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THE'MAGIC BULLET' NANOMEDICINE –AS A MOLECULAR DRUG CARRIER FOR TARGETING INFLAMMATION IN RHEUMATOID ARTHRITIS

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ABSTRACT

With an aim of identifying novel medication, nanomedicine is found be instrumental in enabling early detection, prevention and to drastically improve diagnosis, treatment and follow-up of many diseases. Overall, nanomedicine has more than 70 products under clinical trials, covering all major diseases including cardiovascular, neurodegenerative, musculoskeletal and inflammatory diseases. Rheumatoid Arthritis is characterised as a systemic, immune inflammatory disease characterized by joint swelling, synovial inflammation and joint destruction that leads to significant disability. Innovative nanomedicine targets patients on reducing doses of drugs, limiting their side effects on healthy tissues. Currently, there are few nanotechnology-enabled therapeutic agents already approved by the FDA like liposome nanoparticle (NP) with entrapped doxorubicin was reported by researchers to be 300 times more effective because of better pharmacokinetic ability in treatment of Kaposi sarcoma, Abraxane® drug is considered as a major success story of the nanomedicine approach to treat cancer is a natural alkaloid, Curcumin nanoparticles used as innovative antimicrobial and wound healing agents well adorned for their wide availability and medicinal property. Thus, this present review gives a brief discussion on the role of nanomedicine as therapeutic use for treating rheumatoid arthritis.

KEYWORDS: Nanomedicine, Rheumatoid arthritis, Nanotechnology, drug carriers, drug delivery systems.

INTRODUCTION

The emerging new science has given way welcoming the use of nanoparticles that is an outcome resulted in fusion of nanotechnology and medicine known as Nanomedicine, this current applications of nanomedicine is subjugated to achieve innovation in healthcare such as for the treatment of different types of cancers (prostrate, breast), heart diseases, rheumatoid arthritis, antitumour therapies and others.[1] The new approach in nanotechnology development has become one of the promising research areas, bringing a significant progress into material, device development and has many applications such as in the area of medicine, chemistry, environment, energy, agriculture, information and communication, heavy industry and consumer goods.[2] It uses the properties developed by a spur of atoms and molecules leading to the construction of structures at the nanometer scale size range 10-9 m, which often differ in terms of physics, chemistry or biology from the same material at a bigger scale. Moreover, the nanometric size is also the scale of many biological mechanisms in the human body allowing nanoparticles and nanomaterials to reach the targets quickly and to potentially cross natural barriers to access new sites of delivery and to interact with DNA or small proteins at different levels, in blood or within organs, tissues or cells.[3]

The molecular technology has enormous immediate benefits will continuingly revolutionize the research and practice of medicine and eventually finding an important place in health care.[4] Modern research wanders around using nanoscale science and technology in identifying opportunities and applications to environmental problems, and to evaluate the potential environmental impacts of nanotechnology. Also, approaches are needed to offer new capabilities for preventing or treating highly toxic or persistent diseases, which would result in the more effective monitoring of its progression and their impacts.[5] Further scientific research is required in the development of nanotherapeutics to deliver unmet medical needs.[6]

A novel application of nanoscales is focussing on applications in the cellular and intracellular delivery of therapeutic agents. Medical therapies have become more tailored to specific diseases and patients in recent

years.[7] Cells and tissues are the primary targets for the most pharmaceutical agents. Therefore selective subcellular delivery is likely to have greater therapeutic benefits.[8]

Metallic nanoparticles craving its importance

Nanoparticles are being sighted as fundamental building blocks of nanotechnology. The nanotechnology concept in scientific terms was first introduced by late Nobel physicist Richard Feynman in 1959 and is the basis on which the technology stands today.[9] It got its first formal name as "nanotechnology" by Japanese scientist Norio Taniguchi in 1974. The technology today has found its application in diverse fields[10] and has walked miles thanks to the hand-holding of Drexler. In present years, the technology has become the prime focus for researchers because of its unique properties and multidimensional applications. In the near future the nanotechnology will bring fundamentally transformation offering enhance human health in novel ways to the society.[11]

New applications of nanoparticles and nanomaterials are emerging rapidly with tremendous growth and advances to revolutionize medical treatment with more potent, less toxic, and smart therapeutics that could invade into disease areas like the imperceptible magic bullet.[12] Noble metals such as Gold, Silver, Platinum and Lead play extensively as metallic nanoparticles. The metallic nanoparticles have their unique optical, electronic, mechanical, magnetic and chemical properties that are significantly different from those of bulk materials.[13][14]

Different metals and its physiological functions

There are many metals with many physiological function required to consume as daily diet in a human (from Recommended dietary allowances (RDA) of essential elements in adults from National Institute of Nutrition, ICMR, INDIA). They are as follows.

Table No. 1 Important metals with their physiological function and recommended dietary allowances (mg/day)

Important metals in Human body	Physiological functions *	Recommended dietary allowances** RDA (mg/day)
Magnesium	Structural functions, metabolic pathways	240-420
Chromium	Glucose intolerance, catalytic activity, formation and activation of xanthine oxidase, release and uptake of iron from ferritin, hormone action	0.065
Manganese	Formation of connective tissues, bones, blood clotting factors, sex hormones, fat and carbohydrate metabolism, calcium absorption, blood sugar regulation, normal brain and nerve function	5.5
Iron	O_2 transport and storage, oxidase. Electron, transfer, enzymatic function	28-30
Copper	Performs enzymatic functions, HB synthesis during pregnancy, fertility and reproduction, nerve function, protection against O2 radicals, normal lung function, bone formation, immune-competence, cell signalling	2.2
Zinc	Structure, hydrolase, male fertility(endocrine functions), enzymatic functions, signal transduction, cell signalling	15.5
Selenium	Antioxidant system, sperm motility	0.040-0.070

* [15]

** Courtesy of Recommended dietary allowances (RDA) of essential elements in adults from National Institute of Nutrition, ICMR, INDIA.

Among the Noble metals, silver (Ag) is the metal of choice in the field of biological systems, living organisms and medicine.[16] Silver nanoparticles are the most prominent one. Silver nanoparticles are nanoparticles of silver, i.e. silver particles of between 1 nm and 100 nm in size and have attracted intensive research interest because of low cost and emerging applications. Use of biogenic nanoparticles, being an environmentally benign greener option, is very much preferred in a variety of applications. AgNPs find wider applications as catalyst in the reactions such as heterocyclizations, cyclo addition of imines, oxidation of ethylene to ethylene oxide and methanol to formaldehyde which are industrially important.[17][18]

Preparation of silver nanoparticles has attracted particularly considerable attention due to their diverse properties and uses, like magnetic and optical polarizability, electrical conductivity, catalysis,[19] antimicrobial[20] and antibacterial activities[21], DNA sequencing[22], and surface enhanced Raman scattering (SERS)[23] etc., Silver nanoparticles can be synthesized by various techniques in different chemical composition, sizes, shapes and polydispersity.[24] This includes

chemical reduction of silver ions in aqueous solutions with or without stabilizing agents[25], thermal decomposition in organic solvents[26], chemical reduction and photo reduction in reverse micelles[27], and radiation chemical reduction.[28]

But most of these methods are extremely pricey and also uses toxic, hazardous chemicals, which may create potential environmental and biological risks.[29] Metal nanoparticles are recently synthesized using eco-friendly natural sources such as plant extracts, fruits, fungi, honey and microorganisms. The need for green chemistry raised and included a clean, non toxic and environment friendly method of nanoparticles synthesis.[30]

This eco-friendly way of synthesizing nanoparticles introduced the hypothesis of using pharmacological agents isolated from natural products leading to bio fractionation of active constituents in plant showing, promising activity and application in the experimental field. Currently, about 25-30% of all active principles used in treatment of diseases are extracted from natural products.[31]

The plant kingdom is responsible for the largest share of chemical diversity recorded in the literature to date, and has contributed quite significantly to the research and discovery of new drugs of natural origin and moreover 80% of people in developing countries prefer the medicinal plants as their choice of treatment.[32]

Why natural drugs are opted for curing Rheumatoid arthritis–Inflammatory disease?

Pain is an important symptom of inflammatory disease and is the primary reason why patients pursue specialised treatment. The use of natural drugs as a relief from pain/illness can be traced back over five millennia to written documents of the early civilization in China, India and the Near East, but it is doubtless an art as old as mankind. The potential of higher plants as source for new drugs are still largely not explored. Among the 250,000 – 500,000 plant species, only a small percentage has been investigated phytochemically and the fraction submitted to biological or pharmacological screening is even smaller. [33]

Rheumatoid arthritis is a common chronic autoimmune disease with, progressive disability and destructive arthropathy that cannot be cured and that has substantial personal and socioeconomic costs. The medical cost of rheumatoid arthritis averages $5,919 per case per year in the United States and approximately £2,600 per case per year in the United Kingdom. Current treatment strategies are slow-acting anti-rheumatic drugs, analgesic and anti-inflammatory drugs have limited efficacy and many side effects. Moreover, conventional and biologic disease modifying therapies do not improve the long-term prognosis of rheumatoid arthritis, so there occurs a need for alternative drug treatment which ended in opting for natural drugs which causes fewer side effects.[34]

However, considering that pain therapies from natural sources date back to thousands of years owing to a variety of painful condition and inflammatory injuries, studies aimed at discovering new compounds of natural origin with potential therapeutic effects and minimal side effects have been pursued vigorously.[35]

Rheumatoid arthritis – An overview

Arthritis is the destruction of cartilage, articular structures and subchondral bone. Rheumatoid arthritis (RA) disease is characterized by stiff, painful and inflamed joints occurring in many parts of the body. The autoimmune process that wreaks havoc on the joints can also affect the eyes, lungs, skin, heart and blood vessels and other organs.[36]

Behind cancer and cardiovascular diseases, rheumatoid arthritis (RA) and osteoarthritis (OA) are the most prevalent global diseases. Worldwide statistics confess that RA ranks 42nd highest contributor to global disability, just below malaria and just above iodine deficiency. In Australia the collected data suggest that, by 2050, 7 million Australians and in America by 2020, 18.2% (59.4 million) will be affected by some form of arthritis.[37]

In Europe, there are 3 million RA and 70 million OA patients. The pathology of this joint destruction is characterized by destruction of articular cartilage and marginal and subchondral bone due to change in lifestyle and ageing of the population, the number of arthritic patients is expected to increase, resulting in enormous medical and socioeconomic challenges.[38] Inflammatory cytokines, such as Tumor necrosis factor - alpha (TNF-α), interleukin 1β (IL-1β) and interleukin 6 (IL-6) not only play important roles in the chronic inflammation of human RA, but also associate with various manifestations of inflammation-related angiogenesis (Figure no.1).[39]

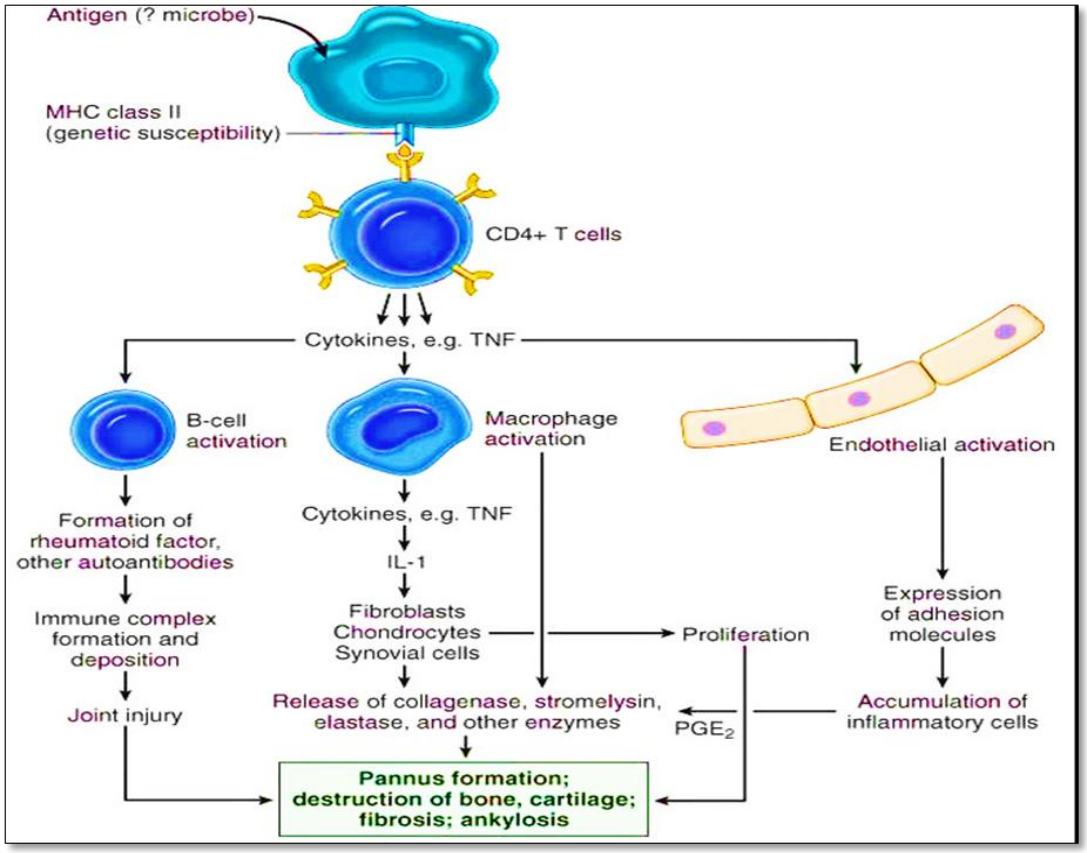

Figure No. 1 Pathogenesis of Rheumatoid arthritis[40]

- Courtesy: Robbins Basic pathology 8th edition

The initiation of rheumatoid arthritis occurs by genetic predisposition or by any initiating agent of microbial origin which acts as self antigen or antigen respectively. CD4+ helper T cells respond to these antigens resulting in production of cytokines. The following changes occur in response.

- Activate macrophages and other cells in the joint spaces releasing degradative enzymes and other factors that perpetuate inflammation.
- Activate B cells, resulting in the production of antibodies, some of which are directed against self-antigens in the joint.
- Activates endothelial cells leading expression of adhesion molecules and accumulation of inflammatory cells secreting prostaglandin (PGE2).

The rheumatoid synovium contains both lymphocyte and macrophage derived cytokines such as TNF promote leucocyte recruitment, IL-1 helps in proliferation of synovial cells and fibroblasts. Other cytokines activate macrophages, stimulate secretion of synovial cells and chondrocytes of proteolytic and matrix degrading enzymes resulting in osteopenia. The large amounts of activated T cells (cytokines) called Receptor Activator of Nuclear Factor κ B (RANK) ligand induces osteoclast differentiation and activation. All these activation, cause joint injury or releases collagenase stromelysin elastase and other enzymes ultimately resulting in pannus formation, destruction of bone cartilage, fibrosis and ankylosis.[41]

The abnormal production of certain inflammatory mediators leads to inflammation and abundant proliferation of synovium giving rise to destruction of several tissues, which includes cartilage, tendons, bones, blood vessels and ligaments. Although the major sites of inflammation and damage are the articular structures, other tissues are severely affected. In RA patients, the observation of IL-1 concentration in plasma is correlated with the activity and acts as indicator of rheumatoid arthritis. It is also observed that patients having erosive rheumatoid arthritis are with elevated synovial and circulating levels of IL-1 than patients without erosive activities of the disease.[42]

IL-1 is a notoriously significant cytokine, which has a wide range of activities within the affected joint and are believed to play a major role in causing painful inflammatory signs and symptoms of rheumatoid arthritis. It is a key mediator of pannus formation and synovial inflammation.[43] It is also believed to be a contributor to the hampering of tissue repair processes and the damage to bone and cartilage in rheumatoid arthritis. Both IL-1 and TNF-alpha have been found to share many biological actions, such as increasing the production of inflammatory mediators like cyclo-oxygenase 2 or COX 2, prostaglandin E2 or PGE2 as well as nitric oxide.

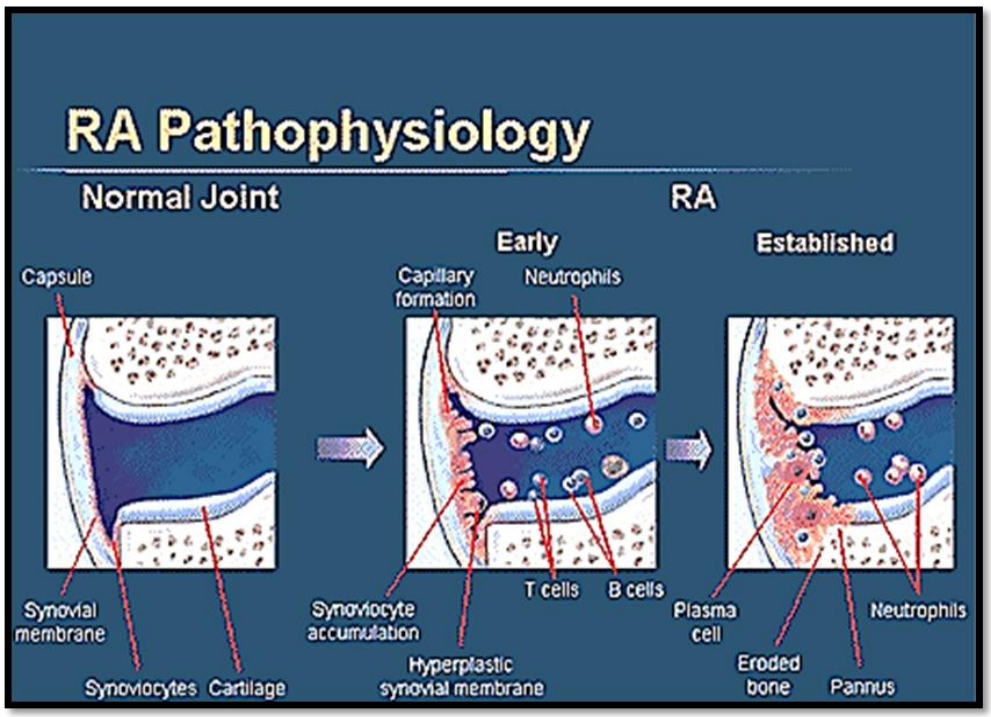

Figure No.: 2 Pathophysiology of Rheumatoid Arthritis[34]

Interleukin (IL)-1 is highly responsible for the signs and symptoms of rheumatoid arthritis. First it mediates inflammation by recruiting neutrophils into the joint, activating macrophages, and stimulating T- and B-cell proliferation and differentiation. Synoviocytes, on their exposure to IL-1, proliferate and produce IL-6, PGE-2 and matrix metalloproteases (MMPs). Further this production of MMPs causes proteoglycan degradation, which ultimately results into cartilage destruction. [34]

Power of Nanoparticle in turning into nanomedicine

Rheumatoid arthritis disease is highly prevalent throughout the world. Despite a staggering series of discoveries and innovations over the last five decades, RA disease remains the leading cause of morbidity, disability, and mortality among the people.[44] The medication available in the market at present aims only at timely relief of the pain and removes emotional distress, but failing as a permanent cure to the disease. Innovative nanodevices might advance drug delivery and therapies in arthritis patients. At the nano-scale, the surface-to-volume ratio is such that the surface properties are becoming an intrinsic parameter of the potential actions of a particle or material. Coating of the particles and functionalization of their surfaces (even on multiple levels) are in this way extremely common to increase the biocompatibility of the particle and its circulation time in the blood, as well as to ensure a highly selective binding to the desired target.[45]

Plant derived nanoparticles for example, be engineered on their surface to reach tissues quickly and release inflammation-reducing drugs. One such example is the EU-funded ‘. These particles which were decorated with antibodies to selectively target Folate-based nanobiodevices for integrated diagnosis/therapy targeting inflammatory diseases’ project which addresses this with surface engineered liposomal and protein-based nanoparticles of 100-400 nm macrophages, certifying high specificity without affecting normal cells and tissues.[47] Simultaneously, particles filled with inflammation-reducing compounds (drug or small interfering RNA) were synthesized and shown to inhibit the signaling pathways occurring during the inflammatory processes.

Modern techniques/experiments supports hypothesis

Natural products have served as an important source of drugs since ancient times and about half of the useful drugs today are derived from natural sources. In recent years, a renewed interest in obtaining biologically active compounds from natural sources has been observed. The standardization of phytomedicines/ herbal products failed and was not so successful in the past due to lack of multidisciplinary approach i.e., by bioactivity guided fractionation which leads to the study of identifying the active principle(s) contained in crude natural plant products/ preparations/ extracts to a biologically or pharmacologically active pure compounds. Due to enormous modern techniques available in chromatography (e.g. HPLC, HPTLC, CCTLC, GC) and spectroscopy (e.g. NMR and MS) over the past two decades, the sensitivity of natural product fractionation has increased dramatically, contributing to this world-wide attention towards formulations based on natural products with low or no toxicity.[47]

Adjuvant induced arthritis is a standard animal model for rheumatoid arthritis in humans.[48] This animal model has been widely used to investigate pathogenic mechanisms

in rheumatoid arthritis, such as bone erosion, pannus formation and infiltration of inflammatory cells, and to evaluate potential new therapeutic agents. The adjuvant induced arthritis model is also characterized by increased numbers of osteoclasts, which is also a feature of human rheumatoid arthritis.[49]

CONCLUSION

Nanomedicine for arthritis will be understood as a key enabling instrument for personalized, targeted and regenerative medicine by delivering the next level of new drugs, treatments and implantable devices to clinicians and patients, for real breakthroughs in healthcare. The application of nanoparticle technologies to drug delivery would be demonstrated with significant impact on inflammation relating to arthritic medicine. Nanomedicine would provide important new tools to deal with the grand challenge of an ageing population and is thought to be instrumental for improved and cost effective healthcare, one crucial factor for making medicines and treatments available and affordable to all. Lack of access to key development phases, the need of extensive safety data to anticipate the regulatory hurdles and the scale-up ability of the production processes are, however, important challenges to unlock the future potential of nanomedicines. Addressing these issues will be as important for developing and validating nanotechnologies in forthcoming projects.

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