PAST, PRESENT AND FUTURE OF MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Abstract

The ancient history of medicinal chemistry records to the use of plants having therapeutic applications and minerals with medicinal properties which were developed through the primordial Chinese cultures, the Mediterranean peoples of antiquity, the Mayans of Central America, and the Hindus during 3rd Century BC. Theophrastus used opium poppy juice for treating and relieving pain while in 10^{th} Century BC. Researchers reported in 'Past, Present and Future of Medicinal Chemistry and Drug Discovery' that the drug is a medicinal agent that is designed and synthesized to show desired biological effect on living organisms. The science that deals with such design and synthesis of biologically active molecules is known as pharmaceutical chemistry. Any advancement in the field of scientific technology catches instantly its applicability in pharmacy, as well as medicine, in drug discovery plus drug development. AI has brought a new prospective to the field of drug discovery and its development. Examples of AI-driven innovations in pharma industries: 1. AI-driven Acceleration 2. High Throughput Screening process embedded with AI Technology. Human biology is extremely multifarious, but AI and Machine learning are helping us to make further sense of it. The outcome is improved medicines, technologically advanced quicker, for the treatment or curing many more patients.

Keywords: Medicinal Chemistry; Drug discovery; Artificial intelligence; High throughput screening.

Authors

Hasti Kenia
BLDEA's SSM College of Pharmacy and Research Centre
Vijayapur. Karnataka, India
hastikenia.25@yahoo.com

Dr. Santosh Karajgi
BLDEA's SSM College of Pharmacy and Research Centre
Vijayapur. Karnataka, India
santosh.karajgi@gmail.com

I. INTRODUCTION

The drug is a medicinal agent that is designed and synthesized to show desired biological effect on living organisms [1]. The science that deals with such design and synthesis of biologically active molecules is known as pharmaceutical chemistry [2]. Medicinal chemistry is sub division of pharmaceutical chemistry which deals with the isolation of compounds from natural resources; discovery of new chemical entities; correlating the activities of isolated and synthesized compounds with the receptors or targets; determination of ADMET properties and their development into useful medicines to treat diseases and disorders [3].

The ancient history of medicinal chemistry records to the therapeuticuse of herbs and plants and inorganic minerals which were originated from the prehistoriccultures of the Chinese, the Mediterranean peoples of antiquity, the Mayans of Central America, and the Hindus [4, 5]. The manuscripts written by Hippocrates, Dioscorides, Pliny and Galenus describe the therapeutic application of plants used by ancient Greeks and Romans [3]. In 2735 BC, The Emperor Shen Nung complied the data including the use of ch'angshang, an antimalarial alkaloid [4, 3] and Ma Huang, diaphoretic and adrenergic agonist recommended for asthma, heart stimulation and nasal congestion. During 3rd Century BC, Theophrastus used opium poppy juice for treating and relieving pain while in 10th Century BC the same was used for treating cough and mental disorders along with pain in the form of pills. The root the plant ipecaccomprisingthe chemical emetine was in use for the cure of dysentery in Brazil.Red Indians of South American origin used to chew coca leaves comprisingthe chemical cocaine and employed mushrooms comprisingthe chemical methylated tryptamine as hallucinogens [3].

The middle age history of medicinal chemistry shifted from the Greco-Roman to the Arabian alchemists [4]. In 1633, extract from the cinchona bark was used for chills and fever by South American Indians. In 6th Century AD Alexander of Tralles, in 11th Century AD Avrienna and in 1763 Baron Anton von Störck recommended Autumn crocus (*Colchicum autumnale*) to relieve thesoreness of the joints and for treating gout [3].

Modern treatment especially for treating CHF began from the extraction of secondary glycosides obtained from the plants *Digitalis purpurea*in addition to*Digitalis lanata* containing digitoxin and digoxin correspondingly [3]. During the 19th Century, the prominence shifted to finding new natural and/or synthetic active ingredients with active pharmacological ingredients. The separation and process of isolation of the drug morphine by Friedrich Sertürner in the year 1803, the process of isolation and separation of the substance emetine from ipecacuanha by Pierre-Joseph Pelletier in the year 1816, and the process of separation and purification of caffeine, quinineand colchicine, in the year 1820 altogether added a great contribution to the augmented use of "purest" materials in the form of therapeutic agents [4]. In the year 1928, accidental discovery of Penicllin by Alexander Fleming entirely changed the overview of the medicinal compounds. In 1940, Woods and Fildes identified the bacteriostatic action of sulphonamides and its analogues which showed p-amino benzoic acid inhibition. This revealed that depending on chemical structure agonistic and antagonistic activities changes [4].

II. PRESENT SCENARIO

Since ancient times to till date, millions of chemical moieties have been studied to explore their pharmacological activities. Most of them may have failed due to their instability or toxicity related issues. Despite the failure, many compounds have emerged as pharmaceutically active moieties. Table 1 shows data of various classes of drugs, their prototype molecule, newer generation molecules and various other drugs that are been used for various ailments (Table 1).

Table 1: Different Classes of Drugs Including the Prototype of the Class, Newer Generation of Drugs and Different Marketed Drugs for the Same Class

Sr. No	Class of drugs	Prototype	Newer generation drugs	Various marketed drugs
	Antimicrobials			
1.	Antimalarials	Chloroquine	Artemisinin	Amodiaquine, Primaquine, Pamaquine, Mefloquine, Cycloquanine, Proguanil, Atovaquone
2.	Anti-tubercular drugs	INH (Isoniazide)	Bedaquiline	Ethionamide, Ethambutol, Pyrazinamide, Para amino salicylic acid
3.	Anti-fungals	Benzoic acid	Albaconazole	Salicyclic acid, Clioquinol, Miconazole, Clotrimazole, Econazole, Nystacin, Natamycin
4.	Anti-viral a. Anti-Herpes b. Anti-Influenza c. Anti-Hepatitis d. Anti-Retrovirus	 Idoxuridine Amantadine Lamivudine Zidovudine	 Pritelivir Peramivir Tenofovir Cabotegravir	Trifluridine, Acyclovir, Famiclovir, Ganiclovir, Cidofovir, Foscarnet Rimantadine, Oseltamivir, Zanamivir Ribavinir, Adefovir, Interferon-α, Didanosine, Stavudine, Lamivudine, Tenofovir
5.	Anti-protozoals	Metronidazole	Tinidazole	Ornidazole, Iodoquinol, Pentamidine
6.	Anthelmintics	Diethylcarbazine citrate	Ivermectin	Mebendazole, Albendazole, Nicolsamide, Oxamniquine, Praziquentel
7.	Antibiotics a. β-lactams (i) Penicillins (ii)Cephalosporins b. Tetracyclines c. Aminoglycosides d. Macrolides	Benzylpenicilin Cefazolin Tetracycline Streptomycin Erythromycin Clavulanic	 Mezlocillin Cefepime Minocycline Paromomycin	Mithicillin, Ampicillin, Amxocicillin, Cloxacillin, Cabencillin Cephalexine, Cefuroxime, Cefprozil, Cefotaxime, Ceftazidime, Cefoperazone

	e. β-lactamase inhibitors	acid	Spiramycin Doripenem	Doxycyclin, Chlortetracyclin, Oxytetracyclin, Demclocyclin Gentamycin, Kanamycin, Tobramycin, Amikacin, Netilmicin Roxithromycin, Clarithromycin, Azithromycin Sulbactam, Tazobactam, Aztreonam
8.	Sulphonamides	Sulfadiazine	Sulfasalazine	Sulfamethoxazole, Sulfadoxine, Sulfamethapyrazine, Sulfacetamide, Mefinide
	Drugs acting on CVS			
9.	Antihypertensives a. ACE Inhibitors b. ARBs c. Calcium channel blocker d. β/ α - adrenergic blockers e. Vasodialators	Captopril Losartan Verapamil Propanolol Hydralazine	Ramipril Telmisartan Benidipine Satolol Diazoxide	 Enalpril, Lisinopril, Reindopril, Fosinopril Candisartan, Irbesartan, Valsartan Dilteazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine Metoprolol, Atenolol, Labetalol, Carvedilol, Esmolol Minoxidil, Sodium nitropruside
10.	Anti arrhythmic a. Sodium channel blockers b. β-blockers c. Repolarizers d. Calcium channel blockers	Quinidine Propanolol Amiodarone Verapamil	Flecainide Carvedilol Ibutilide Benidipine	Procainamide, Disopyramide, Lidocaine, Mexiletine Metoprolol, Atenolol, Labetalol, Esmolol, Satolol Dronedarone, Dofetelide Dilteazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine
11.	Anti-anginal a. Nitrates b. β-blockers c. Calcium channel blockers d. Potassium channel opener	Glyceryl trinitrate Propanolol Verapamil Dipyridamole	Pentaerythritoltetranitrol Carvedilol Benidipine Oxyphedrine	Isosorbide dinitrate, ErythritylTetranitrate Metoprolol, Atenolol, Labetalol, Esmolol, Satolol Dilteazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine

				Trimetazidine, Ranolazine, Ivabradine
12.	Anticoagulants	Heparin	Dabigatran	Fondaparinaux, Danaparoid, Bishydroxycoumarin, Rivaroxaban
13.	Antihyperlipedaemic	Lovastatin	Ezetimibe	Simvastatin, Atorvastatin, Rosuvastatin, Colestipol, Clofibrate, Gemfibrozil, Bezafibrate
	Drugs acting on CNS			
14.	General anaesthetics a. Inhalation b. Intravenous	Ether Thiopentone sodium	Sevoflurane Etomidate	Halothane, Isoflurane, Desflurane Methohexitone sodium, Propofol, Ketamine, Fentanyl
15.	Sedatives and Hypnotics a. Barbiturates b. Bezodiazepines	Barbital Diazepam	Phenobarbitone Triazolam	Butabarbitone, Thiopentone, Methohexitone. Flurazepam, Nitrazepam, Alprazolam, Oxazepam, Clonazepam, Lorazepam,
16.	Anti-epileptics	Primidone	Tiagabine	Phenotoin, Fosphenotoin, Carbamazepine, Valproicaicd, Gabapentine, Lamotrigine
17.	Anti-psychotics	Chlorpromazine	Cariprazine	Triflupromazine, Thioridazine, Haloperidol, Penfluridol, Loxapine
18.	Anti-depressants	Phenelzine	Brexanolone	Moclobemide, Imipramine, Doxepin, Amitriptyline, Clomipramine, Fluoxetine, Fluvoxamine, Citalopram, Venlafaxine, Duloxetine, Mianserine
19.	Anti-parkinsonian	Levodopa	Safinamide	Carbidopa , Benserazide, Ropinirole, Selegiline, Rasagiline, Entacapone, Amantadine
20.	Opioid analgesics	Morphine	Dsuvia	Codeine, Thebaine, Papaverine, Noscapine
	Drugs acting on PNS			
21.	Local anaesthetics	Procaine	Benoxinate hydrochloride	Lidocaine, Prilocaine, Tetracaine, Bupivacaine, Dibucaine
	Drugs acting on ANS			
22.	Cholinergics	Acetylcholine	Arecoline	Methacoline, Carbachol, Bethanechol, Muscarine, Pliocarpine
23.	Anti-	Atropine	Pirenzepine	Hyoscine, Ipratropium,

	Cholinergics			Tiotropium, Clinidium, Pipenzolate methyl bromide, Isopropamide
24.	Adrenergics	Ephedrine	Acebutolol	Phenylephrine, Dopamine, Methoxamine. Isoprenaline, Dobutamine, Salbutamol
25.	Anti-Adrenergics	Phenoxybenzamine	Lofexidine	Ergotamine, Phentolamine, Prazosin, Terazosin, Doxazosin, Tamsulosin, Yohimbine
	Respiratory System			
26.	Cough and Bronchial Asthma	Sodium citrate	Salbutamol	Bromhexine, Guaphensin, Ammonium chloride, Ambroxol, Carbocisteine, Codeine, Noscapine, Chlorpheneramine, Promethazine
	GIT			
27.	Proton pump inhibitors	Pantoprazole	Dexlansoprazole	Rabeprazole, Lansoprezole, Omeprazole, Esomeprazole
28.	Constipation	Bisacodyl	Linaclotide	Sodium picosulphate, Castor oil, Magnesium suphate, Sodium phosphate, Lactulose
	Drugs acting on excretory system			
29.	Diuretics a. Thiazides diuretics b. Loop diuretics c. Osmotic diuretics d. Potassium sparing diuretics e. Carbonic anhydrase inhibitors	Chlorothiazide Ethacrynic acid Urea Spironolactone Acetazolamide	Indapamide Furosemide Isosorbide Triamterene Zonisamide	Htdrochlorthiazide, Benzthiazide, Chlorthalidone, Metolazone Torasemaide, Bumetanide Mannitol Amiloride
30.	Anti-UTIs	Nalidixic acid	Gepotidacin	Norfloxacin, Ciprofloxacin, Ofloxacin, Gatifloxacin, Sparfloxacin, Nitrofurantoin
	Autocoids			
31.	NSAIDs	Paracetamol	Cimicoxib	Aspirin, Ibuprofen, Ketoprofen, Flubiprofen, Piroxicam, Tenoxicam, Ketorolac, Indomethacin, Phenylbutazone,

				Diclofenac, Aceclofenac, Celecoxib, Parecoxib
32.	Anti-histaminics a. H_1 b. H_2	Diphenhydramine Cemitidine	Ebastine Roxatidine	Dimenhydrinate, Promethanzine, Pheneramine, Meclizine, Triprolidine, Clemastine, Loratadine, Cetrizine, Azelatine, Rupatidine Ranitidine, Famotidine
	Hormones			
33.	Corticosteroids	Hydrocortisone	Fluticasone propionate	Prednisolone, Triamcinolone, Betamethasone, Fludrocortisone
34.	Anti-thyroids	Propyl thiouracil	Carbimazole	Mehtimazole
35.	Anti-diabetics	Tolbutamide	Dulaglutide	Glibenclemide, Glipizide, Glimeperide, Repaglinide, Nateglinide, Sitagliptin, Vildagliptin, Alogliptin, Metformin, Phenformin, Pioglitazone, Acrabose, Voglibose
	Chemotherapy			
36.	Anticancer a. Alkylating agents b. Platinum coordination complexes c. Antimetabolites d. Microtubule damaging agents e. Topoisomerase-I inhibitors f. Topoisomerase-II inhibitors g. Antibiotics	Cyclophosphamide Cisplatin Methotrexate Vincristine Topocetan Etoposide Actinomycin D	Procarbazine Oxaliplatin Cytarabine Estramustine Camptothecin Epirubicin. Mitoxantrone	Ifosfamide, Chlorambusil, Melphalan, Busulfan, Lomustine Caboplastin Pemetrexed, Mercaptopurine, Azathioprine, Fludarabine, Capecitabine Vinblastine, Paclitaxel, Docetaxel Irinotecan Doxorubicin, Daunorubicin, Epirubicin, Mitomycin C, Mleomycin

III. FUTURE OF MEDICINAL CHEMISTRY AND DRUG DELIVERY

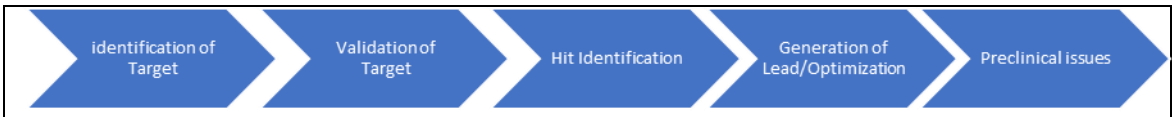
Any advancement in the field of scientific technology catches instantly its applicability in pharmacy as well as medicine and drug discovery plus its development.

Funding in the arena of drug design are sensible since as superior is planned a particular drug contender all through the trial phase, as very less prospective will be for that drug material to be unsuccessful in later platforms when the investigations are much more costly, specifically during the various phases of clinical trials. The COVID virus enforced everyone to reconsider how to speed up the time-lines of drug discovery and development of medicines as well as vaccines. Novel, in effect, even cheaper approaches for process of drug discovery are essential and Artificial Intelligence (AI) ensures the prospective to afford those. AI has the capability to collect and scrutinize huge aggregates of databases in a very small spell, for the selection of suitable targets as well as specific ligands, designing trials and also to accomplish these activities. The definitive aim of this part of drug design in future definitely will be competent for designing and improving a particular, less or non-toxic, more effective and personalized drug candidate concluded a time range of more than a few hours. Even though this goal appears fanciful in the instance, it is absolutely attainable in very near future.

The AI-bound drug discovery industry stays to grow, driven by new participants in the market, noteworthy capital share, and technology evolution. There are more than 250 establishments working in the industry of which more than fifty percent of them are grounded in the United States of America, but crucial hubs are evolving in Western Europe and Southeast Asia in addition. By putting AI at the center of the research set up, firms can transmute research at gauge and bring around theatrical advances in patient outcomes.

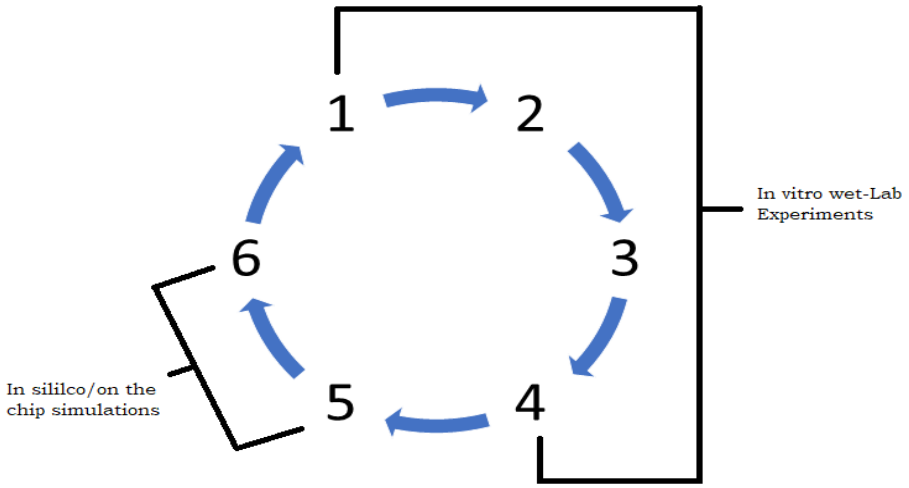
Examples of AI-driven Innovations in Biopharma industries:

1. AI driven Acceleration:



1. Identification of Target: Inputs from data sources to produce novel hypothesis.	2. Validation of Target: In-silico/ phenotypic or cellular models to validate targets and recognise biomarkers.	3. Hit Identification: Automated image analysis for cellular/biological assays through computer vision technology.	4. Lead Generation and Optimization: Molecular structure and property prediction for new target proteins (example: protein binding, toxicity, log P etc.)	5. Preclinical issues: Safety issues and Drug metabolism-Pharmacokinetics data.

2. High Throughput Screening process (HTS) embedded with AI Technology:



- High throughput screen launched with varied sets of compound
- Automated selection of compound and allocation
- Computer fashioned hit selection
- Machine learning model (ML) from screen outputs
- Data library inferencing and prioritizing
- Automated selection of compound centered on ML commendations

IV. CONCLUSION

Drug discovery remains a much challenging pharmaceutical discipline over anextensivepast. A lot of accomplishments already have been achieved in the arena of drug design by the completion of 19th century. Progressively, field of drug design in the present scenario transmuted to a comprehensible and regimented scientific discipline with a compacted theoretic background and practical applicability. Today, drug design is one of best progressive approaches for drug discovery. The terms like Artificial Intelligence, Machine learning, deep learning and neural network etc. will be inseparable and essential paradigm shift in the nous that these tools will touch every distinct feature of how anyone discovers and develops medicines, and speed up and help improve each one of them.

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