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Pharmacology and Pharmacotherapeutics: Finding New Avenues of Research

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Abstract Pharmacology and pharmacotherapeutics assume increased significance in the treatment and management of human diseases. Also, it is evident from the current experiences of the novel Coronavirus pandemic, that specific therapeutic pharmacological agents are essential to successfully treat and manage patients. Having good knowledge of the pathogenesis of various diseases helps us in the direction towards the development of newer and improved pharmacotherapeutic agents. Also essential is to understand the anatomy, physiology, and functions of various organs of the human body like the eye, skin, kidneys, among others. Improved knowledge of the human immune responses to infections, inflammation, poisoning, drug reactions, and the agonistic and antagonistic activities of potential endogenous pharmacological molecules is necessary to discover newer pharmacological agents, improve health, and fight diseases.

Keywords: *pharmacology, pharmacotherapeutics, treatment, management, human diseases, pathogenesis, eye, skin, kidneys, immune responses, drug reactions*

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1. Introduction

Pharmacology is the study that deals with the discovery, development, and therapeutic applications concerning the treatment and management of diseases. The biologically active compounds or the chemicals which are effective in the treatment of diseases are termed pharmacotherapeutics [1]. Belonging to the branch of pharmacology, pharmaceutics involves the study of beneficial as well as the adverse effects of pharmacological agents/drugs. Most pharmacological agents are identified within nature, and few are synthesized/manmade [2,3,4]. Initially, several naturally occurring plants and their parts were found to be effective in the treatment of diseases and they were generally referred to as home medicines. Later, scientists have successfully extracted the core pharmacotherapeutic components from natural substances. Also, scientists were able to develop synthetic chemicals which were biologically active like natural compounds [5,6,7].

Among the several characteristic features of pharmacological substances, their ability to specifically act on the target cell/organ is considered as most significant along with the minimum effect that they cause on the other cells/organs of the host. The substances are chosen for their activities after thoroughly determining the pharmacological and toxicological properties including the absorption, dissemination, metabolism, and elimination (ADME) studies. Some such pharmaceutical agents are synthesized from microorganisms and are available as antibiotics, like penicillin and streptomycin that were extracted from fungi Penicillium notatum, and Streptomyces griseus respectively [8]. A few of them are synthesized manually using the chemicals (Figure 1).

In fact, in the early 20th-century salvarsan, an organic arsenic compound was successfully used to treat syphilis, a venereal disease [9]. There was also evidence that the willow tree extract named salicin has an effective anti-inflammatory activity and was later synthetically produced as acetylsalicylic acid, which is today famous as aspirin [10].

There are some endogenous organic molecules found in the human body like amine autoacids including the histamines and serotonin along with few others (prostaglandins, leukotrienes, platelet-activating factors, bradykinins) that have activities like pharmacological agents and therefore can be used to treat and manage diseases apart from being hazardous in nature if consumed in excess amounts [11,12].

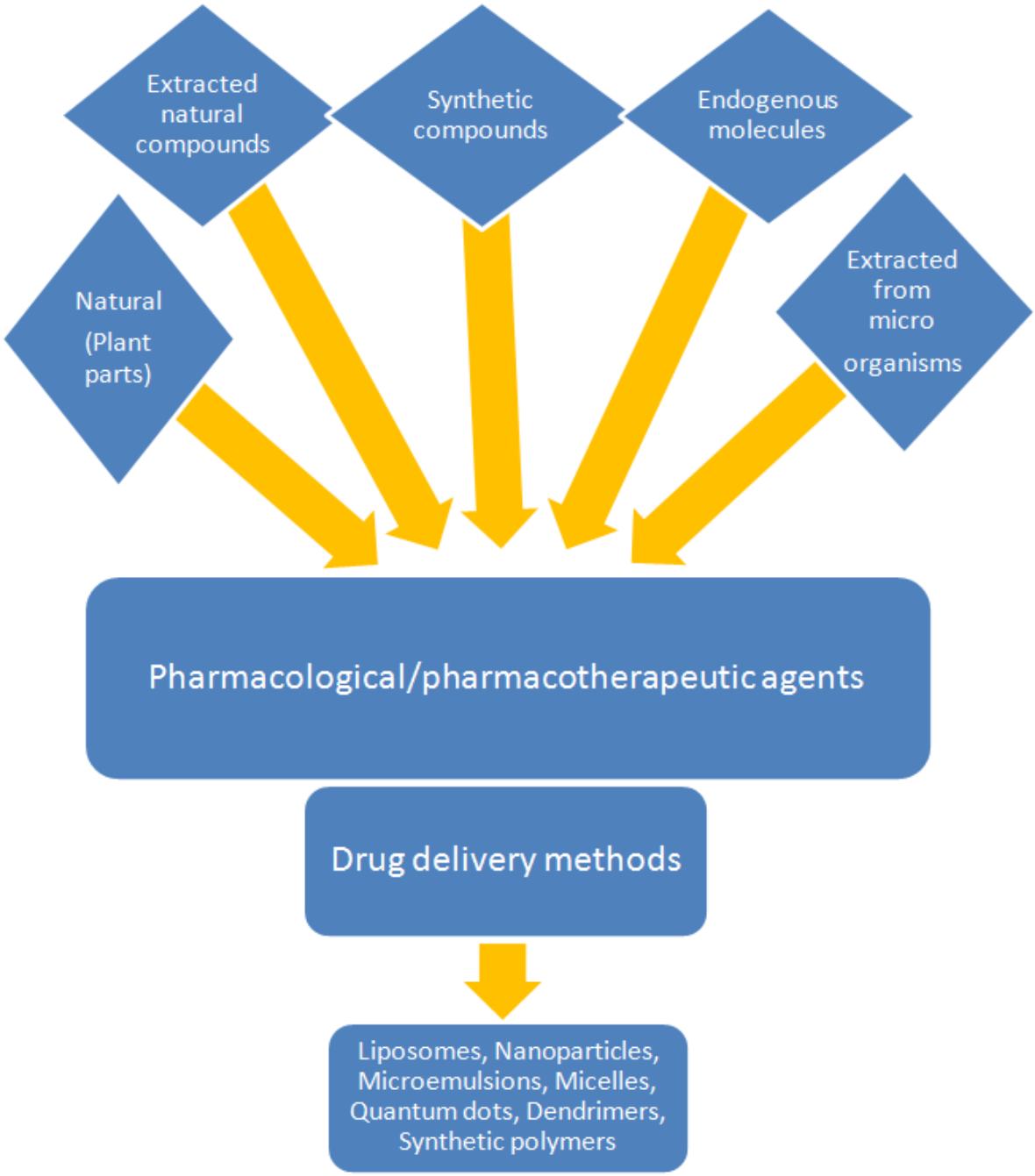

Figure 1. Source of pharmacotherapeutic compounds and drug delivery methods

Currently, drug discovery, development, and clinical research have proven to be beneficial to mankind owing to the improved scientific and technological advances [13,14,15]. Although the time taken for the development of a novel drug has considerably reduced, some pitfalls like adverse drug reactions, potential drug-drug interactions, mode of delivery, and others remain to be completely understood.

In the present review, we delineate the developments in the field of pharmacology and pharmacotherapeutics concerning eye, skin, kidney, hematological, infectious, and immunological disorders. Also, we attempt to summarize the status with regards to the developments in managing poisoning, adverse drug reactions, age-dependent drug dosing, and the pharmacotherapeutic applications of autoacids.

1.1. The Pharmacotherapeutic Preparations for Treating Ocular Diseases

Vision is one of the most essential abilities/functionalities of a human being, with which he/she can live a normal life. Lack of vision is a huge disability and causes severe morbidity in the affected population. Apart from the several causes of eye diseases, the most common diseases of the eye may be caused by its continuous exposure to the air and environmental dust.

The pharmacokinetics of the ocular drugs depends on the anatomy and physiology of the eye, the production and sterilization methods, the routes of administration, and the barriers of absorption. The most common ocular disease is glaucoma, an age-related condition. The age-related macular disease, the cataract, which also is mostly age-

related, the traumatic eye disease, and the other physiological (dry eyes) and infectious diseases of the eye are frequently noted.

In most instances, the ocular diseases may be initiated by the inflammatory responses elicited by the host's own immune system, autoimmunity, or hypersensitivity. This fact has been supported by a recent research report which suggested that the drug discovery and patenting of newer drugs were mostly related to treating allergic eye diseases [16].

Among the challenges in treating ocular diseases, the delivery of the drug to the desired area of the eye (back of the eye) and the adverse effects are the most significant as evidenced from a recent study [17]. Also, studies have highlighted the role of certain vaccines in the development of adverse eye conditions (conjunctivitis, uveitis) [18].

A recent research report emphasized and characterized the ocular microbiome using 16S ribosomal RNA gene sequencing. This study had shown that there is a low diversity microbiota in the eye which maintains its homeostasis [19].

Corynebacterium, *Actinobacteria*, *Pseudomonas*, *Sphingomonas*, and *Streptococcus* species were the microbial species frequently found in the conjunctiva of people as evidenced from the current research results [20].

In a recent experimental study, the efficacy of rapamycin to control the necroptosis initiated by the pan-caspase inhibitor among retinal detachment cases was positively assessed [21].

By understanding the anatomy and the physiology of the eye, which is complex, it must be noted that there are multiple areas of the eye, which can be affected. And treatment for the specific area may be done taking into consideration the drug delivery and portability in the affected area neutralizing the anatomical and physiological drug penetration barriers [22].

There is a research finding which says that topical eye drugs have the least bioavailability and that only 5% of lipophilic drugs are absorbed into the desired site, and only 0.5% of the hydrophilic drug reaches the site of action [23].

So, this is a big area for further research to find out possible ways to increase the bioavailability of ocular drugs, with special reference to treating the anterior chambers of the eye.

An estimated 125 million people use contact lenses, and there is a significant gap, regarding the safety of contact lenses. Finding the biomaterials to synthesize contact lenses that contain/disseminate/release the drug is an emerging area of research as noted by very recent research [24].

Considering the challenges involved in the drug delivery, and bioavailability of ocular drugs, few recent studies have suggested using colloidal carries known as microemulsions (ME) which are sub-micron to nanometer sized (5-200 nm) compounds, polysaccharide nanomaterials, nanogels (NG) composed of high molecular weight chitosan (HCS) crosslinked with sodium tripolyphosphate, and transferosomes made of phospholipids and surfactants [25,26,27,28].

Since ocular drugs, especially the topical preparations fail to reach the posterior segment of the eye, a recent study had suggested using an ex-vivo model consisting of human and porcine tissues for pre-clinical testing of the drugs for their penetration capabilities [29].

Application of novel methods like hybrid liposomal nanocapsules coated with monoclonal antibodies, and liposomal preparations consisting of dexamethasone, and antibiotics like moxifloxacin to treat infections and inflammations of the eye was recently reported [30,31].

1.2. Drugs to Manage and Cure Skin Diseases

Because skin and its appearance are of cosmetic importance, management of skin conditions (insect bites)/diseases (genetic-eczema)/disorders (metabolic-psoriasis/infections (bacterial, viral, fungal, and parasitic infections) assumes greater significance. The most common skin condition is acne, which is usually seen among the population of the pre-pubertal-to-pubertal age. Other frequently noted skin disorders like eczema and psoriasis are complex and require improved understanding of their pathophysiology, and clinical diagnosis for better patient management.

Several therapeutic interventions like pharmaceutical drugs, surgery, transplantations, and other management and supportive therapies are currently available for the treatment of skin conditions. The selection of the best therapeutic intervention depends on the type and nature of the skin disease. Skin conditions may be due to trauma/accident (shock, burns), autoimmune in origin, may be caused by various microbial infections (bacterial, fungal, parasitic, and virus related), or because of drug reactions [32].

Since skin is the largest organ of the body, and that the skin and its health are correlated with the beauty of the person, any disease to skin and its appendages assume greater significance [33].

Skin diseases impose multi-dimensional damage (psychological, social, and financial) on the affected population as suggested by a recent study [34].

Because the skin is the primary protective barrier, its health defines the overall condition of the human body. Also, since the skin is in direct contact with the environment, it may be transiently colonized with microorganisms, like the Staphylococcus species.

Diseases of the skin and its appendages are very common throughout the world. The most frequent condition of skin, eczema, and fungal infections, affects many people throughout the world, and especially in India as noted by a recent study [35].

Skin diseases may have varied etiology from being caused by autoimmune conditions, like eczema, psoriasis, and other skin conditions may be produced by bacterial (staphylococcal), viral (rashes-dengue, measles), fungal (candidiasis), and parasitic infections (larva migrans). Skin diseases may also have a genetic predisposition [36].

Skin diseases have multiple causes, and the therapy is different in each case. Most skin diseases are treated using antibiotics, some are treated using other drugs like the use of anthralin for treating psoriasis. Since anthralin has many side effects like stainability and irritability, it is another area of research, to improve and produce a better drug.

Recently, Baricitinib, a Janus kinase (JAK)/JAK2 inhibitor, interleukin (IL)‑4, and IL-13 inhibitors, and nanomedicines were positively evaluated for the treatment and management of patients suffering from atopic

dermatitis, an immune-mediated chronic inflammatory condition of skin [37,38,39].

Systemic sclerosis is a connective tissue disorder that affects various systems of the human body including the skin. Recent clinical trials have evaluated the efficiency of various drugs in the treatment of such patients. Among several drugs tested Cyclophosphamide, and Mycophenolate mofetil (MMF) were found particularly efficient in improving the lesions. Abatacept, tocilizumab, and nintedanib showed no clinical benefit, and drugs like brentuximab vedotin, pirfenidone, intravenous immunoglobulin (IVIG), and a combination of belimumab+rituximab+MMF are currently under trial [40].

1.3. Pharmacological Preparations to Treat Kidney Diseases

Among the various organs of the body, the kidneys and their function assume increased significance. This is attributed to the filtering ability of the kidneys, which purifies the blood of impurities and retains/absorbs essential minerals/elements, and excretes the unwanted and the excess.

Kidney diseases are among the most common disorders in the developing world like India. Improved understanding of the anatomy, physiology, aetiology, and pathogenesis of kidneys is essential for better management of kidney diseases.

Kidney diseases are of two types that include the acute and chronic kidney diseases. The kidney functions may be compromised due to various factors, which may result in either acute or chronic kidney disease. Management of kidney diseases includes dialysis (hemodialysis and continuous ambulatory peritoneal dialysis (CAPD)), replacement of lost minerals/elements, and other supportive therapies (fluid and electrolyte replacement therapy) [41].

Given the limitations in the therapy and management of kidney diseases, recently there has been continued research for the development of other therapeutic modalities in the areas of stem cell therapy, gene therapy, and tissue engineering [42].

Most kidney diseases are followed by some co-morbidities that include diabetes, hypertension, and others. And all age groups have been affected by kidney diseases. With adults over the age of 50 years being more affected, kidney diseases may be acute, caused by infections or trauma, and maybe chronic or genetically mediated.

The discovery of drugs that inhibit the renin-angiotensin aldosterone system (RAAS) resulted in frequent use to manage kidney diseases [43]. Also, dialysis (peritoneal and haemodialysis) has been commonly used to manage patients with end-stage renal disease (ESRD).

Because the aldosterone pathway was identified to influence kidney function, therapeutic use of aldosterone antagonists (spironolactone, eplerenone, canrenone, prorenone, and mexrenone) paved the way for the management of kidney diseases [44].

Other drugs used include glucocorticoid metabolites (11-dehydrocorticosterone and 11-dehydrocortisol, which is cortisone), mineral corticoid receptor (MR) antagonists [44]. The most recent and novel approach to the treatment of kidney diseases is the use of aldosterone synthase inhibitors [44].

Kidney diseases are among the most common age-related acute or chronic conditions prevalent throughout the world. The presence of co-morbidities may complicate kidney diseases. Patients with diabetes and those with lipid disorders pose a challenge in the treatment of kidney diseases. It is therefore important to understand and treat patients with kidney diseases with associated co-morbidities (diabetes).

The incidences of diabetic kidney diseases are on the rise, especially among older age patients [45,46]. A recent study had evaluated several drugs for their nephroprotective activities. It was noted that sodium-glucose-cotransporter-2 (SGLT2) inhibitors, mineralocorticoid-receptor antagonists, and JAK inhibitors, among others, showed promise [47].

The extracellular nuleotidases like CD39 and CD73 were noted to facilitate the breakdown of proinflammatory adenosine triphosphate (ATP) into adenosine, an immunosuppressive agent. Therefore, CD39, among others can be opted as therapeutic interventions to treat/manage CKD [48].

Applications of the novel nano-based drug delivery systems like synthetic polymers, micelles, protein based nanoparticles, gold nanoparticles, dendrimers, quantum dots, and liposomes in the management of kidney diseases were recently reported [49].

The potential role of gene therapies and stem cell transplantation in the treatment of diabetic nephropathy was recently reported. It was observed that translocase inner mitochondrial membrane-44 (Tim44), a mitochondrial gene could trigger apoptosis of kidney cells. Stem cells like the unipotent, multipotent, pluripotent, and totipotent cells can potentially differentiate into organs/organelles [50].

1.4. Drug Formulations to Treat/Manage Hematological Disorders

Anemia is a condition that is used to describe the decrease in the number of red blood cells (RBCs). Anemia can be of various types including aplastic anemia, megaloblastic anemia, and the anemia caused by other chronic diseases/infectious conditions. Anaemia also emphasizes the clinical relevance and dietary importance of vitamin B12, and folic acid. Megaloblastic and pernicious anemia are the two most common types of anemia.

Hematologic disorders assume greater significance to human health since such abnormalities (anemia, thalassemia major, sickle-cell disorders leukemia, and myelodysplastic syndromes) disturb the homeostasis of the human body.

During hematological disorders, understanding the iron metabolism assumes significance. Deferoxamine, the choice of treatment in thalassemia major patients may cause intolerance. The management of sickle cell anemia with iron-chelation therapy warrants caution due to potential side effects due to impaired liver function and heart failure [51].

The three major types of blood disorders include the red blood cells (anaemias-Thalassemia, sickle cell anemia, hemolytic, iron deficiency, pernicious, aplastic, and other types of anemias), the white blood cells (lymphoma, leukemia, and, myeloma) and the platelets (idiopathic thrombocytopenic purpura, heparin, thrombotic).

Slowly but gradually the applications of gene therapy have been applied to treating hematological disorders. Such a therapy has been attempted using vectors as vehicles for gene therapy. The virus vectors used as vehicles include the adeno associated viruses (AAVs), and the retroviral vectors [52].

Treatment for blood disorders includes the use of growth stimulators for deficient cells, using steroids and suppress the immune system, and the use of chemotherapeutic agents to control the tumors.

Recombinant activated factor VII (rFVIIa), is the most recent therapeutic drug for treating hemorrhage among the non- hemophiliacs that were positively evaluated in a recent study [53].

Multiple myeloma is a plasma cell malignancy where the patients suffer from bone, kidneys, red blood cells (RBCs), and immune system disorders. Apart from the routine treatment with immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs), novel therapeutic interventions like daratumumab, and isatuximab (both anti-CD38 monoclonal antibodies), and Chimeric antigen receptor-T cell (CART) therapies and bi-specific T-cell engager (BiTE) were found both safe and efficient [54].

Polycythemia vera (PV) is a type of blood cancer that causes excessive production of RBCs. Apart from the traditional treatment options, recently the usefulness of histone deacetylase inhibitors (HDACi), and drugs targeting mammalian targets of rapamycin, insulin receptor substrates 1/2, MDM2 protein are being explored in the management of PV [55].

1.5. Pharmacotherapeutic Approaches to Treat Infectious Diseases

Infectious diseases are among the most frequent causes of morbidity and mortality worldwide. There are different groups of antimicrobial agents effective against bacteria, fungi, viruses, and parasites. There are currently several anti-bacterial agents, a few antiviral agents effective against the human immunodeficiency virus (HIV) infection, some antiparasitic drugs (anti-amoebic drugs and the anti-helminthic drugs), and anti-fungal agents. Antimicrobial agents effective against bacteria vary in their functions (cell wall inhibiting-penicillin) and mostly are ineffective against other microbes.

Infectious diseases including malaria, amoebiasis, and soil-transmitted helminthic infections are most common in developing countries like India. The knowledge of therapy and management of microbial infections assumes significance, especially in developing countries like India where the prevalence and risk of infection spread are more owing to low socioeconomic and dense human inhabitation.

The major disadvantage with antimicrobial drugs is the development of resistance by the microorganisms against the most common drugs [56].

Since the discovery of penicillin, antibiotic therapy has been revolutionized with the discovery of more than 100 antimicrobial agents, currently available for the treatment of infectious diseases. Also, the present era is now plagued by the emergence of both new microbial species and the evolution of microbes resistant to commonly used antimicrobial agents [57].

Only recently (April 2019) two new drugs dolutegravir and lamivudine were approved for the treatment of HIV-1 infections. Triclabendazole is another drug approved in 2019, which is effective against fascioliasis (liver fluke infection). Another drug that was successfully got approved for the treatment of malaria is tafenoquine [58].

Because of antimicrobial resistance, and emergent microbial species like the novel Coronavirus (SARS-CoV-2), there is an increased need for the production and the availability of newer antimicrobial agents to combat multi-drug resistance as suggested by the world health organization (WHO) [59].

Therapy for the patients with multi-drug resistant tuberculosis (MDR-TB) and the extremely drug-resistant tuberculosis (XDR-TB) is another avenue where the current concepts may be useful as noted from a recent finding [60].

Advanced drugs possessing long-acting and slow-release formulations have recently been found effective in the treatment of HIV. rilpivirine (non-nucleoside reverse transcriptase inhibitor), and cabotegravir (integrase inhibitor) have been approved as combination drugs for HIV disease management in Canada. Other potential drugs in the line include Islatravir (4'-Ethynyl-2-fluoro-2'-deoxyadenosine) is a novel nucleoside reverse transcriptase inhibitor along with GS-6207 (a capsid inhibitor) [61].

Fungal infections are exceedingly difficult to treat owing to the similarities between the fungal metabolites and the mammalian tissues. Also, there is a potential danger of the host being affected due to antifungal therapeutic agents. Therefore, a recent study had suggested the utility of sphingolipids as potential fungal therapeutic targets. Dihydrosphingosine, glucosylceramide (GlcCer), and inositol phosphorylceramide (IPC) were noted to influence the sphingolipid synthesis pathways, and drugs like acylhydrazones and aureobasidin A derivatives could emerge as potent antifungal agents either singularly or in combination with the existing therapeutic options [62].

According to a recent report, among more than 50 drugs approved by the US-FDA in the year 2018, the antimicrobial drugs, and drugs against cancers constituted the majority followed by drugs against neurological, and hematological disorders, among others [63]. This study highlights the significance of drug interventions against infectious diseases.

1.6. Drugs to Manage Immune System Disorders

Although drugs are used to treat and manage different human diseases, humans are already equipped with a resistance mechanism known as the immune system. The pharmaceutical products/drugs can either stimulate the immune system or suppress it. The immune stimulators cover a broad range of pharmaceutical products also including the naturally available immune boosters in the form of nutrition.

The immune system majorly functions to maintain human health in good condition. It protects against both infections and cancers. The two main arms of the immune system include humoral immunity and cell-mediated immunity.

The responses elicited by immunity can be defined as innate or acquired. Innate immunity is genetic-based and can be inherited, and the acquired immunity develops after exposure to the microorganisms either through natural infections or by vaccination.

The immune stimulators like levamisole, imiquimod, and resiquimod are used to treat some cancerous conditions. Also, there are a different group of pharmaceutical agents which act as immunosuppressants (corticosteroids, cyclophosphamide, methotrexate, azathioprine) use during and after transplantation [64].

The drawbacks of immunosuppressive therapy include susceptibility to microbial infections and tumors. The immune system of humans is innately equipped with defensive mechanisms to combat infection and inflammation. There are few instances where the immune system gets suppressed due to genetic/infectious/drug-induced causes.

Proper nutrition may boost immunity and may act as immune stimulators. Multivalent and multi-specific antibodies were tried as immune stimulants against cancers [65]. The most common immune stimulators are vaccines, which are regularly given to prevent both infectious diseases (tuberculosis-BCG vaccine; Hepatitis B vaccine) and cancers (Human papilloma virus-cervical cancer).

Antibody-drug conjugates and small molecule drug combinations were recently tried for their utility to treat cancers by preventing/minimizing the damage to normal human cells [66].

During and after transplantation, either stem cells/organ transplantation, the patients are prescribed immunosuppressants which facilitate the acceptance of the graft and minimize the possibility of rejection.

Immunosuppressant drugs are also used to treat common autoimmune diseases like psoriasis, systemic lupus erythematosus (SLE), and rheumatoid arthritis [67].

The newer immunomodulatory drugs like the thalidomide analogs, CC-5013 (lenalidomide, Revlimid) and CC-4047 (Actimid) have been known to cause less/no neurotoxicity, as compared to the previous/parent drug [68]. This is another application for research to produce immunomodulatory drugs with the least/no adverse effects.

Atopic keratoconjunctivitis (AK) is a common allergic condition of the eye. AK is generally treated using antihistamines (first line: olopatadine, emedastine, and levacobastine; second line: astemizole, fexofenadine, terfenadine, cetirizine, loratadine, ebastine, mizolastin, bepotastin, rupatadine, and bilastine), corticosteroids (local: Loteprednol etabonate), calcineurin inhibitors (cyclosporin A (CsA), Tacrolimus), mast cell stabilizers (sodium cromoglycate, lodoxamide, olopatadine, ketotifen, azelastine, epinastine, and bepotastine), and immunomodulatory drugs (methotrexate, mycophenolate mofetil, azathioprine, infliximab (anti-TNF-α), alefacept (T cell inhibition), and rituximab (anti-CD20)) [69].

2. Pharmacotherapeutic Approaches to Treat/Manage Poisoning

Substance abuse either intentionally (suicidal attempt, drugs, alcohol), or by accident is amongst the several problems prevalent worldwide. It is important to understand the causes, effects, and management of poisoning. There are several types of drugs (legal, illegal), types of abuse (substance abuse, drug abuse), and the management of such conditions using appropriate antidotes.

In a recent study, it was observed that methanol poisoning caused hundreds of deaths among Iranians, who consumed methanol that they believed will protect them against a potential *Coronavirus* disease-19 (COVID-19) causing severe acute respiratory syndrome *Coronavirus*-2 (SARS-CoV-2) infection. Also, methanol poisoning is a common phenomenon among several developing countries including India.

Owing to the complex metabolic pathway of methanol in humans, it was recommended that either fomepizole or ethanol can be used as alcohol dehydrogenase (ADH) inhibitors to stop the conversion of methanol to its toxic metabolite, formate [70].

Poisoning is one of the most frequent causes of medical emergencies in countries like India. Poisoning may result by accident or due to homicidal/suicidal behaviors. Management of poisoning assumes greater significance to reduce morbidity and mortality.

Accidental poisoning may be due to insect or animal bites (snake), contaminated water, adulteration of food, chemical, gas, and drugs. We need to know the common household substances which a poison can be (kerosene, phenyl) and those which do not cause any harm (toothpaste).

The advantages of having a good knowledge of types of poisoning and the useful antidotes (pharmaceutical agents) will help in the better management of patients. The farmers usually consume organophosphorus containing agricultural chemicals [71].

Poisoning is one of the most common types of medical emergencies in countries like India. Poisoning may be accidental (children) and homicidal/suicidal (adults). The management of such patients is done by using specific antidotes and evacuating the poison from the body before it is absorbed [72].

The atropine, 4-dimethylaminophenol (4-DMAP), tolonium chloride, naloxone, and activated charcoal were the most common antidotes used in the management of poisoning cases [73]. Effective elimination of poisons can be done using hemodialysis, hemoperfusion, multi-dose activated charcoal, and molecular absorbent recirculating system (MARS) [74].

Another common method of poisoning is drug abuse/substance abuse/illicit drug use/abuse. Cathinones and bath salts are a couple of emerging illicit drug abuse requiring therapeutic considerations as noted by a previous study [75]

3. Therapeutic Approaches during Drug Induced Disorders

Although drugs are prescribed by physicians to cure and manage diseases, they may be occasionally responsible for mild to severe forms of adverse effects. These include the hematological disorders (aplastic/hemolytic/megaloblastic anemia, agranulocytosis, neutropenia, and thrombocytopenia) induced by a

different class of drugs [76,77,78]. Drug-induced dermatological and kidney diseases, and hormonal disorders (pituitary, and sex hormones) are also common.

Although a drug may be especially useful to treat the most common to serious diseases/conditions, its safety to human beings remains very important. Adverse drug reactions (ADR's), as we commonly call them, probably because of the drug overdose, its interaction with the host's metabolism, drug interaction with other drugs used simultaneously, or the drug-food interactions [79].

The disadvantages of drug-induced disorders can be best explained by using the human immunodeficiency virus (HIV) infection. In HIV disease, the patients are treated with antiretroviral therapy (ART). Such patients develop several drug-related complications (hematological abnormalities, compromised liver, kidney functions, and cardiovascular diseases) as evidenced by recent research reports [80,81].

Drugs and many other substances (foods from both plants and animal origin) may induce abnormal reactions in human beings. Some substances like coffee, alcohol, cocaine, nicotine and, opioids and drugs including amphetamines, sedatives, and many other commonly used drugs may initiate abnormal reactions in humans [82].

Drug reactions assume increased significance since they are meant to treat the cause rather than cause additional effects after the treatment. Drugs used and their adverse effects need to be carefully considered to minimize the morbidity and mortality associated with them. Research studies indicated the association of some anesthetic drugs and bronchodilators in causing myalgia and joint pains [83].

The current research highlights not only the adverse reactions, but also signifies the importance of drug-drug interactions, drug-food interactions, and other related interactions and adverse reactions [84].

Liver injury may result in the event of drug reaction, drug-drug interactions and it may also be caused by immunological reactions, also known as autoimmune hepatitis. A few existing drugs like ursodeoxycholic acid, and corticosteroids, among others, are used to manage drug induced liver injury [85].

Antibiotics used in the treatment of infectious diseases may result in adverse drug reactions. Antitubercular drugs along with other antibiotics like vancomycin, sulphonamides, among others can frequently cause eosinophilia, liver injury, and other systemic symptoms like a fever [86].

4. Autoacids and Their Pharmacotherapeutic Applications

Serotonin (5-hydroxy tryptophan), eicosanoids-prostaglandins, leukotrienes, and renin-angiotensin-aldosterone system are some of the amine autoacids. Autoacids are pharmacological agents that have either agonistic or antagonistic activities against serotonin. The activities of various serotonergic receptors, their effects on different systems of the human body including the central nervous system, cardiovascular system, gastrointestinal system, and respiratory system require improved understanding.

The autoacids have a wide range of therapeutic applications. The prostaglandins (PG), leukotrienes (LTs), eicosanoids, and thromboxanes (TXs) are not only used as non-steroidal anti-inflammatory drugs, but also are used to treat other vascular, kidney, and metabolic disorders [87].

The angiotensin type 1 receptor (AT1) antagonists are active anti-inflammatory pharmaceutical drugs used to treat oxidative stress, neuroinflammation, and Parkinson's disease [88].

Although the autoacids and their derivates prove to be beneficial in the treatment of diseases like Parkinson's, recent research observed the risk of developing gambling and impulse-control disorders in some patients [89,90].

Autoacids like PGs play a key role both in the health and diseases of humans. Previous research had observed the role of PGs both for and against bone metabolism [91].

The eicosanoids, prostanoids, and leukotrienes have been attributed to the development/cause of inflammatory and allergic conditions in both humans and animals [92].

In a recent research report, the PGs (PGE1, PGE2), TXs (TXB2), and the other eicosanoids (polyunsaturated fatty acids (PUFAs)) were found to cause/initiate airway inflammation [93].

Eicosanoids are the by-products of the biosynthesis of arachidonic acid using the cyclooxygenase (COX) pathway and generating PGs and TXs, lipoxygenase (LO) pathways forming LTs and lipoxins (LXs), and cytochrome P450 (cytP450) pathways giving rise to several epoxy, hydroxy and dihydroxy derivatives [94]. The COX pathway is inhibited during the therapy with non-steroidal anti-inflammatory (NSAID) therapy. Therapy with the COX inhibitors (COXIBs) may stimulate gastrointestinal ulceration and cardiovascular risk (prothrombotic) as noted by a previous study [95].

Recently, the application of Phosphodiesterase inhibitors (PDEIs) and PG analogs were assessed positively for their use in the treatment of several diseases including atopic dermatitis, vitiligo, alopecia, intraocular pressure, rheumatoid arthritis, wound healing, among others [96,97,98,99].

5. Drug Dosage in Varied Population Groups

Pharmaceutical drugs, although are available, it is significant to adjust drug dosage for a positive effect. Given the potential adverse effects, mechanism of action, and the drug metabolism in various organs of the human body, the drug dosage must be carefully selected in varied population groups (pediatric age, geriatric age, pregnant women, patients with compromised liver, heart, or kidney functions).

The most critical aspect of patient management includes drug dosage. It considers the bodyweight of the person, the age of the patient, and the drug interactions with others simultaneously taken by the patient.

Understanding the drug dosage, its metabolism, and the excretion from the human body assumes significance with regards to its efficacy and to avoid any drug-related adverse reactions.

Some drugs like paracetamol cannot be given to people with liver disease, and the drugs, their dosage is different among adults and children. Few other drugs are contraindicated during pregnancy due to their teratogenic effects (fetal anomalies/birth defects).

The pharmaceutical drugs, although are commonly available, the dosage needs to be appropriately adjusted to various age groups, and special groups (pregnancy, organ failures, geriatric). A previous study by the French database of drugs prescribed and dispensed during pregnancy noted that the safety of medication during pregnancy needs extensive studies to confirm/rule out their role in the development of birth defects or effects of drugs on the psychomotor development of the child [100].

Adverse drug reactions among children are noted to be frequent both by the outpatient medication (1.7%) as well as the hospital inpatient therapy (10%) as noted by a German study [101]. This study emphasized the need for increased clinical trials among the children to better understand the drug reactions and adjust the dosage.

Multiple factors including organ dysfunction, co-morbidities, and drug-drug interactions appear to influence the therapeutic consideration among geriatric age group patients [102].

Although, the pharmacological agents are produced with great difficulty and time, the same amount of significance is attributed to their effective use.

Clinicians and pharmacologists need to get sensitized about the usefulness of the drug dosage, and its utility concerning the patient's age and other conditions like pregnancy and others.

Drugs in pregnancy must be carefully selected and used, since they may show the effect both on the mother as well as the fetus present/growing/developing in the womb. A recent study highlights the importance of understanding the pharmacokinetics of various drugs during pregnancy [103].

In the special group of patients like the pregnancy, the drugs may be absorbed and found in the breast milk. This drug in the mother’s milk may affect the neonates after breastfeeding [104]. Therefore, understanding the safety and efficacy of the drugs during lactation assumes increased significance.

Because of improved life expectancy, the geriatric age group patients consume a greater number of drugs also called polypharmacy. Most drugs are organ targeted like the drugs taken for cardiovascular diseases, some are taken for treating kidney failures and others are used for liver or brain diseases.

A better understanding of drug-drug interactions assumes greater significance to reduce the morbidity associated with such interactions as noted from the recent studies, especially among geriatric patients [105].

6. Conclusions

To sum it up, there are areas of concern in drug discovery, delivery, and potential avenues of research for further improvement. There is an ever-increasing demand for the repurposed drugs, which have been applied to treat/manage new and existing diseases for which there is no treatment available. An increased focus on the endogenous molecules and their pharmacotherapeutic potential warrants further research. Advances in the novel drug delivery systems require additional attention for potential applications in healthcare. We, therefore, should focus on potential areas of research for finding and solving the problems/hurdles which we are currently facing and those which may be expected in the future in the form of newer diseases, and pandemics. The scientific and technological advances in the areas of drug discovery, development, and clinical research must be applied to improving preparedness in the event of biological emergencies like pandemics by novel microbial species, and bioterrorism.

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