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Repurposing and Repositioning of Orphan Drugs in Rare Diseases

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ABSTRACT

This article briefly introduces the use of DKK-1 inhibitors, and then focuses on the recent researches for treatment of Systemic Lupus Erythematosus. The major objective of this article is to open the doors of research for use of Orphan drugs in Rare disease.Furthermore, it also discusses uses of Phytochemicals and existing treatment available along with few clinical representations.Use of softwares like SWISS ADMET, sites like Pubechem and docking platforms like Autodock Vina can help in efficient repurposing of drugs In this review, we have systemically reviewed the pathogenesis of Systemic lupus erythematosus (SLE) and highlighted recent advances in host genetic factors, Epidemiology, Causes and symptoms of the same. Moreover, it also encompasses need for repurposing and repositioning of orphan drugs in treatment of SLE.

INTRODUCTION:

Drug repurposing (DR) (also known as drug repositioning) is a process of identifying new therapeutic use(s) for old/existing/available drugs. It is an effective strategy in discovering or developing drug molecules with new pharmacological/therapeutic indications. Drug repositioning utilizes the combined efforts of activity-based or experimental and in silico-based or computational approaches to develop/identify the new uses of drug molecules on a rational basis. It is, therefore, believed to be an emerging strategy where existing medicines, having already been tested safe in humans, are redirected based on a valid target molecule to combat particularly, rare, difficult-to-treat diseases and neglected diseases. Drug repurposing (DR) is also known as drug repositioning, drug re-tasking, drug reprofiling, drug rescuing, drug recycling, drug redirection, and therapeutic switching. It can be defined as a process of identification of new pharmacological indications from old/existing/failed/investigational/already marketed/FDA approved drugs/pro-drugs, and the application of the newly developed drugs to the treatment of diseases other than the drug's original/intended therapeutic use. It involves establishing new therapeutic uses for already known drugs, including approved, discontinued, abandoned and experimental drugs[1]. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with varied natural history and multisystemic involvement. The pathogenesis is multifactorial and complex precipitating the formation of autoantibodies. SLE is a rare disease with an incidence of approximately 1–10 per 100,000 person-years and a prevalence of 20–200 per 100,000 person-years. It predominantly affects young women and middle-aged women. Though there is not much difference between the two sexes in terms of disease manifestation or severity, greater severity is noted at extreme ages of life [2].Thus this article aims to provide new opportunities to researchers for finding out alternatives that can be used in treatment of SLE and thus improve the quality of life for people.Dickkopf-1 (DKK1) is a well-characterized Wnt inhibitor and component of the Wnt/β-catenin signaling pathway, whose dysregulation is associated with multiple abnormal pathologies including osteoporosis, SLE Alzheimer's disease, diabetes, and various cancers. In fact, strategies for developing DKK1 inhibitors can produce encouraging clinical results in different pathological models.

Pathophysiology*:*

The interaction of sex, hormonal milieu, and the hypothalamo–pituitary–adrenal axis modifies this susceptibility and the clinical expression of the disease. Defective immune

regulatory mechanisms, such as the clearance of apoptotic cells and immune complexes, are important contributors to the development of SLE. The loss of immune tolerance, increased antigenic load, excess T cell help, defective B cell suppression, and the shifting of T helper 1 (Th1) to Th2 immune responses leads to B cell hyperactivity and the production of pathogenic autoantibodies. Finally, certain environmental factors are probably required to trigger the disease. The central immunological disturbance in patients with SLE is autoantibody production. These antibodies are directed at several self-molecules found in the nucleus, cytoplasm, and cell surface, in addition to soluble molecules such as IgG and coagulation factors. Antinuclear antibodies are most characteristic and present in more than 95% of patients. Anti-double stranded DNA (ds-DNA) and anti-Sm antibodies are unique to patients with SLE [3]. It is believed that the removal of these apoptotic cells is compromised because of the impaired functioning of phagocytic cells, resulting in suboptimal disposal of dying cells and antigen recognition in patients with SLE. [4]

Causes*:* Genetic, hormonal, immunological, and environmental factors all play a role in the development of SLE. Many drugs such as procainamide and hydralazine, which are aromatic amines or hydrazines, can induce a lupus-like syndrome, especially in individuals who are genetically slow acetylators. Hydrazine itself also occurs naturally in tobacco and tobacco smoke. The ingestion of alfalfa sprouts that contain L-canavanine has been linked to the development of lupus-like symptoms in several case reports [3]. Genetic interactions with environmental factors, particularly UV light exposure, Epstein–Barr virus infection and hormonal factors, might initiate the disease, resulting in immune dysregulation at the level of cytokines, T cells, B cells and macrophage. [7]

Signs and symptoms:

1. Arthritis
2. Mouth and nose ulcers
3. Muscle aches
4. Cognitive dysfunction
5. Fatigue and Lethargy
6. Mild fever
7. Photosensitivity

Epidemiology:

The incidence of SLE varies among ethnic groups and by geographic location, sex, and age. SLE is more common in women, particularly those of child-bearing age. This increased incidence may be attributed to hormones, namely estrogen, as studies have shown women who had an early menarche or who used oral contraceptives or hormonal therapies had an increased risk of SLE. Black persons in Africa have a much lower incidence of SLE than African-Americans in the U.S. [4]

Clinical Presentation*:*

The skin, musculoskeletal system, and pulmonary system are primarily affected. SLE patients who report symptoms involving the skin most commonly have a red rash on the nose and cheeks following exposure to the sun. This "butterfly" rash is identified in a significant number of SLE patients at some point during the disease course [5]. SLE also affects the cardiovascular, gastrointestinal, renal, and haematological systems, as well as the central nervous system (CNS). Cardiovascular effects often include pericarditis, myocarditis, endocarditis, and coronary artery disease.[6]

Treatment Options:

1. NSAIDS: Block prostaglandin synthesis through inhibition of cyclooxygenase enzymes, producing anti-inflammatory, analgesic, and antipyretic effects [7]

2. Corticosteroids: Multiple effects on immune system (e.g., blocking cytokine activation and inhibiting interleukins, γ-interferon and tumor necrosis factor-α) [8]

3. Immunosuppressants: Multiple suppressive effect on immune system (e.g., reduction of T-cell and B-cell proliferation; DNA and RNA disruption [9]

4. Targeted Therapies: Biologic Agents: Introduction of a number of biologic agents that specifically target disease pathways underlying the development and progression of lupus. Some of these therapies, such as rituximab (RTX) and belimumab RTX is a chimeric monoclonal Ab which selectively targets B cell-specific surface molecule CD20.[10] Block binding of BLyS to receptors on B cells, inhibiting survival of B cells, and reducing B-cell differentiation into immunoglobulin-producing plasma cells. [11]

FUTURE SCOPE:

With aid of network pharmacology and Redox pharmacology finding out new phytochemicals, new moieties for networking and management of Systemic Lupus erythematosus.

CONCLUSION:

So in nutshell we can say that repurposing or orphan drugs will aid in finding out new alternatives and subsitutes for better managaement of Rare diseases.Amalgamation of Reverse Pharmacology and Network Pharmacology will help in finding out new moieties for treatment of Systemic Lupus Erythematosus.

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