue flow because of their distinctive size, physical characteristics, and chemical makeup. It can also remain in tissues and organs for a long enough time to improve imaging or carry out other special nanoscale tasks. As a result, the main applications of NPs are for improved medical imaging, targeted drug administration, and targeted delivery to eliminate diseased cells [3]. Nanotechnology can enhance pharmacological efficacy and local and systematic drug delivery to atherosclerotic plaques. Nearly all cardiovascular medications, including statins, antithrombotic, and thrombolytic agents, are still concerned with systemic exposure and drug-drug interactions. To fully understand the impact of nanoparticles on the body and on cardiac tissues, in vivo and clinical trials are necessary. Imaging and diagnostic substances could be delivered by nanocarriers to precisely specified locations. This review article will discuss the primary diagnostic techniques for the treatment of CAD together with the current applications and perspective of nanotechnology. Within the last two decades, a wide variety of nanotechnologies have been created for biomedicine, each with special benefits and qualities. These include the utilisation of nanoparticles, liposomes, dendrimers, micelles, and nanocoatings [4].

ISSN: 0975-3583, 0976-2833 VOL 11, ISSUE 03, 2020

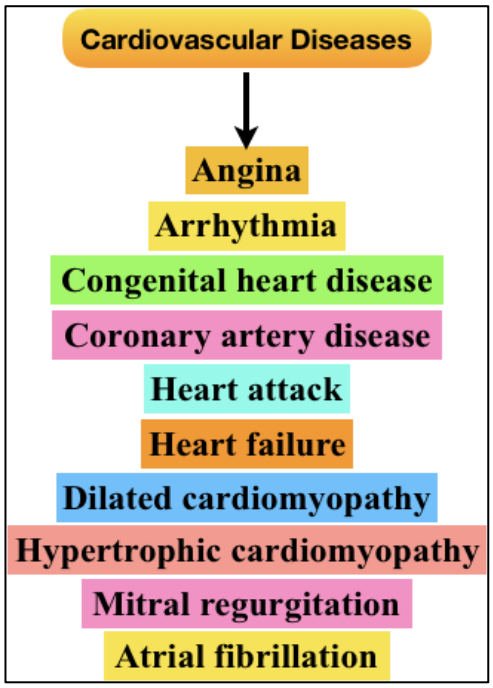

Figure 1: Diseases and disorders that affect the heart

1. NANOPARTICLE DELIVERY SYSTEM

Nanoparticles can be functionalized to target particular tissues or cell populations and have greater ability to pass through epithelium, endothelium in inflammatory areas, and microcapillaries. These nanoparticles (NPs) are appealing for medical applications because of their significant and distinctive characteristics, including their surface to mass ratio, which is significantly higher than that of other particles, their quantum properties, and their capacity to adsorb and transport other substances. Different nanodrug delivery methods, such as dendrimers, nanocrystals, emulsions, liposomes, solid lipid nanoparticles, micelles, and polymeric nanoparticles, have been created to date for diverse routes of administration. Multifunctional drug delivery systems (DDSs) have recently been developed to offer a thorough approach with various features, including controlled drug release, targeted drug administration, and diagnostic imaging. Because the polymer degradation may be closely controlled and consequently connected to drug release, polymeric formulations have been used particularly for their controlled distribution. There are numerous strategies to manage the drug delivery by nanoparticles [5]. They vary depending on how practical the therapeutic intervention is. There are various nano-sized materials as a drug delivery system such as micelles, liposomes, polymeric nanoparticle, dendrimer, carbon nanotube and metallic

ISSN: 0975-3583, 0976-2833 VOL 11, ISSUE 03, 2020

nanoparticle [Figure 2]. In this review, we have been focussed on the use of metallic nanoparticle in atherosclerosis. Atherosclerotic plaques have been identified and assessed using nanoparticles. It is crucial to emphasise recent developments on both sides because successful translation of nanomaterials into cardiovascular applications necessitates a thorough understanding of both nanomaterials and biomedicine.

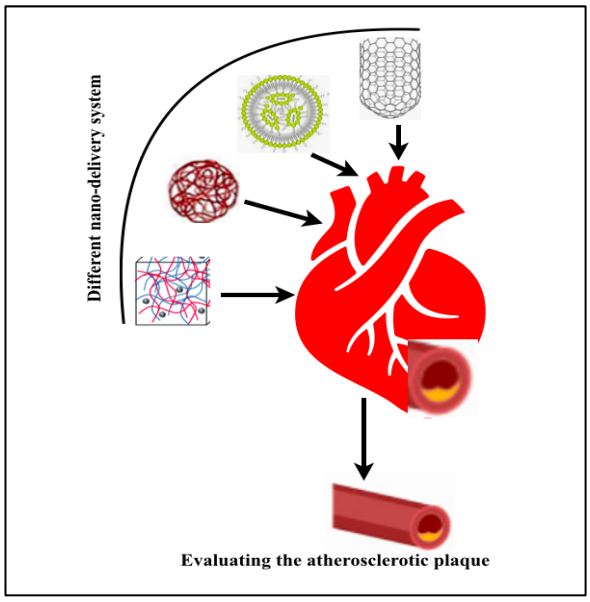

Figure 2: Evaluation of atherosclerotic plaque via different nano-delivery system

1.1. METALLIC NANOPARTICLES

Metallic nanoparticles have captivated scientists for more than a century, and they are now widely used in engineering and biological sciences. They are the subject of attention due to their enormous potential in nanotechnology. Many different types of medical treatments have made extensive use of metallic nanoparticles. Metallic nanoparticles are being more widely used in cancer treatment as novel carriers and contrast agents [6]. Through active and passive targeting, these metallic nanoparticles have been employed for tumour cell imaging. The properties of metallic nanoparticle is explained in figure 3. These nanoparticles are now capable of site-specific targeting and drug delivery. Metal Genetic technologies based on nanoparticles like Gold nanoparticles have received FDA approval. Currently, they play a role in the identification of numerous genetic and molecular indicators. The ability of silver nanoparticles to produce different effects such as cytotoxic effect, phagocytic effects has been

ISSN: 0975-3583, 0976-2833 VOL 11, ISSUE 03, 2020

demonstrated in numerous laboratories. The majority of these effects depend on the experimental duration including concentration, size, biological target, and exposure time [7].

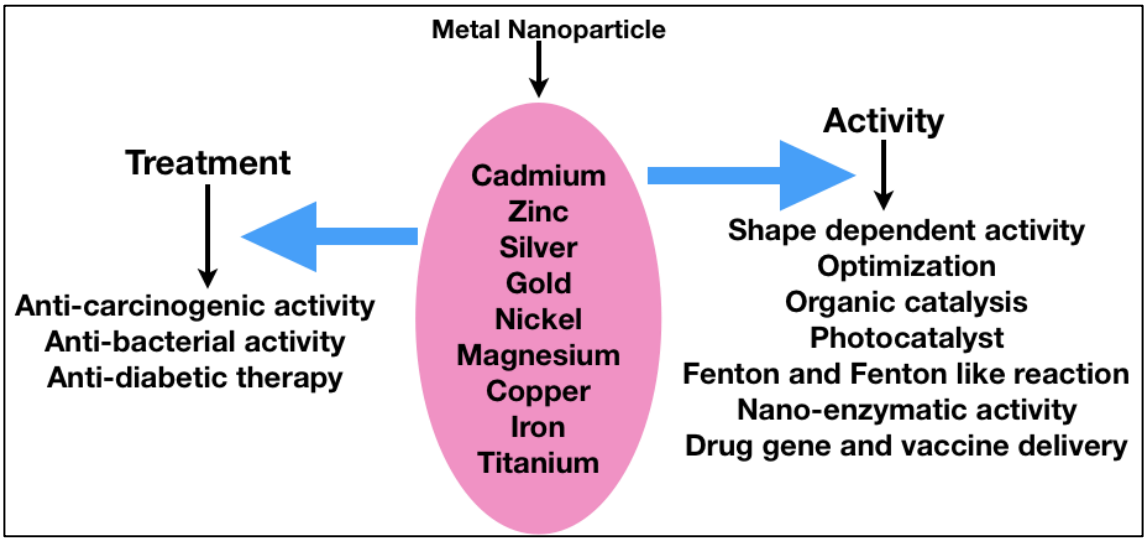

Figure 3: Properties of metallic nanoparticle.

1.2. ACTION OF METALLIC NANOPARTICLE IN ATHEROSCLEROSIS

Metallic nanoparticles appear to have a promising future in improving atherosclerosis detection and treatment by targeting the intimal macrophages, foam cells, endothelial cells, angiogenesis, proteolysis, apoptosis, and thrombosis. This is despite the fact that the currently available therapeutic modalities cannot target specific molecules, cells, and processes in the lesions. Researchers used alpha, beta3, integrin-targeted iron oxide nanoparticles to picture angiogenesis in early-stage atherosclerosis or used iron oxide nanoparticles with conjugated anti-human E-selectin fragments to detect endothelial cells. To visualise the structure of atherosclerotic lesions, magnetic resonance imaging/angiography is a commonly used technique that uses gadolinium chelates/nanoparticles, superparamagnetic iron oxide probes, and ultrasmall superparamagnetic iron oxide as contrast enhancement [8]. Other metal-based substances have been employed for both imaging and treatment, such as gold shell nanoparticles (120 nm). Monocrystaline iron oxide nanoparticles, small iron oxide particles (50 to 500 nm), and ultrasmall iron oxide particles all contain iron that causes strong local disruptions in the magnetic field of MRI scanners. These disruptions increase T2* relaxation, which lowers image intensity in areas where iron particle accumulation has occurred (these effects are known as "susceptibility" effects). These particles have been employed for passive

ISSN: 0975-3583, 0976-2833 **VOL 11, ISSUE 03, 2020**

targeted imaging of pathological inflammatory processes by MRI, such as unstable atherosclerotic plaques, and they have a very long circulation half-life (24 hours) [9]. With their potent antibacterial properties, silver nanoparticles are most frequently employed in biomedicine, textiles, healthcare items, and other fields. AgNPs are therefore more frequently exposed to human bodies than other nanomaterials. AgNPs are extremely hazardous to both cells and animals, however this is becoming more and more clear. As a result, oxidative stress is frequently thought of as AgNPs' most dangerous toxic mechanism. AgNPs can easily enter the bloodstream due to their small particle size. The effect of Ag ionic form as silver nitrate and silver chloride has ben demonstrated in previous study. The researcher showed that the concentrations of 1 part per thousands of Ag ionic form in drinking water elicit cardiac changes in rats, such as left ventricular hypertrophy. In addition, it has been demonstrated that feeding turkeys with 900 parts per million silver nitrate for 4 weeks improved their hematocrit, haemoglobin concentrations, aortic elastin content, and heart size [10]. Atherosclerotic plaques are actively attracting monocytes from the circulation. Monocytes in the plaque undergo macrophage differentiation before becoming foam cells. It has been demonstrated that plaque-dwelling monocytes contain gold nanoparticles. The success of utilising gold nanoparticles as efficient cell labelling contrast agents for CT imaging of monocyte accumulation within plaques is demonstrated by this work. While phagocytosis of nanoparticles and lung inflammation may be involved, an in vivo and in vitro investigation revealed that exposure to ZnO-NPs could cause atherosclerotic changes [11].

Table 1: Possible action of metallic nanoparticle in atherosclerosis

Metallic Nanoparticle	**Pathway**	**Application**	**Reference**
Silver nanoparticles	IKK/NF-κB pathways	Induction of endothelial cell injury and dysfunction	17
Silver nanoparticle	Inflammatory pathway	Induced neutrophil extracellular traps	18
PEGylated gold nanoparticles	Non-invasive detection of macrophages in atherosclerotic lesions	Computed tomography enhanced	19
Gold nanoparticles	atherosclerotic plaques	SPECT/CT imaging	20
Zinc oxide nanoparticles	tumor necrosis factor-α [TNF-α]) and biomarkers of atherosclerogenesis	human coronary artery endothelial cells	21

ISSN: 0975-3583, 0976-2833 VOL 11, ISSUE 03, 2020

Zinc ferrite nanocomplex	atherosclerotic plaques	magnetic resonance imaging (MRI)	22
Iron oxide nanoparticles	Macrophages and endothelial cells	Detecting and imaging	23

1.3. QUENCHING OF REACTIVE OXYGEN SPECIES

The development of subclinical non-atherosclerotic intimal lesions prior to the onset of pathologic intimal thickening and advanced atherosclerotic plaques is crucial. It has been established that oxidative stress has a role in the malfunctioning of endothelial cells and the emergence of atherosclerosis. Endothelial dysfunction, neovascularization, vascular proliferation, apoptosis, matrix degradation, inflammation, and thrombosis are some of the mechanisms that are involved in this intricate process. The primary source of ROS in vascular endothelial cells is electron leakage from the mitochondria. An imbalance in the oxidant/antioxidant processes results in a state of oxidative stress, and endogenous anti-oxidants serve as checkpoints to prevent these undesirable effects of ROS. The imbalance between ROS generation and detoxification by antioxidant defence mechanisms leads to the development of ROS in hypercholesterolemia. ERKs, stress-activated protein kinases, Akt kinases, and NF-kB are possible targets of ROS in endothelial cells and SMC [12]. Similar to H2O2, AgNPs can catalyse the breakdown of H2O2, producing superoxide. Recent research conducted has revealed that superoxide can mediate the reduction of Ag to AgNPs [13]. Due to nanoparticle benefits, research into ROS-based nanoparticles has been done to examine ROS scavenging effects for treating atherosclerosis that are stronger and longer-lasting. Metal nanomaterials have been the most common inorganic nanocarriers employed to treat atherosclerosis in recent years [14]. It has been also observed that the the ZnO play and important role in the maintenance of hematopoiesis, maintaining cell redox balance, enzyme regulation, body's metabolism and regulation of the DNA and protein synthesis machinery. Additionally, ZnO NPs are the best choice for biomedical applications among other metal and metal oxide nanoparticles because of their exceptional wound healing, catalytic, bioimaging, anti-bacterial, and anti-inflammatory characteristics. ZnO NPs' size in the nanoscale range enables Zn to be absorbed readily through biological membranes. It has strong anti-inflammatory properties such as, it an act against anti-inflammatory mechanisms that include inhibiting the expression of the inducible nitric oxide synthase enzyme, inhibiting the release of pro-inflammatory cytokines, inhibiting myeloperoxidase, inhibiting the NF-kb pathway, and

ISSN: 0975-3583, 0976-2833 VOL 11, ISSUE 03, 2020

inhibiting mast cell degranulation [15]. Inhalation of ultrafine particles is one of many risk factors for endothelial cell inflammation and the onset of atherosclerosis that have been discovered. According to a recent study, exposure to TiO2 NP increased cellular oxidative stress and NF-B DNA binding. Furthermore, cells treated to TiO2 NPs showed enhanced phosphorylation of Akt, ERK, JNK, and p38. TiO2 NPs also markedly boosted the induction of vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1 mRNA and protein levels (MCP-1). TiO2 NP-induced MCP-1 and VCAM-1 gene expression was considerably reduced by pretreatment with inhibitors for NF-kB (pyrrolidine dithiocarbamate), oxidative stress (epigallocatechin gallate and apocynin), Akt (LY294002), ERK (PD98059), JNK (SP600125), and p38 (SB203580) [16]. Nanoparticle induces ROS to further proceed apoptosis [figure 4]. However, ROS could become lethal at sufficiently high quantities, typically resulting in cellular necrosis or apoptosis, an effect that is widely used for a variety of medicinal applications. Radiation therapy4, or the application of ionising radiation to treat local malignancies, has the potential to harm cells directly by ionising DNA and other biological components, or inadvertently by producing large amounts of ROS that have a significant cytotoxic effect.

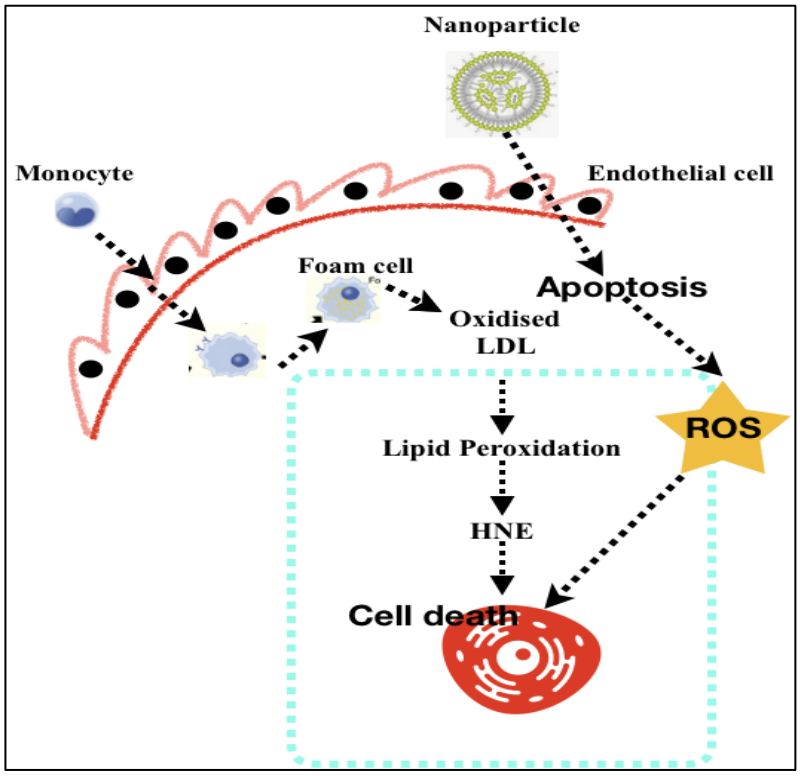

Figure 4: Action of ROS in presence of nanoparticle

ISSN: 0975-3583, 0976-2833 VOL 11, ISSUE 03, 2020

2. FUTURE PERSPECTIVE

Nanomedicines have a lot of potential for the prevention, detection, and treatment of a wide range of illnesses, including atherosclerosis, despite significant restrictions. Being a disease linked to inflammation, atherosclerosis poses a serious healthcare issue. Its cause is still unknown, and myocardial infarctions and strokes are two major causes of morbidity and mortality globally as a result. Unfortunately, medications can't stop plaque build-up in its tracks. There is currently no medication that can completely reverse or cure atherosclerosis, despite the fact that it can reduce the disease's course. Few nanomedicine has been approved by FDA but in the field of cardiovascular diseases, there is a need of clinical trials for the effect of metallic nanoparticle. The nanoparticles discussed in this review needs to be undergo clinical trials for the appropriate result.

ACKNOWLEDGEMENTS

One of the authors M. Kavitha is thankful to UGC-New Delhi, India for financial support in the form of Start-up grant and Head, Department of Chemistry, Osmania University, Hyderabad, India for providing laboratory facilities.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Kumar AS, Sinha N. Cardiovascular disease in India: a 360 degree overview. Medical Journal, Armed Forces India. 2020;76(1):1.
2. K Jain A, K Mehra N, K Swarnakar N. Role of antioxidants for the treatment of cardiovascular diseases: challenges and opportunities. Current pharmaceutical design. 2015,1;21(30):4441-55.
3. Gupta P, Garcia E, Sarkar A, Kapoor S, Rafiq K, Chand HS, et al. Nanoparticle based treatment for cardiovascular diseases. Cardiovascular & Haematological Disorders-Drug Targets (Formerly Current Drug Targets-Cardiovascular & Hematological Disorders). 2019,1;19(1):33-44.
4. Chandarana M, Curtis A, Hoskins C. The use of nanotechnology in cardiovascular disease. Applied Nanoscience. 2018;8(7):1607-19.

ISSN: 0975-3583, 0976-2833 **VOL 11, ISSUE 03, 2020**

5. Aljunaidy, M. M., Morton, J. S., Cooke, C. L. M., & Davidge, S. T. (2017). Prenatal hypoxia and placental oxidative stress: linkages to developmental origins of cardiovascular disease. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *313*(4), R395-R399.
6. Ahmad MZ, Akhter S, Jain GK, Rahman M, Pathan SA, Ahmad FJ, et al. Metallic nanoparticles: technology overview & drug delivery applications in oncology. Expert opinion on drug delivery. 2010,1;7(8):927-42.
7. Gonzalez C, Rosas-Hernandez H, Ramirez-Lee MA, Salazar-García S, Ali SF. Role of silver nanoparticles (AgNPs) on the cardiovascular system. Archives of toxicology. 2016;90(3):493-511.
8. Zhang J, Zu Y, Dhanasekara CS, Li J, Wu D, Fan Z, Wang S. Detection and treatment of atherosclerosis using nanoparticles. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2017;9(1):e1412.
9. Wickline SA, Neubauer AM, Winter P, Caruthers S, Lanza G. Applications of nanotechnology to atherosclerosis, thrombosis, and vascular biology. Arteriosclerosis, thrombosis, and vascular biology. 2006 Mar;26(3):435-41.
10. Zhang Y, Koradia A, Kamato D, Popat A, Little PJ, Ta HT. Treatment of atherosclerotic plaque: perspectives on theranostics. Journal of Pharmacy and Pharmacology. 2019;71(7):1029-43.
11. Yan Z, Wang W, Wu Y, Wang W, Li B, Liang N, et al. Zinc oxide nanoparticle-induced atherosclerotic alterations in vitro and in vivo. International Journal of Nanomedicine. 2017;12:4433.
12. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. Experimental & Clinical Cardiology. 2002;7(1):40.
13. He D, Jones AM, Garg S, Pham AN, Waite TD. Silver nanoparticle− reactive oxygen species interactions: application of a charging− discharging model. The Journal of Physical Chemistry C. 2011;115(13):5461-8.
14. Wang Y, Li L, Zhao W, Dou Y, An H, Tao H, et al. Targeted therapy of atherosclerosis by a broad-spectrum reactive oxygen species scavenging nanoparticle with intrinsic anti-inflammatory activity. ACS nano. 2018,16;12(9):8943-60.

ISSN: 0975-3583, 0976-2833 **VOL 11, ISSUE 03, 2020**

15. Agarwal H, Shanmugam V. A review on anti-inflammatory activity of green synthesized zinc oxide nanoparticle: Mechanism-based approach. Bioorganic chemistry. 2020,1;94:103423.
16. Han SG, Newsome B, Hennig B. Titanium dioxide nanoparticles increase inflammatory responses in vascular endothelial cells. Toxicology. 2013,5;306:1-8.
17. Shi J, Sun X, Lin Y, Zou X, Li Z, Liao Y, et al. Endothelial cell injury and dysfunction induced by silver nanoparticles through oxidative stress via IKK/NF-κB pathways. Biomaterials. 2014,1;35(24):6657-66.
18. 강한구. Mechanism of silver nanoparticle-induced neutrophil extracellular traps and its association with atherosclerosis (Doctoral dissertation, 연세대학교).
19. Qin J, Peng C, Zhao B, Ye K, Yuan F, Peng Z, et al. Noninvasive detection of macrophages in atherosclerotic lesions by computed tomography enhanced with PEGylated gold nanoparticles. International journal of nanomedicine. 2014;9:5575.
20. Li X, Wang C, Tan H, Cheng L, Liu G, Yang Y, et al. Gold nanoparticles-based SPECT/CT imaging probe targeting for vulnerable atherosclerosis plaques. Biomaterials. 2016,1;108:71-80.
21. Yan Z, Wang W, Wu Y, Wang W, Li B, Liang N, et al. Zinc oxide nanoparticle-induced atherosclerotic alterations in vitro and in vivo. International Journal of Nanomedicine. 2017;12:4433.
22. Chaudhary R, Roy K, Kanwar RK, Walder K, Kanwar JR. Engineered atherosclerosis-specific zinc ferrite nanocomplex-based MRI contrast agents. Journal of nanobiotechnology. 2016;14(1):1-7.
23. Schneider MG, Lassalle VL. Magnetic iron oxide nanoparticles as novel and efficient tools for atherosclerosis diagnosis. Biomedicine & Pharmacotherapy. 2017,1;93:1098-115.