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 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 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 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.

**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 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 therapeutic use of herbs and plants and inorganic minerals which were originated from the prehistoric cultures 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 root the plant ipecac comprising the chemical emetine was in use for the cure of dysentery in Brazil. Red Indians of South American origin used to chew coca leaves comprising the chemical cocaine and employed mushrooms comprising the 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 the soreness 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, quinine and 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].

# 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 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:**

## **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 remains a much challenging pharmaceutical discipline over an extensive past. 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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