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An Overview of Aflat Neurological Diseases and Drug Discovery: An Overview

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Abstract

Hundreds of millions of people worldwide are affected by neurological disorders. More than 50 million people have epilepsy; 7.7 million new dementia cases are reported every year worldwide. Over the last decade, fewer new drugs for nervous system disorders have garnered approval in comparison to other therapeutic areas. An important step of the drug development process is the lead identification and lead optimization to develop the best pharmacokinetic profile for the desired formulation and preferred route of administration. It requires Quantitative Structure-Activity Relationship (QSAR) to understand which modifications will best enhance affinity. Computer-aided molecular design (CAMD) is used in innovative strategies assisting in improving the binding affinities of drug candidates to specific receptors. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) have proven to be useful in phases ranging from preclinical development to the initial stages of clinical testing. The high sensitivity of these imaging modalities makes them particularly suited for exploratory investigational new drug development.

Keywords: *Anti-inflammatory, neurotrophins, neurodegenerative, neurocysticerosis, encephalitis*

Introduction

Any damage to nervous system as a result of injury or illness is the main cause of neurological conditions. These conditions have adverse effect on nerves, spinal cord, brain, and muscles in the body. Dissociative (non-epileptic) attack and functional weakness are commonly faced by a few patients, but these symptoms are genuine and not due to the neurological disease. This is actually the way their nervous system works, and the people facing these problems also show symptoms like numbness, weakness, blackouts, fatigue, and sleep problems. A lot of information is still required to understand the reason behind these functional symptoms while no clear indication of brain damage or illness can be observed on scanning or under microscope. In these conditions, nervous system doesn't function properly and exhibit the range of symptoms that make it more challenging for neurologist to determine the exact way of treating patient.

Previous researches indicated that dietary phytochemicals attack neutrophils that helps to stop or reverse the neurodegenerative diseases. Neurotrophins are important for maintenance, regeneration, and survival of specific neuronal population in the brain. These neurotrophins are identified as neuronal survival-promoting proteins in mammals, include: brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and NT-4/5. A decrease in neurotrophins has been associated with physiological symptoms and the pathology of various neurodegenerative diseases (Venkatesan *et al.*, 2015).

Among the neurotrophins, an extensive study has been carried out on nerve growth factor (NGF) because of its strong relationship with the neurodegenerative diseases. Other than NGF, the most common targets are antistress, anti-inflammatory, antioxidant factors, and AChE inhibitors. Neurotrophins are also considered as one of the promising targets for neuroprotetive agents against degenerative diseases, and neurotrophic administration are quite effective against neurodegenerative diseases. Neurotrophin-based treatments are still under preclinical trials, and exhibit challenges during clinical trials; however, phytochemical from natural sources and synthetic derivatives have been proved to have a great potential to control neurotrophin levels. Moreover, an enhancer or modulator like tropomyosin related kinase (TrK) receptors could contribute to reversal of the neurotrophin loss.

Moreover, the compounds with anti-inflammatory and antioxidant activities are more commonly used to treat neurodegenerative diseases. One of the main examples of such compounds is ladostigil, a neuroprotective agent, which is referred to as one of the effective treatments of Parkinson's disease (PD) and Alzheimer's disease (AD). Ladostigil inhibits caspase 3 activation, cholinesterase, MAO-B, Bad, and Bax. Moreover, it also acts on prosurvival molecule Bcl-2 and enhances the availability of ACh and monoamine neurotransmitters in neuroblastoma SK-N-SH cells (Youdim *et al.*, 2006).

Herbal polypheonols impart a significant part in the amendment of neurodegenerative disease interceded by oxidative pressure. Ginsenosides of Panax ginseng shield dopaminergic neurons from 1-methyl-4-phenylpyridinium incited oxidative pressure by extra impact via advancing neurotrophic aspects (Rudakewich *et al.*, 2001; Chen *et al.*, 2005). Peculiarly, ladostigil likewise improves the statement of neurotrophic factors and persistently actuates neuritogenesis. Multitarget medications that deed the neurotrophin-upgrading impact of ladostigil appear to be substantial signal for phytochemicals role in the effectiveness of brain impairment (Weinreb *et al.*, 2007).

Furthermore, phytochemicals can cooperate with neuroinflammatory arbiters and neurotrophins (NT-5, NGF, NT-3, and BDNF). Nutritive Tocotrienols adequately decrease neuronal cell death by controlling NF-κB, COX-2, Phospholipase A2 and lipoxygenase level (Frank *et al.*, 2012).

Generally, lead bioactive phytochemicals give a successful method for preventing neurodegenerative disease. Phytochemicals and derivatives, for example, 3, 7-dihydroxy-2, 4, 6-trimethoxy-phenanthrene, lignin, limonoid, apigenin and quinic corrosive derivatives, diosniposide B, cyanidin-3-O-β-glucopyranoside, quercetin, clerodane diterpenoids incite neuronal cell separation

and upregulate neurotrophic factors, for example, BDNF and NGF.

Lead phytochemicals possibly anticipate and capture neurodegeneration by actuating neurotrophic factors and by boosting the action of specific segments of the cell reinforcement framework, for example, catalase and superoxide dismutase (SOD). Polyphenols actuate neurotrophins and have antioxidative and antiapoptotic exercises in neurons (Hur *et al.*, 2004; Chen *et al.*, 2009). Neuroinflammation-mediated neurodegeneration can also be treated effectively through Floridoside. Floridosisde is an oxidant mostly obtained from Rhodophytes, there in algae it may serve a dual functions: first, to serve as a compatible organic osmolyte in response to elevated salinities and, second, to counter reactive oxygen species produced as a consequence of potential salinity and heat stress.

Molecular techniques are considered as a decision-making tool during initial stages of drug discovery and clinical trials. Nuclear imaging techniques are used in early clinical development to validate the potential drug targets and to study pharmacokinetics of the drug. Moreover, evaluation and assessment of biodistribution and drug-target interaction can also be investigated using nuclear imaging techniques. In addition, its mechanistic aspects linked to the therapeutic intervention (proof of principle) and on proof of concept testing can also be performed using imaging-based biomarker (Rudin and Weissleder, 2003; Willmann *et al.*, 2008).

The clinical benefits provided by the drug-induced biological changes demonstrate the proof of concept. Potential imaging biomarkers labeled with γ-emitting radionuclides and positron have been developed in adequate number and currently going through preclinical or clinical testing. Some of these labeled biomarkers have a huge impact on the development of drug, and provide information regarding drug-target interaction and efficacy of drug in early clinical studies (Richter, 2006; Rudin, 2007).

Single-photon emission computed tomography imaging (SPECT) on small animals exhibit high resolution and sensitivity, which can later be translated during clinical practice into human SPECT imaging. Both of the quantitative and qualitative measurements of physiological processes can be obtained by this method. Various types of isotopes can be used for SPECT scan involving ^{111}In, ^{99}Tc, ^{125}I, ^{123}I that are comparatively less costly with longer half-lives as compared to those used in PET imaging. The longer half-life of these isotopes helps to increase the scanning periods, also eliminates the requirement of secondary isotope administration. That makes it possible to carry out scanning using the lower number of subjects with comparatively smaller amount of isotopes; moreover, large data are obtained over long span of investigation period using small number of animals (Lucignani, 2007).

Positron Emission Tomography (PET) is one of the sophisticated nuclear imaging methods that help the researchers to carry out both molecular and functional imaging on biological and biochemical processes in vivo. Functional imaging is used to monitor any change in metabolic rate caused due to disease or its treatment. PET is actually involved in quantitative examination of cellular events like receptor binding, cell trafficking, and gene expression. Thus, PET plays a major role to explain the

mechanisms linked with drug actions and diseases. Similar to PET, microPET has been designed and introduced that is used to image small animals and considered as a great tool to facilitate basic research and preclinical studies. By using these methods, animal's scarification can be avoided by creating the possibility of longitudinal, non-invasive, and serial studies (Wang and Maurer, 2005).

Neuronal Disorders

Neuronal disorders encompass any disorder in the nervous system including structural, biochemical and electrical disabilities of spinal cord, brain or related nerves exhibiting wide range of symptoms. Paralysis, poor coordination, muscle weakness, seizures, loss of sensation, confusion, and altered level of consciousness are among the major of neuronal disorders.

Dementia

Dementia is a chronic or progressive nature of brain disease that can be detected due to disturbance found in multiple higher cortical functions involving thinking, comprehension, memory, orientation, learning capacity, calculation, judgment and language; however, consciousness remains unaffected. This disorder mainly affects aged people; however, only in less than 2% cases the onset of the disorder can be found in patients before 65 years of age. After this, the prevalence of disorder doubles every five years and attributes to one of the major cause of disability in later life.

Epilepsy

Contrary to dementia, epilepsy affects both sexes of all ages with worldwide distribution. The term 'Epilepsy' is used for a large group of conditions that are collectively characterized by a common symptom 'epileptic seizures' that might be attributed to metabolic, toxic or systemic brain insult. These acute or provoked symptomatic seizures are considered as an acute manifestation of the brain insult that can be completely avoided to reappear by removing the underlying causes, or when acute phase passed (Hauser *et al.*, 1993).

Headache Disorders

Relatively, a small number of primary headache disorders are characterized by a painful headache condition, which is often life-long and widespread. Headache is also recognized as a major symptom of many other disorders hence termed as secondary headache disorder. In short, headache disorders cause substantial disability in world's population making it one of the most common disorders of nervous system.

Multiple Sclerosis

Multiple sclerosis is considered one of the most common neurological disorders of young adults affecting about 2.5 million people around the world, especially in North America and Europe. In Asia, the less prevalence might be attributed to lack of epidemiological studies; however, more cases are being reported now with the advancement and availability of more neurologists and magnetic resonance imaging. A mild disability is found in some of the patients, whereas after 20 years from the onset of the disorder 60% patients cannot walk properly.

Neuroinfections

The term neuroinfections refers to the diseases that adversely affect the nervous system of millions of people, worldwide.

Neuroinfections are considered as sixth main cause of neurological consultation in primary care services. A quarter of WHO's Member States and by half of the countries in some parts of South-East Asia and Africa has reported these diseases. Since ancient times, neuroinfections were given a huge importance. Especially in developing countries, it is still considered as one of the major challenges of the world even after the discovery of antibiotic and vaccines (Ferri and Ames, 2004).

Viral Diseases

The causative agent of acquired immunodeficiency syndrome (AIDS) is a retrovirus commonly known as human immunodeficiency virus (HIV), which causes impairment in body immune system against infection and disease. The progression of HIV virus may take years to make a person seriously ill. During this time, different viruses, bacteria and parasites take benefit of the impaired immune system of HIV-infected person that makes the body of the infected patient weaker, leaving him or her vulnerable to various diseases like tuberculosis, pneumonia and mycosis. The person is considered as AIDS patient when he or she starts developing infections from attack of opportunistic infections. The time span taken by a HIV-infected person to develop AIDS depends upon health and nutritional status before and during HIV infection. For an average adult with no antiretroviral therapy (AVT), it takes approximately 10 years for full-blown AIDS after the start of HIV infection. Women are more likely to develop AIDS as compared to men, and the disorder can also be found in children (Saunders *et al.*, 1993).

Viral Encephalitis

Acute viral encephalitis commonly affects children and young adults, and is often considered as an unusual manifestation of viral infection. With the passage of time, more kinds of viruses are now associated with encephalitis. The variable presence of encephalitis depends on geographical zone, age group, and patient's state of health and season of the year. In the USA, incidence of viral encephalitis are approximately 3.5-7.4 cases per 100,000 population. Moreover, some causes of the viral encephalitis was also estimated; for example, herpes simplex encephalitis (HSE) exhibited the yearly incidence of approximately one per million.

Patients infected with viral encephalitis exhibited an acute onset of a febrile illness along with the clear symptoms of focal neurological signs, meningeal irritation, seizures, behavioral and speech disturbance and alteration of consciousness. The diseases can be diagnosed through electroencephalography, neuroimaging technique, and immunological test and in some cases brain biopsy.

All types of encephalitis are not curable and the patient can only be supported through medication. The severity of sequlae and death rates mainly depend on causative agent of the disease. The mortality rate of herpes virus encephalitis is estimated as 70%, and severe sequaele among survivors may also be exhibited. Medical therapy used for herpes virus encephalitis includes the use of vidarabine and acyclovir. The disease can be avoided by using preventive measures like vector control by reducing water holding objects and old discarded tyres. A few vaccines are also being used as

preventive measure that includes western equine encephalitis, eastern equine encephalitis and Venezuelan equine encephalitis in horses. Different viruses may also spread through international trade and travel that was mainly observed during 1999 outbreak of West Nile virus in New York with following spread to other states (Aziz *et al.*, 1997).

Poliomyelitis

The causative agent of poliomyelitis might be one of the three related viruses i.e. poliovirus 1, 2 or 3. The poliovirus is mainly spread through the fecal-oral route. The poliovirus may enter along with the infected food when a person ingest any food already contaminated with feces,

When the virus reaches to the intestine, it multiplies there and enters into the blood stream and ultimately cause damage to various types of nerve cells. This virus can be easily spread in areas where people follow poor hygienic practices. Poliomyelitis can be commonly found in any person with paralytic illness and the child below 15 years of age with acute flaccid paralysis.

Rabies

Rabies is one of the most frequently reported diseases in medical literature and considered as one of the oldest and most feared disease of that time. It is actually an animal disease having an ability to transmit into humans and considered as a viral zoonosis, which belongs to genus Lyssa virus. Several wild and domestic animals that act as reservoir species are responsible to maintain this disease in nature that include foxes, dogs, raccoons, mongooses, skunks and some species of bat. As concerned with human health, dogs are considered as the most dangerous reservoir that accounts for 99% of human deaths. It is estimated that 50 thousand people die from rabies disease annually while most of such cases are reported in Africa and Asia.

Mycobacterial and other Bacterial Diseases

Tuberculosis

Nervous system tuberculosis is quite hard to diagnose because of the limited access of methods to confirm the disease and its nature of great simulator (Carpio *et al.*, 2005). The diagnosis of this disease mainly depends on clinical and epidemiological findings and collected data obtained during neuroimaging, cerebrospinal fluid (CSF) and bacteriological studies. Peripheral neuropathy might be observed in patients suffered from tuberculosis; however, it is not the direct consequence of the disease. Peripheral neuropathy might be attributed to the side effects of tuberculosis treatment through isoniazide, and more profound side-effects can be observed in alcohol users, malnourished or HIV infected patients.

Leprosy Neuropathy

Mycobacterium leprae is the major causative agent of leprosy that attributes to the most common treatable neuropathy in the world. The incubation period of the bacterium is reported as five years; however, the symptoms can appear even after 20 years. Nerves can be infected from the bacterium either via direct invasion or the immunological reactions. In rare cases, leprosy neuropathy might be present without any appearance of skin lesions (neuritic form of leprosy) that makes it hard to be diagnosed. In such cases, patients only exhibit the symptoms of muscle weakness,

sensory impairment that makes it difficult to be diagnosed especially in those areas where nerve biopsy, bacilloscopy and elctroneruomycography are not available.

This delay in diagnosis sequentially cause delay in the treatment that may result in serious disability even after elimination of mycobacteria. The long term leprosy may affect the patients to the extent that they ultimately become unable to use their feet or hand due to repeated injury caused by the loss of sensation. WHO recommended the early diagnosis and treatment with multidrug therapy (MDT) to avoid the progression of disease that may ultimately results in disability.

Bacterial Meningitis

In children and adults, one of the very common causes of mortality, morbidity and neurological complication is *Bacterial meningitis*, which is comparatively more common among children. For every 100,000 adults of age above 16 year, 4 to 6 cases are reported yearly. In developing countries 33-44% case-fatality rate was reported which increases up to 60% in adults (Meyer *et al.*, 2010). Around 80% of all cases in developing countries are caused by *Streptococcus pneumoniae* and *Neisseria meningitides* (Dua *et al.*, 2005).

Tetanus

The exposure to the spores of the bacterium *clostridium tetani*, commonly found in soil, is considered as the main cause of the disease tetanus. The growth of bacteria in dead tissues produces neurotoxins which are mainly responsible for the disease. Those dead tissues can be found in either dirty wounds of umbilicus following non sterile delivery in case of neonatal tetanus. The disease is not easily transmitted from one person to another. At the end of the 1980s, neonatal tetanus was one of the major public health problems. According to a report released by WHO, 787,000 newborn children were died from neonatal tetanus in 1988 that means 6.5 cases were reported per 1000 live births. In 2002, worldwide death numbers were reduced to 213,000 out of which 198,000 children were younger than five years. The reported cases were further reduced in subsequent years and only 13,448 cases were reported during 2004 (Begley *et al.*, 2000).

Parasitic Diseases

Neurocysticercosis

A parasitic disease, cytocercosis is one of the major health problems of developing countries in Asia, Africa and Latin America. Tourism and the high immigration rates from endemic to non-endemic areas have spread the neurocysticercosis in those countries too that was previously free from the disease. In some low income countries, neurocysticerosis remains endemic and considered as the main cause of acquired epilepsy despite the advancement in diagnostic and therapeutic techniques. Annually, 50,000 reported deaths are caused due to neurocysticercosis, while those who survived exhibited an irreversible damage of their brain, while up to 70% patients exhibited seizures. A few reports from Latin America has presented and association between cytoceriosis and about 30% from all of the seizures (Kwan and Brodie, 2002).

Cerebral Malaria

Malaria is one of the major human's health problems in tropic areas like Africa. There are four different species of

Plasmodium that have the ability to infect humans; however, only *Plasmodium falciparum* may enter into the capillaries of central nervous system and cause cerebral malaria. The parasite is inoculated into the skin when anopheles mosquito stings the skin of human. Some cerebral malaria patients exhibit small hemorrhages, diffused cerebral odema and occlusion of cerebral vessels by parasitized red cells. Thus, falciparum malaria not only cause mortality and infection but may also involve in causing neurocognitive sequelae (Kwan and Sander, 2004). The presence of *P. falciparum* is determined by examining the blood smears with Giemsa stain. Repeated blood examination is required because of cyclical nature of parasitemia. The disease may also be diagnosed via neuroimaging studies exhibiting cerebral infracts and brain swelling of small hemorrhages in severe cases. Drug administration involves the use of quinones and arteminisinin derivative in order to treat cerebral malaria. Despite all treatment strategies mortality rate is quite high in patients suffering from cerebral malaria (Engel Jr, 1997).

Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoal parasite, which is the main causative agent of the disease toxoplasmosis. The disease either follow oral or transplacental mode of transmission. The disease is caused by the direct entry of infective oocytes in vegetables contaminated by feline feces, or through the consumption of meat which is not properly cooked and contains viable tissue cyst (mainly lamb and pork). The transplacental infection might be transmitted if the mother suffered from acute infection, or the latent infection is reactivated in immune-suppressed patients. In immunesuppressed mother, a primary infection during the early stages of pregnancy may cause the death of the unborn baby (fetus) or severe postnatal effects may also be observed. However, if the mother is infected at later stages it shows either mild or subclinical fetal diseases. In most of the adults, *T. gonidii* infections are subclinical; however, in immunocompromised patients like those suffered from malignancies and AIDS exhibit severe infections. The organs affected by *T. gonidii* may include white and gray matter of brain, alveolar lining of lungs, retina, skeletal muscles and heart.

Neurological Disorders Associated with Malnutrition

Malnourishment is one of the major causes of the increased risk of disease and early death. Around 800 million people around the world are facing the problem of malnourishment. It mainly affects those who have poor living standards and doesn't have enough food to eat, having inadequate access to clean water and health education. In low income countries, inadequate amount and diversity of the food is mainly responsible for serious health issues that includes retarded growth, child malnourishment and a severe deficiency in micronutrients like minerals, vitamins or trace elements. However, most of the neurological disease associated with malnourishment is preventable.

Preventive Strategies for Neurological Disorders

Primary Prevention

The primary prevention includes the prevention from the onset of disease to avoid certain conditions. One of the main

examples of primary prevention is the use of polio vaccines to eradicate indigenous poliovirus from all over the world but four countries. Similarly, different measures adopted to control cholesterol level, blood pressure, diabetes mellitus, to reduce the use of tobacco and to promote healthy physical activities and improved diets helps a person to avoid neurological stroke and considered as some important means of primary prevention. In Japan, government mainly focus on health related educational campaigns that helps treat high blood pressure and reduce the blood pressure. The stroke rate in their country has reduced to 70%. Motorcycle helmet can also be considered primary preventive measure that helps to lower the rate of head injuries resulting from the cycle and motorcycle crashes. It has been reported that the use of helmet reduces the risk of severe injuries in motorcyclist about 70% and death by 40% thus lower the budget required for health care associated with such accidents.

Secondary Prevention

The secondary prevention includes accurate diagnosis at early stages, proper treatment, risk factor management and compliance. The adequate treatment of epilepsy with first-line antiepileptic drugs leaves 70% patients free of seizure. In comparison to a general ward, mortality and disability is greatly reduced by patient's management by an organized unit.

Tertiary Prevention

Tertiary preventions include care, rehabilitation, self-support group, social integration, treatment of complications and reduction of stigma and discrimination. The target to depression and stress among caretakers of dementia patients involving counseling and training to caretakers has shown positive results for the management of dementia. In many low income countries various community-based rehabilitation strategies has been implemented. Its practice has immense influence to the participation and quality of disable person's life. Various methods were applied in African community to decrease the stigma related to epilepsy which in turn altered the attitudes towards epilepsy. The cultural beliefs regarding epilepsy were became weak and the fearless attitude progress that improve the acceptability of epilepsy patients in the society.

Bioactive Lead Compounds

Phlorotannins show various striking properties on biological systems, specifically cancer preventing agent, militating, against unfavorably susceptible, antimicrobial, anticancer and antidiabetic actions. Additionally, phlorotannins likewise show an imperative job in neuroprotection through various mechanisms (Barbosa *et al.*, 2014). Dieckol down-regulate the NF-κB, activate p38 kinase or inhibit ROS signal in microglial cells and hence effectively reduce the release of pro-inflammatory cytokines and mediators. Dieckol regulate the neuroinflammation and oxidative stress. Indicated by experiments it was noted that, dieckol, triphlorethol A, phloroglucinol, eckol and aeckstolonol were effective in hippocampal HT22 cells against H_2O_2-induced neurotoxicity (Kang *et al.*, 2012). Polyphenolic compounds extracted from Macroalgae have great potential in controlling neurodegenerative processes.

Alkaloids display multiple pharmacological effects like growth regulation, neuromodulator, cytotoxicity,

neurotransmission, angiogenesis, and antioxidant, together with antifungal, larvicidal and antiviral activities. Two novel bisindole Aacemosins A and B, bisindole alkaloids were assessed *in vitro* for neuroprotective action against Aβ-induced SH-SY5Y cell damage. The human neuroblastoma cell line SH-SY5Y is presently applied in neuroprotection studies as *in vitro*-simulated ischemia model. SH-SY5Y cells are generally recognized sensitive to oxidative stress and to direct glutamate receptors. The two complexes displayed a assured degree of neuroprotection, racemosin A existence the most powerful agent, which suggests that the characteristic scaffold of this certain alkaloid can be accountable for the inflection of significant progressions intricated in neurodegeneration (Liu *et al.*, 2013; Barbosa *et al.*, 2014).

Sargachromenol, a plastoquinone secluded from *Sargassum macrocarpum* indorse nerve growth factor (NGF)-dependent neurogenesis in PC12 cells, in a dose-dependent manner. NGF has vital role in regeneration, differentiation and survival by exciting neuritis outgrowth in neuronal and rat phaeochromocytoma cells. The neuroprotective influence by sargachromenol valored by the stabilization of microtubule amassing and extension of neuritis *via* protein kinase A (PKA) and MAPK signaling conduits (Tsang *et al.*, 2005; Wang *et al.*, 2005). Sargachromenol and sargaquinoic acid were studied as NGF-potentiating constituents might adjust cellular responses, such as neuroprotection, neuronal differentiation and repair in the CNS.

Fucoxanthin is able to attenuate neuronal cell damage in cortical neurons under hypoxia and re-oxygenation. Ever since ROS generation is reflected to ensue after hypoxia and oxygen reperfusion, it was implicated that the neuroprotective commotion of fucoxanthin is primarily grounded on its scavenging potential (Lee and Jeon, 2013). Fucoxanthin subdues indices of oxidative damage and inflammation in microglial cells, dynamics that implicated in the pathogenesis of neurodegenerative diseases. The properties were arbitrated through attenuation of the phosphorylation MAPK signaling pathway, as well as by the free radicals scavenging ability of fucoxanthin and its capability to normalize the endogenous antioxidant system (Barbosa *et al.*, 2014).

Chlorophylls are lipid-soluble pigments operationally categorized by the presence of a relieved tetrapyrrole with a centrally bound magnesium atom; the porphyrin tetrapyrrole is additionaly esterified to a diterpene alcohol, phytol for chlorophyll formation (Ferruzzi and Blakeslee, 2007).

Chlorophylls are subtle to great temperature and pH conditions, permitting the development of numerous derivatives, like pheophytins. Pheophytin A, a chlorophyll *a*-related constituent of certain macroalgae species, displayed robust neurodifferentiating constituents. Several *in vitro* and *in vivo* investigations resulted that C-PC scavenge numerous radicals, like alkoxyl, hydroxyl and peroxyl, to inhibit lipid peroxidation, prevent oxidat C-PC protect SH-SY5Y cells from iron toxicity (Bermejo-Bescós *et al.*, 2008; Barbosa *et al.*, 2014).

Numerous *in vitro* and *in vivo* experiments displayed fucoiden neuroprotective effects (Cui *et al.*, 2010; Park *et al.*, 2011). K-carrageenan with 3,6-anhydro-α-d-galactopyranose showed protuberant biological effects, comprising anti-inflammatory, antitumor and

antioxidant activity. κ-carrageenan could possibly be applied for averting the neurodegenerative progressions of several CNS diseases (Barbosa *et al.*, 2014).

PUFAs are linked to membrane fluidity and integrity. DHA that is a key omega-3 PUFA, it's supply is indispensable for apposite brain, eye, and nerve functioning. Therefore such PUFAs as significant nutraceutical defenses against neurogenerative disorders (Ward *et al.*, 2012). Possible reason of dementia is the high consumption of SFA and Low intake of PUFAs. DHA amplify cortical brain derived neurotrophic factor (BDNTF) and its ethanolamide metabolites displayed to endorse neuritis development and synaptogenesis.

Molecular Targets for Drug Development

The technological breakthrough inferring advanced computational and experimental methods have majorly contributed in the process of drug designing. These drug design methods are proved to have an immense importance to predict identification of hits, biological profiles, generation and optimization of lead into drug candidates. Molecular imaging techniques are most widely used to investigate the drug development process.

Quantitative Structure-Activity Relationship (QSAR)

One of the most famous computer based tool used in medical chemistry for the discovery of drug and lead optimization are quantitative structure-activity relationship (QSAR) modeling. Since the time of its first introduction, QASR methods have gain a lot of public interest. They are more widely applicable when the 3D structures of specific drug targets are absent.

Since 1868, chemical structure of compounds is correlated with their biological activities, and various methods have been proposed for this purpose (Selassie and Verma, 2003). During early stages, physicochemical properties were commonly used for QASR analysis, like hydrophobic constant (π).

Today, a few requirements need to meet in order to construct and apply QASR models. For applicability, it requires a compound set that has already been tested under the similar experimental conditions against an identified molecular target, tissue, cell or even microbes, and exhibit a minimum variance in observed response (Roy *et al.*, 2015).

After the selection of suitable dataset, QASR modeling follows main steps that involve molecular /physicochemical properties, variable selection model generation from various algorithms and the process validation via external of internal dataset.

The QASR model can be used to predict biological activities of newly collected samples and physicochemical interpretation of the observed phenomena could also be conducted that helps to provide a detailed insight to construct new bioactive chemicals and/or their mode of actions. QASR model exhibit wide applications, and are widely used in different steps of drug design process, especially, it helps to determine the binding affinity of any compound with specific molecular targets. This modeling also helps to understand general phenomena like toxicity related end points and pharmacokinetics (Tong *et al.*, 2004).

Even today, animal test models are considered quite important in order to evaluate chemical safety, thus the testing of chemical toxicity and the development of alternative methods may improve our understandings of disease at various biological levels (Patlewicz *et al.*, 2016; Pradeep *et al.*, 2016). Various methods have been developed that represent many layers of human metabolism and physiology of both healthy and diseased body (Tomic *et al.*, 2000; Patlewicz *et al.*, 2016). Some research groups have also built local QASR models to explain the problems of hepatotoxicity, sensitization and DNA harming agents. It can be predicted that future advancement will bring the improvement in validation techniques, and the generated data will grow because of the improvement in quality of data which in turn lead to broader QSAR models.

Computer-Aided Molecular Design (CAMD)

Computer Aided Molecular Design (CAMD) along with computational chemistry is considered as one of very efficient disciplines of chemistry with striking projections. The cost of experimental synthesis has greatly reduced due to virtual designing of novel compounds with well-defined properties, which in turn promotes more investment in the field of theoretical research. The designing of chemical structure with well-defined desirable therapeutic characteristics has greatly promoted CAMD.

A lot of advantages are associated with the use of CADD in drug discovery including cost reduction and time-to-market showing that CADD prediction may help in selection of promising lead candidates which greatly contribute to save the time spent on dead end compounds with no valuable outcome. Moreover, for researchers, CADD also provide a thorough understanding of drug receptor interactions. In addition, CADD uses structure or ligand based virtual screening that helps to identify hits, optimization of hit-to lead for affinity and selectivity (SBDD, LBDD) and maintenance of the affinity by optimization of other pharmaceutical properties of lead.

Single-Photon Emission Computed Tomography (SPECT)

Single-photon emission computed tomography (SPECT) helps to investigate multiple molecular or cellular events because of its distinctive capability of imaging isotope labeled multiple probes (Gomes *et al.*, 2011). Previously, SPECT was solely employed for human use; however, this system is scaled down to small animals for providing their high resolution imaging that make it possible in early stages of development to screen and investigate the potential drugs. The challenges related to camera sensitivity, image reconstruction, spatial resolution and quantification are needed to be addressed.

Recently, designed system offers a comparatively better quantitative accuracy and high quality image with submilimeter spatial resolution by using tomographic reconstruction methods and pinhole collimation (DiFilippo, 2008).

Nowadays, multimodality imaging combining SPECT with computed tomography (CT) in a dual-modality system (SPECT/CT) provides accurate quantification and localization of radiolabeled imaging probe that makes it possible to acquire detailed and functional anatomical information. A huge interest has been arisen due to its application in

preclinical research and medical sciences using small animals (O'Connor and Kemp, 2006. This technique may help to translate the research from bench to bedside because of its use in both animals and human that increases the speed of process and contribute majorly to reduce the cost of the new drugs introduced in the market.

Nuclear Medicine techniques like SPECT and PET can be employed in vivo to image the trace quantities of radiolabelled candidate drugs. The higher sensitivity of the technique makes it possible to detect even nano and pico range of radiolabelled drug.

Such a minute quantity of drug doesn't exhibit any pharmacological effect thus reducing the risk of any negative effect in volunteers or patients.Depending on radionuclides and ligands, the target properties of radiolabelled drug can be assessed using microdosing imaging approach, which can help to generate pharmacokinetic data. Thus, the evaluation of the drug under development leading to early approval process can be possible by employing this tool. In ideal conditions, the physicochemical properties of radiolabelled molecule remain same as parent molecule, which can be possible through direct radiolabeling by the replacement of stable atom by a radioactive isotope as in PET molecule 12 C is replaced by 11C. For SPECT imaging, a few small drug novel molecules were developed that contain γ-emitting radioisotopes.

Positron Emission Tomography (PET) Imaging

Positron Emission Tomography (PET) is a type of quantitative and functional imaging that helps to quantify radiotracer's behaviors in vivo. Moreover, the biochemical interaction between the target protein and radiotracers can be determined.

Four major categories of drug development includes: (a) The detection of tissue kinetics and drug distribution when the drug molecule is labeled with positron-emitting radioisotopes (b) Proof of target- to determine either the drug reaches to specific target or not (c) Proof of Mechanism- to determine either the specific target interact with a sufficient level of drug required to stimulate pharmacological effect. (d) Proof of Efficacy- to determine the effect of drug to alter the pathology of disease being treated. However, sometimes a single PET imaging serve as dual purpose like providing information for both the proof of target and proof of mechanism (Huang and Carson, 2012).

Conclusion

An important step of the drug development process is the lead identification and lead optimization to develop the best pharmacokinetic profile for the desired formulation and preferred route of administration. Molecular techniques are considered as a decision-making tool during initial stages of drug discovery and clinical trials. The technological breakthrough inferring advanced computational and experimental methods have majorly contributed in the process of drug designing. Furthermore these drug design methods are proved to have an immense importance to predict identification of hits, biological profiles, generation and optimization of lead into drug candidates.

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