

## EVOLUTION OF DRUG : A HISTORICAL PERSPECTIVE

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### ABSTRACT

To trace out the first person who discovered the first medicine is extremely difficult. Perhaps the origin of medicine and drug and its early history has been lost in myths. The use of medicinal plants dates back not only to human civilization but to ancient people also. Plants have been crucial in sustaining human health and well being of mankind. The word Drug, taken from French word Drogue which means Dry Herb, strongly suggests that earliest drugs were taken out from plant sources. Earliest people used to treat diseases by some unconventional methods, using plants, animal products and minerals, of them plants were given priority. World's ancient systems of medicine e.g. Chinese Medicine, *Ayurveda* and Greek Medicine, despite, having wider differences in their principles of treatment agree upon the point, that disease is due to imbalance within the constituents of the body and that the aim of treatment is to restore the balance with the help of herbs. So, herbs played vital role in the development of Pharmacology and Pharmacy. The splendid architect of today's advanced Pharmacology was not built in a day, but its foundation stone has been laid on old base. Pharmacology from its very beginning to the age of Chemotherapy and on words, has traversed long voyage. In this article travelogue of the Pharmacology has been discussed briefly.

**Key words:** Papyrus, Shamanistic medicine, Humors, Alchemy, Renaissance, Magic bullet

### Introduction

It is very difficult to trace out the first person on the earth who discovered the first medicine. The origin of medicine and early history of its progress are lost in the mythical stories. Dr. Ryan's assertion, "All medicine is derived from God, and without His will, it can't exist or be practiced", is universal truth.<sup>20</sup> Plants played key role in therapeutics, which is evident from their use in all systems of medicine, for example, Western Medicine, originated in Mesopotamia; Unani Medicine, originated in Greece; Ayurveda, originated in India; Chinese Medicine, originated in China and many others. In fact, the knowledge about the plants and their uses as drug came to us following the oral transmission from generation to generation and then through papyrus, manuscripts,

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printing and finally electronic storages.<sup>9</sup> All theories relating to origin of medicine are object of imagination and have mystical basis. The only fact is that when early man would have fallen ill he would have discovered some remedy for his illness. Those people's remains contain evidences of attempts at medical care. The most striking of these are skulls with cut holes probably, to allow the disease to escape from the body. Herbal medicine was also practiced from the earliest time which, can be seen in apes, chewing herbs that are not part of their normal diet probably, for their medicinal effects.<sup>22</sup> From the earliest time, herbs have been crucial in the health of mankind. The remains of herbs are not uncommon in ancient burials. A 60000 years old burial site excavated in Iraq was found to contain eight medicinal plants, including *Ephedra sinica*, Stapf. which, is still in use.<sup>1</sup> In ancient period diseases were supposed to be due to some supernatural causes, hence, treated by some unconventional methods. Plants, animal products and minerals remained in use from earliest time. Plants were given priority in treating the patients. Apart from medicinal values, plants were considered to have souls. Even, Aristotle, the great Greek philosopher considered that plants had Psyche. In many cultures, some plants have been given ritual importance In Hinduism, many plants are sacred to specific divinities, e.g. Bael tree (*Aegle marmelos* Linn.), is sacred to Shiva. The Doctrine of signature shows that there was a connection between how plant looked God's "signature", and used medicinally, e.g. *Juglans regia* Linn. looked like Brain tissue, so, considered as Brain tonic. Native people of Andes in S. America believe in coca plant, that it is a spirit and must be respected. Even, today many traditional societies believe in Shamanistic medicine. In fact up until 20<sup>th</sup> century every rural community had it's own wealth folklore, but what was the origin of these folklore, there is no definite answer. Observations coupled with trial and error, good and bad effects, eating of a particular root, leaf or berry and watching of animal behavior might have been played roles in identification of plants as drug.<sup>1</sup>

The use of plants as drug, dates back not only to civilization but to early people also. Parts of the plants, such as roots, leaves, fruits, flowers etc., were used as food. Harmless parts were kept in the category of food, while harmful parts were discarded.<sup>2</sup> Nevertheless the adverse effects of the plants paved the way for the evolution of drug, e.g., purgative effects of "Rhubarb", was tested for treatment of constipation. Plants or parts of the plants, which proved extremely fatal, were considered to be poison. On the basis of this differentiation, edible things were classified as food, drug and poison. The

word, Drug, taken from a French word, Drouge, meaning, Dry herb, suggests that the earliest drug was obtained from plant. source. As civilization grew from 3000 B.C. onwards, in Egypt, India and China, plants were used in more sophisticated forms and written accounts of them were made. The awareness about conventional medicinal plants began in Egypt, India, China, Greece and Rome.<sup>2</sup> The Egyptian "Ebers papyrus" of 1500 B.C., is the earliest and oldest surviving example of medical text, about 20 meter long, describing many disease and remedies including over 700 drugs and 800 medicine recipes, instruction for mixing up medicines into ointments, poultices, uses and their actions.<sup>22</sup> Though many of drugs had little effects, but some are still familiar to day e.g., Opium, Cannabis, Myrrh, Garlic and Castor etc. In India, the Vedas written, thousand of years earlier are series of Hindu text, probably, based on much older stories, also contain rich herbal materials and disease including herbal remedies, prayers and magic rituals.<sup>22</sup> The Vedas were followed by Charaka in about 700 BC. The Ayurvedic medical treatise, Charaka Samhita, includes details of around 350 herbal medicines.<sup>1</sup> Indians were aware of anti-leprotic action of Chalmugra; tonic property of Amla and sedative property of Asgandha. The Vedic medicine was practiced by about 1000 BC. After this new school of medicine, still based on Vedas, but taking ideas from Buddhism and other systems of medicine, started in India, known as Ayurveda. By about, AD.1000, final version of Charaka Samhita was written. In A.D.1000, Islamic Physicians brought new medical practices to India, and in AD. 1500 Europeans brought western medical ideas to India. An other traditional system, the Chines Medicine developed over thousand of years without outside influences, is as old as other systems. Nei Ching, an ancient medical work by Huang Ti. has been written in about 200 BC. Shen Nong 2700 BC. discovered herbal medicine and described some important drugs, e.g. Cheng Sheng, an anti-malarial drug along with 365 different medicinal plants. These three ancient civilizations and their medical systems differing widely from each other, all consider the disease due to imbalance within constituents of body and that the aim of treatment is to restore balance with the help of herbs.<sup>22</sup>

Modern concept of medicine has its origin in 500 BC. Medicine, in this period began to separate from spiritual and magical world. Hippocrates (460-370 BC.), the Greek, Father of Medicine, considered the illness due to natural causes and felt that medicine should be given without ritual connection. He, for the first time, gave scientific approach to the art of healing and liberated it from the clutches of dogmatism and opened

doors for more scientifically based researches, but he too believed in humors. His theory of humors survived to 1800s, in Western Medicine. Later on Aristotle, gave a classification system to animals. His pupil, Theophrastus suggested the idea of classification of plant kingdom.<sup>2</sup> He systemized knowledge of herbs and plants, describing their medicinal values. The Greeks were most civilized from where Greek Medicine emerged, which later became Greek-to-Arab Medicine, that is presently known as Unani Medicine. The famous Greek School at Alexandria, remained center for medical teaching, even after, Romans conquered the Greeks. They followed the ideas of Greeks in medicine and employed most Greek doctors, one of them is Claudius Galen, who moved to Rome in AD.162, had profound influence on development of herbal medicine. He was so influential that his writings were accepted for 1500 years. Hippocratic Theory inspired him, but unlike other Greeks, he believed in experimenting.<sup>22</sup> He described the methods of preparation of drugs from plants and animals. He stated that plant products provide essential elements for health. People followed his ideas for centuries. In fact, his work was base for compilation of *Materia Medica*, on the basis of sources, dosages identification, and indication and contra-indication of drugs.

The period 300 BC.-600 AD. was foundation of major herbal trade. By 2<sup>nd</sup> century BC., Europe, China, and India were already set for trade. Trade routes between these countries favored exchange of knowledge about herbs. The trade and interest in herbal drugs was based on the same line as mentioned in ancient records. It was Dioscoridos, (1<sup>st</sup> Century A.D.), a Roman botanist, some say, Greek physician, who wrote the first herbal, *De-Materia Medica*, known as, *Kitab al-Hashais*, in Arabic. He was the first person to take botany in its applied form, following which, science of Pharmacy developed.<sup>7</sup> *De-Materia Medica* is a milestone in the science of Pharmacology and Pharmacy. Dioscoridos's intention was to present an accurate and authentic work on herbal medicine, and he was successful. This text contains about 600 herbs, which influenced the Western Medicine and was principle source of reference until 17<sup>th</sup> century. It was translated in many languages, like Arabic, Persian, English and Hebrew etc. In AD. 512, *De Materia Medica* became first pictured herbal containing nearly 400 color illustration.<sup>1</sup>

In the middle ages, Folk Medicine was also practiced and this would have meant nothing to do with traditional systems of medicines of India, Greek and China. The folk people had sophisticated knowledge of plant drugs. This folk remained also unaffected

by revolutionary forces of history.<sup>1</sup> Though, Greek Medicine suffered a major setback with the decline of Roman Empire, but during the period of Byzantine Empire, Greek and Roman works on medicine were collected and some works were translated into Persian and Syrian. At the same time, Arab Empire was expanding and growing. The Arabs conquered Persia and Syria. In the beginning they preferred their own systems but later they turned to Greek ideas and put it into Arabic, which were later translated into Latin, and used in European medical schools from 1200 A.D. Thanks to Arabic culture (A.D. 500-1300) in which the remains of Greek and Roman were preserved. The spread of Islamic culture led to establishment of medical schools. The Arabs were interested in alchemy. They experimented to find many drugs. They also developed methods of purifying chemicals. They were expert in Pharmacy and mixing herbs. Their relation to India and China made them to have wide range of knowledge of herbs. Avicenna (A.D. 980-1037), the author of *Cannon of medicine*, is most famous Arabic scholar. Among the Arabic scholars many were Persian, Jews and Christians, living within Arab empire. Razhesh was Persian, who compiled huge medical compendium, *Alhawi*. Arab pharmacists compiled long list of herbal remedies. Some have described more than 3000 different drugs. The techniques for extractions of active parts (Distillation), introduced by alchemist, led to establishment of modern pharmaceuticals. Many drugs of modern age are synthetic or version of plant extract. On the other hand the 7<sup>th</sup> century B.C., was a golden period of herbal medicine in India. Establishment of Nalanda University and other medical centers attracted thousands of students for learning Ayurveda. Scholars recorded medical achievement, developed hospitals and established herbal gardens. The Arabs worth special mention, because it was Greek-Arab-Medicine, which affected Western Medicine. We will come to know how Western Medicine (Greek Medicine) later changed in Arabian Medicine. In fact the system of medicine which, we call, Arabian Medicine, was Greek Medicine, modified by various factors and rehabilitated in Arabic Script<sup>5</sup>. Its foundation was laid by translation of Greek Medicine in Golden Period (750-850 A.D.) The Greek-Arab Medicine is now known as Unani Medicine. Modern medicine is Greek Medicine, which developed in Europe after Renaissance.<sup>3</sup>

The Arabian medicine means the body of medical doctrine enriched in books written in Arabic, mostly of Greek Origin. With decay of Greeks, the reliable source of Greek wisdom is Arabian medicine from which Europe developed scientific ideas.<sup>4</sup> The greatest contribution of Arabs to medical science was in Pharmacology. The word

Drug, it self, has its origin in Arabic. Alcohol, Alkali, Syrup, Sugar, and many other terms have their roots in Arabic. Benzoin, Camphor, Saffron, Myrrh, Musk, Senna and many more drugs are of Arabian origin. Alchemy (Chemistry) intimately, is associated with Pharmacology. The Arabs invented methods of Distillation, Sublimation, Crystillation and other processes familiar to chemists of today.<sup>8</sup> If the Arabs did not invest their valuable time in search of potable gold, they could have done more useful works. Jabir Ibn Hayan is the father of Arabic Alchemy. Another genius among Arabs is Al-Biruni who, in fact was one of greatest cultural historian, but deserves to be recalled the father of Arabic Pharmacy. Al-Biruni is the first in Islam and perhaps in any culture to trace the history of Apothecary art. He gave systemic, clear, rational and objective interpretation of definition of Pharmacology. He apposed majority of pharmacists of his time who were blind followers of what the others say. He emphasized on practical training of pharmacy rather than study of books.<sup>11</sup> Besides, Chemistry and Pharmacy, Arabs contributed in Pharmacology to a wide extent, which is evident from many Arabian scholars. Firdaws al-Hikmat (Paradise of Wisdom) by Rabban Tabri; al Hawi (Liber continent) by Rhazes; al-Qanoon-fi-al-Tibb (the Cannon of Medicine) by Avicenna, Kitab al-Jami-li-Mufradat-al-Advia-wal Aghdhia (the Corpus Simples) by Ibn Baitar; Tadhkirah (the Memorial) by Antaki- and many others are living examples of Arabian contribution towards Pharmacology.<sup>15,21</sup> In the later days a large number of books were compiled by Unani scholars, but most are replica of one another. By Arabian medicines means the contribution of those who knew Arabic and translated Greek works in Arabic. Some historians by a contrivance intension named it Arabic Medicine to distinguish it from Greek Medicine, which later changed in Modern Medicine after renaissance.

Up to the late 13<sup>th</sup> century medicine in Europe was practiced on the basis of Greek writings rather than practice. After that, there was a period of renaissance that lasted from 1400 A.D.-1600 A.D. People in this period experienced the most terrible condition, the world has ever seen. From the mid 14<sup>th</sup> century onwards, Plague killed millions of people, known as Black Death. Plague was not the only disease to strike the people. Besides, Syphilis and Leprosy were common. European doctors were not successful to combat these diseases, especially that of Plague. For these diseases no herbal or mineral drug was available. The old treatment was some times worst than disease itself. Europeans raised questions on old writings and started revising ancient medical texts. One of important European figure of 17<sup>th</sup> century was Paracelsus (1493-

1541), who rejected Galenic theories. He told, "I have not borrowed from Hippocrates, Galen or any one else". He wrote, "Having acquired my knowledge, from the best teacher, that is, by experience and hard work". Paracelsus was a driving force in the future development of Chemistry, Conventional Medicine and Herbal Medicine. By the end of 16<sup>th</sup> century, Paracelsus had become the superman of new Chemical Medicine. In those days importance of vital force was being diminished and medical understanding of bodily functions, on the basis of biochemical level was gaining ground. In the beginning the renaissance was a rebellion against Arabism.<sup>19</sup> Paracelsus started the campaign of reform by burning the works of Gallen and Avicenna. The renaissance indicates the movement of Europe, which divides the medieval period from the modern period.<sup>3</sup> It does not mean that renaissance totally discarded the herbal drugs rather than it started more scientific based uses of herbs. From the 16<sup>th</sup> century onwards, isolated drugs were developed from herbal sources. The discovery of medicinal value of Foxglove (*Digitalis purera*) is a case when traditional herbal knowledge led to major advance in medicine. From early 19<sup>th</sup> century, chemical laboratory became versus nature. No doubt, important drugs like Morphine, Cocaine, Curare and many others are plant products. Isolation of Morphine from Opium (*Papaver somniferum*), Salicylic acid (Aspirin) from white willow bark (*Salix alba*) etc. separated the Herbal Medicine from Biomedicine. Understanding of mechanism of action, dosage formulation etc. brought the era of synthetic drugs. Synthesis of drugs like Phenacetine, Aspirin, Procain, Anaesthetics, Sedatives and Hipnotics were centrifugal point. The Pharmacology expanded beyond previous boundaries and became rational rather than trial and error. Physics, Chemistry, Biochemistry and other branches of science played key roll in the development of modern Pharmacology.<sup>13, 18</sup>

Despite, tremendous advancement in the science of drug, it was nothing but production of fast acting drugs that give symptomatic relief to the patients. There was no magic bullet, which could eliminate the cause of infective diseases. i.e microorganisms. It was not until first half of 20<sup>th</sup> century, when an era of Chemotherapy resulted in the discovery of antimicrobials, which proved great blessings to mankind. Though, some antimicrobials were known to man for centuries. Fungi, grown on shoes and moulded curd on boiled soya were used for wounds.<sup>2</sup> Ancient Greeks used male fern and *Chenopodium* as intestinal anthelmintics. But in true sence, Pasteur's work, Ehrlich's idea, Dogmak's experiment and Fleming's discovery are strongest stimuli in uprising

the Chemotherapy. Pasteur and Joubert were the first to recognize the potential of microbial products as therapeutic agent.<sup>10</sup> In 1877 they published their observations, that some microorganisms could be capable of inhibiting the growth of Anthrax bacilli in Urine. Later on series of reports on the subject were presented. Tindal, 1881; Emmerich 1887, and Buchard, 1889 reported similar actions. But the history of modern rational Chemotherapy did not begin until the use of Dye-Intermediate. Paul Ehrlich developed the idea that Aniline dye could selectively kill the bacteria, stained by it, and thus, he introduced the term Chemotherapy.<sup>14, 16</sup> He, in this way, pioneered the scientific approach to drug discovery. He also standardized experimental dosages with concept of minimal lethal dosages. He assumed the production of maximally parasitotropic and minimally organotropic antimicrobials.<sup>17</sup> His dreams proved true, because now we have much selective antimicrobials. Dogmack's discovery of Sulphonamide (1935) brought the Chemotherapy one more step ahead. Fleming (1928) established the term Antibiosis. He was a proponent for research of more antimicrobials. His discovery of Penicillin led to the discovery of other antimicrobials like Chloramphenicol, streptomycin and Chlor-tetracycline etc. In the 20<sup>th</sup> century Pharmacology became truly scientific when experiments confirmed the usefulness and uselessness of drugs. Shot-gun prescriptions became of bygone era.<sup>6</sup> Understanding of chemical structures of drugs, pharmacological actions and toxic effects made the scientists able to produce more useful drugs. The idea of structure - activity relationships (SAR) resulted into many new drugs, and toxic effects were also minimized by this technique.<sup>2</sup> Modern pharmacology entered into new field where antibiotics, vaccines and other drugs are being produced by Biotechnology.

It is to be noted that, this article is not aimed to a specific or particular system of medicine rather than it covers the historical background of evolution of drugs. Here it would be justified to give a brief account of sources of drugs. The traditional systems are entirely based on drugs from plant, animal and mineral origin, but the Modern system of Medicine covers other sources too. Irrespective of different systems of medicine, we can classify the sources of drugs into more or less six groups-plants, animals, minerals, synthetic, Biotechnology and Human gene therapy.<sup>12</sup>

### **Plant Source**

Plants always remained important source of drugs for all systems of medicine. In traditional systems, parts of the plants or whole plant is used as drug, but in Modern system of Medicine isolated active principles are used. Alkaloids, found in plants, are landmark in the history of Pharmacology. Reserpine, Atropine and Morphine etc. are

few examples. Other principles, like Glycosides and Glucosides etc. are also used. Digoxin, a cardiac glycoside, is milestone in the history of pharmacology. Chemical structures of these active principles provide basis for semi-synthetic drugs, having different actions. Important drugs used in Modern system of Medicine, are debts of plants.

### **Animal source**

Animals always sacrificed them selves in uprising the Pharmacology to fame, because they have not only been used as drug sources, but in experiments also to up grade researches for new drugs. In traditional systems animals or their parts or products are used as drug. Hormones, like Insulin and Thyroxin etc. were first obtained from animal sources.

### **Minerals, Synthetic Source, Biotechnology and Human gene Therapy**

In traditional systems, minerals are extensively used as drug in inorganic forms, but in Modern system of Medicine, minerals are not used alone, instead, have been replaced by synthetic organic compounds, which is the largest of source of drugs. Now a days laboratory has become actual means of drugs. A comparison between old and modern Pharmacology will impart beneficial. Traditionalists claim that natural drugs, when, used in crude forms, exert beneficial effects only, and side effects are counter acted by other substances present in that particular drug. Although, such substances and their mechanism of action are to be known yet. The Innovatives say that synthetic drug prepared on the basis of SAR, are safer than natural compounds, as harmful parts could be removed by this technique. The authentication of traditionalist may be proved by tea and coffee. Both have same amount of Caffeine, but coffee is more stimulant than tea, because the later has more tannin, which renders the absorption of caffeine. This may prove the hypothesis, but it may not always be true rather than such substances may hinder the action of active constituents making the drug less effective. Modern Pharmacology has adopted new techniques. Antibiotics, vaccines and other drugs are being produced by Biotechnology and Human gene therapy has been instituted in genetic disorders.

### **Conclusion**

The stepwise evolution of the drugs shows that from the beginning of traditional therapy to the age of modern therapy, Pharmacology has long voyage. With emergence of Modern system of Medicine, some political expediency divided the drug into modern

and traditional system Needless, to say that modern Pharmacology is nothing but a developed form of traditional Pharmacology. It is offshoot of old systems especially that of Greek Medicine or Unani Medicine. Be, it art, literature or science, all have preliminary forms, that with passages of time reach the destination. Past with all its particulars imbibes in the present and the present with all its possibilities continuously changes in future. The factors of the past become logical base of present, which with present decides the direction of future. This is true for Pharmacology too. The traditional systems of medicine have a treasure of drugs, which is neither a succession nor a compendium of hypothesis. It came up after exhaustive researches based mainly on clinical observation. The Modern system of Medicine on the other hand has opened many doors of more scientifically based researches, while traditional systems are bound to the principles made centuries ago, due to which these systems are lagging behind. If the followers of traditional systems of medicine bring small change in their ideas, methodology and adopt today's scientific parameters, their systems would be in a position to rationalize and convince the scientific world.

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## सारांश

### औषधि का विकास : एक ऐतिहासिक दृष्टिकोण

अब्दुल वदूद, पी.वी.वी. प्रसाद, एम.एम. राव एवं अला नारायण

उस व्यक्ति के बारे में जिसने सर्वप्रथम औषधि विज्ञान की खोज की, बता पाना अत्यंत कठिन है। ऐसा प्रतीत होता है कि इस विज्ञान की उत्पत्ति एवं इसकी आरंभिक कहानी कथाओं में खो गयी है। पेड़-पौधे सदा से ही मानव जीवन के उत्थान एवं स्वास्थ्य के सम्बन्ध में अग्रसर रहे हैं। इनके उपयोग की कहानी उतनी ही प्राचीन है जितना कि मानव जीवन। “ड्रग” शब्द फ्रेंच भाषा से लिया गया है जिसका अर्थ होता है, सूखा पौधा। यह बताता है कि प्रथम औषधि पेड़-पौधों से ही प्राप्त की गयी होगी। संसार के प्राचीनतम चिकित्सा विज्ञान अर्थात् चाइनीज चिकित्सा विज्ञान, आयुर्वेद एवं ग्रीक चिकित्सा विज्ञान उपचार विधियों में एक दूसरे से भिन्न होते हुए भी इस बिन्दु पर एकमत हैं कि शारीरिक दोषों में असंतुलन के कारण रोग होते हैं जिनका उपचार वानस्पतिक औषधियों द्वारा किया जा सकता है और दोषों को पुनः संतुलित किया जा सकता है। वनस्पति विज्ञान चिकित्सा विज्ञान का मुख्य अंग रहा है। आधुनिक नवीनतम औषधि विज्ञान की जड़ें प्राचीनतम औषधि विज्ञान में निहित हैं। आरंभ से लेकर आज तक औषधि विज्ञान ने एक लम्बी यात्रा तय की है। इस लेख में इसी यात्रा की संक्षिप्त कहानी का वर्णन किया गया है।