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Title Page Should Contain: Title of the manuscript, Short title, Authors names with superscripts representing their affiliation clearly marked *corresponding author with Telephone, Fax and E-mailaddress.

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NEUROPSYCHIATRY IN ISLAMIC MEDICINE

SHAHEED HAKIM MOHAMMED SAID

The history of psychomatic and nervous disorders can be divided into two principal periods: that of the primordial age when man had begun to cull the fruits of knowledge and that of enlightenment which continues to our own age.

The period preceding the age of enlightenment in its earlier stages is spread over three epochs: (a) the inchoative age in which we find traces of medical and surgical practices, e.g. the Egyptian, Babylonian, Chinese, American, Greek and the Roman civilizations; (b) the age in which philosophy – especially the problem of ontology and teleology dominated and which was Greco-Roman; and (c) the dark ages which prevailed in Europe during the Medieval-age Europe. But the age was illumined here and there by the light of Islam.

Rudimentary ideas about the disease of the brain were known to the ancients. Hence the practice OF trepanning, which was practiced on large scale in Peru. The early age of enlightenment offers us positive evidence for the treatment of psychosomatic diseases. We find epileptic fits, insanity, headaches, and neuralgia listed among the disease of ancient India in the Atharvaveda.

Firm Territory

With the advent of Greeks, however, we come up the terra firma of medicine. The rational is extricated from the superstitious. This corpus of knowledge was completed by the Arabs. Pythagoras of Samos (d. 497/6) especially raised mathematics to the rank of science and established correlation between the physical and the biological aspects of life. He was followed by the Hippocrates of Cos (b. about 460 B.C), the first physician who established that the brain was the source of intellect, and that an outward manifestation like epilepsy was a physical disease. Nor is it something strange or an irrational manifestation and it is totally inane to consider it to be a "sacred disease". He further showed that dementia, insanity, melancholia, manic depression, paranoia and uncontrolled laughter were the manifestation of mental disorders.

E.D Phillips has quoted a few cases from Hippocratic book of case-histories, Epidemics.Some cases were noted for their mental symptoms. A certain Nicanor was eager to drink at parties but was frightened of the flute girl when she began playing. He was beset by terrors, and said that he could hardly contain himself at night. But if he heard the sound by day he was not disturbed at all. Democles, who was with him, seemed to have his sight obscured and to be

unable to tense his body; he would never pass near a precipice or over a bridge, but he could walk along the ditch itself. This continued to happen for some time. These physicians were evidently familiar with irrational terrors.[1]Galen (d. 199 A.D.) was a physician of remarkable ability whose influence upon human anatomy persists even to this day. His ideas are similar to those of Hippocrates. He has, however, made additions to the Galenic corpus. Thus he believed that the brain was insensitive, and that it possessed a movement synchronous with respiration; the latter process served to drive the pneuma out of the ventricles into the nerves. The meanings were the support and covering and united the blood vessels. The spinal cord conducted sensation and movement. It was, in effect, a sort of smaller brain, controlling the parts below the head and sending out nerves in streams. He distinguished sensory, motor and mixed nerve trunks which is a very major contribution to human physiology. He further traced connection between the vagus and the sympathetic, and showed the importance of recurrent nerves in the production of voice. Above all else, he showed that the nerves had no power in themselves, but merely conducted impulses to and from the brain and spinal cord. He is a great believer in ethical conduct and any disruption that creeps into the ethical makeup of man leads to sickness.

The Roman Age

We then come across physician to the Roman Age, like Cornelius Celsus (1st century A.D.), Soranus the Elder (98-138. A.D.) and Aretaeus (2nd century A.D.). He especially had something original to contribute to the aetiology of epilepsy. He stated that ancients attributed epilepsy to human influence as a punishment upon wicked people for their crimes, whence it was called "sacred disease". Aretaeus was against the popular belief that epilepsy was sacred disease. . He regarded it as resulting from natural cause , having its seat in the brain whence a cold phlegm or pituita was secreted and passed down the blood vessels, there it encountered the pneuma, causing coagulate obstruction, thus producing a convulsion.[2]

Asclepiades (b. 124 B.C.) was the first physicians to treat mental patients wit gentleness. He ordered them to be moved in to the sun, where they would be treated wit music and songs instead of being kept in the dark cells. He has differentiated between delirium and emotional disturbance. In some cases he has prescribed music, in others bath and, still in others, provision of pleasures.

Celsus has specially mentioned the clinical experiments conducted by himself. For Example, in epilepsy he recommended cupping around the occiput or scarifying in two places – over the occiput and over the first vertebra of the neck.

The symptoms which he has described in the cases of manic-depressive illness are remarkable. Sometimes they are inherited and sometimes they are not. One suffering from such illness lives in the world of phantasy, prefer solitude, and is afraid of crowds. Sometimes psychometric disease may be ameliorated through flogging or harsh treatment. Aretaeus believes that hysteria and similar uteral diseases stem from local disorders of the uterus.

All of these physicians who belonged to the antiquity regarded the origin of psychosomatic and nervous diseases to the nervous system. In this sense except for the development of neuro therapy and further progress in psychiatry, mainly through the pioneering work of Freud, Jung, and Adler, their views are closer to those of modern physicians.

Ibn Sina

Ibn Sina is perhaps the first physicians to correlate disease with movements. e.g., gestures, postures, and attitudes. Thus he holds that the states of the body are revealed by its movements or absence of movement. In this way the motionlessness

of the body as a whole would indicate apoplexy, epilepsy (coma),), syncope, and palsy, while unusual movement would be symptomatic of shivering, tremor, twitching, sneezing, yawning, stretching, cough, trembling and spasms. Some of these movements are physiological, e.g.; hiccough, whereas others are symptomatic, e.g.; convulsion or spasm. While some are realized by the senses, e.g. shivering, but some, e.g. quivering, jactitation, are not. Moreover, these movements vary with regard to their nature; thus cough is intrinsically more energetic and powerful than quivering. But on the other hand the extent of sneezing is greater in as much as the act of sneezing entails movements of the head as well as the chest. Further in a key statement he says:

Dry hiccough is associated with the greater degree of mental anxiety than the movement of coughing, though the latter is more vigorous, being reinforced by the natural faculty. In some cases the movement is aided by an essential primary instrument; thus, defecation is aided by the abdominal muscles; in other cases the aid is extraneous: thus the natural act of coughing may be aided by the atmosphere; in origin. These movement vary (a) according to the faculties involved (jactitation originates in the vegetative faculties; the act of coughing originates in the sensitive faculties); (b) according to the human concerned (thus, cough proceeds from an excretion; twitching from a gaseous agent.)[3]

If we substitute "foreign bodies" for external atmosphere, we have a key to what Ibn Sina means. The classic work of J.W black and associates has shown that stomach ulcers are due to the release of excessive histamine in the stomach; and histamine is also released under stress and fear, as in the phenomenon of gooseflesh or excessive histamine release as in asthma and ulcer.

Anecdotes

We came across number of anecdotes regarding nervous diseases in al-Tabari's *Firdaws al-Hikmah*. Al-Razi also dealth with psychosomatic medicines rather comprehensively. Thus, following Galen, he recommended lettuce, mandragora, and opium as a cure for insomnia; phlebotomy, dietary regulation, purgation and messaging for nightmares; and diversion, fasting, physical exercise and wine for sickness due to disappointment in love. He found that vertigo could arise from the brain as well as from the stomach. *Ilaj- i nafsani* (psychotherapeusis) is associated with the name of Al – Razi in particular. Borwne in this context notes:

… elementary method of psychotherapeusis from the subject- matter of no less than four of the narratives, and several of these have passed into general Persian literature, even poetry, and have thus attained considerable notoriety. We may take first two of the best known, wherein the emotions of the anger and shame are employed respectively in the treatment of rheumatic affection of the joints.[4]

The first anecdote runs as follows:

Al-Razi was summoned to Transoxania to attend the Amir Mansur who was suffering from a rheumatic affection of the joints which defied cure by all of his medical attendants. Arriving at the Oxus, al-Razi taken aback by the size of the river and the small and fragile appearance of the boat in which he was invited to embark, decline to proceed further until the King's messenger bound him and foot, throw him into the boat, and ferried him across by force, though otherwise they showed him the utmost deference and even apologized for the use of violence, begging him to bear no grudge towards them. Al-Razi assured them that he harbored no resentment and explained the motives of his resistance.

"I know every year many thousand persons cross the Oxus safely, but, had I chanced to be drowned, people would have said,

'What a fool Mohammad ibn Zakariyaa was to expose himself to this risk of his own free will: But, being carried across by force, had I then perished

people would have pitied, not blamed, e". On arrival at Bokhara he tried various method of therapy upon the Amir but without any success. Finally, he tried a state gem. He said to the Amir, "Tomorrow I shall attempt a new treatment, but it will cost you to the best horse and best mule in your stables". The Amir agreed and placed the animal at his disposal. Next day, al-Razi brought Amir to a hot bath outside the city, tied up the horse and the mule, saddled and bridled, outside, an entered the hot room of bath alone with his patient, to whom he administered douched of hot water and a draught which he had prepared "till such time", says the narrator, "as the humor of his joints were matured. Then he went out, put on his clothes, and taking a knife in his hand, came in, and stood for a while reviling the Amir, saying. "Thou didst order me to be bound and cast into the boat, and didst conspire against my life. If I do not destroy thee as a punishment for this, my name is not Muhammad Zakariyya!' The Amir become furious, and partly from anger, partly from fear, sprang to his feet. Al-Razi at once fled from the bath to where his servant was waiting for him outside with the horse and the mule, rode off at full gallop, and did not pause in his flight until he had crossed the Oxus and reached Merw, whence he wrote to the Amir:

"May the life of the king be prolonged in health and authority? Agreeably to my undertaking I treated you the best of my ability. There was, however, a deficiency in the natural caloric, and this treatment would have been unduly protracted, so I abandoned it in favor of psychotherapeusis *(ilaj-I nifsani)*, when the peccant humors had undergone sufficient coaction in the bath, I deliberately provoked you in order to increase the natural caloric, which thus gained sufficient strength to dissolve the already softened humors. But henceforth it is in expedient that should meet."

The Amir, having recovered from his anger, was delighted to find himself restored to health and freedom of movement, and caused him to be searched everywhere but in vain.

On the seventh day his servant returned with the horse and mule and the above quoted letter. As al-Razi was adamant in his decision not to return, the Amir rewarded him with the robe of honor, a cloak, a turban, arms, a male and a female slave and a horse fully caparisoned, and further assigned to him a princely pension of 2,000 gold dinars and 200 as loads of corn.

Crossed in Love

This anecdote is quoted in the famous work, Akhlaq-I Jalili, composed three hundred years after the Chahar Maqalah of Nizami 'Arudi. There is, of course, a famous anecdote about Ibn Sina in which he identified the disease of the prince of Jurjan as due to being crossed in love. Browne describes it as follows: When in his flight from Mahmud to Ghazna he came incognito to Jurjan … by the Caspian Sea, a relative to the ruler of that province lay sick of a malady which baffled all the local doctors.Avicenna, though his identity was then unknown was invited to give his opinion, and, after examining the patient, requested the collaboration of someone who knew all the districts and towns of the province, and who repeated their names while Avicenna kept his finger on the patient's pulse. At the mention of the certain town he felt a flutter in the pulse. . "Now", said he, "I need someone who knows all the houses, streets and quarters of this town". Again where a certain street was mentioned the same phenomenon was repeated, and once again when the name of inhabitants of a certain household were enumerated. Then Avicenna said, "It is finished. This lad is in love with such-and- such a girl, who lives in such-and-such a house, in such-and-such a street, in such-and-such a quarter of such-and-such a town; and the girl's face is the patient's cure". So the marriage was solemnized at a fortunate hour chosen by Avicenna, and thus the curve was completed.[5]
Ibn Sina elaborates this aspect in the Canon. After describing the symptons and especially the irregularities of pulse, he says:

And hereby it is possible to arrive at the identity of beloved person, if the patient will not reveal it, such knowledge affording one means of treatment. The device wherby this may be affected is that many names should be mentioned and repeated while the finger is retained on the pulse, and when it becomes very irregular and almost ceases, one should then repeat the process. I have tried this method repeatedly, and has discover the names of the beloved. Then, in like manner, mention the streets, dwelling, arts, crafts, families and countries, joining each one with the name of the beloved, and all the time feeling the pulse, so that when it alters on the mention of any one thing several times, you will infer from this all particulars about the beloved as regards name, appearance and occupation, we have seen case where health and strength were completely restored and flesh regained, after the patient had become greatly attenuated and suffered from severe chronic diseases and protracted accesses of fever from lack of strength resulting from excessive love , when he was accorded union with his beloved… ijn a very short time, so that we were astonished threat and realized the subordination of human nature to mental imagination.[6]

Ibn Sina has listed 63 cardiac drugs in his tract on cardiac drugs. Many of the drugs found employment as psychosomatic drugs, e.g. frankincense, common polyploidy (which expels the melatonin matter), and peony (which has a property of purging the atrabilious and phlegmatic humors from the brain and its vicinity).

Muslim Contribution

K.S. Durrany in connection with the Muslim contribution to neuropsychiatry states:

The Arab physicians introduced the grana paradise in therapeutics for neuropsychiatry. This substance is claimed to have been used for epilepsy, syncope and headache. Serapion discussed hellebore and is reported to have recommended the use of mandrake before amputation. In specific neural conditions, he included tremors, vertigo, lethargy, headache, apoplexy, phrenitis, epilepsy, sciatica and vertebral caries. This is an account of Serapion Senior, a contemporary of Rhazes who was a strong advocate of such remedies. Haly 'Abbas in (the) treatment of neuropsychiatric matters appears to have followed his predecessors so closely that he only detectable differences consist of a very fanciful description of lycanthropy, which, in his Latin editions is entitled *Canine Melancholy,* and of his employment of Indian nut for epilepsy, hemicranias and paralysis.

Avicenna's philosophic speculations exerted a profound influence upon neuropsychiatric theory. But it is doubtful (whether) his clinical observations, which are diffused and unoriginal, exerted any effect upon the therapy. He recommended cashew (Anacadium) for psychiatric and neutral affections, especially aphasia, Artemisia… for hiccup, cubebs for impotence and deodar (a variety of pie) for paralysis.[7]

Considering the fact that the tools of knowledge at their disposal were few, the practical contribution of the Muslims to neuropsychiatry was considerable. For example, al-Razi was instrumental in having set up a block where music was played for neurotic patients for soothing their nerves.

Jibril Bakht Yashu, on the authority of Ibn abi Usaybi'ah *(Uyun al-Anba)* regarded hysteria as non-somatic disease *(ghayr jismi)*; Moses Maimonides described in detail the principles of health. It was in 707 A.D. tahat the hospital for mental patients was set up during the reign of the Umayyad Caliph, Abd al-Malik b. Marwan. This was followed seventy nine years later (786) by the establishment of another mental asylum during the reign of Caliph Harun al- Rashid and was christened the Bimaristan Rashid. Several mental insitutions were set up, the most famous among them being the Bimaristan Al-'Adudi, set up by the Buwayhid sultan' Adud al-Dawlah in the west Baghdad. In 259 A.H. were established the Bimaristan Ahmad bin Tulun and in 578 A.H. the Bimaristan Salah al-Din Ayyubi.[8]

9th-14th Centuries

From the 9th century to 14th, the Muslim physicians dominated in both East and West. Ibn Zuhr (Avenzoar), for instance, wrote on mental disorders, and condemned cautery (a device to kill poisonous tissues through the application of hot substances) which the Arabs used on their patients suffering from mental ailments. Under exceptional circumstances trepanning was also recommended by al-Zahrawi. Ibn Rushd, a confirmed Aristotelian, tried to reconcile his religious faith with rational philosophy. His compromise was important from the view point of medical phycology, since it established the tradition of a medical man keeping his religious convictions and still believing in important discoveries.

When we speak of the Muslim contribution to the cure or at least keeping in check mental ailments, we have o take account of the situation in the Europe of the middle ages. There was no treatment worth any name given to the insane; they were either quarantined or burnt at the stake. Chains and shackles were not taken off them till as late as 19th century. In the new World witch-hunting had assumed terrible proportions as depicted by Arthur Miller in his remarkable drama. *The Cruicible*. Gradually, with the advent of the 16th century, the Hippocratic-Galenic scientific reasoning asserted itself in Paracelcus, Agrippa, and others who questioned the concept of demoniacal seizures. In the 17th century, Bacon realized the function of the mind as a part of his concern with the natural order of the universe. The emergence of the natural philosophical reasoning and ratiocination began to exert effect on medical thought. The theories of Locke, Hume, Descartes, Hobbes, Berkeley and others made sense and perception the touchstones of the knowledge. Phillipe Pinel (1745-1826), a French physician, a launched humanitarian movement for the reformation of the mentally sick. Patients were provided with sun-lit rooms in place of dungeons and allowed to perform exercise within the precincts of the hospitals. Naturally this led to positive results.

Activities during the period 1800-1900 gave rise to what we call the modern school of psychiatric thought, e.g. the schools of analysis psychobiology, psychosomatic medicine. It would not be true to say that Greco-Arab medicine has lagged behind in this fields. The example of Rauwolfia serpentine Benth, is a case in point. Ahmed Ali Khan has provided a hand-list of simple and compound drugs employed in Islamic Medicine.[10]

Recent Development

The recent development which has occurred in psychiatry in the West owe their origin to archetypal myths, religions and philosophy. Further research in to the mental makeup of man, human anatomy, psychology, pathology, chemistry and bacteriology led to the discovery of specific brain lesions for various forms of mental illness. The cause of pellagra psychosis, For example, was pinned to vitamin deficiency, while the recognition of delirious reaction was correlated with malnutrition and pernicious anemia. Medical scientists made significant observations on cellular changes in the brain which accompany the prehensile and senile psychoses. In the 19th century several pathological factors associated with medical retardation were discovered. The approach adopted by Freud, viz. analysis of the patients mind, had already been adopted by al-Razi and Ibn Sina.

What Freud did was to formulate a complex model. Jackson's work on epilepsy and other brain disease is also notable; his conclusion was that the function of the nervous system ere integrated with the highest level of function located within the cerebral cortex.

While Freud emphasis the role of sexual impulses in neurotic disease, Jung advocated a deeper analysis of the spiritual factors. Adler, on the other hand, emphasis the concept of inferiority complex.

However, newest discoveries have been made in the field of psychiatry and are associated with Claude Bernard, e.g. the digestive action of pancreatic juice;

the glycogenic function of the liver; and the discovery of vasomotor nerves. The vasomotor tissues are distributed through all the tissues of the organism. Nervous disorder involves the whole of the organism and "there is evidence to show that stress leads to emotional tension and on to general tension in the organs, thereby altering visceral responses which disturb the internal secretions and metabolism". According to this view, there can be no confusion as regards the absoluteness of the mind and the body. Each individual is an indivisible organism.

More recent studies have shown – and it should be borne in mind that this kind of study was pioneered by Ibn Sina that many diseases formerly thought to be unassociated with the brain have psychosomatic origins. Thus Averill define emotion as a socially constituted syndrome which is based on an individual's appraisal of the situation, and which is interpreted as a passion rather than as an action.[12] According to this analogy, both emotion and disease refer to complex syndromes, the latter being a set of responses which co-vary in a systematic fashion. There is a variety of ways in which emotions affect us, e.g. electro physical changes in the muscle of the faces, changes in the electrical activity of the brain, in the circulatory and respiratory systems, activation of the autonomic nervous system which changes the flow of glandular secretions, enzymes, hormones and autacoids. Psychosomatic symptoms may also be manifested if emotion-relevant cognitions and actions are blocked.[13]

Vohra states in this context:

The classical experiments of (the) *Canon* on the physiological effects of fear, hunger, pain and rage lend the basis for many of the psychosomatic studies. It is well-known from every day experience that emotion e.g. fear, anger, resentment, guilt or embarrassment have definite physiological effects.[14] Physical effects of the emotions are medicated through the autonomic nervous system; the sympathetic is chiefly connected with mechanism which sub serves the function of "fight or flight" and the parasympathetic section with functions that are associated with "ease and relaxation "Pituitary adrenal and hypothalamus are fundamentally involved in mechanism concerned with adjustment to acute and chronic emotional stress. Gastric secretion, bile secretion, autacoids, hormones, secretion of the sweat glands, peristalsis, heart rate, qualitative and quantitative changes in urine, blood sugar, blood pressure, peripheral circulations etc. are known to affect and be affected by various situations of emotions stress.

Weiss and English worked out in detail several disease resulting from fear and stress, including cardiac diseases, hypertension gastrointestinal disturbances, endocrine and metabolic diseases, male and female sexual disorders, respiratory disease, disturbances in the central nervous system, skin disorders, arthritis, dental extractions and anxiety attacks. [15]

Our knowledge, then, resting as it does on the relation between psyche (or pneuma of the ancients) and soma (body) is greatly indebted to Muslim scientists and philosophers who, it now appears in hind-sight, possessed a remarkable degree of prescience.

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Pharmacotherapeutics review on Herbal Bioenhancers: A New Approach

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Abstract

Utilization of herbal medicine has been amplified globallyattributable to their effectiveness and low undesirable effects associated with contemporary drugs. Despite of impressive *in-vitro* finding of herbal drug and herbal extracts demonstrated low *in-vivo* absorption and poor bioavailability. In recent time advancement of technology and improvement in the drug delivery system, open the door for increasing the bioavailability of herbal drugs. Last decade witnesses the numerous novel carrier like liposomes, ethosomes, transferosomes, lipid based system, nanoparticles, microspheres for modified drug delivery of many herbal drugs. Piperine, lysergol, aleovera, curcumin, glycyrrhizin, nitrile glycosides and quercetin are the herbal compounds that have ability to improve the bioavailability. The main emphasis of this review is to compile mechanism of action as well as the bioavailability of enhancers of natural origin.

Keywords:

Herbal Bioenhancer, bioavailability, mechanism of action, drug delivery system.

1. INTRODUCTION

Herbal bioenhancers are the phytomolecule or the agents that have ability to enhance the bioefficacy and bioavailability when combined with drug or with any nutrient. These agents do not exhibit own pharmacological activity at the dose used (Atal, 1979). Despite of impressive *in-vitro* finding of herbal drug and herbal extracts demonstrated low *in-vivo* absorption and poor bioavailability. In recent time advancement of technology and improvement in the drug delivery system, open the door for increasing the bioavailability of herbal drugs (Francis AO, 2018). Several reports signify that the use of herbal medicinal products as part of complementary and Alternative medicine is very widespread in developing countries (Ekor M, 2014). The revival of interest in herbal medicine has been attributed to number of factors such as these are safer in use, cost effective and sometime might be more

effective in treatment of certain disease where conventional therapies have proven to be ineffective (Anquez-Traxler C, 2011; Lynch N and Berry D, 2007).

Several plant extracts and phytoconstituents showed reduced in vivo activity due to the inappropriate molecular size, poor aqueous solubility, poor intestinal permeability of the bioactive constituent results in decreased absorption and poor bioavailability. Extract of the plant *Azadirachtaindica*, which is used for the treatment of malaria exhibits high *in vitro* activity against various strains of *Plasmodiumfalciparum* but required high doses to produce in vivo response. Similarly, *Silybummarianum* has silymarin as major bioactive compound and it is used for oral therapy of chronic liver disorder, but due to poor aqueous solubility, exhibited poor bioavailability (Isah AB et al., 2003; Yang KY et al., 2013). The bioavailability of such compound can be improved by using different novel drug delivery system like liposomes, ethosomes, transferosomes, lipid based system, nanoparticles, microspheres (Uchegbuand Vyas, 1998; Moussaoui*et al*., 2002).

1.1. Bioefficacy enhancing activity

Bioenhancing activity is defined as, a substance with low dose, combine with medicine or with nutrient enhance the availability of drug and reduce the intake of drug. The drugs which are poorly bioavailable are subtherapeutic drugs because the dose never reaches to the plasma or it can only produce its therapeutic effect at a very high dose which leads to serious adverse effects. Bioefficacy of many nutraceuticals including metals and vitamins are improved by the use of bioenhancers (Qazi*et al*., 2007).

Bioavailability improvement can be done by the following ways.

1. Fostering the absorption of drug through GIT.
2. Reducing the rate of bio transformatin.
3. Reducing the overall requirement of the drug by modifying the immune system.
4. Enhances the penetration into the pathogens.
5. Inhibiting the ability of pathogens to reject the drug.
6. Modifying the signaling process.
7. Boosting the binding of the drug with the receptors.

There are number of approaches by which the modern drug development processes attain bioavailabilityimprovement.

a. Through chemical modification increases the polarity of drug.
b. Complexation or salt preparation
c. Prodrug formation
d. Micro or nanonization
e. Controlled delivery of drug through fil coating

1.2. Mechanism of action of bioenhancers of natural origin

Among the various mechanism of action postulated for bioenhancer of natural origin includes, reduction in the hydrochloric acid, increase blood supply to the GI, prevention of GI transient and gastric emptying time, modification gastrointestinal epithelial cell membrane permeability, suppression of first pass metabolism of drug and inhibition of metabolizing enzymes of drug, stimulation of ã- glutamyltranspeptidase activity which enhances the uptake of amino acids (Table. 1).

Table 1: Mechanism of action of bioenhancers of natural origin

Mechanism of action	References
Bioenergetic properties	Reanmongkol*et al*., 2009; Jamwal and Singh 1993
Enhances GI blood flow and reduces HCl secretion	Annamalai and Manavalan 1990
Stimulation of GGT (γ-glutamyltranspeptidase) activity	Johri*et al*., 1992
Cholagague and thermogenic activity	Majeed*et al*., 1996
Inhibition of gastric emptying time	Bajad*et al*., 2001
Drug metabolizing enzyme inhibition	Atal et al., 1985; Bhardwaj *et al*., 2002; Reen*et al*., 1988
Modification in GI membrane permeability	Khajuria*et al*., 2005

1.3. Herbal Bioenhancers

1. *Lysergol*. Lysergol,is obtained from *Ipomoea spp*. (Morning glory). It has been isolated from the plants like *Ipomoea muricata, Ipomoea violacea,* and *Riveacorymbosa*. It increases the activities of different antibiotics (rifampicin, tetracycline and ampicillin). The extent of lysergol as a bioavailability enhancer is 1-10ìg/ml, with a dose level of 10ìg/ml. The antimicrobial effect of antibiotic enhances 2-12 folds by lyergol (Khanuja*et al*., 2007).

2. *Aloe Vera Gel. Gel*is obtained from *Aloe barbadensis*(Aloe Vera). It enhances the absorption of two important vitamins (C and E) as well as their plasma concentration. Whole leaf extract and gel improved the absorption of vitamin E, especially by 8 hours and also increase the absorption of ascorbate. The plasma concentration is significantly prolonged even for 24 hours and following fasting. The gel should be considered as nutritional herbal bioenhancers because of its unique ability to enhance the bioavailability of both these vitamin (Vinson *et al*., 2005).

3. *Curcumin*. Curcumin is the main principle curcuminoid obtained from *Curcuma longa*(Turmeric). The effect of curcumin was evaluated in animal model (rabbit) before the agent was administered on pharmacokinetic of norfloxacin. The results revealed that after oral administration curcumin treated rabbit had significantly higher AUC (area under the curve). Treatment with curcumin reduces the loading and maintenance doses by 26% and 24% respectively (Pavithra*et al*., 2009)

4. *Carvone*. Carvone is the main component of *Cuminumcy minum* (Cumin). The dose of 0.5-25 mg/kg is responsible for the bioenhancing activity. The dosage level of extract of *C. cyminum* is 10-30mg/kg, while bioactive fraction dose is 2-20mg/kg (Qazi*et al*., 2003; Qazi*et al*., 2009).

5. *Glycyrrhizin*. Glycyrrhizin is a glycoside obtained from *Glycyrrhiza glabra* (Liquorice). It is known for its expectorant action and used for the treatment of bronchitis and sore throat. Glycyrrhizin improved the bioactivity of different antibiotic used against gram positive and negative bacteria like *Bacillus subtilis* and *E. coli*. It also enhances the activity of antifungal drug i.e., clotrimazole against *Candida albicans* (Khanuja*et al*., 2005; Khanuja*et al*., 2006)

6. *Niaziridin*. Niaziridin is a glycoside obtained from *Moringaoleifera*(Drumstick). The

activity of commonly used antibiotics such as ampicillin, rifampicin, tetracyclin and nalidixic acid against *Bacillus subtilis* and *E. coli* enhances by niaziridin (Shanker*et al*., 2007). It enhances the activity of antibiotics against Gram-positive bacteria by 1.2-19 fold and activity of azole antifungal drugs by 5-6 fold (clotrimazole). It also assists the uptake of Vitamin B12, thus also effective as bioavailability enhancer (Khanuja*et al*., 2005: Khanuja*et al*., 2008).

7. *Piperine.* Piperine, is one of the important alkaloid attained and isolated fromtwo species i.e, *Pipernigrum* (Black pepper) and *P. longum* (Long pepper). It is used as a condiment in all savory dishes to enhance the flavor. The compound acts as an antimicrobial bioenhancers. It enhances the bioavailability as well as bioefficacy of drug by acting on drug metabolism. Acting on the gastrointestinal tract it increases the bioavailability and absorption of nutrients. It was reported that piperine improves the bioavailability of aflatoxin B1 in rat tissues (Allameh*et al*., 1992). Some studies also revealed that piperine inhibit several cytochrome P450 mediated pathways and phase II reaction in experimental models. The administration of piperine also enhances the plasma concentration of different drugs like phenytoin, propranolol, rifampicin, sulfadiazine, and tetracycline in human.The pharmacokinetic profile of phenytoin with piperine was studied using the healthy volunteers.The recommended dose is 5 mg/kg/day. FDA listed piperine as safe herb, it can be safely used as spice, seasoning or flavoring (Dhanukar*et al*., 1983).

8. *Gingerol.*Gingerol, is a major pungent compounds foundin *Zingiberofficinale*(Ginger). It is converted to shogaols, zingerone and paradol (Govindarajan 1982). The presence of volatile oil (1-3%) in the ginger is basically responsible for its odor (Jolad et al., 2004). It has powerful effect on GIT mucous membrane. Ginger not only helps in the regulation of intestinal function but also facilitate absorption. The extract of *Z. officinale*can be used in a dose of 10 to 30 mg/kg.

9. *Caraway oil.* Caraway oil is obtained from the dried and crushed seeds of *Carumcarvi*(Caraway).It enhances the bioavailability of many antibiotics and essential anticancerous drugs. The dose of the bioenhancers extract is 5-100 mg/kg.In different combination it showed pronounced activity ranging from 25 - 95% (Qazi et al., 2003; Qazi et al., 2007).

10. *Sinomenine*. Sinomenine is a principle ingredient of Chinese traditional medicine obtained from *Sinomeniumacutum.*This alkaloid is widely used for rheumatoid arthritis in China and Japan. Experiment was conducted in Sprague-Dawley rats (250–300 g) which indicated that Sinomenine hydrochloride (90 mg/kg) significantly enhances the absorption of paeoniflorin (150 mg/kg) in rats by 1.5 fold (Table 2). The proposed underlying mechanism of sinomenine for the improvement of bioavailability of paeoniflorin was it could decrease the efflux of paeoniflorin by P- glycoprotein (Liu *et al*., 2005; Chen *et al*., 2006).

Table 2. Pharmacokinetic profile of paeoniflorinwith Sinomenine (Liu *et al*.)

$n = 6$, mean ± SD; $^{*}P < 0.01$, $^{**}P < 0.001$, $^{***}P < 0.05$

Parameters	Paeoniflorin	Sinomenine + paeoniflorin
AUC_{0-8} (μg·h/ml)	124.62 ± 36.91	1540.43 ± 548.96**
C_{max} (μg/ml)	1.26 ± 0.23	6.03 ± 2.45*
t_{max} (min)	45 ± 5.0	77.30 ± 17.50*
$t_{1/2}$ (min)	19.58 ± 9.01	53.78 ± 22.17***
Cl_B (ml/kg/min)	1301.83 ± 429.03	110.44 ± 45.61*
V_d (ml/kg)	102044.14 ± 46608.43	16064.25 ± 17189.33***
MRT (min)	133.12± 38.63	224.07 ± 26.62*

11. *Genistein*. Genistein is anisoflavone obtained from *Glycine max* (soybean) and *Puerarialobate* (kudzu). Cotreatment of genistein with epigallocatechin gallate on HT-29 human colon cancer cells increased cytosolic EGCG by 2-5 folds as compare to the EGCG alone. A research was conducted to evaluate the effect of orally administered genistein (10 mg/kg) on the pharmacokinetics profile of paclitaxel administered orally (30 mg/kg) and intravenously (3 mg/kg). Genistein significantly increased the C_{max} and reduced the clearance of intravenous administered paclitaxel (Li X and Choi JS 2007; Lambert et al., 2008).

12. *Capsiacin*. Capsiacin is the active constituent of *Capsicum annum* (chilli pepper). Capsiacin causes burning sensation in any tissue with which it comes into contact. Chilli pepper reduces the bioavailability of aspirin after oral administration in rats (Cruz *et al*., 1999).

Table 3: Recent Patents Bioenhancers

Active ingredients	*Novel system incorporate*	*Patent number*
Alkaloids	Transdermal	US6896898 B1
Flavonoids	Microgranules	US patent 7569236132
Isoflavones	Microencapsulated formulation	Us6890561 B1
Ginsenosides	Microencapsulated formulation and controlled release	US 6340478 B1
Opioid analgesic and aloe	Nasal spray	US 5948414
Ginger	Tablet form	US patent 2007/0042062 A1

1.4. Future Prospective

The use of bioenhancers minimizes the dosage frequency as well as drug resistance. Bioenhancers are also beneficial on ecological point of view. Those therapeutic important drugs that are obtained from slow growing plants in these cases bioenhancers are the choice. Challenges related to the new herbal bioenhancers are needed to be solved. There is a regulatory control of the physiochemical and pharmacokinetics properties of nano drug products.

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Attitudes of Pharmacy Students towards Online learning during COVID-19 Lockdown: A Cross Sectional Survey

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Abstract

The COVID-19 is a pandemic everywhere in the world. The pandemic caused schools, colleges and Universities to close immediately leading to lock down situation to stop the spread of the virus. In Pakistan, all educational institutes were shut down on 13th March, 2020 due to the COVID-19 flare-up. In this situation HEC instructed Universities to switch towards online mode, which was considered as the most adaptable option. The current paper is based on questionnaire based analysis to determine the attitudes of University Pharmacy students of both public and private sector in Karachi towards e-learning during the lock down in Karachi, Pakistan. In survey more than 60% students in favor of on campus lecture because collaboration with other students adds to the logic that there is a community of learning and delivers supplementary support for the student to magnify his or her understanding of the lecture handout.

Keywords:

COVID-19 lockdown, online learning, Pharmacy students, attitudes

1. INTRODUCTION

The COVID-19 pandemic is a gigantic challenge to education systems all over the world. The pandemic caused schools, colleges and universities to shut down their campuses globally so that students could strictly follow social distancing measures in order to stop the spread of the infection (Toquero, 2020).

In Pakistan, authorities closed all educational institutions across the country on 13th March 2020 (Ali, 2020) due to the coronavirus outbreak. Government had ordered institutions to switch the teaching towards online mode, which was considered as the best possible solution for the safety of both the faculty and the students in this condition and was adapted by many countries including Pakistan (Basilaia, G. and Kvavadze; 2020: Peters et al, 2020).

Pakistan's Higher Education Commission (HEC) requested universities to quickly develop their

own learning management system and start online classes in order to prevent the loss of studies in view of the coronavirus situation in the country. At the same time, this online system was quite new for teachers as well as students which totally transformed the traditional way of learning into modern form. Teachers were taking suitable actions to conduct effective e-learning via e-lectures, e-tutorials, e-case based learning, etc. so that education can be continued during the lockdown period without getting much effected (Abbasi et al, 2020).

Despite this, there are some challenges regarding online education in Pakistan as most of the students don't have smart phones and internet facility especially students in remote areas are facing these problems more.

However, in different Universities of Pakistan survey based studies have been carried out to find the opinion of student's about online education in Pakistan. The main issues highlighted by the students were lack of face-to-face interaction with the instructor, response time and poor internet facilities (Adnan and Anwar 2020). The main aim of the present questionnaire based analysis was to determine the attitudes of University Pharmacy students of both public and private sector in Karachi towards e-learning during the lock down and to highlight the challenges and problems of online learning faced by higher education students in Karachi, Pakistan.

2. MATERIAL AND METHODS

An online survey technique was used to collect the data about the knowledge and attitudes of Pakistani higher education students regarding COVID-19. This study was conducted among Pharmacy students of Universities in Karachi including both private and public sector. Students from all Prof. (1st to 5th Year) participated in the survey. The duration was April, 2020 to June, 2020.

2.1. Venue of the Study:

Karachi is the biggest and most heavily populated city of Pakistan and is the capital of Sindh province. There are 3 public sector and 6 private sector institutes. The total intake of pharmacy students is 1070 as per the current information. (https://www.pharmacycouncil.org.pk/PI.php) (https://www.pharmacycouncil.org.pk/doc/recognition.jpg).

2.2. Target population and Exclusion criteria:

The target population for this study was pharmacy students of Pakistan from both private and public sector. It included those participants who were currently enrolled in Pharm. D (Doctor of Pharmacy) program in a Pakistani Pharmacy institution. Those pharmacy students who withdraw during the studies were also not included. Students enrolled in post graduation studies in Pakistan were also not included. Those questionnaires whose data were missing are not part of our study.

2.3. Statistical Analysis

All the data was added by using Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). Chi square test was applied and $p<0.05$ was considered significant.

3. RESULTS AND DISCUSSION

The objectives of the present study were to acquire a broad view of students' experiences and inclinations in e-learning in Pakistan (Karachi),

to assess for which purposes of students favor online modules and for which they favor face-to-face mechanisms in learning progression. The aims of the study was not to investigate exact courses but to survey a large and representative sample of students appearing in Pakistani universities in order to achieve a comprehensive image of their experiences in e-learning system. Consequently, a survey was accompanied with a sample of 143 students from all universities in Pakistan that deal e-learning courses and from assortment of universities of pharmaceutical sciences (undergraduate and postgraduate)(Fig 1. and Table -1). Hence, the outcomes of this exploration can be comprehended as not good indicator for e-learning as in Pakistan (Karachi).

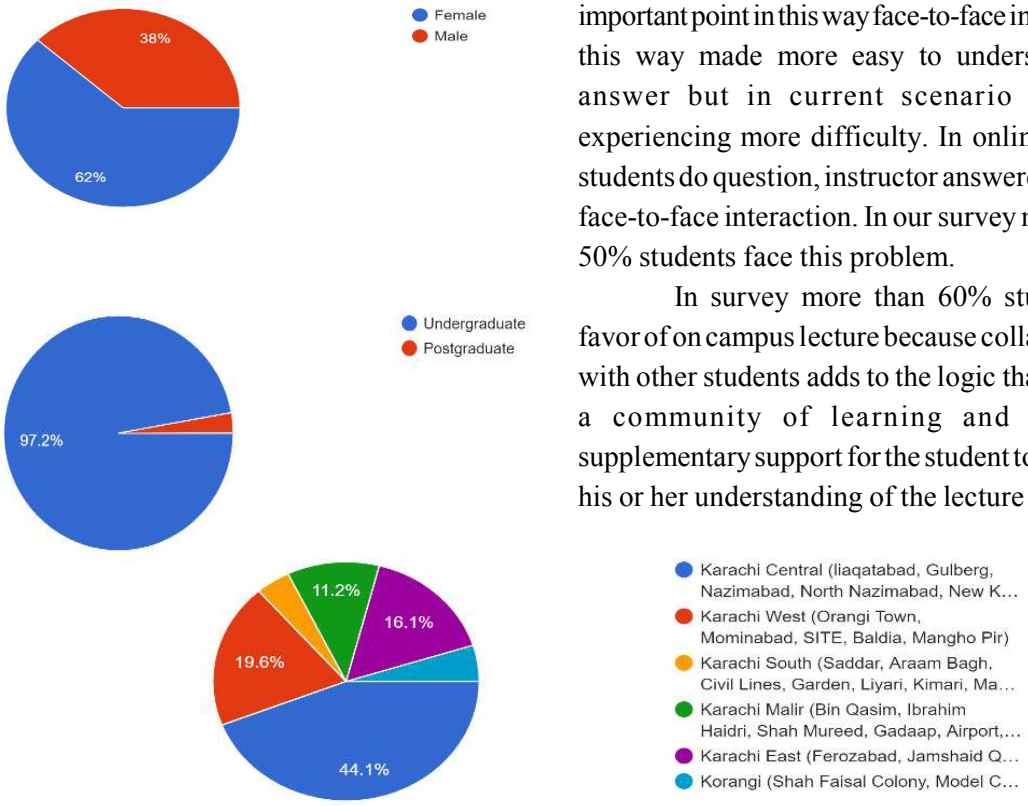

Fig. 1: Graphic representation of demographic evidence of study group

50 to 70 %, students stated a high extent of dissatisfaction with e-learning in their homes due to many circumstances like, electricity issues, internet connectivity, devices storage issues, etc. It was observed that students are under stress due to this Online system of education.

In this investigation, issues of appropriateness and mentor's availability were also elevated but to a minor degree than lucidity and mentor's capability to excellently usage of technology in online programs.

In this assessment, it was understandable that students experience the absence of collaboration with the mentor and with their fellows in the online learning management system.

In classroom students have chance to do question and mentor explain very well and most important point in this way face-to-face interaction, this way made more easy to understand the answer but in current scenario students experiencing more difficulty. In online system students do question, instructor answered but not face-to-face interaction. In our survey more than 50% students face this problem.

In survey more than 60% students in favor of on campus lecture because collaboration with other students adds to the logic that there is a community of learning and delivers supplementary support for the student to magnify his or her understanding of the lecture handout.

Table 1: Distribution among undergraduate and postgraduate students Pharmacy

Question	Responses	%age
Are you ever taken online class before this semester?	• Yes • No	96.5% 3.5%
How difficult was the online class curriculum for you?	• Very difficult • Difficult • Neutral • Easy • Very easy	46.9% 32.2% 18.2% 2.1% 0.7%
How often were you evaluated in the course of your online class?	• Always • Very often • Sometimes • Rarely • Never	15.4% 20.3% 42.7% 11.9% 9.8%
Do you think the online class provided the right amount of theoretical experience?	• Yes • No	22.5% 77.5%
Do you think the online class teachings will be helpful for the growth in your career?	• Yes • No	19.6% 80.4%
How much time spent on education is done using computer?	• 1 -2 Hour • 3- 4 Hours • 4 - 5 Hours • More than 5 hours	23.8% 36.4% 9.8% 30.1%
Do you like the online lecture format?	• Yes • No	27.3% 72.7%
You can ask with teacher, questions and receive a quick response during Internet activities outside of class.	• Yes • No	54.9% 45.1%
Do you feel comfortable composing text on a computer in an online learning environment?	• Yes • No	27.5% 72.5&
Are you satisfied with the quality of online teaching?	• Satisfied • Somewhat satisfied • Not satisfied	8.4% 46.2% 45.5%
Do you able to manage your study time effectively and easily complete assignments on time.	• Yes • No	39.4% 60.6%
You are willing to actively communicate with my classmates and instructors electronically	• Yes • No	44.8% 55.2%
What do you consider to be the drawbacks of taking an online class?	• Interaction with the instructor is not as good • Interaction with classmates is not as good • None, I have not experienced any drawbacks • Other (please specify)	56.7% 11.3% 16.3% 15.6%

The following comments from the survey are illuminating.

1. I'm as a student of University online classes is a big no. Students that lack motivation, need to force themselves to sit and study, still they can somehow get distracted easily whereas in a classroom there is a complete serious environment, we can interact with teachers and students, can easily solve our queries, there are group discussions that helps a lot and in the end when they come out of the classroom they might have learnt something.
2. I request not to repeat this again as learning level is 0. It's not a game to pass online exams being a medical student without proper classes and labs.
3. Normal classes are more comfortable than online classes.
4. Interaction with the instructor is not good; you have to always get in touch with your device to get to know if there is any new update etc.
5. There is many difficulties sometime network problem, power supply, etc.
6. Face to face learning in class is far better than online learning.

Pinto and Anderson (2013) found that the more the student felt a part of the class, and the more interaction there was between students, the more satisfied the student reported to be with the hybrid format. As in this survey, interaction was important between mentor and students.

As retention is key to the success of online programs in higher education, the relationship between students' satisfaction with their e-learning experiences and student retention is clear (Lorenzo, 2012). It is this role that makes ongoing studies of satisfaction with online education important.

4. CONCLUSION

The outcomes of current study indicate that Pharmacy higher education student's attitudes towards online teaching are not satisfactory. Although the students towards the pandemic are optimistic but there are several constraints related to online teaching that are problematic for students such as internet, smart phones, lack of face to face interaction and group discussion. However the fact must be kept in mind that many universities around the world are rapidly turning to digital on line system during pandemic situation. As the current scenario about Covid-19 is uncertain therefore in this connection future recommendation will have to focus on Pharmacy academicians for improving on line education. HEC should ask recommendations from pharmaceutical expert because they are directly connected to students and understand their issues.

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A Significant Correlation Between Convulsion and Ferrula Foetida Exudate

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Abstract

Ferula asafoetida, an oleo gum resin was evaluated for anticonvulsant activity at various doses using seizureinducing model, Pentylenetetrazole(PTZ) test .The test drug showed significant dose dependent anticonvulsant effect without sedative effects as observed in Phenobarbitone (standard) group while the toxicity test represented safety margins of drug.

Keywords:

Phenobarbitone, LD_{50},Pentylenetetrazole, Anticonvulsant.

1. INTRODUCTION

Medicinal plants provides immense health not only to individuals but also to different population in the world. These indigenousmedicinal plants have been utilized as spice and food componentswhich contains numerous bioactive molecules exerting profound physiological action on body of humans. (Edeoga*et al.,*2005) Genus Ferula belongs to family Umbelliferae has 133 species which is dispersed widely throughout different mediteranean and Asian regions. From centuries *Ferulaasafoetida* (Fig-1) has been used traditionally as anticonvulsant, antispasmodic, carminative, digestive, expectorant, antihysteric, laxative, aphrodisiac, antiseptic, and analgesic agent.The dynamic pharmacological potential of this herb is due to sulfide, sesquiterpene and monoterpene compounds which includes á-pinene, phellanderene,á terpineol and other flavonoids and luteolin (Bagheri *et al.,*2010; Kiasalari*et al.,*2013) The gum contain some skin friendly compounds i.e ferulic acid which has well known antioxidant activities, protects the skin from UV damage and ultimately produce antiwrinkle or antiaging effects. Azulene another compound in exudate of Ferula prevents skin irritation and used widely in cosmotological products(Moghadam et al., 2017) Asafoetida is the major flavoring agent in various cuisines and because of its peculiar taste it is used in many spice mixtures. It produces flavor in meatballs

and pickles Curries. The whole plant is regarded as a fresh vegetable. Commercially, the adhesive property of gum makes it fixative agent in perfumeries.(Mahendra, and Bisht., 2012).

In neurological disorders, epilepsy is the most common problem which effects 5-10% people world wide, If this disorder is untreated can cause compromised cognitive activities or psychopathological problems. Many synthetic antiepileptic drugs like phenobarbital, phenytoin, valproic acid, felbamateare used frequently but all of them have marked side effects and toxicity therefore, natural antiepileptics is a better choice which not only cure the disorder but elicits minimal side effects (Fatehi *et al.,*2004).

2. MATERIALS AND METHODS

2.1. Plant Material

Ferula foetida gum resins was purchased from local market in 2018 and identified by Prof. Dr. Ghazala H. Rizwani, Dean Research, Hamadard University.The voucher specimen was deposited in hebal museum , Hamdard University Karachi . The gum was powdered using electrical grinder and sieved with cotton cloth to remove impurities. The sample drug obtained was stored in air tight container. The gum resin was freshly dissolved in distilled water before administered orally.

Fig-1: Plant of Ferula asafoetida (i) Gum resins (ii)

2.2. Animals

Male albino mice, (21-32) g., were reared in the animal house of Hamdard University Karachi. and kept under controlled standard laboratory conditions .i.e light and dark and temperature 20±2°Cwere maintained during whole experimental period. The mice had free excess to standard food and tap water except during the actual test. The dose of the drug was determined by preliminary screening at a doses of 5, 15, 25, 35,45mg/kg weight. Since the animals were protected against PTZ induced convulsions at 45 mg orally therefore lower and higher dose viz. 35, 45 and 55 mg /kg were used.

2.3. In vitro PTZ induced method

Evaluation of anticonvulsant activity of Asafetida gum resins against pentylenetetrazol (PTZ) induced convulsions in albino mice was carried out according to the method described earlier, Mitchell and Kealing (Robert , 1965 ; Emmanuel and Thompston,1990).

Male albino mice were divided into five groups(n=6 per group). Group I (control) was pretreated with distilled water 0.20ml/25gm of animal by oral route, while group II (standard group) was pretreated with Phenobarbitone 30 mg/kg orally. The test groups III, IV and V were pretreated with the test drug at of 35, 45 and 55 mg/kg respectively. One hour later, all the animals were administered with PTZ (60 mg/kg) subcutaneously in the scruff of the neck (Akula, et al., 2009) Convulsions in each group was observed immediately. Number of mice protected/ not protected from convulsions, number of episodes, time of onset, duration of convulsion, nature and severity of convulsion were recorded.

2.4. Determination of LD_{50}

Albino mice were divided into groups(n=6 per group), each having six animals .The animals were kept on fasting overnight. Each group was administered the test drugs orally with subsequent two fold increment of therapeutic dose (55 mg/ kg)viz. 110,220,440, 880 mg, 1.76 g, 3.5 g, 7g, 14g and finally overnight mortality was recorded. The therapeutic index was calculated to determine the margin of safety of test drug.

3. RESULTS AND DISCUSSION

In control and treated animals the onset of effect of PTZ-induced convulsions were observed after 5.20 minutes and the convulsions were seen after the mean time 7.03 minutes and the duration of convulsion was recorded as 8.2 seconds. In one animal of this group died after12th minute.The individual records are shown in Table -1and group results are presented in (Table -2)

Table -1: Arbitatory scale of observed effects, showing the behavioral

Dose gm/kg	Restlessness	Alertness	Body posture	Limb posture	Grip strength	Staggering gait	Death
6 animals /dose	Normal score*	0	4	4	4	4	0
0.11		0	4	4	4	4	0
0.22		0	4	4	4	4	0
0.44		0	4	4	4	0	0
0.88		0	4	4	4	0	0
1.76		0	4	4	4	0	0
3.5		4	6	4	4	0	0
7		6	3	2	2	4	1
14		8	0	0	0	8	5
12		8	1	0	1	7	3

*4 for a normally present showing increase to 8 for increase in the characteristics and decreas to 0 for diminution of the characteristics. Sigma normally absent at 0 and relative activity of the drug is recorded as an increase in score up to 8.

The animals after administration of phenobarbitone injection were immediately observed for convulsionsfor 30 minutes. There were no convulsions and 100% protection was recorded. Marked sedation was observed in 45 minutesafter Phenobarbitone treatment. (Table 2) and at 35 mg/kg convulsions presented was observed only in two animals at mean time 13.05 and duration of convulsion was recorded 5.50 sec (Table-2).

At 45mg /kg, one animals were protected from convulsion. Convulsions appeared in 10 minutesfor only four seconds and then after 13.40 minutes. Straubs tail, stormy jerky movement generalized colonic convulsion was recorded for 05 seconds later animal was exhausted and after one hour death occurred.(Table 2).

The animals after treatment with 55mg/ kg were under observation for one hour. No convulsion was noticed, and 100% protection was recorded (Table 2) .The test groups of dose 35, 45, and 55 mg/kg, orally exhibited 66.7%, 83.3%,and 100% protection, respectively, against PTZ induced convulsions (Table 2).

The median protective dose (ED_{50}) was calculated by Arithmetical method of Reed and Munech was 33mg/kg (Robert., 1965). In the test for determination of LD_{50} the test drug with the dose of 110mg, 220mg, 440mg, 880 mg and 1.76g/kg administered orally, did not show any behavioral changes. At the dose of 3.5 g and 7.5g/kg orally, restlessness, ataxia, deficient gripping and extreme restlessness were evident. After 30 minutes decrease in alertness and extension in limbs were also observed. All the animals were observed for 6 hrs and overnight. All animals recovered fully after 4 hrs except one which was died.

At a dose of 14 g/kg marked restlessness was observed after 20 minutes of it's administration for 10 minutes. After 30 minutes marked staggering gait, loss of grip strength and limbs were noticed to be paralyzed and finally loss of body posture and loss of alertness appeared in five animals. Since the mortality at 14 g/kg was 83.3% therefore a reduced dose i.e 12 g/kg was administered and recorded.

At dose of 12 g/kg orally, the restlessness was observed for 15 minutes, after 20 minutes of drug administration and loss of grip strength, marked ataxia, and flexed limbs were observed. After 45 minutes abnormal body posture and marked reduction in alertness appeared .Three animals died overnight three were recovered. The observed effects were scored over an arbitatory rating scale from 0-8.4 for a normally present allowing increases to 8. For an increase in characteristics and decrease to 0 and the relative drug is recorded as an increase in score up to 0-8.(Table -1). The mortality was recorded at 110, 220, 440, 880 mg /kg, 1.76 g, 3.5g, 7g, 14 g, and 12 g/kg respectively (Laurence and Bacharach.,1996).The LD_{50} of the test drug was found to be 12g/kg.

Table -2: The effect of Phenobarbitone and different doses of ferrula asafetida gum resins on the convulsions induced by PTZ in mice

S.no	Groups	Convulsions		Nature and Severity	Convulsions Protected	Death Out of 6
		Onset Mean+ S.E (Mins)	**Duration** Mean+S.E (Mins)			
1	**Cotrol +PTZ**	7.03±0.32	8.2±0.69	Jerky movements, straub's tail and generalized clonic convulsions	0/6	1/6
2	**Phenobarbitone + PTZ**	0	0	No convulsion	6/6	0/6
3	**Asafoetida gum (35 mg/kg)**	13.05±0.02	5.5±0.28	Delayed Jerky movements and convulsion	2/6	0/6
4	**Asafoetida gum (45 mg/kg)**	13.40±0.10	5±0.30	Delayed Jerky movements and convulsion	1/6	0/6
5	**Asafoetida gum (55 mg/kg)**	0	0	No convulsion	6/6	0/6

In the present study Asafoetida was investigated for anti convulsant effects by employing potent seizure induced model i.e. PTZ test which provided remarkable protection against convulsions.

The WHO estimates that there are 50 million people suffering from epilepsy worldwide.This prevalence is around 4-10 per 1000 population .The treatment gap, the percentage of patients with active epilepsy untreated estimated to be 50% world over, much higher in developing countries as compared to developed countries (Sanders,1996).The ideal drug for treating epilepsy is expected to have an ability to suppress convulsions, furthermore such an agent which correct any underlying defect and predisposes the patient to paroxysm of abnormal neural activities resulting in seizures (Nigam and Sachan 2013).

In this study the treatment group showed convulsions in only two animals in 13.05 minutes and the duration was 5.3 seconds. While the convulsions appearedonly in one animal after 13.4minutesand duration was 5 seconds.

Test group showed no convulsions in any animal. The absence of sedationafter treatment proves is a better choice than phenobarbital. The test drug therefore exhibited significant dose dependent anticonvulsant effects without sedation as observed in standard group.The safe dose calculated to be 33 mg/kg .In the test for determination of LD_{50} the mortality was recorded to be 0, 0, and 0,0,0,0,01,05,03 respectively. Thus the LD50 of asafetida gum resins was found to be 12 g/kg in male albino mice.

4. CONCLUSION

It is concluded that asafetida gum resins at 35,45 and 55 mg/kg orally provided protection against PTZinduced convulsions respectively. The protection from convulsion at 55 mg/kg without any sedation is most promising property.Thus, further investigations are required to isolate the active moiety followed by detailed mechanism ofaction along with safety profile to be included in the drug development programme.

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Bioinformatics Tool and Application for Analysis of Omics

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Abstract

Bioinformatics tools and applications are computational program that help to analyze the one or more sequences at the same time. There are dizzying or wide varieties of bioinformatics tool available on web that can analyze sequence to find the protein domains (Pfam), or that can search through databases of millions of sequences to find ones that are slimier (BLAST) or that can find potential protein-coding region (ORF-Finder).or we can say that bioinformatics gather, store, analyze and integrate the complex omic (genomics, transcriptomics, proteomics, and metabolomics) information that applied for the developmental biology, evolutionary biology, or to gene base drug development.

Advancement in molecular biology has opened the new era for rapid sequencing like human genome project. Bioinformatics helps in the analysis of sequencing data by computer applications and tools is known as "Computational Biology".

Keywords:

Bioinformatics, computational tools and application, database for omics, genomics, transcriptomics, proteomics, metabolomics, epigenomics, and pharmacogenomics.

1. INTRODUCTION

The science of bioinformatics, the modified form of molecular biology with computer science which help to understanding the genomic information of human disease or disorder and mechanism of action against these disorder or disease by the new molecules, in the discovery of new molecules or regime and vaccine stud. Despite in the development of molecular biology, research institutes and pharmaceutical firms in collaboration work on it and create the bioinformatics data sharing for curing of disease and new drug development. Now the biotechnology is being considered as essential part of pharmaceutical as well as diagnostic lab. Studying the cellular level of existing and new molecules acted on it including

human, plant and microbe. Molecular biological and pharmaceutical
scientists have unraveled the massive information generated by large scale sequencing; efforts are underway in research laboratories around the world.

Bioinformatics is concerned with the creation and maintenance of database to store biological information's of omics such as genomics, transcriptomics, proteomics, and metabolomics as mentioned in fig1.Researchers and scientists both could access existing as well as submit new revised data by bioinformatics tools. Bioinformatics tool and technique helps to identify the cellular level of molecular action which tends to regulate human cells response to a disease signal, by identifying the gene and the numerous protein expressions in cells to determine which responds in specific disease. Its involvement includes hepatitis C, bronchitis, cancerous tumors, rheumatic diseases, and allergy. Application of bioinformatics tool and technique in various disciplines as describe in fig.2.

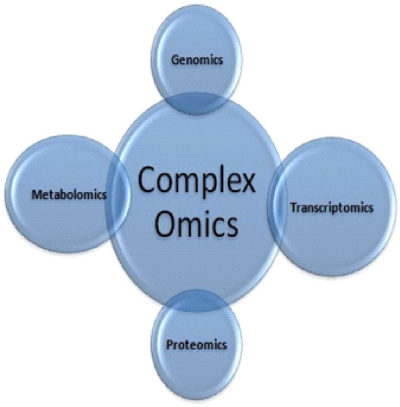


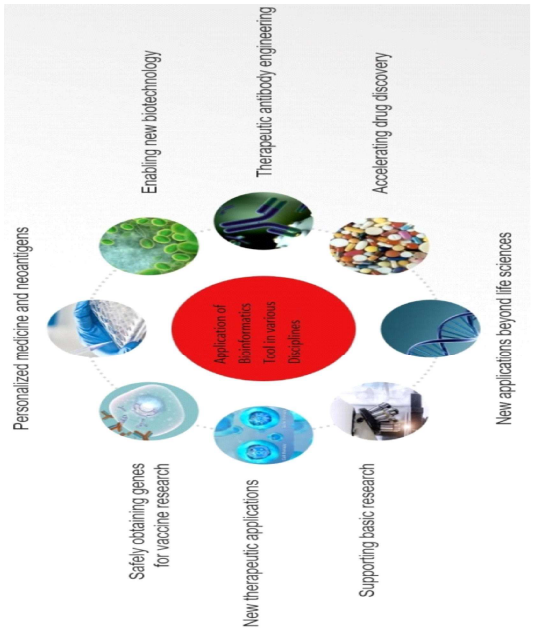
Fig.1. A complex omics consist of bioinformatics

Therefore bioinformatics is an excellent tool and application for biology or biotechnology as well as pharmaceutical sector (particularly responsive proteins determination and vaccine / drug development.

2. MATERIALS AND METHOD

2.1. Genomics:

An organism having complete set of DNA is called genome. Genomics refer to the study of whole genomic sequencing and estimated every single cell in the tissues contains a complete copy of approximately 3 billion DNA base pairs that make up the genome. Among the advancement in technology of the past one decade which made the sequence of large DNA easy and established molecular database (EMBL nucleotide database library) for comparison of DNA and protein sequence with the help of alignment tools and application including smith waterman algorithm and FASTA/ BLAST package. Genomic refers to the study of gene and their functions, including genes mapping and sequencing the DNA which help to understand the disease. It includes,



Genomic, Transcriptomics, Proteomic, and Metabolomics.

Fig.2.Application of bioinformatics tool and technique in various disciplines.

1. Functional genomics: the characterization of genes and their mRNA and protein products.
2. Structural genomics: the analysis of the architectural features of genes and chromosomes.
3. Comparative genomics: the evolutionary relationships between the genes and proteins of different species.
4. Epigenomics (epigenetics): it is a multitude of chemical compound that can tell the genome what to do. Epigenome is made up of chemical compounds and proteins that can attach to DNA and direct such actions as turning genes on or off, controlling the production of proteins in particular.

Table 1. Bioinformatics analysis for genomics.

Methods	Whole genome sequencing by *De-novo*	Whole genome re-sequencing	Exome sequencing and Target region sequencing	RAD sequencing	Optical Maping
Bioinformatics analysis	• Sequence depth analysis. • Gene size estimation. • Repeat annotation. • Gene prediction. • Phylogenetic analysis. • WG alignments. • Prophage prediction.	• Statistics of data production. • SNP calling, annotation and statistics. • Population structure analysis. • Complex disease advanced analysis. • Cancer and advanced analysis. • Mandelian disorder analysis.	• Data filtrating. • Alignment summary of data producer. • Haploview. • Somatic SNP detection for paired Normal-tumor sample. • NGS-GWAS for complex dieses.	• Basic seq. data analysis. • Phylogeny tree analysis. • SNP detection. • Principle component analysis.	• Enzyme digestion result. • Optical map. • Comprative genetic.

Table.2. Bioinformatics tools available on website for genomics.

Tools	Description	Website
Bowtie	Ungapped alignment use of FM Index using the BWT Fast and memory-efficient alignment Quality value output	http://bowtie.cbcb.umd.edu/
LALIGN	It finds multiple matching sub-segments in two sequences. It provides or assigns one with % identity for different sub segments of the sequence.	http://www.ch.embnet.org/software/LALIGN_form.html
CoreGenes	It is designed to analyze two to five genomes simultaneously, it also generates a table of related genes i.e. orthologs and putative orthologs. It has a limit of 0.35 Mb. It has an updated version of core gene 2.0	http://binf.gmu.edu:8080/CoreGenes1.0/
MATCHER	It is also a part of EMBOSS. It finds the best local alingment between two sequence .	http://mobyle.pasteur.fr/cgi-bin/portal.py?#forms::matcher
ClustalW	It is a Multiple Sequence Alignment search tool. It provides one with a number of options for data presentation, homology matrices and presentation of phylogenetic trees.	http://www.ebi.ac.uk/Tools/msa/clustalw2/
VISTA	VISualization Tools for Alignments - this URL allows one to align two genome - length sequence.	http://genome.lbl.gov/vista/mvista/submit.shtml

Table.3. Bioinformatics analysis for Transcriptomics.

Methods	RNA Sequencing (Transcriptome)	RNA Sequencing (Quantification)	Digital Gene Expression Tag Profiling (DGE)	Small RNA Sequencing	Degradome Sequencing
Bioinformatics analysis	• Statistical analysis and evalution of data. • Assembly results. • Assessment of sequencing. • Gene expression and annotation. • Prediction of novel transcripts. • Other analysis content is the same as transcriptome.	• Sequencing and basic data processing. • Expression pattron analysis of differentially expressed gene (DGEs). • Gene antology analysis of DEGs. • Pathway enrichment analysis DEGs.	• Novel transcript detection. • Antisense transcript annotation. • Protein-Protein interaction network analysis.	• Length distribution of small RNA with insert size of 18-30 nt. • Small RNA distribution across genome analysis. • Alignment of small RNAs to rRNAs, tRNAs, snRNAs, and snoRNAs. • Alignment of small RNAs to the known miRNAs in the miRNAs database. • Known miRNAs in the miRNAs family analysis.	• Statistic data assessments. • Remove polyN reads. • Categorization and annotation of degradome fragments. • Identificatio of mRNA degradation.

Table.4. Bioinformatics tools available on website for Transcriptomics.

Tools	Description	Website
Gene Expression Omnibus (GEO)	Feasable for both type microarray and sequencing data.	https://www.ncbi.nlm.nih.gov/geo/
ENCODE: Encyclopedia of DNA Elements	Public ENCODE Consortium data	https://www.encodeproject.org/
European Nucleotide Archive (ENA)	only for Sequencing data	https://www.ebi.ac.uk/ena
DDBJ Sequence Read Archive (DRA)	only for Sequencing data	https://www.ddbj.nig.ac.jp/dra
RNAmicro	It recognizes the miRNA precursors in Comparative Genomics Data. It is available as a standalone program and as webbased program.	http://www.tbi.univie.ac.at/~jana/software/RNAmicro.html
Mireval	It is a comprehensive tool, easy to use and very informative.	http://tagc.univ-mrs.fr/mireval/

Table.5. Bioinformatics tools available on website for Proteomics.

Methods	Proteome Profiling	Quantitative Proteomics	Targeted Proteomics	Phosphoproteomic Analysis	Protein Identification
Bioinformatics analysis	• Statistical data and quality control. • Protein identification. • GO, COG and pathway analysis of protein.	• Expresion pattern cluster analysis of multi samples (more than three samples). • Comprative analysis of proteomic and transcriptomic.. • Protein-Protein interaction network analysis. • Protein COG analysis. • GO enrichment analysis of differential proteins.	• Target protein selection. • Transition predicition. • Transition protein identification. • Transition protein quantification.	• Database search. • Statistical analysis of database search results. •Detection and identification of phosphorylated proteins.	• Statistical analysis. • Protein GO category analysis. • Protein COG category analysis.

Table.6. Bioinformatics tools available on website for Metabolomics.

Tools	Description	Website / URL
IMPALA	Integrated pathway-level analysis from gene or protein expression and metabolomics data Identification of additional pathways from the combined datasets Accepted inputs: gene or protein expression and metabolomics data.	http://impala.molgen.mpg.de/
MetaboAnalyst	metabolomics data processing, normalization, multivariate statistical analysis including SNPs, locations, and pathways.	http://www.metaboanalyst.ca/faces/home.xhtml
MetScape	Gene, enzyme, and metabolite networks analysis with emphasis on metabolic pathways.	http://metscape.ncibi.org/
WGCNA	Integrated analysis of correlation and network topology.	http://labs.genetics.ucla.edu/horvath/CoexpressionNetwork/Rpackages/WGCNA/
huge	Fast computation for high-dimensional data using lasso estimate of the inverse covariance matrix.	https://cran.r-project.org/web/packages/huge/index.html

Table.7. Bioinformatics tools available on website for Metabolomics.

Tools	Description	Website
SWISS-MODEL (Swissprot)	An automated comparative protein modelling server. It require a viewer such as DeepView - Swiss-PdbViewer, Rasmol , Cn3Dv 3 . 0 or webmoljava PDB.	http://swissmodel.expasy.org/
Coils	It helps in prediction of Coiled Coil Regions in Proteins.	http://www.ch.embnet.org/software/COILS_form.html
D A S	Transmembrane pediction server.	http://www.sbc.su.se/~miklos/DAS/
OCTOPUS	This tool uses a novel combination of hidden Markov models and artificial neural networks. It predicts the correct topology for 94% of the dataset of 124 sequences with known structures.	http://octopus.cbr.su.se/
YASPIN	It is built on three individual web servers: cons-PPISP, PINUP, and Promate. It is known as the meta web server and is used for protein-protein interaction and site prediction.	http://www.ibi.vu.nl/programs/yaspinwww/
Tmpred	Prediction of Trans-membrane Regions and Orientation	http://www.ch.embnet.org/software/TMPRED_form.html

Cells including DNA methylation patterns, imprinting and DNA packaging.

5. Pharmacogenomics:it refers to the study in which how an individual gene affected and how they respond on medication. It is a part of precision medicine which tends to new biological targets and new ways to design **drugs** and **vaccines**.

Some bioinformatics analysis and its tool for genomics are mentioned in Table.1 and Table. 2.

2.2. Proteomics:

The name itself indicates that the study of entire protein produced by a cell type in order to understand its structure and function. It is the recent field for protein analysis with high throughput approach to protein expression analysis of a cell or organism and in proteomics gene expression at protein level can be analyzed by chromatography, large scale 2D gel electrophoresis, and mass spectrometry. It helps in diagnostic and precise medication for individual.

Some bioinformatics analysis and its tool for proteomics are mentioned in Table.5 and Table. 6.

2.3. Metabolomics:

Metabolomic refer to identify the wide range of different classes of molecules such as metabolite in a cell and the statistical tool is used to analyze and interpret the data. It is a powerful tool for understanding biology and developing new hypothesis. It can be used to determine the composition in food and nutrition. Bioinformatics analysis for metabolomics include, metabolomic analysis by UHPLC-Q-TOF/MS, Partial least square discriminate analysis (PLS-DA).

Identification of additional pathways from the combine datasets, Gene expression and metabolite data, metabolite identification translation for a 200 common biological database.

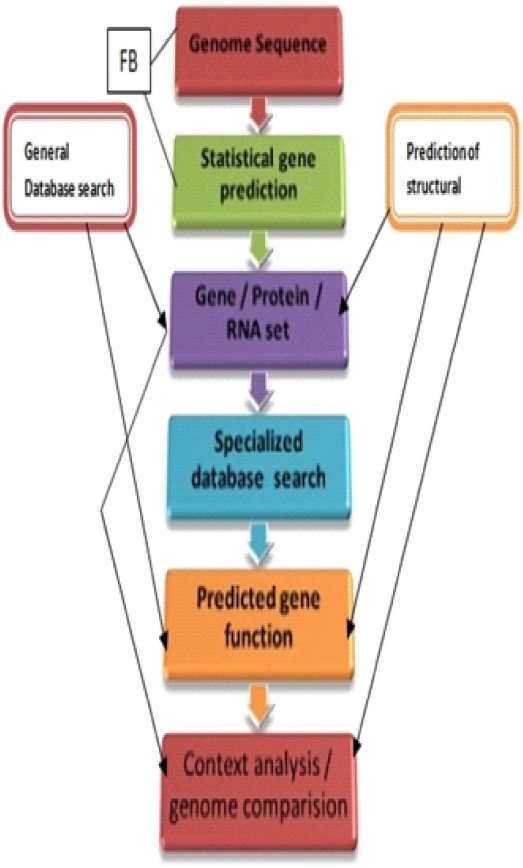


Fig.3:A general flow diagram for bioinformatics of omics annotation.

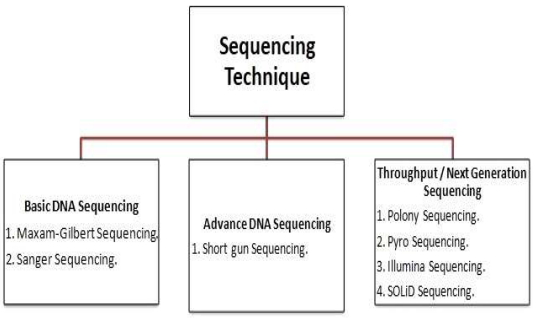


Fig.4: Flowdiagram of sequencing technique generally used in sequencing.

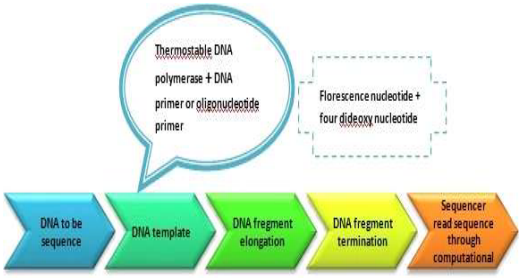


Fig.5: All the reaction occur in thermocycler i.e. (PCR) except the sequence read and the core principle of DNA replication in PCR is to **denaturing** the protein or DNA at 95°C then **annealing** at 50 to 65°C where the primer is attached to specific region on single strand of DNA followed by **extending** at 70-80°C where polymerase enzyme (Tag polymerase) acted on it and new DNA formed.

Some bioinformatics tools for metabolomics are mentioned in Table.5 and Table. 7.

Bioinformatics for Omics can be described by a general flow diagram as mentioned in fig.3.

2.4. Sequencing:

DNA sequencing means determination of nucleotide sequencing of DNA strands by gel electrophoresis followed by DNA amplification through PCR and then sequence read through sequencer by Computational graphs that is called sequencing methods. It contains information about the protein and amino acid. Following steps are followed for PCR based amplified DNA products in (fig.5).

Different types of sequencing techniques are using for sequencing which is briefly describe in flow diagram (fig.4).

2.5. Sequencing Methods:

There are more than nine different types of sequencing methods some of which are described as follows.

2.5.1. Restriction fragment length polymorphism (RFLP):

This method can be detected variation in DNA sequence by cleavage the DNA into pieces with restriction enzyme and analyze the size of fragment by gel electrophoresis. RFLP can identify the differences in sequence at restriction site. RFLP acts as important tool in gene mapping, chromosomal location of particular disease gen which is transferred by inheritance, risk for disease, likely to be carrier of mutant gene, breeding patterns in population of animal.

2.5.2. Amplified fragment length polymorphism (AFLP):

AFLP use restriction enzyme to cut the genomic DNA into restriction fragments and these fragments are then amplified using primer at restriction fragment site. Amplified fragments are visualized on denaturing by polyacrylamide gel either through autoradiography or fluorescence methodologies.

AFLP has higher reproducibility, resolution, and sensitivity at the whole genome level as compare to other technique. This method is widely use for the identification of genetic variation in closely resembled of plant species, fungi, microbe and

animals and used in criminal and paternity as well.

2.5.3. Random amplification of polymorphic DNA (RAPD):

This method is used for primary assay that helps in screening the differences in DNA sequences. It is used in sequence of random amplification of DNA fragments and using short single primers at low annealing temperatures, the DNA is cut and PCR amplified at random segment of genomic DNA. The disadvantage of this technique over RFLPs is due to low annealing temperatures and easier reaction conditions.

2.5.4. Variable number tandem repeat (VNTR):

It is found in genome where organized a short nucleotide sequence as a tandem repeat. It is used in analysis of genetics and biological research, forensic, and DNA fingerprinting.

2.5.5. Micro satellite polymorphism or Simple Sequence Repeat (SSRs):

Simple sequence repeats are microsarellites and show high degree of polymorphism. They are isolated using hybridized probes followed by their sequences.The advantage of SSRs over RFLPs is that less amount of DNA is required.

2.5.6. Single nucleotide polymorphism (SNP):

In this method variation in DNA sequence occur when single nucleotide in genome differ between member of a species. These are used to determine the response to pathogen, chemicals, drugs, vaccines and other reagent in human.

2.5.7. Short tandem repeat (STR):

Polymorphism occur when pattern two more nucleotide are repeated and repeated sequence are adjacent to each other and with the pattern from 2 to 10 base pair (bp) in length. It is under studied and discussion the use of this technique in transmissible agent of canine transmissible venereal tumor (CTVT).

2.5.8. Inter simple sequence Repeat (ISSRs):

It is a specific primer-based polymorphism detection system, where a terminally anchored primer specific to a particular simple sequence repeat (SSR) is used to amplify the DNA between two opposed SSRs of the same type.

2.6. Some basic concepts for Bioinformatics:

The very important basic concepts for bioinformatics are as follows,

1. Similarity.
2. Homology.
3. Phenotype.
4. Genotype.

2.6.1. Similarity:

Degree of likeness between two sequences usually expressed as percentage of similar or identical.Sequences are just compared by same method logically weaker.

2.6.2. Homology: Statement about common evolutionary history / ancestor of two or more sequences. It is hypothetical base and can only be true or false. Compared sequence results have profound impact.

2.6.3. Phenotype: The term phenotype is used in genetics refer to all observable characteristic in organism as a result of the interaction of genotype with environment. It indicate the observable physical characteristics in organism like its height, hair color and texture, eye color, and facial texture ant its color. It covers the organism's

morphology, physical form and structure, its behavior, biological and physiological properties of the organism.

2.6.4. Genotype:

The term phenotype is used in genetics refer to genetic composition of an individual consisting of heritable gene. For example two alleles that are inherited for a particular gene, one is dominant and the other is recessive allele.

2.7. Gene Sequence Label:

DNA or protein (sequence) has chemical function whenever the coding containing single letters reduce to its fraction also function as unique label like barcode.

The sequence label can be sued to search the information related to particular gene, its role in cellular label. Sequence label can help user connect information about gene that are slightly or even dramatically different sequence. Simple label were all that was to make sense biological data you could just registered sample data followed by instruction to gene bank ID to give a unique accession number to every DNA sequence and be done with it.

2.8. Alignment:

The matching of codon with its ancestral protein called alignment. It represents evolutionary relationship between the protein sequences. We can also say that "sequential arrangement of DNA, RNA and protein on top of another where the residues are entitled to have a common evolutionary origin". If the alignment is correct, it represent the historical past. The sequence can be correct, it represent the historical past. The sequence can be correct or check the alignment to reconstruct the sequence to get the ancestral sequence by several means known as mutation, it includes,

i. Elimination of nucleotide (in DNA) Deletion.
ii. Introduction of nucleotide (in DNA)- Insertion.
iii. Replacement of nucleotide (in DNA)

2.9. Currently three different types of Alignments existed as mentioned,

i. Global Alignment
ii. Local Alignment.
iii. Multiple Alignment.

2.9.1. Global Alignment: Alignment of two proteins or genes basically similar or it is the paired alignment of entire sequence includes all residues of both the sequence. For example,

```
Seq. 1    EARDF- NQYYSSIKRS GSIQ
          . . :    . : : : : : : : . . .
Seq. 2    LPKLF    IDYYSSIKRT
MG-H
```

Highest similarity in the highlighted region including residues both the sequences.

The tools and technique is used for a global alignments is ALIGN.

2.9.2. Local Alignment: Merely compares the part that have good similarity or it is the paired alignments of subsequences from sequence include identical and similar residue matches.

```
Seq. 1    NQYYSSIKRS
          . : : : : : : : : .
Seq. 2    IDYYSSIKRT
```

Portion of two sequences that have highest regional similarity.

The common tools and technique is sued for a local and other alignment is BLAST / FASTA as mentioned in Fig.6.

2.9.3. Multiple Alignment: It is the set at sequence (homogenous) arrange and unite in column and similar in figure or table. The matrix tools are used for multiple sequence substitution

or alignments includes 1. Clustal W. 2. MUSCLE. 3. MEGA-X.

2.10. Biological Database:

It is a structural collection of record store in a computer system and consists of number of files which contain many records of biological information (sequence). Genomic database usually store DNA or protein sequence as well as annotated about the sequence and many database also provide bioinformatics tool, such as BLAST, for finding specific sequences or annotations. There are several thousand types of genomic database, few are comprehensive in these, but are not carefully curate (GenBank) while other are carefully curate, but are narrow (FlyBase). Researcher's point of view data store in database

2.11. Derived Data:

It contain two types of database that is primary database and secondary database.

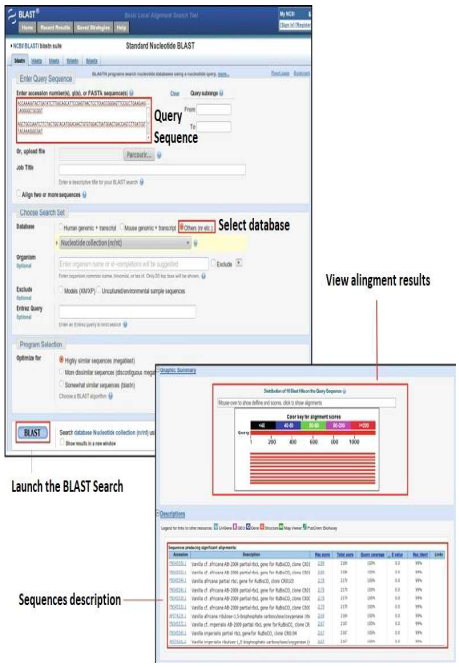


Fig.6: BLAST / FASTA technique is used for alignment of sequences by NCBI.

and the results obtained needs to be easily accessed through standard means. Biological database are classified on the basis of biological information are as follows.

2.12. Fundamental types of Biological data:

It contain the following information like nucleotide sequence, protein sequence, protein sequence pattern, micro-molecular 3D structure, metabolic

pathway. Database consist of gene expression data, relational database, objected oriental database in the form of Flat file and exchange/ publication format such as FTP, HTML, CORBA, XML.

2.12.1. Primary Database:

Primary database is also known as archival database and are populated with experimentally derived data such as nucleotide sequence, protein sequence or macromolecular structure. Experimental results are submitted directly into the database by researchers and the data are essentially archival in nature. Once given a three dimensional database accession number and the data in primary databases can never be changed and it becomes a part of the scientific record. Examples of primary database are ENA, GeneBank, NCBI and DDBJ (nucleotide sequence), array express Archive and GEO (function a genomics data), Protein Data Bank (PDB; coordinates of macro-molecular structures) etc.

2.12.2. Secondary Database:

Secondary database comprise data derived from the results of analyzing primary data and it often draw upon information from numerous sources, including other databases (primary and secondary), controlled vocabularies and the scientific literature. They are highly curate, often using a complex combination of computational

algorithms and manual analysis and interpretation to derive new knowledge from the public record of science.Examples of secondary database reinterpret (protein families, motifs and domains), unipart Knowledge base (sequence and functional information on proteins), Ensembl (variation, function, regulation and more layered onto whole genome sequences), Swiss port and Mega etc.

2.13. Gene Bank: is an international organization which collects the data of Omics sequences from the entire world, including taxonomy database, and alternate access point for protein sequence and structure data. Few of the examples of official international gene bank includes:

1. National centre for Biotechnology information (NCBI-NIH) America.
2. China National GeneBank (BGI) China.
3. GeneBank Project, NARO Japan.
4. European GeneBank Europe.

The Most common searching data through Gene Bank search engine or database includesfig.7.

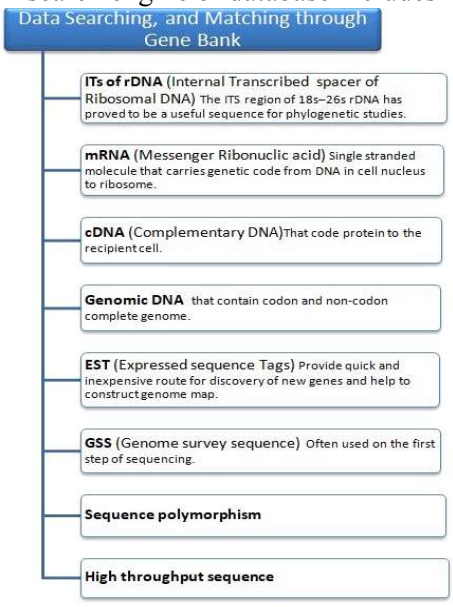


Fig.7: Collection of sequence data from Gene bank

2.14. Protein Data Bank:

The protein databank is responsible to collect only one type of molecular data (molecular structure of molecule) and to a growing extent the underlying raw data set from which the molecular structure is molded. Searching match protein sequences through gene bank as FastA file by BLAST while some other searching tool and technique includes Swiss-
Pdb, Cyrill2 system, BioMOBY and RASMOL.

Structure Prediction of Protein:

The complete sequence of amino acid and protein in hand to predict the structure of protein by using a process of range of data and CPU-intensive computer analysis. For best protein analysis followed the following pattern.

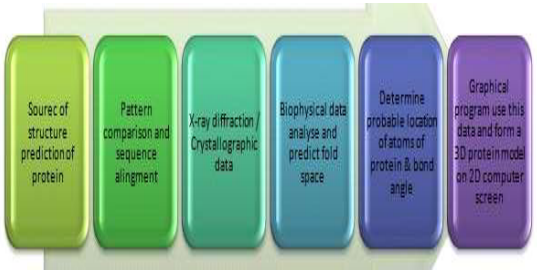


Fig.8: Cascade for structural prediction of protein.

3. CONCLUSION

We conclude the discussion related to bioinformatics tool and application in the field of medicine, microbiology, biochemistry, biotechnology and genetics make an easy to understand the sequencing and the interaction of molecules at the cellular level hypothetically. These approaches in Pharma's gene and cell therapy ambition will kick into high gear in 2020. Despite some major hurdle faces pharmaceuticals. Now at that time at least 800 genes therapy in the pipeline of biopharmaceuticals according to FDA.As spokesperson of FDA Commissioner Scott Gottlieb predicted that agency would be

approving between 10 and 20 gene and cell therapies per year by 2025. In late stage several companies develop their gene and cellular therapies achieve a key milestone or FDA approval. Biopharmaceutical companies expected to use "Biomarin" for cellular and gene therapy in this and next year. A recent advent of molecules which is derived from the biomarin named cubimicin, effective for deadly virus *candida auris*. Biopharmaceutical and researchers have been worked simultaneously on various project jointly for valoctocogeneroxaparvovec to treat hemophilia, Sarepta and its gene therapy for Duchenne muscular dystrophy, and CAR-T for the treatment of cancer including Bristol-Myers Squibb and Gilead.

Enormous upfront investment is required for the gene and cellular therapy in complex manufacturing process as well as innovation approach such as Novartis spend 2 million dollar for gene therapy of Zolgesma to treat spinal muscular atrophy. Hence the bioinformatics and its tool serve the purpose of molecular study or research that is potentially significant in drug development. Therefore multinational pharmaceutical firms are interested in the use of these advanced tooling for their existing and new

CONFLICT OF INTEREST

There is no conflicts of interest.

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Abbreviation and its definition:

Codon: A codon contain triplet of nucleotide that codes for specific aminoacid.

MEGA (Molecular Evolutionary Genetics Analysis)**:** Software providing tools for exploring, discovering and analyzing DNA and protein from an evolutionary perspective.

Clustal W: It is general purpose multiple sequence alignment program for DNA or protein. Website: http://www.ebi.ac.uk/clustalw/.

MUSCLE: It is a program for generating multiple alignments of amino acid and nucleotide. Alignment with high accuracy in all tests like T-coffee.

BLAST (Basic Local Alignment Search Tool)**:** it is a program to compare the nucleotide or protein sequence to sequence database and calculate statistical significance of matches which is used for functional and evolutionary relationships between sequences and identify member of gene family.

FASTA: This program was designed for protein sequence and its similarity searching. It is used as alignment tools for "FASTA-P" (protein) and "FASTA-N" (Nucleotide).

FASTA Format: It is a text based format representing a sequence (either nucleotide or protein) starts with single line description, followed by lines of sequence data.

EMBL (European Molecular Biology Laboratory)**:** Maintain bioinformatics data in collaboration with DNA databank Japan (DDBJ) and gene bank (USA).

SAGE (Serial Analysis of Gene Expression)**:** Technology used for analysis of gene expression.

MPSS (Massively Parallel Signature Sequencing)**:** It is an open ended platform that analyse the level of gene expression in a sample

by counting the number of individual mRNA molecules produced by each gene.

UHPLC-Q-TOF/MS (Ultra-High Performance Liquid Chromatography-Quadrupole time-of-flight Mass Spectrometry)**:** It is used for metabolic analysis of biomarker.

FTP (File Transfer Protocol)**:** It is a standard network protocol used for transfer of computer file between a client and server on a computer network.

HTML (Hyper Text Markup Language)**:** is standard markup language for creating web page or document designed to be displayed in a webpage.

CORBA (Common Object Request Broker Architecture)**:** It is a standard developed by the object management group to provide interoperability among distributed objects.

XML (Extensible Markup Language)**:** It was designed to store and transport data. Tool used in bioinformatics for data exchange. It currently represents a diverse set of biological data from nucleotide and protein sequence to protein-protein interaction and signal transduction pathway.

Bio-Moby: is a web service to support clustering of co-regulated gene based on similarity of promoter configurations.

RASMOL (Molecular Graphic Visualization)**:** Rasmol is a computer program for graphic visualization of molecules intended to use for exploring biological macromolecule structure such as those found in protein databank.

Swiss-Pdb: is an application used to analyze several proteins at the same time including, amino acid mutation, H-bonding, angles and distance between atoms. It is linked with Swiss-Model and isan automated homology modeling server developed within the Swiss Institute of Bioinformatics (SIB) in associationwith GlaxoSmithKline R&D and the Structural Bioinformatics Group at the Biozentrum in Basel.

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