Past, Present and Future of Medicinal Chemistry and Drug Discovery

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ABSTRACT

 The ancient history of medicinal chemistry records to the use of therapeutic plants and minerals which were derived from the ancient civilizations of the Chinese, 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 10th 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 science and technology catches instantly its application in pharmacy, in medicine, in drug discovery plus development. AI has given a new prospective to the drug discovery and 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.

**Key Words –** Medicinal Chemistry; Drug discovery; Artificial intelligence; High throughput screening.

#  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 synthesised 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 use of therapeutic plants and minerals which were derived from the ancient civilizations 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’ang shang, 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 ipecacuanha root containing emetine was used in Brazil for the treatment of dysentery. South American Indians chewed coca leaves containing cocaine and used mushrooms containing 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*) for relief of pain of the joints and for treating gout [3].

Modern treatment especially for treating CHF began from the extraction of secondary glycosides from *Digitalis purpurea* and *Digitalis lanata* containing digitoxin and digoxin respectively [3]. During the 19th Century, the prominence shifted to finding new natural and/or synthetic active ingredients with active pharmacological properties. The isolation of morphine by Friedrich Sertürner in 1803, the isolation of emetine from ipecacuanha by Pierre-Joseph Pelletier in 1816, and his purification of caffeine, quinine, and colchicine in 1820 all contributed to the increased use of “pure” substances as therapeutic agents [4]. In 1928, the 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].

# 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** |
|  | Antimalarials | Chloroquine | Artemisinin | Amodiaquine, Primaquine, Pamaquine, Mefloquine, Cycloquanine, Proguanil, Atovaquone |
|  | Anti-tubercular drugs | INH (Isoniazide) | Bedaquiline | Ethionamide, Ethambutol, Pyrazinamide, Para amino salicylic acid |
|  | Anti-fungals | Benzoic acid | Albaconazole | Salicyclic acid, Clioquinol, Miconazole, Clotrimazole, Econazole, Nystacin, Natamycin |
|  | Anti-viral1. Anti-Herpes
2. Anti-Influenza
3. Anti-Hepatitis
4. Anti-Retrovirus
 | IdoxuridineAmantadineLamivudineZidovudine | Pritelivir  PeramivirTenofovir Cabotegravir | Trifluridine, Acyclovir, Famiclovir, Ganiclovir, Cidofovir, FoscarnetRimantadine, Oseltamivir, ZanamivirRibavinir, Adefovir, Interferon-α, Didanosine, Stavudine, Lamivudine, Tenofovir |
|  | Anti-protozoals | Metronidazole | Tinidazole  | Ornidazole, Iodoquinol, Pentamidine |
|  | Anthelmintics | Diethylcarbazine citrate | Ivermectin | Mebendazole, Albendazole, Nicolsamide, Oxamniquine, Praziquentel |
|  | Antibiotics1. β-lactams
2. Penicillins
3. Cephalosporins
4. Tetracyclines
5. Aminoglycosides
6. Macrolides
7. β-lactamase inhibitors
 | BenzylpenicilinCefazolinTetracyclineStreptomycinErythromycinClavulanic acid | MezlocillinCefepimeMinocyclineParomomycinSpiramycinDoripenem | Mithicillin, Ampicillin, Amxocicillin, Cloxacillin, CabencillinCephalexine, Cefuroxime, Cefprozil, Cefotaxime, Ceftazidime, CefoperazoneDoxycyclin, Chlortetracyclin, Oxytetracyclin, DemclocyclinGentamycin, Kanamycin, Tobramycin, Amikacin, NetilmicinRoxithromycin, Clarithromycin, AzithromycinSulbactam, Tazobactam, Aztreonam |
|  | Sulphonamides | Sulfadiazine | Sulfasalazine | Sulfamethoxazole, Sulfadoxine, Sulfamethapyrazine, Sulfacetamide, Mefinide |
|  | **Drugs acting on CVS** |
|  | Anti-hypertensives1. ACE Inhibitors
2. ARBs
3. Calcium channel blocker
4. β/ α - adrenergic blockers
5. Vasodialators
 | CaptoprilLosartanVerapamilPropanololHydralazine | RamiprilTelmisartanBenidipineSatololDiazoxide | Enalpril, Lisinopril, Reindopril, FosinoprilCandisartan, Irbesartan, ValsartanDilteazem, Nifedipine, Felodipine, Amlodipine, NitrendipineMetoprolol, Atenolol, Labetalol, Carvedilol, EsmololMinoxidil, Sodium nitropruside |
|  | Anti-arrhythmic 1. Sodium channel blockers
2. β-blockers
3. Repolarizers
4. Calcium channel blockers
 | QuinidinePropanololAmiodaroneVerapamil | FlecainideCarvedilolIbutilideBenidipine | Procainamide, Disopyramide, Lidocaine, MexiletineMetoprolol, Atenolol, Labetalol, Esmolol, SatololDronedarone, DofetelideDilteazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine |
|  | Anti-anginal1. Nitrates
2. β-blockers
3. Calcium channel blockers
4. Potassium channel opener
 | Glyceryl trinitratePropanololVerapamilDipyridamole | Pentaerythritol tetranitrolCarvedilol BenidipineOxyphedrine | Isosorbide dinitrate, Erythrityl TetranitrateMetoprolol, Atenolol, Labetalol, Esmolol, SatololDilteazem, Nifedipine, Felodipine, Amlodipine, NitrendipineTrimetazidine, Ranolazine, Ivabradine |
|  | Anticoagulants | Heparin | Dabigatran | Fondaparinaux, Danaparoid, Bishydroxycoumarin, Rivaroxaban |
|  | Antihyperlipedaemic | Lovastatin | Ezetimibe | Simvastatin, Atorvastatin, Rosuvastatin, Colestipol, Clofibrate, Gemfibrozil, Bezafibrate |
|  | **Drugs acting on CNS** |
|  | General anaesthetics1. Inhalation
2. Intravenous
 | EtherThiopentone sodium | SevofluraneEtomidate | Halothane, Isoflurane, DesfluraneMethohexitone sodium, Propofol, Ketamine, Fentanyl |
|  | Sedatives and Hypnotics1. Barbiturates
2. Bezodiazepines
 | BarbitalDiazepam | PhenobarbitoneTriazolam | Butabarbitone, Thiopentone, Methohexitone. Flurazepam, Nitrazepam, Alprazolam, Oxazepam, Clonazepam, Lorazepam,  |
|  | Anti-epileptics | Primidone | Tiagabine | Phenotoin, Fosphenotoin, Carbamazepine, Valproic aicd, Gabapentine, Lamotrigine |
|  | Anti-psychotics | Chlorpromazine | Cariprazine | Triflupromazine, Thioridazine, Haloperidol, Penfluridol, Loxapine |
|  | Anti-depressants | Phenelzine | Brexanolone | Moclobemide, Imipramine, Doxepin, Amitriptyline, Clomipramine, Fluoxetine, Fluvoxamine, Citalopram, Venlafaxine, Duloxetine, Mianserine |
|  | Anti-parkinsonian | Levodopa | Safinamide | Carbidopa , Benserazide, Ropinirole, Selegiline, Rasagiline, Entacapone, Amantadine |
|  | Opioid analgesics | Morphine | Dsuvia | Codeine, Thebaine, Papaverine, Noscapine |
|  | **Drugs acting on PNS** |
|  | Local anaesthetics | Procaine | Benoxinate hydrochloride | Lidocaine, Prilocaine, Tetracaine, Bupivacaine, Dibucaine |
|  | **Drugs acting on ANS** |
|  | Cholinergics | Acetylcholine | Arecoline | Methacoline, Carbachol, Bethanechol, Muscarine, Pliocarpine |
|  | Anti- Cholinergics | Atropine | Pirenzepine | Hyoscine, Ipratropium, Tiotropium, Clinidium, Pipenzolate methyl bromide, Isopropamide |
|  | Adrenergics | Ephedrine | Acebutolol | Phenylephrine, Dopamine, Methoxamine. Isoprenaline, Dobutamine, Salbutamol |
|  | Anti- Adrenergics | Phenoxybenzamine | Lofexidine | Ergotamine, Phentolamine, Prazosin, Terazosin, Doxazosin, Tamsulosin, Yohimbine |
|  | **Respiratory System** |
|  | Cough and Bronchial Asthma | Sodium citrate | Salbutamol | Bromhexine, Guaphensin, Ammonium chloride, Ambroxol, Carbocisteine, Codeine, Noscapine, Chlorpheneramine, Promethazine |
|  | **GIT** |
|  | Proton pump inhibitors | Pantoprazole | Dexlansoprazole | Rabeprazole, Lansoprezole, Omeprazole, Esomeprazole |
|  | Constipation | Bisacodyl | Linaclotide | Sodium picosulphate, Castor oil, Magnesium suphate, Sodium phosphate, Lactulose |
|  | **Drugs acting on excretory system** |
|  | Diuretics1. Thiazides diuretics
2. Loop diuretics
3. Osmotic diuretics
4. Potassium sparing diuretics
5. Carbonic anhydrase inhibitors
 | ChlorothiazideEthacrynic acidUreaSpironolactoneAcetazolamide | IndapamideFurosemideIsosorbideTriamterene Zonisamide | Htdrochlorthiazide, Benzthiazide, Chlorthalidone, MetolazoneTorasemaide, BumetanideMannitolAmiloride |
|  | Anti-UTIs | Nalidixic acid | Gepotidacin | Norfloxacin, Ciprofloxacin, Ofloxacin, Gatifloxacin, Sparfloxacin, Nitrofurantoin |
|  | **Autocoids** |
|  | NSAIDs | Paracetamol | Cimicoxib | Aspirin, Ibuprofen, Ketoprofen, Flubiprofen, Piroxicam, Tenoxicam, Ketorolac, Indomethacin, Phenylbutazone, Diclofenac, Aceclofenac, Celecoxib, Parecoxib |
|  | Anti-histaminics* 1. H1
	2. H2
 | DiphenhydramineCemitidine | EbastineRoxatidine | Dimenhydrinate, Promethanzine, Pheneramine, Meclizine, Triprolidine, Clemastine, Loratadine, Cetrizine, Azelatine, RupatidineRanitidine, Famotidine |
|  | **Hormones** |
|  | Corticosteroids  | Hydrocortisone | Fluticasone propionate | Prednisolone, Triamcinolone, Betamethasone, Fludrocortisone |
|  | Anti-thyroids | Propyl thiouracil | Carbimazole | Mehtimazole |
|  | Anti-diabetics | Tolbutamide | Dulaglutide | Glibenclemide, Glipizide, Glimeperide, Repaglinide, Nateglinide, Sitagliptin, Vildagliptin, Alogliptin, Metformin, Phenformin, Pioglitazone, Acrabose, Voglibose |
|  | **Chemotherapy** |
|  | Anticancer1. Alkylating agents
2. Platinum coordination complexes
3. Antimetabolites
4. Microtubule damaging agents
5. Topoisomerase-I inhibitors
6. Topoisomerase-II inhibitors
7. Antibiotics
 | CyclophosphamideCisplatinMethotrexateVincristineTopocetanEtoposideActinomycin D | ProcarbazineOxaliplatinCytarabineEstramustineCamptothecinEpirubicin.Mitoxantrone | Ifosfamide, Chlorambusil, Melphalan, Busulfan, LomustineCaboplastinPemetrexed, Mercaptopurine, Azathioprine, Fludarabine, CapecitabineVinblastine, Paclitaxel, DocetaxelIrinotecanDoxorubicin, Daunorubicin, Epirubicin, Mitomycin C, Mleomycin |

# FUTURE OF MEDICINAL CHEMISTRY AND DRUG DELIVERY

Any advancement in the field of science and technology catches instantly its application in pharmacy, in medicine, in drug discovery plus development. Investments in the arena of drug design are advisable since as superior is designed a particular drug candidate all through the investigational phase, as less prospective is for the drug substance to be unsuccessful in the later platforms when the investigations are much more expensive, specifically during the clinical trials. The COVID pandemic enforced us to reconsider how to accelerate the time-lines of discovery and development of medicines and vaccines. Novel, effective, and cheaper approaches for drug discovery are essential and Artificial Intelligence (AI) has the prospective to afford those. AI is capable to collect and scrutinize huge aggregates of data in a very short spell, to select suitable targets and specific ligands, to design trials and to accomplish them. The definitive aim of the drug design in future is to be competent to design and improve a particular, less or non-toxic, effective and patient-tailored drug candidate over a period of more than a few hours. Even though this goal appears fanciful at the instance, it is absolutely attainable in the 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 half of them are grounded in the United States, but crucial hubs are evolving in Western Europe and Southeast Asia in addition. By putting AI at the centre 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:**

## **A. 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. |

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

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1. High throughput screen launched with varied sets of compound

2. Automated selection of compound and allocation

3. Computer fashioned hit selection

4. Machine learning model (ML) from screen outputs

5. Data library inferencing and prioritizing

6. Automated selection of compound centered on ML commendations

# CONCLUSION

Drug discovery is a much complex pharmaceutical discipline with a lengthy history. Many accomplishments have been made in the arena of drug design ever since the end of 19th century. Progressively, field of drug design has been transmuted into a comprehensible and regimented science with a solid theoretic background and practical applicability. Today, drug design is one of the most progressive approaches for drug discovery. 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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