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RESEARCH ARTICLE

SYNTHETIC AND APPLICATION OF NANOPARTICLES DRUG DELIVERY SYSTEMS PRESENT AND FUTURE PROSPECTIVE

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Abstract

Materials in the nanoscale range are used as diagnostic tools or to deliver therapeutic medicines to precisely targeted locations using nano delivery systems, a relatively new but fast emerging field of medicine. By delivering precise medicines to specified sites and targets, nanotechnology has the potential to significantly improve the treatment of chronic human diseases. Recently, there have been a number of remarkable uses of nanomedicine (chemotherapeutic agents, biological agents, immunotherapeutic agents, etc.) in the treatment of various disorders. Clinical uses of nanomedicines, both current and potential, are reviewed, as are the advantages and disadvantages of nanomedicines for drug delivery from synthetic/natural sources. We have also included data on future predictions and developments in the field of nanomedicine.

Introduction:-

Natural materials derived from plants have been widely used by humans as medication against a wide range of illnesses since ancient times. Herbal remedies are the basis of many modern pharmaceuticals, which in turn are based on centuries-old techniques and expertise. Natural resources provide close to 25% of the principal medicinal chemicals and their derivatives now in use [1,2]. Natural chemicals from a variety of molecular origins provide a platform for the development of new therapeutics. The focus in generating synthetically tractable lead compounds that mirror their counterpart's chemistry has been a recent trend in natural product-based drug discovery [3]. Natural products have many advantageous qualities, such as low toxicity and a wide range of useful chemical and biological properties at the macromolecular level. This makes them promising starting points for finding new medicines [4].

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Additionally, target-based drug discovery and drug delivery are just two examples of next-generation drug discoveries made possible by computational studies.

Natural product-based drug development and drug delivery systems have various benefits, but pharmaceutical corporations are unwilling to spend more in them [5]. Instead, they prefer to scour the libraries of existing chemical compounds in search of novel medications. Cancer, diabetes, cardiovascular, inflammatory, and microbial disorders are only some of the major health problems for which natural chemicals are being investigated as potential treatments. This is mostly due to the fact that natural medications offer a number of benefits not seen in synthetic alternatives. The greater difficulty in employing natural chemicals as medicine arises from worries about their biocompatibility and toxicity. Thus, many natural substances are failing to go through clinical trial stages due to these issues [6,7,8]. Tonic ineffectiveness, difficulty in reaching the intended target, poor absorption, and the potential for adverse effects are just some of the problems that arise when using large materials in the administration of medications. For this reason, emerging drug delivery systems for targeting treatments to specific body locations may provide an option that may address these important concerns [9, 10]. As a result, nanotechnology is essential to the creation of state-of-the-art pharmaceuticals, the advancement of targeted drug delivery systems, and the achievement of controlled drug release and delivery.

Nanotechnology has been shown to remove the barrier between the medical and physical sciences through the use of nanostructures and nanophases in various scientific fields [11]. Such particles are of particular relevance in nanomedicine and nano based drug delivery systems [12, 13]. Nanomaterials, or substances with a size between 1 and 100 nm, have an impact on the cutting edge of nanomedicine in many different areas, including biosensors, microfluidics, drug delivery, microarray tests, and tissue engineering [14,15,16]. Therapeutic agents can be implemented at the nanoscale with the help of nanotechnology in nanomedicines. The biomedical industry, which includes nanobiotechnology, drug delivery, biosensors, and tissue engineering, has been spurred by nanoparticles [17]. Nanoparticles are typically small nanospheres [18] because they are composed of materials manufactured at the atomic or molecular level. Therefore, smaller materials have greater mobility within the human body compared to their larger counterparts. Particles on the nanoscale display unusual characteristics in their structure, chemistry, mechanics, magnetism, electricity, and biology. The increased interest in nanomedicines can be attributed to the nanostructures' potential to encapsulate drugs, attach therapeutic ingredients, and deliver them to target tissues with higher precision and controlled release [10, 19]. Nanomedicine is a relatively recent field that utilises the discoveries and methods of nanoscience for medical biology and the treatment and prevention of illness. Nanorobots, nanosensors for diagnostic, delivery, and sensory purposes, and actuating materials are all hinted to as being involved in cellular processes (Fig. 1). As an example, nanoparticle-based approaches have been developed that can be used for both cancer treatment and diagnosis using imaging [20]. Lipidomic systems, which include liposomes and micelles, were among the first nanoparticle-based medicines approved by the FDA [21]. Liposomes and micelles can enclose inorganic nanoparticles like gold or magnetic nanoparticles [22]. The beneficial properties of inorganic nanoparticles have led to their extensive use, especially in the medical disciplines of drug delivery, imaging, and treatment. It has also been suggested that nanostructures can help keep drugs from becoming polluted in the digestive tract and speed up the delivery of treatments that aren't very water soluble to where they need to go. Oral administration makes nanodrugs more bioavailable than injectable ones since they are absorbed by the body in the same way as conventional drugs.

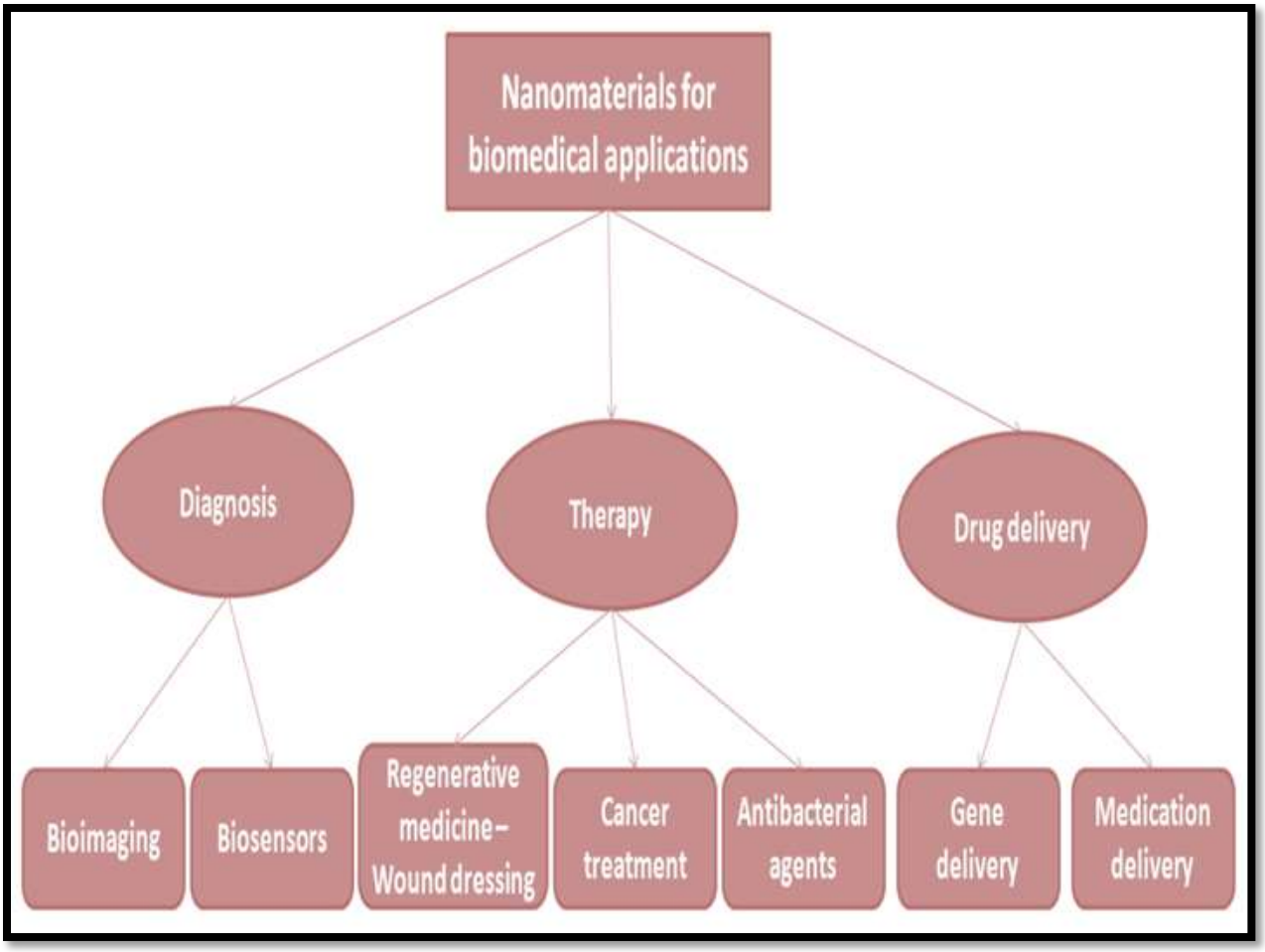

Fig 1:- Nanomedicine potential and aspirations in various fields of biomedical study.

Nano based Drug delivery system

Intracellular transport, epileptic transport, and other mechanisms have been proposed for the delivery of nanomedicines. Intercellular transport is facilitated and regulated in part by intracellularization, transporter-mediated endocytosis, and permeability mediated by interactions based on particle size and/or cell surface [15,16]. Additionally, the particle size of the medicine plays a role in how well it is absorbed, disseminated, and eliminated; smaller particles facilitate intercellular movement, which in turn facilitates cell penetration. The efficiency with which a cell takes up a nanomedicine via transporter-mediated endocytosis depends on the size of the molecule. Also, endothelial macrophages help speed up the process of opsonization and the removal of large particle sized nanomedicines from the bloodstream. Recent studies have shown that macrophages' ability to effectively clear large particles from the bloodstream depends on factors such as the particle size of nanomedical products and the susceptibility of nanomedical cell surface transporters to these products. Due to their hydrophilicity, non-charged polymers, surfactants, and polymer coatings that degrade in vivo are beneficial for nanomedicines because they can link with cell surface receptors or ligands. Combining with bioadhesive polymers or chelates, nanomedicines improve intracellular delivery of active medicinal components. Tight junctions can be opened and/or membrane permeability can be increased, both of which contribute to the enhanced intracellular mobility of active medicinal compounds linked with various proteins, antibodies, and other in vivo polymers. Chemotherapy would be more effective with the addition of pharmaceuticals that play this role in the targeting of tumour cells, normal cells, and cancerous cells, as well as in the treatment of brain tumours that are resistant to therapies linked with tight junctions. This approach has the potential to improve the efficacy of nanomedicines against cancer while decreasing their cytotoxicity toward healthy cells. It has been proven that decreasing the amount of time nanomedicines spend being degraded and absorbed by lung mucosa or macrophages improves their processing time and translocation to destination. The EPR effect improves the efficacy against cancer because it allows more of the drug to enter and remain in the tumour for a longer period of time. To directly transmit nanomedicines to target tissue, the EPR can be

used in conjunction with an antigen, enzyme, peptide, or polysaccharide to modify the delivery of nanomedicines to the target tissue via receptor/ligand interactions or other physiologically sensitive cell regulation interactions, drug efficacy modification, or adverse reactions. Hydrophilic coated nanomedicines have a greater half-life because they are not as prone to opsonization or aggregation in mucus. Nanomedicines can be retained in vivo, for example in lung tissue, for prolonged periods of time [17] by avoiding disruption by macrophage-induced or mucosal disruption and elimination by mucus ciliates. The lung mucosa may suffer microscopic damage or suffer macroscopic damage as a result. There have been numerous formulations developed, each employing a unique delivery strategy to regulate the pharmacokinetics and pharmacodynamics of nanomedicine.

Nanotechnology-based drug design techniques

Nanomedicine is the medical specialty that uses nanoscale materials, like biocompatible nanoparticles and nanorobots, to detect, process, observe, and act upon living organisms. Reduced bioaccess after oral ingestion, decreased diffusion potential into the outer membrane, increased intravenous dosing requirements, and unwanted side effects in the absence of the conventionally formulated vaccine method are just a few of the biopharmaceutical distribution challenges posed by very poorly soluble drugs. Many of the disadvantages of the current medication delivery system, however, could be averted by adding nanotechnology. Since there is so much to gain from manipulating nanoparticle qualities like solubility, drug release patterns, diffusivity, bioavailability, and immunogenicity, this is where the field of nanoparticle applications has developed the most. This opens the door to the development of new routes of administration with improved efficacy, safety, tolerability, biodistribution, and shelf life for the drug. Therapeutic substances can be activated in a controlled fashion at a precise site with the help of an engineered drug delivery system. Their creation calls for self-assembly, a process in which predetermined structures or patterns are formed out of seemingly random arrangements of building parts. The mononuclear phagocyte cell's opsonization and subsequent sequestration of the target is another obstacle that must be surmounted. Nanostructures can be used in either passive delivery or self-delivery of drugs. The latter's hydrophobic action is what allows medications to be inserted into the structure's interior. The nanostructure materials are directed to specified areas, where the low drug content, protected by a hydrophobic environment, is released in the desired volume. Conversely, the medications that are meant for release are coupled to the carrier nanostructure material in a way that facilitates rapid diffusion. The medicine will not penetrate the target location and disassociate from the carrier very rapidly if it is not released from its nanocarrier device at the proper time, reducing its bioactivity and effectiveness. The utilisation of nanomaterials or nanoformulations as drug delivery methods, which is further subdivided into active and passive categories, is another key aspect of drug targeting. The goal of successful targeting is to bind drugs to receptor complexes that are expressed at the target site. Through factors like pH, temperature, molecular site, and shape, the prepared drug carrier complex is directed to the target site as it circulates through the bloodstream. Cell membrane receptors, lipid membrane components, and cell surface antigens or proteins are the primary targets in the body. Currently, cancer therapy and prevention account for the primary focus of medication delivery systems facilitated by nanotechnology. Significant progress has been made in the development of delivery systems to transport medicinal agents or active chemicals derived from natural sources to their intended sites of action in the treatment of various ailments. Although numerous medication delivery systems have been put into place with great success in recent years, there are still a number of issues that need to be fixed and new infrastructure that needs to be created before drugs can be distributed to their intended populations. Research into nano-based drug delivery systems is ongoing to pave the way for the creation of a more complex drug delivery system.

Principles and Practices of Drug Development and Discovery

Potential novel therapeutic entities are uncovered through the drug discovery process. Despite advancements in biotechnology and our increased understanding of biological processes, the drug discovery process remains painfully lengthy, prohibitively expensive, convoluted, and wasteful. With the understanding of a biological target, drug designers can creatively discover new therapeutic agents. Drug design, at its most fundamental, entails the creation of molecules that interact with and bind to a molecular target by virtue of their shape and charge being complementary to that target. In the age of big data, computer modelling methods and bioinformatics approaches are often used but not required in the design of drugs. Increases in affinity, selectivity, and stability of these protein-based therapeutics [3] have been achieved in large part through the use of computational methods, making biopharmaceuticals and therapeutic antibodies an increasingly important category of medicines. Clinical trials in humans are the final stage of medication development and discovery after extensive testing in cell-based and animal models. After hits are identified by screening, they are subjected to medicinal chemistry in order to increase their affinity, selectivity, efficacy/potency, metabolic stability (to lengthen the half-life), and oral bioavailability. When a

molecule meeting these criteria has been found, medication development leading up to clinical trials can commence. An extensive docking investigation of autotaxin was published by Dimitra Hadjipavlou-Litina and colleagues in their publication "Boronic Acid Group: A Cumbersome False Negative Case in the Process of Drug Design". They discovered that vast virtual libraries of boronic acid derivatives do not dock in a natural fashion when tested in a virtual screening environment. Both the binding poses and the values of the scoring function that would normally be used to identify them as positives are ignored. The authors were able to more precisely characterise the generated binding between Ser/Thr residues as a polar covalent bond by using natural bond orbital calculations, as opposed to a simple nonpolar covalent bond. This article presents work that employs computational screening of chemical libraries rich in boron to identify potential leads for new medication designs.

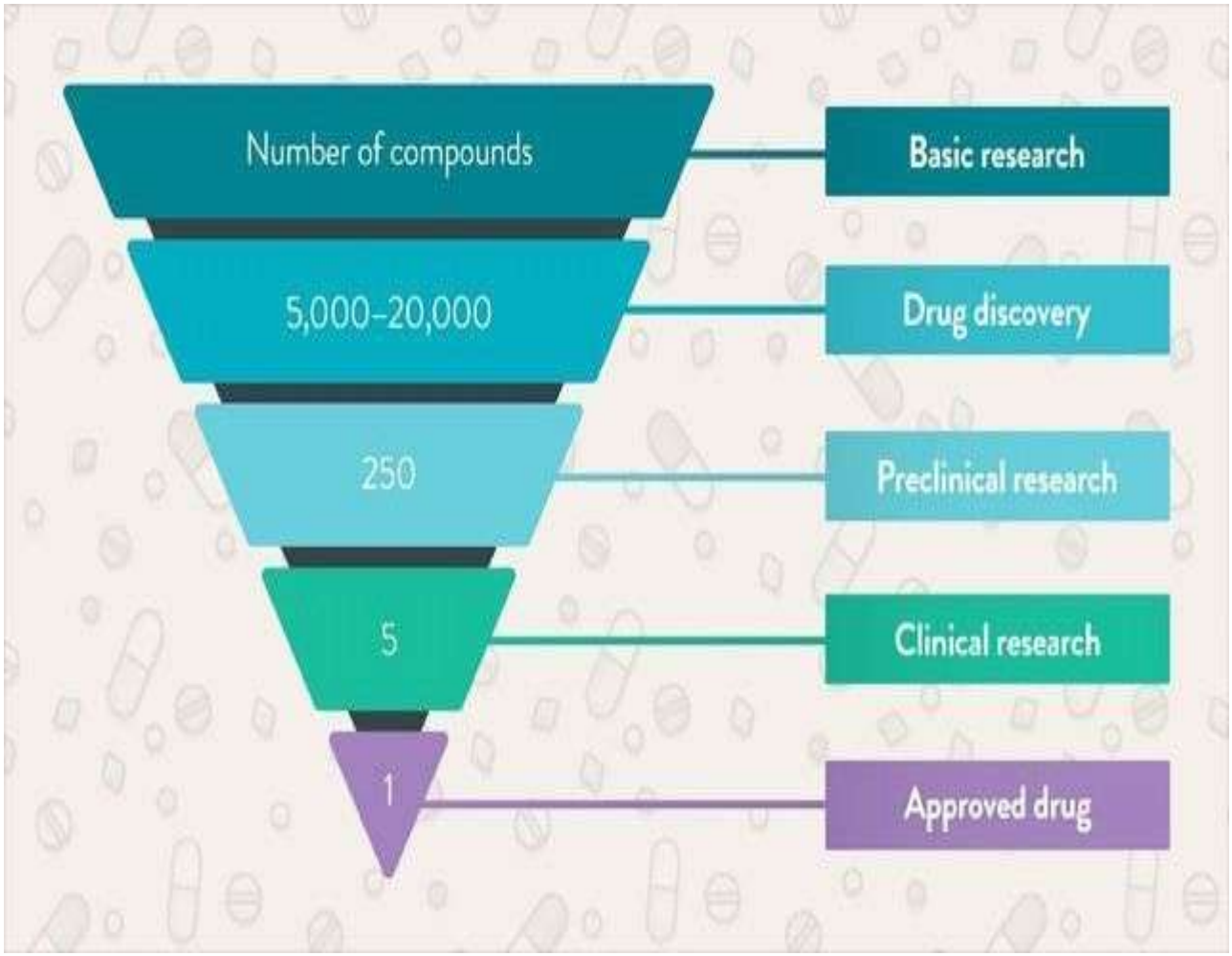

Fig 2:- Drug discovery timelines.

The anti-proliferative activity and cellular uptake of two promising anti-tumor drug candidates, evodiamine (EVO) and rutaecarpine (RUT), were evaluated in 3D multicellular spheroids and compared with those obtained from 2D monolayer cultures of MCF-7 and SMMC-7721 cells by Feng Xu and colleagues (Antiproliferative Activity and Cellular Uptake of Evodiamine and Rutaecarpin Using 3D multicellular spheroids and the fluorescence of chemicals, the researchers gained a novel perspective on the anti-tumor activity of EVO and RUT, which they believe could be valuable for drug screening and cytotoxicity studies.

Malaria is a serious public health issue in parts of sub-Saharan Africa, Southeast Asia, and South America. In the absence of an effective malaria vaccine, the need for constant research into novel antimalarial drugs is especially pressing due to the toxicity and possibility for drug resistance associated with the use of aminoquinolines over extended periods of time. Rizk E. Khidre and colleagues set out to create and evaluate a new class of quinoline

compounds for their ability to combat malaria. Their findings are described in the book New Potential Antimalarial Agents: Design, Synthesis, and Biological Evaluation of Some Novel Quinoline Derivatives as Antimalarial Agents.

In their publication titled "Novel (E)—Farnesene Analogues Containing 2-Nitroiminohexahydro-1,3,5-triazine," Xinling Yang and coworkers discuss the introduction of a series of such analogues by replacing the conjugated double bonds of EF with 2-nitroiminohexahydro-1,3,5-triazine. Conjugation and In bioassays against the green peach aphid, several analogues shown a wide range of repellant and aphicidal effects (Myzus persicae). In addition, they performed early structure-activity relationship (SAR) research, which revealed instructive hints for the creation of novel EF analogues.

In an effort to identify prodrug analogues of clopidogrel with improved metabolic properties and antiplatelet bioactivity, Yan Yang, Jingkai Gu, and colleagues synthesized and evaluated a series of clopidogrel related vicagrel analogues selectively group refers at the benzylic methyl ester group. Research on the compounds' ability to suppress ADP-induced platelet aggregation and the pharmacokinetics from rats following oral dose are described in "Significant Improvement in Metabolic Characteristics and Bioactivities of Clopidogrel and Analogs by Selective Deuteration".

As a non-invasive method of drug delivery, intranasal administration is gaining a lot of attention. Since the respiratory mucosa is so delicate, not only the active substances but also the additives must undergo toxicity testing in suitable models. In order to increase the residence time, the permeability, and the solubility dissolving rate of pharmaceuticals, Rita Ambrus and her colleagues investigated the cytotoxicity of six pharmaceutical excipients. Sodium hyaluronate at 0.3 percent and polyvinyl alcohol at 1 percent were found to be safe for use in nasal formulations, as was reported in the communication titled "Cytotoxicity of Different Excipients on RPMI 2650 Human Nasal Epithelial Cells".

Proteins in the epididymal luminal fluid were analysed by Li-Juan Qu, Yan Zhu, and colleagues in order to determine the effects of dutasteride, a dual 5-reductase inhibitor, on sperm maturation in infertile rats. This research could lead to the development of more effective contraceptives and treatments for infertility. Their research is the first to demonstrate that dutasteride modifies the protein expression profiling in rat luminal fluids, which they argue identifies new epididymal targets for male contraceptive and infertility therapy. The study's results were published under the title "Identification of New Epididymal Luminal Fluid Proteins Involved in Sperm Maturation in Infertile Rats Treated with Dutasteride using iTRAQ."

According to the paper "Synthesis and Evaluation of Ester Derivatives of 10-Hydroxycanthin-6-One as Potential Antimicrobial Agents," Jun-Ru Wang and colleagues have been investigating a new series of ester derivatives of 10-hydroxycanthin-6-one utilising a simple and effective synthetic method. They performed a structure-activity analysis, described the antibacterial properties of each molecule, and settled on a candidate chemical that was effective against all of the tested bacterial and fungus strains. Chun-Mei Jin, Zhe-Shan Quan, and collaborators wrote a paper titled Synthesis and Biological Evaluation of Novel Benzothiazole Derivatives as Potential Anticonvulsant Agents. Due to the urgent need for the development of more effective antiepileptic drugs with an enhanced safety profile, the authors investigated new benzotriazoles with mercapto-triazole and other heterocycle substituents and tested the anticonvulsant activity and neurotoxicity of each compound using maximal electroshock, subcutaneous pentylenetetrazole, and rotarod neurotoxicity tests. The accompanying article elaborates on their findings. Non-steroidal anti-inflammatory medications (NSAIDs) are first-line treatment for inflammation and pain. However, its use is associated with a number of drawbacks. In order to lessen these risks, Ahmed M. Gouda and coworkers synthesised a series of N-(4-bromophenyl)-7-cyano-6-substituted-H-pyrrolizine-5-carboxamide derivatives as dual COX/5-LOX inhibitors and tested them on animals and humans. Their findings suggest that these novel pyrrolizine-5-carboxamide compounds can serve as a starting point for developing more secure dual COX/5-LOX inhibitors, which could have far-reaching medical applications. Check out their work titled "Design, Synthesis, and Biological Evaluation of Some Novel Pyrrolizine Derivatives as COX Inhibitors with Anti Inflammatory/Analgesic Activities and Low Ulcerogenic Liability" to learn more about their findings.

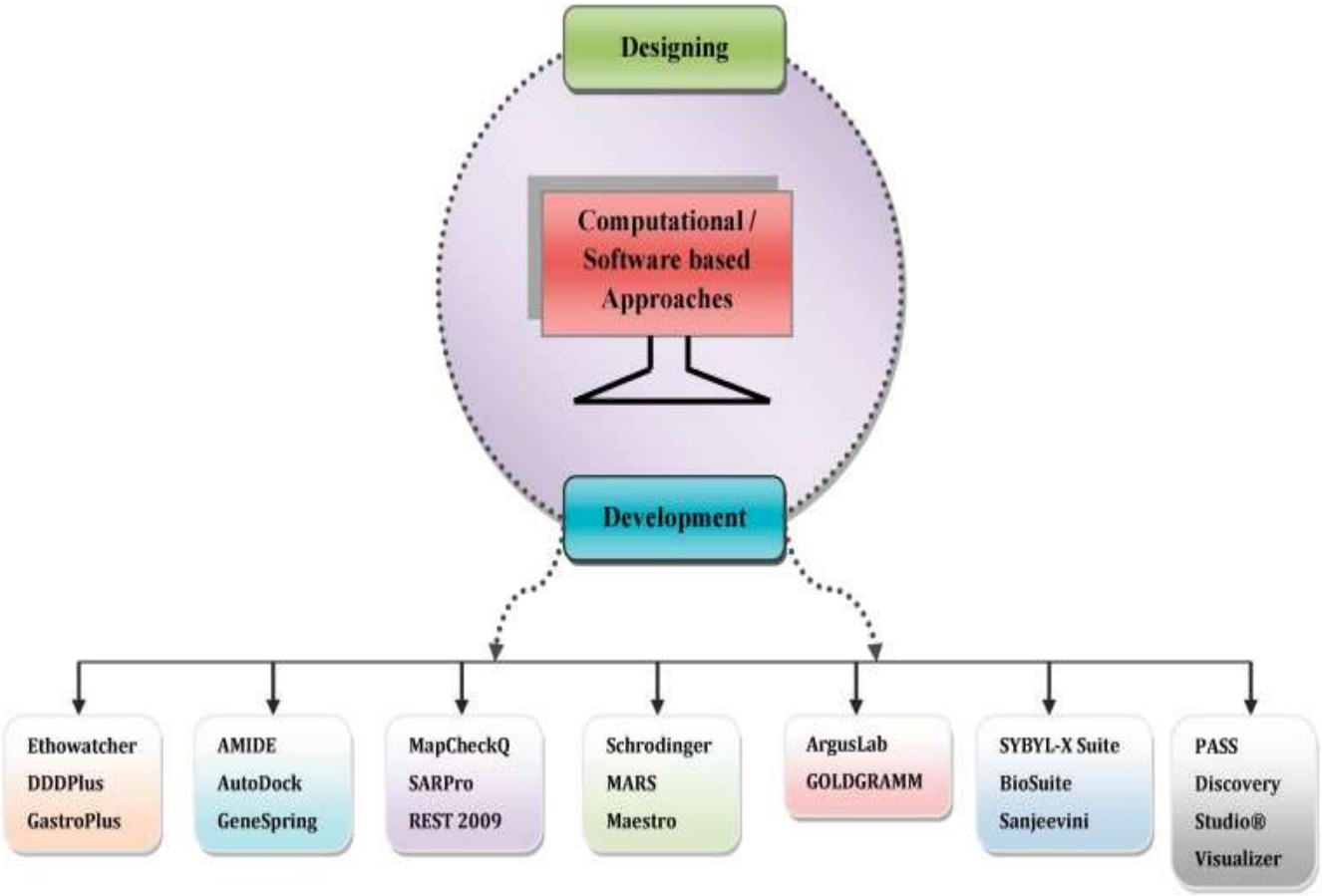

Fig 3:- Methods in medication development and design that depend on computer systems.

Finding tiny, highly selective molecules that bind to a therapeutic target with high affinity is the most important part of the drug development process. An inexpensive machine learning approach to performing compound selectivity classification and prediction was proposed by Hany E. A. Ahmed and colleagues in their article "Self Organizing Map-Based Classification of Cathepsin k and S Inhibitors with Different Selectivity Profiles using Different Structural Molecular Fingerprints: Design and Application for Discovery of Novel Hits". They compiled a selective database of 153 compounds that inhibit cathepsin K and S and were found to be active in previous studies to create a medicine of interest. The results showed that the approach could be used to build more highly active and selective inhibitors for other targets. Although nephrotoxicity is a well-known side effect of the routinely prescribed antibiotic vancomycin, its molecular targets and underlying processes are not well understood. For a more holistic and integrative understanding of vancomycin's effect, Zhi-Ling Li and Shu-Feng Zhou investigated its molecular targets in HK-2 cells derived from human proximal tubule epithelium, with a particular emphasis on the cell cycle, apoptosis, autophagy, and epithelial to mesenchymal transition (EMT) pathways. Utilizing a quantitative SILAC-based proteomic approach, we discovered that vancomycin affected a wide range of critical functional proteins and related molecular signalling pathways in HK-2 cells, thereby influencing cell proliferation, the mitochondria-dependent apoptotic pathway, autophagy, and EMT. By better identifying molecular targets and clarifying the underlying mechanism of vancomycin-associated nephrotoxicity, this study shows promise as a first step toward greater treatment effect and reduced side effect in clinical settings. In "A SILAC-Based Approach Elicits the Proteomic Responses to Vancomycin-Associated Nephrotoxicity in Human Proximal Tubule Epithelial HK-2 Cells," the researchers detail these findings in greater detail.

Protein-protein interactions and their binding sites are a crucial part of understanding the networks in living organisms. With the deluge of protein sequences being generated in the postgenomic era, it is critical that computational methods for identifying protein-protein binding sites (PPBSs) based on the sequence information alone be developed as soon as possible. This information can be used in biomedical research and drug development.

To address this issue, Jianhua Jia, Bingxiang Liu, and colleagues created iPPBS-Opt, a novel predictor that uses the concept of pseudo amino acid composition (PseAAC) to generate protein sequences that are difficult to predict. While the PseAAC has been used to build protein sequences in the past (for example, see), this is the first time the stationary wavelet transform technique has been applied to reflect the roles of low-frequency phonons in proteins, which were deduced roughly 40 years ago.

Article: "Synthesis of Canthardin Sulfanilamides and Their Acid Anhydride Analogues via a Ring-Opening Reaction of Activated Aziridines," by Mei-Hsiang Lin et al., discusses the synthesis of these compounds as well as their pharmacological properties. A new class of anticancer compounds was discovered through the interaction of activated aziridine ring opening on cantharidinimide. The most potent cytostatic compound, N-cantharidinimido-sulfamethazine, was shown to be toxic to both HL-60 and Hep3B cells. The results of their extensive investigation are presented in this article.

Chemical structure-related drug-like criteria of globally approved drugs is the title of an article written by Jian Li and coworkers. They discovered two things: 1) the ideal ratio of aromatic to non-aromatic rings is 2:1, and 2) the most promising functional groups for potential novel drugs are -OH, -COOR, and -COOH, in that order, whereas -CONHOH, -SH, -CHO, and -SO3H are less promising options. Thirdly, the R value of potential CNS treatments should be as low as possible within the range of 0.05–0.50 (preferably 0.10–0.35), which is the preferred range for candidate medications. According to the authors, the three chemical structure-related criteria can be used prospectively in the search for new drug candidates and will serve as a theoretical foundation for the development of novel chemical entities with desirable drug-like qualities.

Using phenylhydrazine and ethyl 3-oxobutanoate as starting materials, Jin-Xia Mu, Xing-Hai Liu, Bao-Ju Li, and coworkers synthesised a wide range of novel pyrazole amide derivatives to identify potent pyrazole amide molecules. They described the structures and antifungal activities of the compounds after performing DFT simulations to study structure-activity relationships. Some of the compounds with the title showed some mild antifungal activity, as reported in their paper titled "Design, Synthesis, DFT Study, and Antifungal Activity of Pyrazolecarboxamide Derivatives."

The eighteen articles in the special issue "Drug Design and Discovery: Principles and Applications" highlight these principles and applications, ranging from computer-aided drug discovery and development to drug design and synthesis approaches to pharmacological and toxicological evaluations in vitro and in vivo. While making important theoretical and methodological contributions, these studies also provided a wealth of useful tools for the pharmaceutical sector. These studies' findings showed that enhanced pharmacological, pharmacokinetic, and toxicological properties of lead candidates can be found in the drug development process by combining in vitro and in vivo research with computational methodologies.

Delivery medications via nanotechnology and biological products

Herbal remedies derived from plants have a long history of usage in traditional medicine. In the pharmaceutical industry today, natural products or their derivatives account for around a third of the top sellers. 1–3 Though many modern pharmaceuticals have their origins in natural ingredients, big pharma has not given them the attention they deserve. Natural goods had enormous success in the years following World War II as antibiotics, and the two concepts have become synonymous. This may account for the lack of interest. 1 Smaller pharmaceutical firms are beginning to investigate the potential of natural products for treating cancer, microbial infections, inflammation, and other disorders, while larger pharmaceutical firms have traditionally preferred screening synthetic compound libraries for drug discovery. 4,5 The main concern with using natural compounds in illness treatment is their poor bioavailability, which has hampered clinical trials. Oral administration of curcumin in 5 subjects resulted in blood concentrations of 11.1% nmol/L only when the dose was 3.6 g/day. Patients given smaller doses of curcumin had undetectable quantities of the compound in their blood plasma. Similar findings have been seen for other widely used natural compounds as polyphenols and flavonoids. In the realm of drug delivery, nanotechnology has shown to be an outstanding success. There has been much discussion on what constitutes a nanoparticle, but no consensus has yet been established on a universal definition. Particles between 1 nm and 100 nm in size are often considered nanomaterials according to many different sources. Although size is an important factor, there is more to the concept of a nanomaterial than that. The varied features and interactions at the nanoscale structure are the source of nanotechnology's advantages. Thus, particles larger than 100 nm can be deemed nanomaterials due to their ability to display these novel characteristics. Examples of suitable delivery systems include polymer nanoparticles with

diameters between 10 nm and 1 m. 5,11 Polymer nanoparticles, solid lipid nanoparticles (SLNs), crystal nanoparticles, liposomes, micelles, and dendrimers are the most widely utilised nanoparticles for drug delivery (Figure 1A). As a vehicle for transporting drugs, each of these nanoparticles comes with its own set of pros and cons.

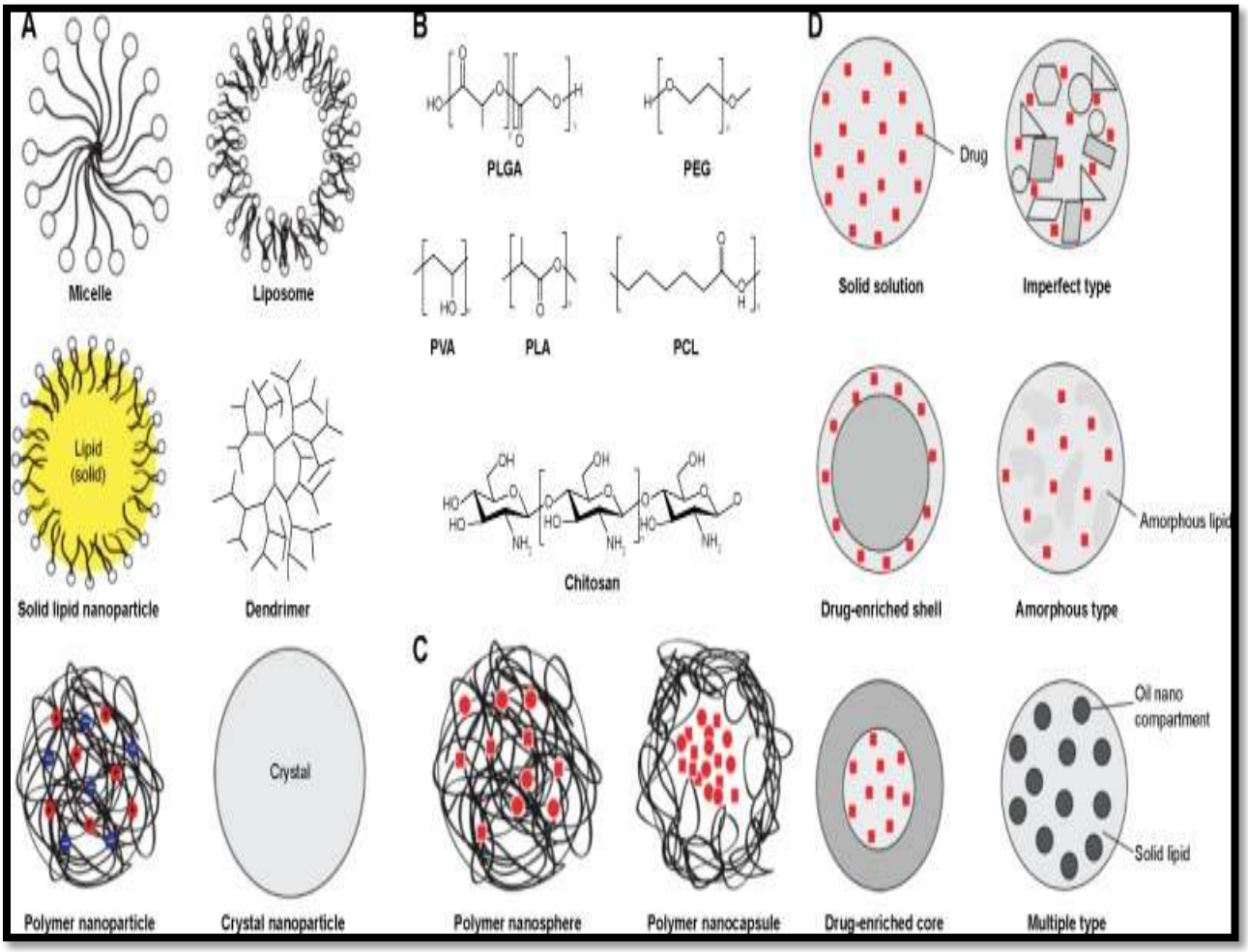

Fig 4:- Schematic depictions of nanoparticles. A) Schematic depictions of the most prevalent nanoparticle classes. Some polymer nanoparticles have charges, and they are shown by red and blue circles. (B) The typical chemical make-up of polymer nanoparticles. (C) Illustrations of the contrasting polymer nanoparticles. Red signifies pharmaceuticals included. Types of nanostructured carriers (right) and drug-incorporation models in solid lipid nanoparticles.

One type of natural product-based material is used to treat a variety of ailments by being delivered to specific places where it can do its work, while another type is used mostly in the synthesis process. Since cancer is currently the leading cause of death around the world, the vast majority of research efforts are focused on finding effective treatments for the disease. Researchers nowadays are focusing primarily on developing nanomedicine to specifically target malignant cells due to the widespread nature of the disease's effects. However, a variety of other applications of nanomedicine to other disorders are also in development. Surface charge, particle size, size dispersion, shape, stability, encapsulation potential, and biological activity all play a role in classifying these delivery systems so that they can be used most effectively. Figure 5 describes the nanomedicine applications of some biological substances extracted from higher plants. The pharmaceutical industry has always been interested in exploring new technological possibilities for the creation of cutting-edge medicines and the improvement of existing ones. New formulations have been developed thanks to the rapid progress of nanotechnology in areas like drug delivery (nanopharmaceutics), imaging and diagnostics (nanodiagnostic), implantable medical materials (nanobiomaterials), and combined diagnosis and treatment of diseases (nanotheranostics)

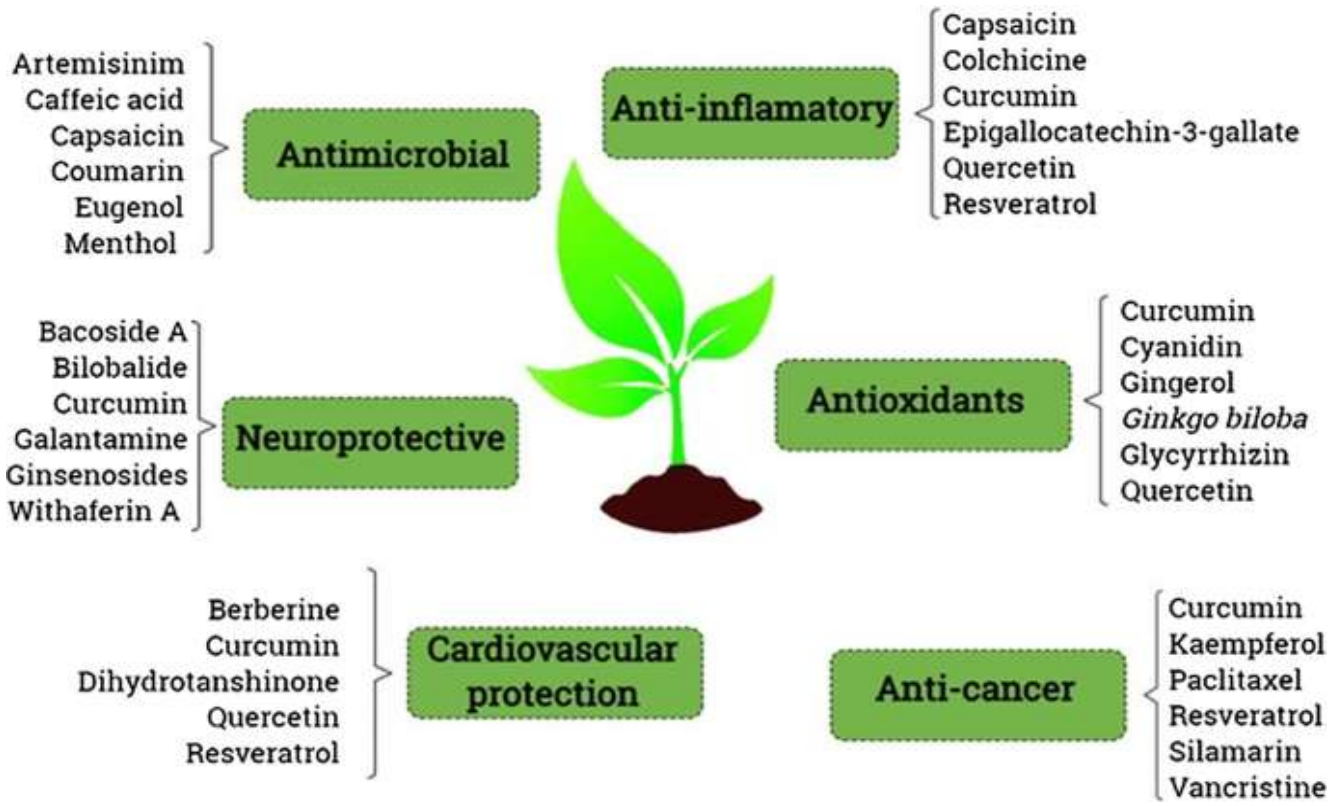

Fig 5:- Natural chemicals isolated from higher plants utilised in nanomedicine with various goals as examples. The scientific community is actively studying some of these extracts while others are already on the market or in clinical trials.

Regulation of nanotechnology and market availability of goods produced

The process of creating new drugs and getting them approved can take up to twenty years if it continues at the current rate. Having enough qualified scientists and medical professionals who are willing to devote at least ten years of their lives to a single project is one of the criteria that a project needs to meet in order to attract investors. Other criteria include having a novel scientific premise that has sufficient intellectual property protection and having a convincing economic business plan. It is necessary to do an exhaustive analysis of the needs of the market, and the ratio of potential rewards to potential dangers must be satisfactory. Additionally, there is a need for greater information regarding the distribution of therapeutic medications as well as the duration of their effects. Intellectual property, technological issues, general costs, and the ethics and regulatory matters associated with the topic are briefly treated here as some of the most essential steps along the method. This is because these are some of the most critical steps along the route. Evaluation of the market by industry professionals is essential for determining the needs of the market as well as the opportunities it presents, both of which may be utilised to lessen the likelihood of failure.

From laboratory to market

To protect the efforts of researchers and businesses, avoid expensive legal fights, and ensure a return on investment, patents should be filed at every stage of the medicine development and commercialization process. The maximum period of patent protection is only 20 years (varies by country), reducing the period of commercial exclusivity to 12 years or less. This is due to the lengthy process of obtaining regulatory permission, completing clinical studies, and releasing a new pharmaceutical to the market. Because of this, the maximum period of patent protection is only 20 years. The window of opportunity for the company to turn a profit is small, and it is not always in a position to take the necessary risks. In light of the additional complexities that are presented by nanopharmaceuticals, the government is obligated to take action regarding this problem. When one takes into consideration the ethical concerns, the economic impact of the clinical trials on the total cost of creating nanopharmaceuticals, the problem of preclinical in vivo studies on animals, and the issue of human clinical trials, extending the duration of market exclusivity for a longer period of time is justifiable.

Techniques

Larger firms has the resources necessary to take a pharmaceutical from its development stage in the laboratory to its sale on the market. The funding comes from investors and the sale of pharmaceuticals that are already on the market. Meanwhile, scientists and engineers work on the research, and engineers and attorneys design production methods and handle the filing and defence of patents. In addition, the possibility of suffering a loss is mitigated by the fact that the research carried out on nanomaterials likely accounts for a negligible part of the total assets held by these businesses. On the other hand, small start-up enterprises might not be able to fund expensive nanopharmaceutical projects due to the processes and resources that were described above. In academic labs, where preliminary research is frequently financed by grants from the government and, as a result, has minimal overhead costs, many of these enterprises receive their start. However, large pharmaceutical companies can also profit from government backing, particularly for the treatment of so-called "orphan diseases." Big companies sometimes purchase out the smaller companies that are working on revolutionary nanoformulations. This provides the researchers with the funding they require to move on to larger and better things, while also allowing the companies to make a quick buck. When compared to other industries, the nanopharmaceutical industry may not be able to make the trade-off between quality and economy. Substantial amounts of time and resources must be committed in order to guarantee acceptable quality assurance in the pharmaceutical market.

Costs

Lifecycle costs for any new drug (including nanopharmaceuticals) include the initial idea and preclinical research (which is typically conducted in academia and funded by the government and tax payers), industrial development, the "valley of death," which includes the period of highest expenses for human clinical trials and finally gaining regulatory approval, and the phase of commercialization and marketing of the drug. A recent study conducted by the Tufts Center for the Study of Medication Development estimated that the total cost to get from the beginning of drug development to the point when the drug is profitable (excluding advertising and special marketing expenses) is approximately $2.87 billion. This estimate does not include the costs associated with special marketing or advertising the drug (in 2013 US dollars). The clinical trials phase of producing a product that is authorised by the FDA can cost anywhere from around $1012 million to $1,744 million. After taking into account the effects of inflation and discount rates, as well as the length of time it takes to bring a product to market and the possibility that any linked patents will expire, the total cost comes out to $2558 million. After a drug is released onto the market, the research costs that are incurred can be added to the cost of the next drug that is in the development stage. Bear in mind that these high prices not only account for the money invested, but also the time and effort that was spent on projects that were ultimately abandoned. The Washington Post asserts that the organisation that published the report received money in part from pharmaceutical manufacturers. This raises worries that the data are biassed and may have been inflated in order to justify the high cost of drugs to individual consumers. Because the pharmaceutical classes that were chosen for this study were not mentioned, it is possible that the conclusion is incorrect. This is despite the fact that 80–90 percent of drugs ultimately fail to receive final approval after clinical trials (with an actual estimate of 11.8 percent success rate). Budgets for research that is financed by the government or by private organisations are not included, nor are tax advantages or subsidies. Given the large percentage of abandoned projects, the ever-increasing costs associated with manufacturing a novel medication are, to some extent, comprehensible. This is of utmost significance because of the one-of-a-kind characteristics that nano pharmaceuticals possess. When developing novel nano pharmaceuticals, it is of the utmost importance to keep in mind the aforementioned legal, ethical, and cost-management procedures. Despite the fact that the high rate of failure has dissuaded some large companies from investing in this sector, opportunities still exist for researchers and businesspeople to capitalise on. The commercialization of authorised nano pharmaceuticals, given their superior efficacy, may lead to substantial profits if they are successfully brought to market.

Ethics

It is important to take ethical concerns into account while developing regulatory frameworks for nanopharmaceuticals. Regrettably, there is frequently a dearth of awareness regarding the safety profile and potentially detrimental effects of these products (on patients, production workers, and the wider environment). It is essential to perform a cost-benefit analysis on the potential outcomes. Due to the absence of a framework or clearly articulated norms for the evaluation, the investigation of this ratio itself presents its own unique set of difficulties. Because of this, decisions need to be made based on inaccurate premises and difficult-to-estimate risks connected with each specific case and type of patient. Patients who participate in the majority of human clinical trials (especially those for cancer) are typically at an advanced stage of their condition and have very few or no other treatment choices open to them at this point. Therefore, it is essential for the people running the experiment to fully

explain the procedures (informed consent), and they must also be careful not to raise the patient's expectations beyond what is reasonable. It is essential for the sake of patients' confidence to notify them about the existence of NPs in the treatment, despite the fact that doing so may reduce the possibility of them signing the consent forms. This is because some stakeholders are hesitant to use the word "nano," but doing so is essential for the sake of patients' confidence. In spite of this, the ethical considerations that need to be made for these clinical studies of nanopharmaceuticals are the same as those that need to be made for any clinical study of a novel drug. Because it is ultimately up to the patients to determine whether or not they want to take a risk, it is the role of regulatory bodies to analyse how the benefits compare to the potential downsides. It is recommended that these organisations seek advise from data safety monitoring committees, stakeholders, and outside experts in addition to receiving it from the government. It is essential that every precaution be taken to avoid giving in to public pressure that is overly cautious about the potential dangers posed by nanopharmaceuticals (and that can even be outright untrue), which would put an end to the research and development of these medications completely. It is not only the safety of the patients themselves that is important; the safety of anybody who comes into contact with the nanomaterial, such as the staff and family members, should also be investigated and dealt with in an ethical manner.

Regulations for approving nanopharmaceuticals (FDA rules & regulations)

A paper defining restrictions for nanopharmaceuticals was just just made available by the Food and Drug Administration (FDA) (or the category of nanomaterials in general). On the other hand, in August of 2016, a document was produced that included broad legislation for all nanomaterial goods related to cosmetics, food additives, and animal feedstuff. These laws were intended to cover nanomaterials. The Food and Drug Administration is not yet completely persuaded that the behaviour of nanopharmaceuticals is significantly distinct from that of other small-molecule drugs, which is why there is no specific regulation in place for these products (save for certain characteristics). Research indicates that nanomaterials are distinct from their bulk counterparts not only in terms of size and surface area, but also, and perhaps most importantly in the context of therapeutics, in terms of biodistribution, toxicity, pharmacokinetics, and excretion characteristics. Rather than this, the research suggests that nanomaterials differ from their bulk counterparts not just in terms of size and surface area. Because of the materials' variable behaviour in a variety of settings, the testing methods that are now in use are unable to provide conclusive answers to the following questions about nanopharmaceuticals (particularly in vivo). Because of this, companies are required to conduct extensive testing of their innovative drugs before filing an application for regulatory approval. This presents a difficulty for the industry. It is necessary to investigate the prospective applications of each pharmaceutical component. A treatment that is administered intravenously to a patient would have to be tested in the blood of the patient, whereas a pill would have to be evaluated in solutions that are intended to replicate the digestive tract. The classification system that the FDA uses for pharmaceuticals is one example of such a dilemma. Different groups of items, such as pharmaceuticals, medical devices, blood products, biologic agents, and others, are each governed by their own unique sets of FDA regulations. The criterion that is utilised for the categorization of combination materials is referred to as the "primary mode of action." If, for instance, nanoparticles or nanotherapeutics are incorporated into a prosthetic bone cement, then the latter can be categorised as both a device and a drug. This is just one example. When it is uncertain what the major mode of action of a product is, the product is forwarded for evaluation to the Office of Combination Products. When conducting a safety analysis, researchers are required to take into account not just the possible threat that nanopharmaceuticals offer to human health, but also the influence that these compounds may have on the natural world. The interactions that occur between different nanomaterials have been identified by researchers as the primary source of concern; pristine samples render their evaluations meaningless. The United States National Research Council has decided to develop a new strategy for environmental risk assessment, primarily based on the "key aspects of nanomaterial interactions," in order to address the potential environmental dangers and public hazards posed by nanoparticles. This decision was made in order to address these potential risks. It's vital to keep in mind that nanomaterial research is still in its infancy despite the fact that bringing a new drug to market could take anywhere from ten to twenty years. Because of this, it is required to continue post-market surveillance even after receiving clearance from the FDA. This is due to the fact that the full repercussions of long-term exposure on humans, animals, and the environment have not been determined. The usage of nanomaterials and nanosimilars brings up an additional intriguing question regarding "nonbiological complicated drugs," which are complex structures in and of themselves. It is strongly recommended that the Food and Drug Administration (FDA) and other organisations of a similar nature keep and improve the regulatory frameworks they have in place for these chemicals. Many patients already make consistent use of the numerous nano-based drugs that have just very recently become available on the market (Fig 6). These products, which are manufactured by businesses located all over the world, serve as evidence of the existing and (most likely) upcoming success of nanoparticles as therapeutic agents. In the following, we will classify some of the most well-known nanopharmaceuticals according to the sort of nanoformulation they employ. These categories include not just

nanoparticles (NPs), but also liposomes and lipid-based systems, polymeric systems (including pegylated biologics, gels, and emulsions), protein-based systems, and metallic NPs.

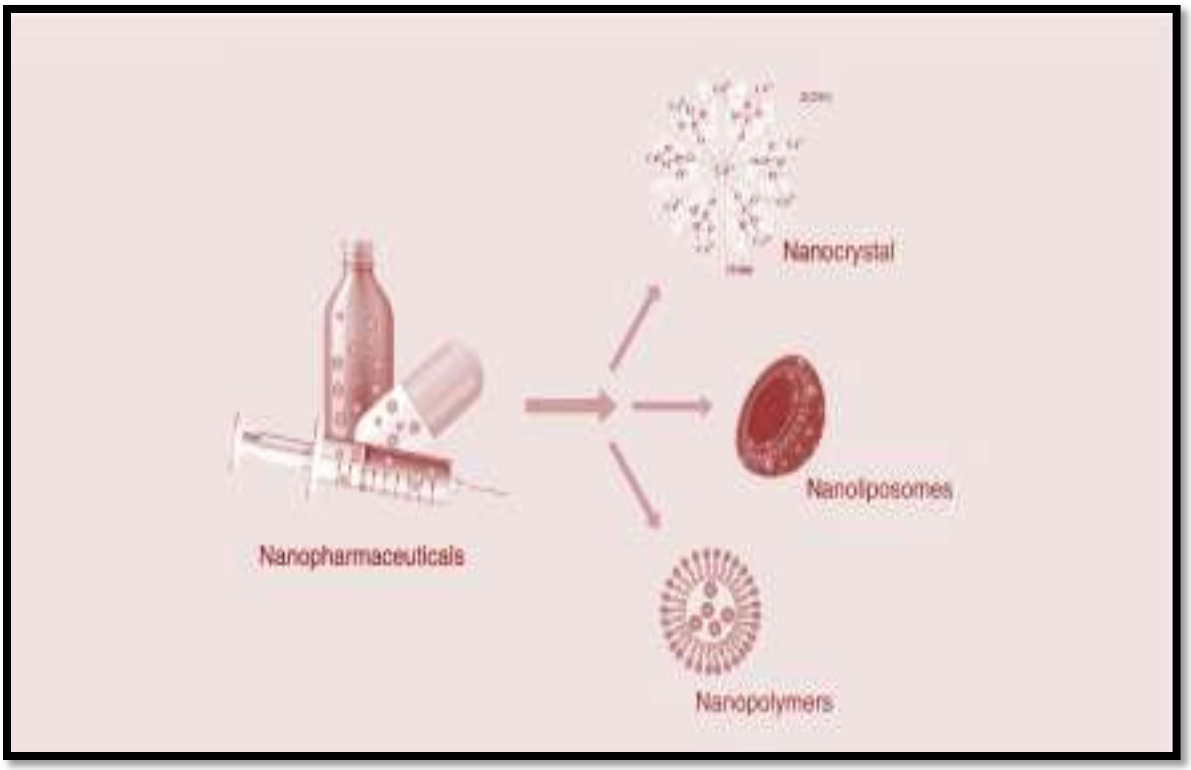

Fig 6:- This diagram shows a simplified representation of three types of nanopharmaceuticals currently on the market.

Conclusion:-

This article provides a summary of recent advancements in the field of nanomedicine. Topics covered include innovative methods for the delivery of medication as well as cutting-edge diagnostic procedures. Nanorobots and nanosensors are just two examples of the nano-scale materials that have been described for their potential to diagnose, transport precisely to targets, sense, or activate components in a real-world system. Other examples of these nano-scale materials include quantum dots, carbon nanotubes, and graphene. The pharmaceutical industry was one of the first to use nanotechnology, which was utilised to improve the delivery of medications at the time of its adoption. Even though there are many unknowns in the process of developing nanodrugs and the search for pharmacologically active compounds in nature is less of a priority today than it was fifty years ago, it is now common practise to use nanotechnology to enhance the efficacy of natural bioactive compounds that have already been established. Therapeutic applications of nanotechnology include berberine, curcumin, ellagic acid, resveratrol, and quercetin, among others; nevertheless, this list is not exhaustive. Nanocarriers such as gold, silver, cadmium sulphide, and titanium dioxide polymeric nanoparticles, solid lipid nanoparticles, crystal nanoparticles, liposomes, micelles, superparamagnetic iron oxide nanoparticles, and dendrimers have been incorporated into these natural remedies, which has significantly increased their efficacy. Unique natural biomaterials are in high demand because they have a variety of desirable properties, some of which are biodegradability, compatibility with living beings, abundance in nature, renewability, and low toxicity. In addition, novel natural biomaterials are abundant. Recognizing natural biopolymers, such as polysaccharides and proteins, and developing techniques, such as crosslinking, to make them more stable in industrial processing settings and biological matrices are at the forefront of current scientific inquiry. This is because of the importance of natural biopolymers in a variety of applications. There are a variety of methods available for the production of polymeric nanoparticles, including emulsion polymerization, solvent evaporation, and surfactant-free emulsion polymerization, to name a few (nanocapsules and nanospheres). Since the 1990s, the FDA has given the go-ahead for a wide array of goods and clinical studies based on nanotechnology. Some of them include protein nanocrystals, nanocrystals, synthetic polymer particles, and

liposome formulations. The process of medication discovery and delivery in biological systems has already been transformed as a result of nanotechnology. Future research will focus on refining the regulatory mechanisms that are already in place as well as undertaking more comprehensive toxicity and risk evaluations. This is all because to nanomedicine, which has made it possible to diagnose diseases and has combined the process of diagnosis and therapy into a single step.

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