

Drug repurposing novel approach for treatment of rheumatoid arthritis

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Abstract: The approach of using existing drugs originally developed for one disease to treat other indications has found success across medical fields. Many of drug repurposing promises faster access of drugs to patients while decreasing costs in the long and difficult process of drug development. but, the number of active drugs and diseases, in concert with the heterogeneity of patients and the diseases, notably including cancers ,rheumatoid arthritis can make repurposing time consuming and inefficient. The identification drug repositioning targets through computational methods and experimental method has the potential to provide a fast, inexpensive alternative to traditional drug discovery process. Finally, challenges and opportunities in drug repositioning are discussed from multiple perspectives, including technology, commercial models, safety, patents and investment.

Keywords: Drug repurposing, Rheumatoid arthritis, Network based, Artificial intelligence.

Introduction:-

Drug repurposing, also called as old drugs for new use, is an effective strategy to find new indications for existing drugs and is highly efficient, low-cost and risk less. Traditional drug development strategies usually include five stages: innovation and preclinical or the clinical investigate, safety review, and FDA post-market safety monitoring. There are four steps in drug repositioning: compound identification, development and FDA review, compound achievement.[1,2].

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by joint synovial tissue inflammation associated with disability of affected joints[3] . the treatment of RA mainly rests on the use of disease -modifying antirheumatic drugs, and has improved outcomes in RA patients significantly .Despite significant therapeutic advances in improving the lives of RA patients ,RA remains a hard clinical problem because of the accumulated and persistent disease[4,5].

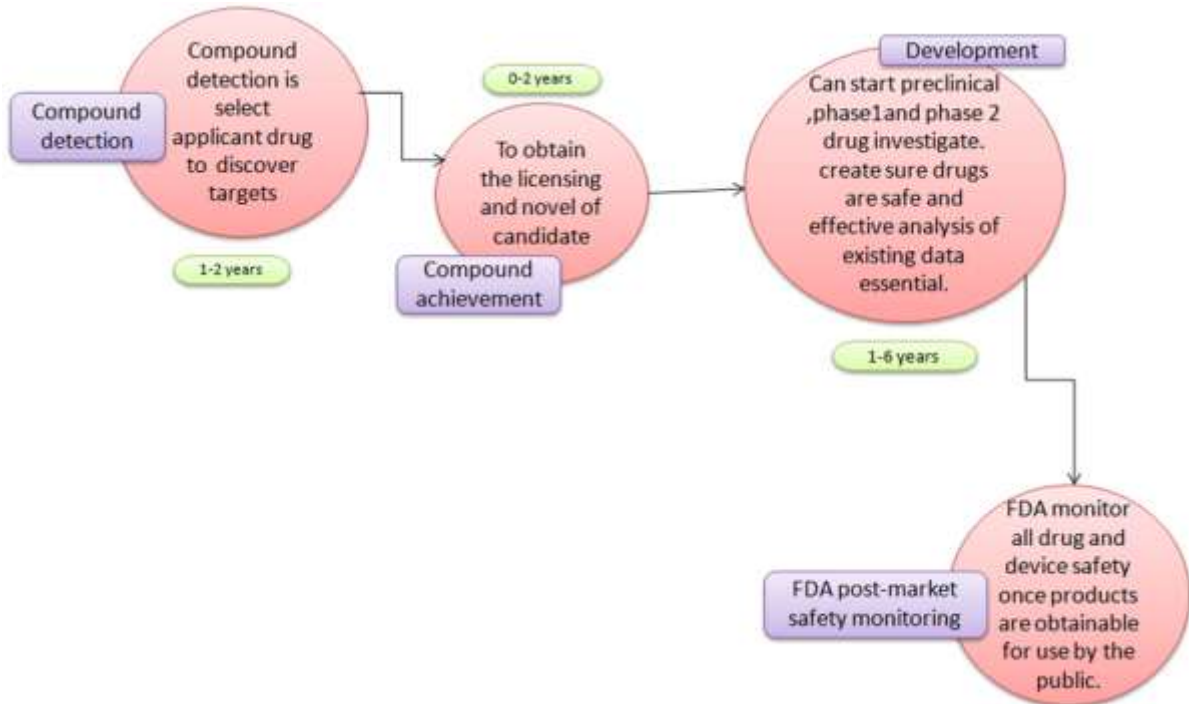
The administration of RA patients needs new drugs for protective orcurative therapies. In the current review article, we are focusing on cancer drugs repurposing for rheumatoid arthritis. Studies emphasizing the emerging role of cancer therapies for usage against rheumatoid arthritis is a verdict for our decision. This review provides a foundation upon which further research can be implemented on the use of cancer drugs in rheumatoid arthritis. [6]

Drug repurposing:-

The main issue in drug repurposing is the detection of novel drug-disease relationships. To address this subject, a variety of approaches have been developed including three main approaches computational approaches, biological experimental approaches and mixed approaches. drug repurposing has major consideration from the pharmaceutical companies industry and research institutes. Relative to the traditional drug development process, drug repurposing repositioning replenishes the drying out drug pipelines by reusing marketed drugs and clinical candidates for new uses, such as treating another disease[7].

These repurposed drugs with identified bioavailability, safety profiles and well consider pharmacology can enter clinical trials for alternative indications more rapidly and less risk. Currently, multiple computational approaches have been established for drug repurposing. [8,9,10]

Figure No. 1:- Flow plan of drug repurposing



Method of drug repurposing:-

The methodologies adopted in DR can be divided into three broad groups depending on the number and quality of the pharmacological ,toxicological and biological activity information available .these are mainly i) drug –oriented ii) target oriented and iii)Disease/therapy –oriented[11].

Figure No. 2 :- A) Disease module identification and module enrichment:-

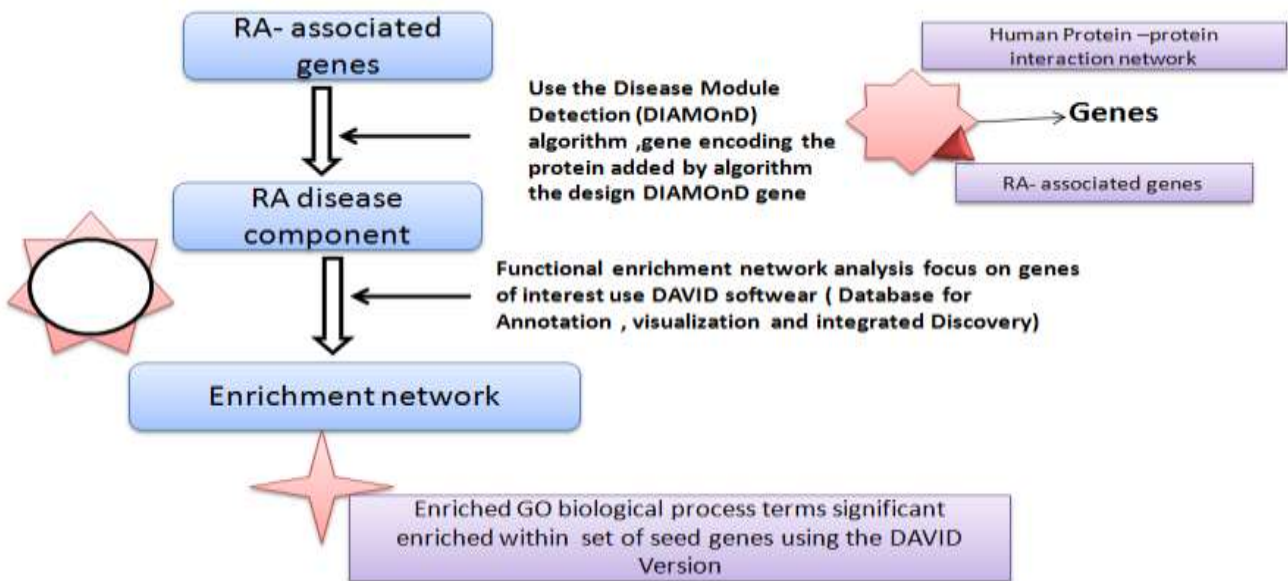
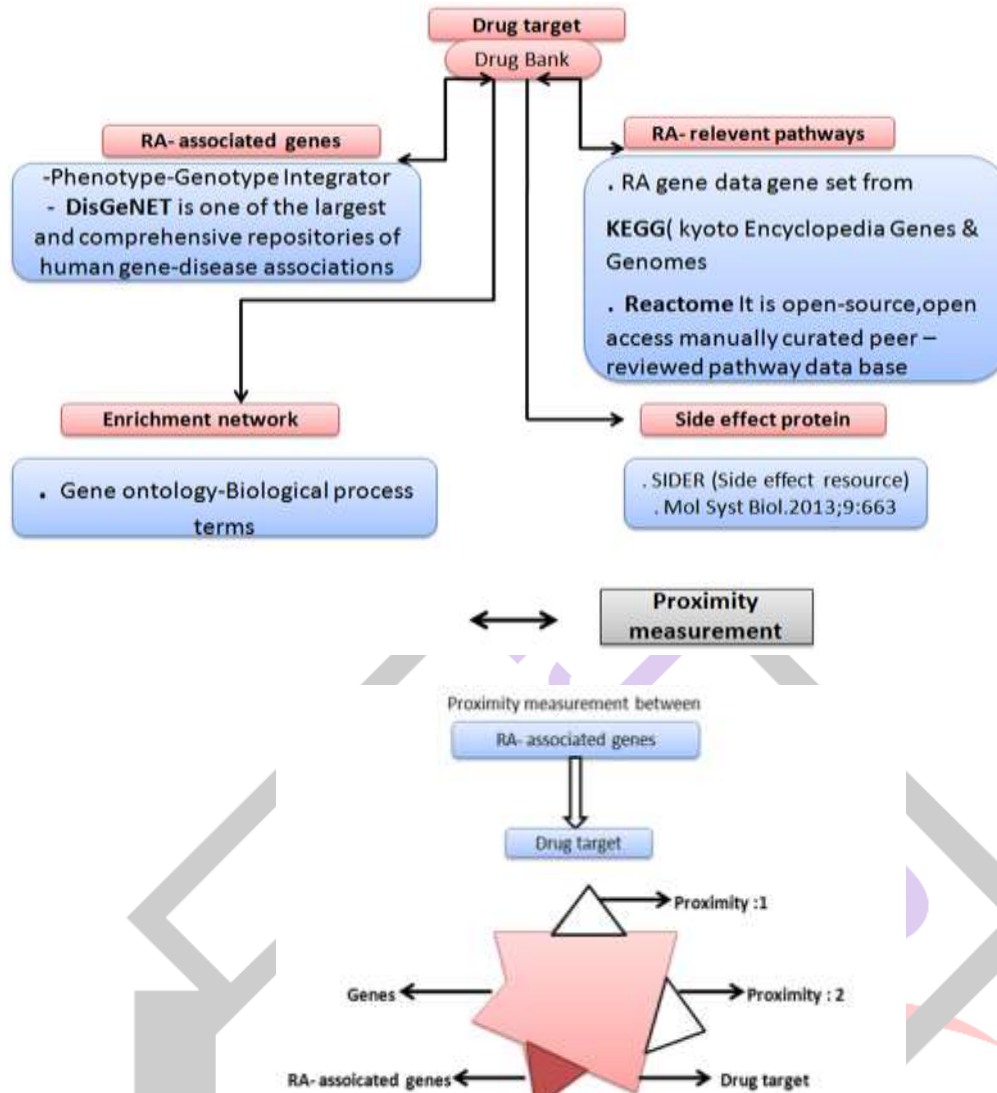


Figure No.3:- B) Network proximity measurement:



- A) The RA - associated genes are used as seen for identification of RA disease module ,by using the DIAMOND module finding algorithm on the human interactome network .once the RA disease module have been constructed ,GO biological process is performed through DAVID for assessment of the related biological processes
- B) Overview of the network proximity data source and methodology [12].

Network –based method:-

Network-based for drug repurposing that takes into account the human interactome network, proximity measures between drug targets and disease-associated genes, potential side-effects, genome-wide gene expression and disease modules that emerge through pertinent analysis. Use of disease omics data, available signal or metabolic ways, and protein interaction networks to reconstruct disease-specific path - ways that provide the key targets for repositioned drugs.

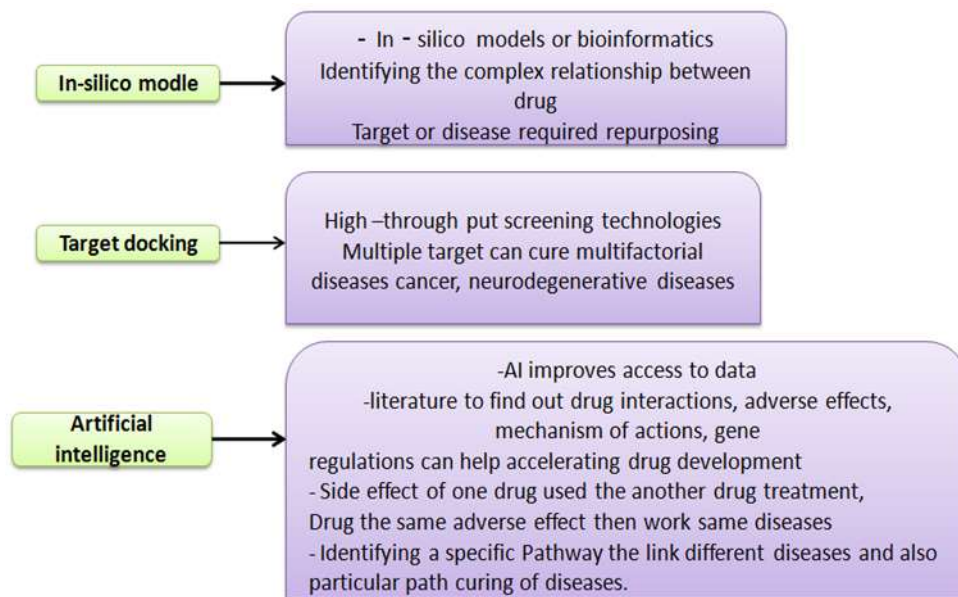
The significance of these methods is that they can slight down general signal networks from a large number of proteins to a specific network with a few proteins [11].

Drugs used in this study:-

Methotrexate, Rituximab, hydroxychloroquine, celecoxib, prednisolone, sulindac, Azathioprine.

Strategies for accelerating drug repurposing:-

Figure No.4:- Flow chart of strategies for Accelerating drug repurposing [13,14,15,16]



Approaches of drug repurposing:-

Drug repurposing important the two approaches, first one is Activity-based approach is also known as experimental –based approach and second one in silico-based approach [11].

Figure No.5:- A) Activity-based approach:-

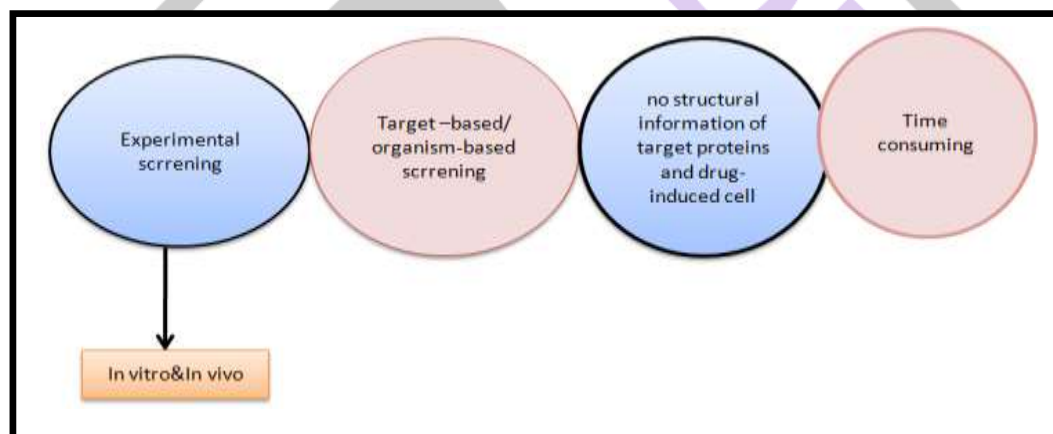
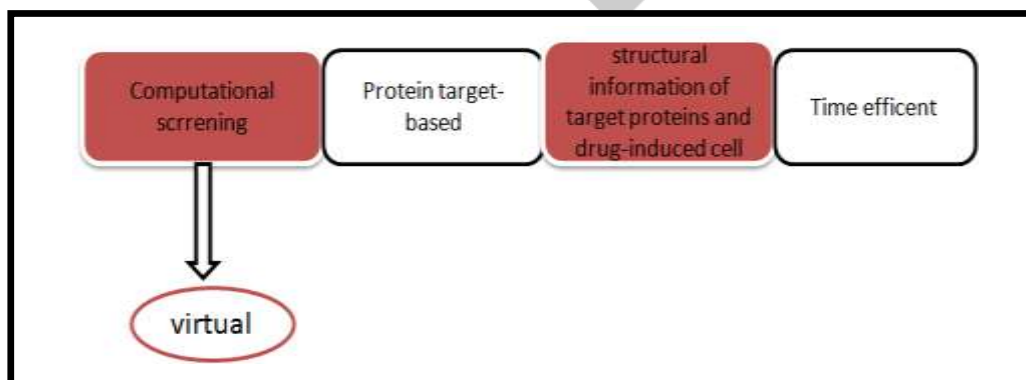


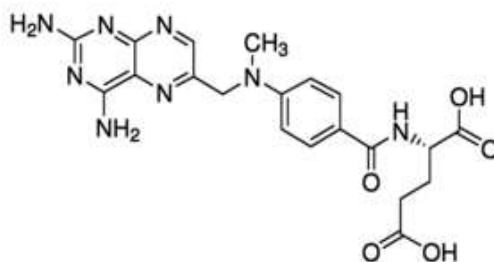
Figure No.6:- B) In silico-based approach:-



List of drug with potential repurposing capabilities:-

The list of potential drugs includes Methotrexate, Rituximab, hydroxychloroquine, celecoxib, Prednisolone, sulindac, Azathioprine.

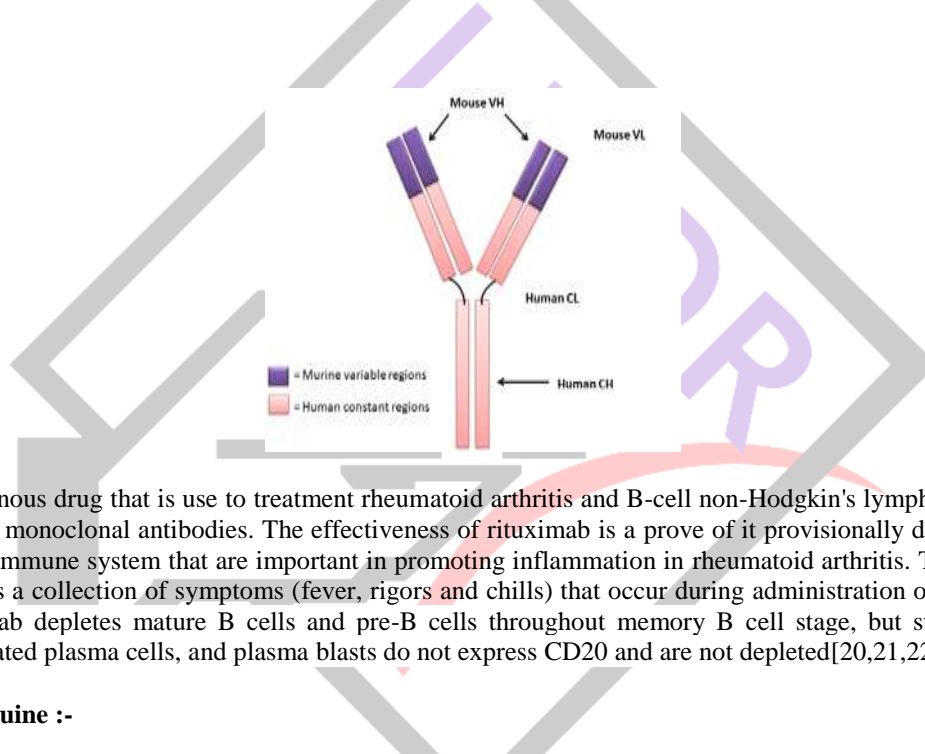
1. Methotrexate:-



Methotrexate is useful to treatment rheumatoid arthritis in adult. It is also used to treat active polyarticular-onset juvenile rheumatoid arthritis RA in children. Methotrexate may reason injury or death to baby and should not be used during pregnancy to treat **arthritis** or **psoriasis**.

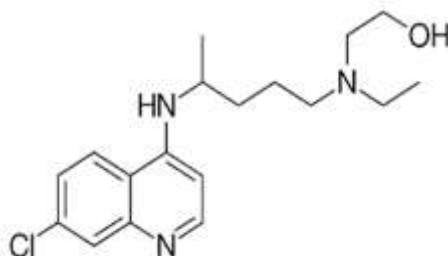
Methotrexate this is dihydrofolate reductase inhibitor has prominent immunosuppressant and anti-inflammatory property mechanism in RA given that methotrexate increases adenosine levels and on engagement of adenosine with its extracellular receptors an intracellular flow is activated promote an overall anti-inflammatory. On the other side , the efficacy of less quantity of doses methotrexate used in RA patients is unaffected by the administration of folic acid and it is in fact almost invariably part of the RA medication regimen to minimize the unwanted methotrexate side effect[17,18,19].

2. Rituximab:-



Rituximab is intravenous drug that is use to treatment rheumatoid arthritis and B-cell non-Hodgkin's lymphoma. It belongs near a class of drugs called monoclonal antibodies. The effectiveness of rituximab is a prove of it provisionally depleting the number of B-cells, cells of the immune system that are important in promoting inflammation in rheumatoid arthritis. The most common side effect of rituximab is a collection of symptoms (fever, rigors and chills) that occur during administration of the first dose of drug mechanism Rituximab depletes mature B cells and pre-B cells throughout memory B cell stage, but stem cells, pro-B cells, terminally differentiated plasma cells, and plasma blasts do not express CD20 and are not depleted[20,21,22,23] .

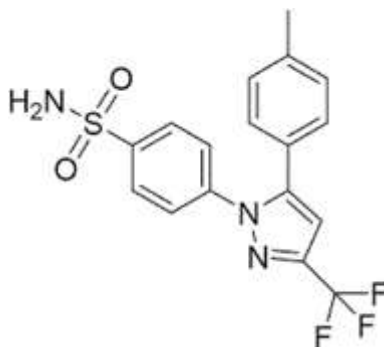
3. Hydroxychloroquine :-



Hydroxychloroquine is further more used to treatment symptoms of rheumatoid arthritis and discoid or systemic lupus erythematosus. For the treatment of acute and chronic rheumatoid arthritis

The mechanism of action of antimalarials in the treatment of patients with rheumatoid arthritis is unknown but is thought to involve changes in antigen production or effects on the innate immune system. Antigen processing may be interfered with. Lysosomal stabilization and free radical scavenging are the other proposed mechanism. The most important toxicities are on the eyes: corneal deposits, extraocular muscular weakness [24,25].

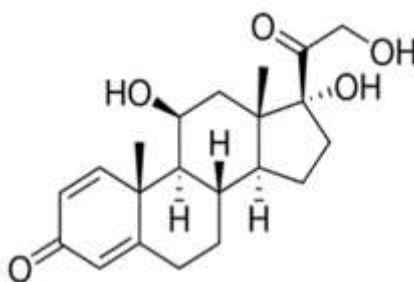
4. Celecoxib :-



The COX-2 selectivity of celecoxib is modest and similar to the that diclofenac . Nonsteroidal anti-inflammatory drugs (NSAIDs) be used to treat citizens with rheumatoid arthritis. Celecoxib is a selective NSAID which may help to reduce symptoms of rheumatoid arthritis[26].

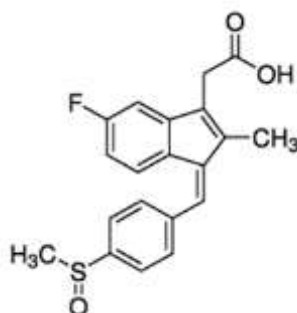
mechanism of action of celecoxib is suitable to selective inhibition of (COX-2) cyclooxygenase-2 , which is responsible for prostaglandin synthesis, an integral fraction of the pain and inflammation path[27]. This action gives celecoxib its analgesic, anti-inflammatory, anti-cancer, and antipyretic action. Side effect Stomach upset or gas may take place. Rise in blood pressure , severe headache, symptoms of kidney problems, symptoms of heart failure ,allergic reaction some edema , rash , fever [28,29,30].

5. Prednisolone :-



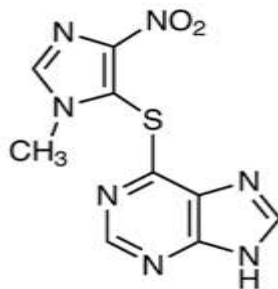
They help decreases the inflammation levels in body that make your joints swollen, stiff, and painful. In case with single or a few joint involvement with severe symptoms, intra articular injection of a soluble glucocorticoid afford release for numerous weeks, joint damage may be slow [31]. Side effect of risk of bacterial and viral infection, weight loss, hyperglycemia ,high blood pressure [32]. to decrease RA symptoms while a person is waiting for disease-modulating anti-rheumatic drugs (DMARDs) or biologics to reduce pain and discomfort [33,34].

6. Sulindac :-



Sulindac trade name Clinoril and marketed name also. Sulindac blocks the enzyme to makes prostaglandins (cyclooxygenase), consequential in lower concentrations of prostaglandins. As a inflammation, pain and fever are reduced .It is used to reduce pain, swelling, and joint stiffness from arthritis. It is also used to treat arthritis [34]. This medication is known as a non-steroidal anti-inflammatory drug (NSAID) and aryl alcanoic acid class .side effect this drug upset stomach , nausea, vomiting, dizziness, or headache . sulindac is contraindicated in hypersensitivity to sulindac or the excipients[35,36,37,38] .

7. Azathioprine:-



This purine synthase inhibitor act after getting converted to 6- mercaptopurine through enzyme thiopurine methyl transferase (TPMT) induced in small fraction of RA it is less commonly use and mostly in autoimmune diseases rheumatoid arthritis, ulcerative colitis as well as an organ transplantation.side effect vomiting ,nausea, mouth and throat ulcer.[39,40,41]

Advantages of drug repurposing:-

1. Already passed a number of toxicity and other tests in drug repurposing.
2. Its safety
3. The risk of failure for reasons of adverse toxicology are decrease[42].

Benefits of Drug Repurposing:-

- 1) Reduction in Cost
- 2) Reduction in Time
- 3) A number of drugs are being repurposed for rare diseases or conditions which leads to many developers being attracted by the incentives associated with obtaining orphan drug designation. Both the FDA and EMA supply incentives to encourage research into these conditions as, without these incentives, the small numbers of potential patients would mean that they would be less commercially viable.
- 4) Lower cost of clinical trials and a shorter development time, drug repurposing is associated with a higher success rate from Phase II to launch [43,44,45] .

Conclusion:-

In this study, predicted several drugs for RA treatment repurposing .When repurposed therapy improved efficacy, safety and cost over the standard treatment of care, most of the benefit included this articles. Drug Repurposing is use future of modern medicine. Proper strategies and techniques its beneficial.

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