ONLY NEWS PAPER PUBLISHED IN INDIA FOR SCIENTIFIC COMMUNITIES
NESA NEWSLETTER
NATIONAL ENVIRONMENTAL SCIENCE ACADEMY
Vol. 23 Issue - 12 (MONTHLY) December 2020

PHARMACOGENOMICS: THE PROMISE OF PERSONALIZED MEDICINE

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Pharmacogenetics is the study of variability in drug response due to heredity. It refers to genetic differences in metabolic pathways which could affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects. It is the science that examines the inherited variations in genes that dictate drug response and explore the ways in which these variations can be used to predict whether a patient will have a good response to a drug, bad response to a drug or no response at all. In oncology, pharmacogenetics historically refers to germ line mutations (e.g., single-nucleotide polymorphisms affecting genes coding for liver enzymes responsible for drug deposition and pharmacokinetics).The term comes from the words pharmacology (the science of drugs) and genomics (the study of genes and their function) and is thus the intersection of pharmaceuticals and genetics.

More recently, with the fashion for adding the suffix 'omics' to areas of research, the term 'pharmacogenomics' has been introduced. The term pharmacogenomics was introduced in 1995. Starting from 1950s until the completion of the Human Genome Project in 2001, the term used for this field was actually pharmacogenetics. Due to new knowledge from the Human Genome Project however, it is now referred to as "pharmacogenomics". Pharmacogenomics evaluates molecular determinants at the genome, transcriptome, and proteome levels. The history of pharmacogenetics stretches as far back as 510 B.C., when it was noted that ingestion of fava beans caused potentially fatal reaction in some, but not all individuals. During World War II it was observed that the soldiers given anti-malarial drug developed anaemia, due to lack of glucose-6-phosphate dehydrogenase enzyme. This basically means that the genetic composition of an individual not only leads to adverse effects from drugs but it also determines whether the drug will actually work or not.

Pharmacogenomics is the study of how an individual's genetic inheritance affects the body's response to drugs. It combines traditional pharmaceutical sciences such as biochemistry with annotated knowledge of genes, proteins, and single nucleotide polymorphisms. The term comes from the words pharmacology and genomics and is thus the intersection of pharmaceuticals and genetics. Environment, diet, age, lifestyle, and state of health can influence a person's response to medicines, but understanding an individual's genetic makeup is the key to create personalized drugs with greater efficacy and safety. It uses genetic information to predict whether a drug will help in making a patient well or ill. While the former term is largely used in relation to genes determining drug metabolism, the latter is a broader based term that encompasses all genes in the genome that may determine drug response.

The terms pharmacogenomics and pharmacogenetics are used interchangeably, and a precise, consensus definition of either remains elusive. Pharmacogenomics is the study of how genetic differences in multiple genes influence variability in drug response. Pharmacogenetics is generally regarded as the study or clinical testing of genetic variation that gives rise to differing responses to drugs, while pharmacogenomics is the broader application of genomic technologies to new drug discovery and further characterization of older drugs. Pharmacogenetics is the study of how genetic differences in a single gene influence variability in drug response. Researchers in this field study genes that produce drug metabolizing enzyme in the body. Many drugs are altered by the body by metabolizing those using enzymes. In some cases, an active drug is made inactive or less active through metabolism and vice versa. Utilizing an individual's genetic profile in prescribing medications for various diseases will prevent unwanted side effects and allow drug to work more efficiently. Pharmacogenomics is viewed as a highly important area for improving drug therapy and prescribing in future. Whether this promise is fulfilled and to what extent will only become evident with time. The main interest or application of pharmacogenomics is to permit the drugs to be tailor-made for every individual and adapted to each person's own genetic makeup, making a way for creating personalized drugs with greater efficacy and safety.

Variation within the human genome is seen about every 500–1000 bases. Although there are a number of different types of polymorphic markers, the attention is focused on single nucleotide polymorphisms (SNPs, pronounced snips), and the potential for using these to determine the individual drug response profile. SNPs occur at a frequency of 1% or greater in the population. A consortium between the pharmaceutical industry and charities such as the Wellcome Trust was formed to create a library of 3, 00,000 SNPs. This has recently resulted in the publication of SNP map comprising 1.42 million SNPs at an average density of one SNP every 1.9 kilo bases. The database is publicly available. Theoretically, this could be used to create individuals SNP profiles that correlate with individual's drug response. Currently, drugs are according to the model that 'one dose fits all'. Using SNP profiling, it may possible to tailor drug prescription and drug dosage to the individual, thereby maximizing efficacy and minimizing toxicity. The promise of personalized medicines is also of obvious interest and importance to the pharmaceutical industry, since it may allow streamlining of the drug development, drug testing and drug

registration process, thereby reducing the time from chemical synthesis to introduction into clinical practice . This could reduce the cost of the drug development process. Genetic variation in an individual comes in the form of 23 pairs of chromosomes, one of each pair contribute by each parent. The DNA sequence (nucleotide base sequence) on these chromosomes, encode for different cellular proteins and can vary by as few as single nucleotide base substitutions or many as long insertions or deletions. Such alterations can markedly influence the ability and sequence of genes to be expressed, which can significantly impact the final protein product. These proteins govern many aspects of a drugs disposition like absorption, distribution, metabolism, elimination and efficacy. Therefore, a thorough knowledge on gene expressions and genetic inheritance are the basic principles for the scope of pharmacogenomics. A large number of human diseases like cardio vascular diseases, respiratory diseases, infectious diseases and oncology, haematology, transplantation, psychiatric related diseases are complex in etiology and are related to genetic variation of individual. The important facts that inter patient variability in drug response are not a monogenetic trait but more likely to involve contributions from multiple genes involved in the relevant pharmacokinetics and pharmacodynamics. This genetic variation is the main criteria of pharmacogenomics. Pharmacogenomics accomplished many difficult tasks and it accomplished great achievements by using human genome sequencing, International HapMap project, the Encode project, micro array and many other technologies. It accumulates tremendous data by using genetic markers, DNA chips, genotyping, disease mapping and statistical and computational pharmacogenomics, etc. Pharmacogenomics has a greatest history of achievements in various fields through treating simple and complex diseases and excellent works in cancer therapy. It accounts in diagnosing genetic information thus helping to predict not only patients drug response but also many other affects like adverse drug effects and their interactions and thus diseases related to that genes. Through pharmacogenomics we can certainly say that we can achieve “specific person, specific gene, specific disease, specific drug, and specific treatment leading to personalized medicine.

Methods of Pharmacogenomics

Pharmacogenomic methods are based on recent technological advances that brought the possibility of highly parallel analysis of genetic information of human as well as model organisms. Bioinformatics methods along with mathematical and statistical apparatus that enables the overview and analysis of resulting multidimensional biological data and sometimes bioinformatics methods as the main tool of investigation for example *in silico* analysis (computer analysis) of genomic data in the publicly available databases. The global mapping of single nucleotide polymorphisms (SNP) on the whole genome level after the finished sequencing quest is one of the promising directions of today. These efforts are based on fact that out of the total predicted 11 - 15 million of genetic polymorphisms in humans the SNPs account for more than 90% of them. In publicly available Single Nucleotide polymorphism Database (db SNP) there are nowadays (build 125 from 29.9.2005) over 5 million of identified SNPs and their number is growing on day to day basis. Recent studies have suggested that the human genome is organized into blocks of haplotypes , and efforts to create a genome-wide haplotype map of single-nucleotide polymorphisms (SNPs) are underway. One of current opinions on human genomic variability states that chromosomes are mainly built out of short segments that during the short evolution history of the humankind were subjected to minimal amount of recombination changes and therefore these segments can be characterized just by few common haplotypes in majority of people. For those regions with high linkage disequilibrium and low diversity of haplotypes (haplotype blocks) it is enough to identify only few "tags" (sometimes just single SNP) that represent the given haplotype. It can be presumed that when the project of haplotype mapping of the human genome (International HapMap project) is finished, the databases dealing with pharmacogenetics as PharmGKB (pharmcogenetics and pharmacogenomics knowledge base), will be used for analysis and identification of the risk haplotypes for specific drug or drug class. So it probably will not be necessary to know the whole "SNP constellation" for a given individual to predict and hopefully prevent adverse side effects through pharmacogenetic and nutrigenetic interactions. Nowadays it is possible to analyze a few thousand SNPs at the same time using a SNP chip. For example Affymetrix Company distributes chip for detection of 1,00,000 SNPs at the same time that requires just a few hundreds of DNA in nanograms and this company will soon introduce a new chip for detection of 5,00,000 SNPs.

AmpliChip

Affymetrix announced "Affymetrix GeneChip System 3000Dx" approved from FDA for *in vitro* diagnostic purposes. The joint product of Affymetrix and Roche based on the above mentioned system - AmpliChip CYP450 Test - acquired the CE certification that enables its use in clinical diagnostics in EU countries. The first AmpliChip system in the central Europe was installed at the Institute of Clinical Biochemistry and Laboratory Diagnostics of the First Medical Faculty of Charles University and General Teaching Hospital. DNA (or RNA) chips are tools that enable to test several tens of thousands of genes at the same time in one sample. On the area of the chip itself (one squared inch) the short segments of known sequence of single-stranded DNA (oligonucleotide probes) are extremely densely packed. Following the principle of complementarities of bases, the fluorescently labelled DNA from the analyzed sample specifically binds to the oligonucleotide probes. After the laser detection of the signal acquired from the probes that hybridized with sample DNA, the analytical software generates a database of results for further analysis. The above mentioned AmpliChip CYP450 Test is focused on two genes that are most important for the metabolism of up to 25% of all commonly administered drugs, gene coding for cytochrome P450 2D6 and CYP2C19 gene. The 15,000 probes placed on a chip enables to distinguish 29 different polymorphisms, duplications and deletions of CYP2D6 gene, 2 polymorphisms of CYP2C19 gene and based on the information it could directly predict the type of drug metabolism - from the slow to "ultra fast". This chip research, gave clinical medicine one of the first pharmacogenetic tools that should help to prevent potential side effects of pharmacotherapy for the predisposed individuals. It mainly aims to become technological milestone on the path of individualized therapy based on genetic background of the patient. The relatively high price (350-400 USD per chip, per one analysis) of diagnostic tool and the price of the system of Affymetrix Company are the main limiting factor in the massive use of this diagnostic tool. The crucial information that enabled the possibility of parallel analysis of expression of thousands of genes at the same time (in some microorganisms of all existing genes) was the verification of dynamic nature of the genome. There is no mechanistic relationship in between the DNA sequence and gene expression; many regulation processes are involved as well as the changes in all the steps of realization of genetic information (post-transcriptional, post- translational, RNA dependent regulation of expression, and others). Detailed description of those mechanisms is beyond the scope of this article, but in summary on the cellular level the signals coming from both the outside and inside environment are integrated and analyzed and only based on that information the time and space specific form of answer is being chosen, this answer includes among others, the setting of expression levels of given set of genes. After just turning off one

gene as it is in knock-out mice models or just by adding one signal in the form of a drug into the media of cellular culture, the adaptive shift can be detected in expression of not one, but hundreds up to thousands of genes. On the transcriptome level the cRNA and cDNA express chips (microarrays) with high density of probes are being used. Therefore, for humans, mice and rats the chips with all annotated genes as well as expressed sequence tags are available. Analogically, proteomics studies i.e. the expression at the level of proteins utilizing modern technologies based on mass spectrometry, and metabolomics studies involving expression at the metabolite level are available. The discussion is still whether these techniques will be implemented into practical routine life. The biological material needed for the analyses can be isolated from blood or urine, saliva, breast milk, or from biopsy of the tissues where the relevant genes are expressed. If the "gene expression signatures" specific for e.g. side effects of a drug commonly used in biological material is not found, the importance of these methods apart from genotyping will remain in experimental area.

Pharmacogenetic Interactions

Majority of the original pharmacogenetic observations dealt with situations where there were radical differences in the drug concentrations in blood or in drug excretion via urine and these could be explained using simple Mendelian inheritance. These polymorphisms could be explained by the changes in pharmacokinetics where due to the defect in the molecule of a given transporter that metabolizes the enzyme or other factor of absorption, distribution, interaction with target structure and finally modification with excretion, resulted in high or low concentrations of the drug in the organism. The above mentioned classical example is the polymorphism in N-acetyltransferase 2 (NAT2) gene, polymorphisms in the cytochrome P450 2D6 (CYP2D6) gene or in thiopurine S-methyltransferase (TPMT). The latter enzyme is involved in metabolism of thiopurines, e.g. of azathioprine (used as an immunosuppressive agent in transplant recipients and in treatment of acute lymphoblastic leukemia). TPMT became one of the first genes with commercially available genetic test. The warning considering the possible side effects in patients with a genetically variant coding for low activity of TPMT was approved by FDA and is present on the package. Of course, there is possibility of a more complicated situation in case, the genetic polymorphism influences the pharmacodynamic processes or is dependent on interaction of more genes. Then even if there is an adequate dosage of the medicament, its efficacy is dependent on factors like expression level of the gene in target tissue. The gene expression can be systematically lower or higher in different ethnic groups (e.g. BiDil has been introduced recently as a drug aimed at heart failure treatment specifically in African-American patients) or it can depend on the developmental stage (newborns, adolescents, adults). The latter possibility might be the reason why paroxetin, an antidepressant from the group of selective serotonin reuptake inhibitors (SSRI) causes suicidal behaviour in patients younger than 18 years, though no such effect can be seen in paroxetin-treated adults.

Heterogeneity as a complicating factor

The research of pharmacogenetic interactions has to deal with similar problems as the analysis of genetic component of complex diseases, i.e. traits with significant genetic and environmental components (the latter including diet and drugs). One of such hindrances is incomplete penetrance (non-appearance of the trait in spite of the presence of the underlying genetic variant), genetic heterogeneity of the analyzed population, phenocopy (appearance of the trait in spite of absence of the underlying genetic variant) etc. There are two basic types of genetic heterogeneity, the first is the allelic heterogeneity, i.e. the association between the given trait (disease, reaction to medication) and two or more alleles of a single gene - >1000 mutations of CFTR gene leading to cystic fibrosis or multiple alleles of cytochrome P450 may serve as paradigmatic examples. The second is the trait heterogeneity, when a vague definition of a disease comprises several genetically distinct conditions, e.g. in autism or hypertension. These factors have to be naturally reflected in the use of new statistical models and approaches as most of the so far used methods are based on mathematical apparatus calculating with simple monogenic inheritance. Thus, various variant of clustering, principal component or Bayesian methods of data analysis are being developed to deal with the above mentioned matters.

The examples of pharmacogenetic models

The detailed functional genomics analysis of genetic polymorphisms in the frame of complex relations of pharmacogenetic interactions is sometimes ethically and practically impossible in the human subjects. So, different parts of the research have to be performed *in silico* (computer-based), *in vitro* (cell culture) and *in vivo* (experimental, mostly mammalian models) and only then the results are validated in human. The simplest physical model is the cells expressing particular variants of human genes introduced by transfection of cDNA. These studies aim at resolution of the question as to how individual polymorphisms influence the expression and function of the coded protein (e.g. receptor). In spite of undeniable successes of this approach, the relevance of the outputs of such studies is complicated by several issues. First and foremost, the most common models are cell lines easily amenable to the transfection-mediated expression of the gene and protein, but these lines lack numerous characteristics of the original tissue. Moreover, cell culture studies take the cells out of their natural context of the particular tissue, organ and organism, formed adaptive and regulatory networks and signals that all together shape the relevant gene expression both in health and disease situation as well as in response to medication. Thus a great importance is attributed to experimental animal model use, currently the most utilized ones being mouse and rat. The traditional role of the latter two models was further supported by the sequencing of their genomes showing greater evolutionary relatedness of human to these models than expected. Under standard environmental conditions, it is feasible to follow on the organism level the effects of such changes like transgenic expression of a gene of interest or a gene "knock-out" and more recently, a gene "knock-down" with complete or partial silencing of the gene expression.

One particular example of the animal model suitable for the pharmacogenetic and nutrigenetic research is the polydactylous rat strain. This highly inbred strain has been kept at the Institute of Biology and Medical Genetics of First Faculty of Medicine, Charles University since 1969. The spontaneous mutation of the Lx gene gives rise to the polydactyly-luxate syndrome. The effect of the Lx gene is modified by the genetic background, but also by its interaction with various teratogens (bromdeoxyuridine, thalidomide, retinoic acid). Even this pharmacogenetic interaction is further affected by the genetic background. This strain is therefore a unique model for the analysis of morphogenetic processes as well as pharmacogenetics /genomics of teratogenesis. In 1993, this strain was found to display high levels of triglycerides and more detailed studies lead to establishment of PD/Cub as model of metabolic syndrome (because of the simultaneous presentation of hypertriglyceridemia, hyperinsulinemia, increased indices of central (visceral) obesity, high concentrations of non-esterified fatty acids and substantial insulin resistance of peripheral tissues). Only recently it has been revealed that PD/Cub possesses unique pharmacogenomic profile in response to several classes of

transcription-modulating drugs. The administration of fenofibrate, a hypolipidemic drug acting mainly on nuclear receptor PPAR (peroxisome proliferators-activated receptor alpha), lead surprisingly to deterioration of glucose tolerance together with high concentrations of insulin. Isotretinoin, a drug used to treat acne acting on another couple of nuclear receptors RAR and RXR, induced a substantial increase in triglycerides in PD/Cub, corresponding to one of the often described side effects of isotretinoin administration in humans. This side effect is though not universal, suggesting genetic predisposition is necessary for its manifestation and so, the polydactylous strain could make a useful model for a more detailed study of this phenomenon. Following example of use of experimental models in pharmacogenetics involves yet another class of agonists of nuclear receptor, this time acting on PPAR (e.g. thiazolidinediones pioglitazone and rosiglitazone). Spontaneously hypertensive rat (SHR), major rodent model of human primary hypertension, did not respond to administration of pioglitazone by improvement of its glucose tolerance. It was eventually found that mutant allele of the gene coding for fatty acid translocase (Cd36/Fat) was responsible. This was proven by the derivation of transgenic and congenic animals carrying wild-type allele of Cd36 on SHR genetic background - all these responded to pioglitazone by improvement of glucose metabolism in peripheral tissues, in contrast to SHR. Again, particular form of effect of the mutant Cd36 (expressivity) depends on the genetic background it operates on. In SHR.BN-congenic strain (Il6-Cd36), where Cd36 of SHR origin is introgressed within a small segment of chromosome 4 into the genetic background of normotensive and normolipidemic Brown Norway strain, non-responsiveness of glucose tolerance to rosiglitazone administration, accompanied by lack of increase of adiposity, which was observed both in control Brown Norway rat and in the pioglitazone-treated SHR.BN –congenic strain. Because of the relatively frequent type 2 diabetes in human carriers of CD36 mutation, the above mentioned pharmacogenetic interaction may have clinically relevant implications for pharmacotherapy of such patients.

Pharmacogenomics in drug development

Besides the possible applications of pharmacogenetics and pharmacogenomics for understanding interactions and optimization of the therapy of currently used drugs, the attention of drug manufacturers is shifting towards the use of new technologies in development and control of new drugs. One of the more obvious approaches is scanning the available DNA sequences of human and model organisms for characteristic motifs common to genes, for which there are large libraries of test chemicals available ("drug-able targets"). These groups include e.g. nuclear receptors or kinases. Before this approach was available, there were about 500 such target structures and it was presumed that there were about 5000 more, hundreds of which may become relevant in therapy of human diseases. The only phase of this research that is not amenable to automation and robotization, is DNA sample acquisition with as detailed and accurate characteristics of subjects (cases and controls) as possible, moreover, the widely-based prospective cohorts with such detailed annotation are missing. Another field open for future pharmacogenomic applications is the primary phase of drug clinical trials. If the tested compounds are effective in a subset of subjects and overall the effect is ambivalent in respect to placebo, the continuation of the trial becomes financially very demanding and the whole project is often stopped at this stage. Profiling could identify the genetic commonalities in the groups that respond to the therapeutic action of the drug and if proven in the subsequent phases of the trial, the condition of testing positive for particular allele in a predictive genetic test would become mandatory for prescribing the drug. There are many reasons why there is no example of a drug with clear-cut specifications on the side of the patient's genetic constitution that would guarantee both efficacy and safety. The reverse side of the coin is identification of a genetic marker (SNP, haplotype, allele, transcription profile) associated with the side effect of the drug administration. Four percent of 11500 people treated with Tranilast (N-(3'4'-demethoxycinnamoyl)-antranilic acid (N-5) an investigational drug for the prevention of restenosis developed hyperbilirubinemia in Phase III. Large-scale genetic testing eventually found this reaction to be strongly associated to an allele of the gene coding for UDP-Glucuronyltransferase 1A1. In people carrying single allele with 7 repeats Tranilast elicited mild hyperbilirubinemia, in those with two alleles with 7 repeats severe hyperbilirubinemia developed, while carriers of two alleles with 6 repeats were protected from this side-effect. Using the 100,000 SNP array, only 10-20 cases compared to 3,000 controls would suffice to exact identification of the genomic region. Of course more complicated interactions render the resolution to be more complex. The transition from the globally administered drugs "for the particular disease" to drugs "for the particular patient" within the paradigm of personalized medicine will therefore be only gradual, relatively slow.

Predicting drug-drug interactions

Much of current clinical interest is at the level of pharmacogenetics, involving variation in genes involved in, drug metabolism with a particular emphasis on improving drug safety. The wider use of pharmacogenetic testing is viewed by many as an outstanding opportunity to improve prescribing safety and efficacy. Driving this trend are the 106,000 deaths and 2.2 Million serious events caused by adverse drug reactions in the US each year. As such ADRs (adverse drug reactions) are responsible for 5-7% of hospital admissions in the US and Europe, lead to the withdrawal of 4% of new medicines and cost society an amount equal to the costs of drug treatment.

Comparisons of the list of drugs most commonly implicated in adverse drug reactions with the list of metabolizing enzymes with known polymorphisms found that drugs commonly involved in adverse drug reactions were also those that were metabolized by enzymes with known polymorphisms.

Scientists and doctors are using this new technology for a variety of things, one being improving the efficacy of drugs. In psychology, we can predict quite accurately which anti-depressant a patient best will respond to by simply looking into their genetic code. This is a huge step from our previous way of adjusting and experimenting with different medications to get the best response. Antidepressants also have a large percentage of unresponsive patients and poor prediction rate of ADRs (adverse drug reactions). In depressed patients, 30% are not helped by antidepressants. In psychopharmacological therapy, a patient must be on a drug for 2 weeks before the effects can be fully examined and evaluated. For a patient in that 30%, this could mean months of trying medications to find an antidote to their pain. Any assistance in predicting a patient's drug reaction to psychopharmacological therapy should be taken advantage of. Pharmacogenetics is a very useful and important tool in predicting which drugs will be effective in various patients. The drug Plavix (clopidogrel bisulphate) is anti-platelet drug medication to prevent blood clotting, is the second best selling prescription drug in the world, however, it is known to warrant different responses among patients. Genome-wide association studies (GWAS) have linked the gene CYP2C19 to those who cannot normally metabolize Plavix. It is given to patients after receiving a stent in the coronary artery to prevent clotting. Stent clots almost always result in heart attack or sudden death; fortunately it only occurs in 1 or 2 % of the population. That 1 or 2% are those with the CYP2C19 SNP. This finding has been applied in at least two hospitals, Scripps and Vanderbilt

University, where patients who are candidates for heart stents are screened for the CYP2C19 variants.

Another new found use of Pharmacogenetics involves the use of Vitamin E. The Technion Israel Institute of Technology has reported that vitamin E can be used in certain genotype of patients to lower the risk of cardiovascular disease with diabetes, but in the same patients with another genotype, vitamin E can raise the risk of cardiovascular disease. A study carried out, showed vitamin E to increase the function of HDL in those with the genotype haptoglobin 2-1 who suffer from diabetes. HDL is a lipoprotein that removes cholesterol from the blood and is associated with a reduced risk of atherosclerosis and heart disease. However, if one has the misfortune to possess the genotype haptoglobin 2-2, the study shows that this same treatment can drastically decrease HDL function and cause cardiovascular disease.

Pharmacogenetics is a rising concern in clinical oncology, because the therapeutic window of most anticancer drugs is narrow and patients with impaired ability to detoxify drugs will undergo life-threatening toxicities. In particular, genetic deregulations affecting genes coding for DPD, UGT1A1, TPMT, CDA and Cyp2D6 are now considered as critical issues for patients treated with 5-FU/capecitabine, irinotecan, mercaptopurine/azathioprine, gemcitabine/capecitabine/AraC and tamoxifen, respectively. The decision to use pharmacogenetic techniques is influenced by the relative costs of genotyping technologies and the cost of providing a treatment to a patient with an incompatible genotype. When available, phenotype-based approaches proved their usefulness while being cost-effective.

In the search for informative correlates of psychotropic drug response, pharmacogenetics has several advantages
The genotype of an individual is essentially invariable and remains unaffected by the treatment itself. Molecular biology techniques provide an accurate assessment of the genotype of an individual. The ease of accessibility to genotype information through peripheral blood or saliva sampling and advances in molecular techniques has increased the feasibility of DNA collection and genotyping in large-scale clinical trials. A recent breakthrough in pharmacogenetics identified a polymorphism near a human interferon gene that is predictive of the effectiveness of an artificial interferon treatment for Hepatitis C.

For genotype 1 hepatitis C treated with Pegylated interferon-alpha-2a or Pegylated interferon-alpha-2b (brand names Pegasys or PEG-Intron) combined with ribavirin, it has been shown that genetic polymorphisms near the human IL28B gene, encoding interferon lambda 3, are associated with significant differences in response to the treatment. This finding, originally reported in Nature, showed that genotype 1 hepatitis C patients carrying certain genetic variant alleles near the IL28B gene are more possibly to achieve sustained virological response after the treatment than others. Later report from Nature demonstrated that the same genetic variants are also associated with the natural clearance of the genotype 1 hepatitis C virus

Integrating pharmacogenetics into the health care system

Despite the many successes, most drugs are not tested using a genome-wide association study (GWAS) also known as whole genome association study (WGAS). However, it is estimated that over 25% of common medication have some type of genetic information that could be used in the medical field. If the use of personalized medicine is widely adopted and used, it will make medical trials more efficient. This will lower the costs that come about due to adverse drug side effects and prescription of drugs that have been proven ineffective in certain genotypes. It is very costly when a clinical trial is put to a stop by licensing authorities because of the small population who experiences adverse drug reactions. With the new push for pharmacogenetics, it is possible to develop and license a drug specifically intended for those who are not the small population genetically at risk for adverse side effects.

Technological advances

As the cost per genetic test decreases, the development of personalized drug therapies will increase. However, as of now, we only have access to single-gene test, which is currently quite expensive. In future, more advanced sequencing will be able to test for multiple genes in short time. A disposable DNA sequencing device, under $900 has recently been announced. This device has a size of a USB memory drive to make it portable and easy to use. Likewise, companies like deCODE Genetics, Navigenic and 23andMe offer genome scans. The companies use the same genotyping chips that are used in GWAS studies and provide customers with a write-up of individual risk for various traits and diseases and testing for 500,000 known SNPs. The costs range from $995 to $2500 and include updates with new data from studies as they become available. The more expensive packages even include a telephone session with a genetic counsellor to discuss the results.

Anticipated benefits of pharmacogenomics
More Powerful Medicines - Pharmaceutical companies will be able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases. This accuracy not only will maximize therapeutic effects but also decrease damage to nearby healthy cells.

Better, Safer, Drugs the First time -Instead of the standard trial-and-error method of matching patients with the right drugs, doctors will be able to analyze a patient's genetic profile and prescribe the best available drug therapy from the beginning. Not only will this take the guesswork out of finding the right drug, it will speed recovery time and increase safety as the likelihood of adverse reactions is eliminated. Pharmacogenomics has the potential to dramatically reduce the estimated 1,00,000 deaths and 2 million hospitalizations that occur each year in the United States as the result of adverse drug response.

More Accurate Methods of Determining Appropriate Drug Dosages- Current methods of basing dosages on weight and age will be replaced with dosages based on a person's genetics --how well the body processes the medicine and the time it takes to metabolize it. This will maximize the therapy's value and decrease the likelihood of overdose.

Advanced Screening for Disease- Knowing one's genetic code will allow a person to make adequate lifestyle and environmental changes at an early age so as to avoid or lessen the severity of a genetic disease. Likewise, advance knowledge of particular disease susceptibility will allow careful monitoring and treatments can be introduced at the most appropriate stage to maximize their therapy.

Better Vaccines- Vaccines made of genetic material, either DNA or RNA promise all the benefits of existing vaccines without all the risks. They will activate the immune system but will be unable to cause infections. They will be inexpensive, stable, easy to store, and capable of being engineered to carry several strains of a pathogen at once.

Improvements in the Drug Discovery and Approval Process- Pharmaceutical companies will be able to discover potential therapies more easily using genome targets. Previously failed drug candidates may be revived as they are matched with the niche population they serve. The drug approval process should be facilitated as trials are targeted for specific genetic population

groups --providing greater degrees of success. The cost and risk of clinical trials will be reduced by targeting only those persons capable of responding to a drug.

Decrease in the Overall Cost of Health Care- Decreases in the number of adverse drug reactions, the number of failed drug trials, the time it takes to get a drug approved, the length of time patients are on medication, the number of medications patients must take to find an effective therapy, the effects of a disease on the body (through early detection), and an increase in the range of possible drug targets will promote a net decrease in the cost of health care.

Barriers to pharmacogenomics progress

Pharmacogenomics is a developing research field that is still in its infancy. Several of the following barriers will have to be overcomed before many pharmacogenomics benefits can be realized.

Complexity of finding gene variations that affect drug response - Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A,T,C,or G) in the genome sequence is altered. SNPs occur every 100 to 300 bases along the 3-billion-base human genome, therefore millions of SNPs must be identified and analyzed to determine their involvement (if any) in drug response. Further complicating the process is our limited knowledge of which genes are involved with each drug response. Since many genes are likely to influence responses, obtaining the big picture on the impact of gene variations is highly time-consuming and complicated.

Limited drug alternatives - Only one or two approved drugs may be available for treatment of a particular condition. If patients have gene variations that prevent them using these drugs, they may be left without any alternatives for treatment.

Disincentives for drug companies to make multiple pharmacogenomic products - Most pharmaceutical companies have been successful with their "one size fits all" approach to drug development. Since it costs hundreds of millions of dollars to bring a drug to market, will these companies be willing to develop alternative drugs that serve only a small portion of the population.

Educating healthcare providers - Introducing multiple pharmacogenomic products to treat the same condition for different population subsets undoubtedly will complicate the process of prescribing and dispensing drugs. Physicians must execute an extra diagnostic step to determine which drug is best suited to each patient. To interpret the diagnostic accurately and recommend the best course of treatment for each patient, all prescribing physicians, regardless of specialty, will need a better understanding of genetics.

Application

The main interest or application of Pharmacogenomics is to permit the drugs to be tailor-made for every individual and adapted to each person's own genetic makeup, so that making a way for creating personalized drugs with greater efficacy and safety. Pharmacogenomics has applications in illnesses like cancer, cardiovascular disorders, depression, bipolar disorder, attention deficit disorders, HIV, tuberculosis, asthma, and diabetes.

In cancer treatment, pharmacogenomics tests are used to identify which patients are most likely to respond to certain cancer drugs.

In behavioral health, pharmacogenomic tests provide tools for physicians and care givers to better manage medication selection and side effect.

Pharmacogenomics is also known as companion diagnostics, meaning tests being bundled with drugs. Examples include KRAS test with cetuximab and EGFR test with gefitinib.

Beside efficacy, germline pharmacogenetics can help to identify patients likely to undergo severe toxicities when given cytotoxics showing impaired detoxification in relation with genetic polymorphism.

In cardio vascular disorders, the main concern is response to drugs including warfarin, beta blockers, and statins.

Improvements in drug discovery, design, and development are obvious applications for pharmacogenomics. A deeper understanding of the genetic factors which cause variance in drug metabolism can aid in the design of drugs with improved potency, reduced toxicity, and fewer side effects.

Pharmacogenomics can identify potential drug targets, and determine which targets are least prone to genetic variance. By selecting drug targets which are not prone to genetic variance, drug designers can create drugs which are more likely to have standard, expected, and safe reactions in people who take it.

Achievements

Pharmacogenomics has a greatest history of achievements in various fields through treating simple and complex diseases and excellent works in cancer therapy. It accounts in diagnosing genetic information thus helping to predict not only patients drug response but also many other affects like adverse drug effects and their interactions and thus diseases related to that genes.

Through Pharmacogenomics we can certainly say that we can achieve “specific person, specific gene, specific disease, specific drug, and specific treatment “leading to personalized medicine.

In non-small-cell lung cancer, pharmacogenomic approach has a potential to great improvement in survival of subpopulation of patients. To overcome the resistance to drug is one of many challenge of current cancer. It helps to identify patients more likely to benefits from which chemotherapy regimen is to be used. With the help of DNA micro array, gene expression of different cancer in human can be identified. It also plays a role in the optimization of cancer chemotherapy.

In cardiovascular therapy management of hypertension, it has a role in identification of genetic markers of drug response for better control of blood pressure and also in identification of polymorphism in blood pressure by receptors.

Pharmacogenomics have great impact on statin therapy for coronary artery diseases (CAD). Pathophysiological mechanism of adverse effects as a result of it was identified.

Research status of pharmacogenomics in India

Pharmacogenomics in India is in developing stage and requires lot of funds and looking future for personalized medicine. It is a new field and has good scope, as it is very essential to know what kind of toxicity and efficacy a drug has on the human body. The subject will focus on the effect of drugs on an individual basis as every individual has a different kind of metabolism. Though we have the required instruments and equipment in the Biotechnology and Microbiology departments, we need some streamlining of equipment before a great future and success of this field in India. At present many colleges are trying to include pharmacogenomics as a academic course, for example MSU (university) has decided to introdue as a PG course.

Future Scenerio

What makes pharmacogenomics possible today? Sequencing of the human genome reveals 2.9 billion base pairs that are constant, narrowing down variability to about 3 million base pairs, of which 100,000 capture the full human variation and <10,000 may be pharmaceutically relevant. Advances in genome sequencing technology made possible addressing those individual base pairs. Automatization and miniaturization significantly resulted in

down cost of DNA sequencing reaction. Computer technology and computer networks facilitated handling of data. Pharmacogenomics may drive new business models based on developing preventive therapy for patients with genetic predispositions to disease. Blockbuster drugs of today were probably not possible if individual genetic variation becomes integrated with drug prescription, due to reduced market sizes. Incorporation of genetic information into the diagnosis of disease and prescription of drugs will lead to new service industry. Pharmacogenomics will foster safer, less toxic drugs.

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ADOPTION OF INTEGRATED PEST MANAGEMENT PRACTICES IN BASMATI RICE IN WESTERN U.P.

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Rice, *Oryza sativa* L., is the important cereal crop which is grown in 117 countries and is a staple food for people in 39 countries, which includes 2.70 billion people in Asia alone (Sardesai et al. 2001). Its productivity is severely affected by numerous biotic and abiotic factors. About 52% of the total global production of rice is lost annually owing to the damage caused by biotic factors, of which nearly 21% is attributed to the attack of insect pests (Brookes and Barfoot 2003). Basmati Rice is a long-grain aromatic rice grown in several States of India and Pakistan. India is the leading exporter of the Basmati rice to the global market and cultivated in about 2.0 million hectares. Basmati rice crop suffers severely due to attack of various insect pests, which reduces its yield and quality. In general, yield loss due to insect pest of rice has been estimated at about 25% in different rice ecosystem.Findings of conducted surveys revealed excessive and injudicious use of chemical pesticides and fertilizers by farmers that aggravated the pest menace, secondary pest outbreaks, residue problems in grains, soil and water, environmental degradation and rejection of many export consignments. To achieve sustainable quality production of Basmati rice, it is important to manage the damage and yield loss by rice pests and options for the appropriate pest management practices. Hence, IPM should be treated as a yardstick for the productivity of a crop.

Rice is the major food grain crop in India. There is significant development in researching new varieties and other package of practices in relation to nutrient management, water management, weed management, pest & disease management, farm mechanization etc. No doubt, all these technologies really brought out significant increase in productivity in rice. Each technology developed by the scientists in this area had its own contribution as sole and also in combination with different technologies. Of all technologies, special focus on Integrated Pest Management (IPM) is required as it is the central role for all the technological developments. Hence, IPM should be treated as a yardstick for the productivity of a crop.

Insect pests associated with basmati rice in western plain zone of Uttar Pradesh were studied during Kharif 2014 at Crop Research Centre, Sardar Vallabhbhai Patel University of Agriculture and Technology, Meerut (U.P.), India.

Basmati rice is cultivated in about 2.0 million hectares. In 2014-15, out of the total production of 8.70 mt of Basmati rice from 2.10 million hectares, 3.7 mt worth INR ` 275.979 billion was exported. The states namely Punjab,Haryana and Western UP account for about more than 70 per cent of total Basmati grown in India. The yield potential of commonly grown Basmati cultivars viz., Pusa Basmati 1, Taraori Basmati and Dehraduni Basmati is severely hampered by biotic stresses as there is no inbuilt resistance in them to any of the pests.

Findings of conducted surveys revealed excessive and injudicious use of chemical pesticides and fertilizers by farmers that aggravated the pest menace, secondary pest outbreaks, residue problems in grains, soil and water, environmental degradation and rejection of many export consignments.

An inter-disciplinary and inter-institutional team took up the challenge at NRCIPM to address these problems through holistic IPM tactics.IPM strategies were synthesized and validated at village level in Basmati growing areas of Uttar Pradesh, Haryana and Uttarakhand.

IPM validation was initiated at Baraut (Dist. Baghpat, UP) during 1997-98 in an area of 10 ha with cv. Pusa Basmati 1. The baseline information collected from the farmers, which had shown indiscriminate use of chemical pesticides (phorate, endosulfanetc) to an extent of 4-6 sprays for suppression of insect-pests and diseases.

After the success of IPM validation at Shikohpur in Pusa Basmati1, the technology was taken up in ChhajpurKhurd (Panipat) village, Haryana with Taraori local Basmati variety. At Chhajpur a total of 28, 80 and 140 ha area was under IPM during kharif 2002, 2003 and 2004, respectively. Gradually the technology by its own spread to 25 adjoining villages.

During 2005 to 2010 the technology was validated in Uttarakhand State at Tilwari and Doodhali villages (Dehradun) in 40 and 25 ha, respectively, with Dehraduni Basmati (Type 3) and Kasturi.

During 2005 the high yielding variety of Basmati cv. Pusa 1121 introduced by ICAR-IARI became very popular among farmers. Presently, this variety has spread to over 84% of the total Basmati area in Punjab, 78% in Western Uttar Pradesh, 68% in Haryana, 30% in Uttarakhand, 8% in Jammu and Kashmir and is grown over 1000 ha area in hill state of Himachal Pradesh.

The IPM module developed by the Centre for pest management in rice was found to be very effective for reducing the incidence of pests and diseases in the village Bambawad which adopted IPM programme. Some of the farmers of the area were very happy for IPM programme.

There is immense scope for proven Basmati Rice IPM technologies in India to sustainable pest management, quality production, reduction of chemical consumption and enhancing farmers' income and empowerment.

Besides these it has social impacts as it takes care about workers health, safety and welfare. The adoption of IPM technologies is always a great challenge to the researches and scientists. Adoption of IPM is very complex in nature and influenced by the socio-economic, cultural, marketing, access of IPM information availability of IPM information and advisory services, training and timely availability of critical inputs, extension support services and availability of proven IPM technologies and policy support.
IPM is also knowledge intensive need specific extension approaches and intensive training. The adoption of IPM depends on the coordination of all the IPM stakeholders. The involvement of local community for in IPM also very important because of IPM is community approach because IPM will not impact in isolation like other technologies. Therefore the involvement of farming community, school, social institution for environmental awareness and moving towards community pest management instead of individual pest management.

The involvement consumer who is the end user of IPM produce and King should take care choice and preference of consumers and also make aware the attributes of IPM produce in comparison of non-IPM produce. Government Policy also influence the adoption of IPM in large scale it is urgent need to institutionalize the IPM commodity associations for mounting pressure on government for to getting premium prices of IPM produces and subsidy on IPM inputs.

Therefore, an inter-disciplinary and inter-institutional team took up the challenge at NCIPM to address these problems through holistic IPM tactics. IPM strategies were synthesized and validated at village level in Basmati growing areas of Uttar Pradesh, Haryana and Uttarakhand. IPM validation was initiated at Baraut (Dist. Baghpat, UP) during 1997-98.The IPM module developed by the Centre for pest management in Basmati rice was found to be very effective for reducing the incidence of pests and diseases in the village Bambawad which adopted IPM programme. Some of the farmers of the area were very happy for IPM programme. There is immense scope for proven Basmati Rice IPM technologies in India to sustainable pest management, quality production, reduction of chemical consumption and enhancing farmers' income and empowerment. Besides these it has social impacts as it takes care about workers' health, safety and welfare. The adoption of IPM technologies is always a great challenge to the researches and scientists. Adoption of IPM is very complex in nature and influenced by the socio-economic, cultural, marketing, access of IPM information availability of IPM information and advisory services, training and timely availability of critical inputs, extension support services and availability of proven IPM technologies and policy support. Integrated Pest Management (IPM) is an approach that can help lower production costs, reduce exposure to pesticides, and improve long-term sustainability of the agricultural system.The NCIPM national primer IPM research institution in India has developed and promoted IPM technologies to manage pests in Basmati Rice in the villages of Uttar Pradesh, Uttrakhand, Haryana, Punjab through participatory approach. Despite of several advantages of these technologies the adoption at the farmer level is not very encouraging. Besides, the use of innovative extension approaches including farmer field schools (FFSs), field days, exposure to other farmers, and written media (e.g. pamphlets) for wide area approach of IPM adoption. Basmati Rice production is associated with heavy use of chemical pesticidesto manage pests and optimize profits. Commercial pressures on farmers to use pesticides, and the idea that pesticides companies disrupt IPM research and implementation activities could be important in specific cases. Concerns have emerged about the adverse consequences of pesticide over use. These consequences include short and long-term health hazards and environmental degradation.

Conclusion

So, it is of utmost necessity for the scientific community to analyze the field level constraints (as perceived by the farmers) in the adoption of IPM technologies especially in the Rice cultivation in the third world countries where excessive and indiscriminate use of the pesticides were reported by various researchers.Therefore, it is very pertinent to identify the barriers and constraints directly relate to the low adoption of IPM technologies in vegetable crops. The study can help promote better technology transfer and adoption of IPM, in so doing, effectively help sustain Basmati Rice production.

SUSTAINABLE BEEKEEPING INDUSTRY IN FIJI

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The drier and intermediate rainfall regions of Viti Levu and Vanua Levu,Fiji have the best environment for honey production given the unexploited native forest and mixed land-use areas. Honey as a high valued commodity is of greater demand than supply in Fiji. This would enable greater profits for the industry in the value chain of Fiji being a developing economy of 330 islands (Lloyd and Hinton 2019; Caldeira 2019). Beekeeping is predominantly subsistence in Fiji having 1-40 hives. As reported by the Ministry of Agriculture in first quarter of 2018-19, a total of 950 beekeepers are registered, holding over 12,000 hives and producing 109 tons of honey (Hinton, *et al* 2019). Also an approximate of 800 beekeepers are managing 17,000 Langstroth hive. The twenty beekeepers having 100+ hives were producing 90% self-sufficient honey (Caldeira 2019). Based on official figures, average honey production of 22-25kg/hive with up to 40kg/hive was achieved on some outer islands. In February 2016, the number of farmers, hives, and production levels were seriously affected by Tropical Cyclone Winston (Lloyd and Hinton 2019). About 35% colony were lost from this category 5 Cyclone Winston (Caldeira 2019).

Biosecurity regulations in Fiji are restricting the importation of honey (excluding some large manufacturers of food products), due to the threat of bacterial and parasitic diseases. Therefore domestic production of all honey sold in retail outlets in the country benefited Fijian beekeepers. The restricted supply resulted in increasing demand and higher prices for honey producers in the country. The wholesale per-kilogram price of honey in Fiji increased near world market prices. High-valued Fijian honey made greater profitability for beekeepers (Hinton et al. 2019; Caldeira 2019; Roper and Gonzalez 2013). Honey produced in Fiji is mostly consumed locally. The domestic consumer market who use honey as a table food product and in cooking is the main market for packaged honey. There is either 220 grams or 440 grams per year per capita consumption of honey in Fiji. It is lower compared to 800-900 grams per capita in Europe but higher than 4 grams of purchased honey per capita in PNG. Recently while honey imports to Fiji is banned, artificial/adulterated honey sales were reported which is potential to cause reduced domestic sales due to price competition or lack of consumer confidence in local honey quality (fear of adulteration). Small packaged 45-85g medicinal honey bottles were observed in supermarkets, mini markets and pharmacies. These are primarily used for cultural purposes as part of Hindu rituals or alternatively for medical purposes (i.e. wound dressing). It costs higher price at $39-55per kilo, though a smaller niche market (Lloyd and Hinton 2019).

In some time honey harvested during or after the sugar cane harvesting season did not meet the Codex Alimentarius standards due to positive tests of honey adulteration with sugar. The National Honey Standard for domestic market was then recommended by the Fijian government to help sustain growth of the honey industry thereby protecting consumers and the integrity of the product (Roper and Gonzalez 2013). At the moment, constraints for beekeepers include: pest and disease (American Foul Brood, Varroa mite, cane toads, insects and ants); limited technical skills and knowledge; limited access to quality training programs; limited access to beekeeping equipment (bee suits, bee hives and other accessories); and, poor quality queens (age and genetics).For community beekeeping development programs, assistance is needed in: training and extension on bee management and business development; understanding of cooperative models and group work dynamics; and, how to optimise uptake and success of beekeeping programs under differing social and economic structures. Challenges being faced by small-scale processors include:

Figure 1: Fiji Beekeeper's Association Beekeeping Mentor Program (Caldeira 2019; https://www.fclc.org.fj/ fiji-beekeepers-association-2/).

inconsistent or low supply of honey; limited coordination between producers; and, limited access to proper storage, processing and packaging equipment. This makes it inherently difficult for processors to supply consistent, high quality products and obtain safe food handling standards that are required to access international markets (Lloyd and Hinton 2019).

Demonstrating and maintaining a high bee health status is crucial to continue to develop the commercial beekeeping industry and expand and export bee products. Imported bee products and used beekeeping equipment could introduce exotic bee diseases which, if established, could threaten the wellbeing of the beekeeping industry in Fiji. Existing import protocols for honey don't provide a very high level of protection. The 2013 survey funded by PHAMA inspected 523 managed European bee colonies (6.5%) out of approximately 8800 hives. No evidence was seen of Asian bees on either Viti Levu or Vanua Levu andno Chalkbrood seen as well. Fiji remains one of the few countries free of this fungal disease. However, wax moths were again identified as a serious pest (Roper and Gonzalez 2013). While, the first Varroa jacobsoni was found in 2018. This incursions would result in weaker bees, a greater susceptibility to viruses, and losses of honey bee population (Hinton, et al 2019; Caldeira 2019; Lloyd and Hinton 2019).

It is believed that European missionaries probably first introduced the North-Western European dark bee (*Apis mellifera mellifera*) or the German 'black' bee, into the Pacific during the mid 19th century. Early attempts to establish national apiculture industries were largely unsuccessful until the 1970's when projects were initiated in Niue, Papua New Guinea, Samoa and Fiji. Bees were undoubtedly introduced in Fiji, if not for the first time, in 1872 by James Carroll, a Queensland beemaster. Fiji needs to improve its genetic honey bee stock as they were more defensive and less productive. During the 1970-80s, New Zealand aid programs attempted to improve the genetic stock by importing Italian bees, which then cross-bred with the German black bee. Beekeeping developed with foreign assistance from Australia, New Zealand, EU, USA, and Japan(Hinton, et al 2019; Caldeira 2019; Lloyd and Hinton 2019; Roper and Gonzalez 2013; Barrett 2010).

With high interest in beekeeping, the Fiji Beekeeper's Association (Fig. 1) is working to increase beekeepers' honey production and grow related businesses. The Beekeeping Mentor Program is an EU-funded pursuit through the International Trade Centre where most successful beekeepers began with help frommentors. Beginning beekeepers are paired with experienced local beekeepers. Mentors teach prescribed set of beekeeping skills during a 12 month period. Thirteen mentors and 20 trainees were compensated with hive equipmentto develop skills in hive assembly and splitting colonies (Caldeira 2019; https://www.fclc.org.fj/fiji-beekeepers-association-2/). Approximately one-quarter of the beekeepers in Fiji wereboth indigenous and Indo-

Fijian women (Barrett 2010). The Fiji Beekeepers Association estimated between 25-35% overall participation of women (Caldeira2019). There is a great opportunity to increase the participation of Fijian women in beekeeping activities as a less labor-intensive activity. This is feasible through targeted training and extension support accessible to women for income generation and improved livelihoods (Hinton et al. 2019). Fiji has significant potential in creating a productive, profitable and viable honey industry. Employment and income-generating opportunities exist at various stages along the value chain. Emphasis needs to be on capacity building for beekeepers and supporting institutions, which would produce flow-on benefits along the value chain. Further strategies were identified to increase value-addition and competitive advantage throughout the industry (Lloyd and Hinton 2019).

GROW GUAVA IN SODIC SOIL

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Guava, the "poor man's fruit" or "apple of the tropics" was a popular fruit bearer of the tropical and subtropical climates. Guava was considered as one of the most delicious and luscious fruits. It is often included in the category of super fruits, being rich in its dietary Fibre, Vitamin A, Folic Acid and the Dietary Minerals of Potassium, Copper and Manganese. It is highly nutritious and rich in anti-oxidants (496 mg/100g) (National Institute of Nutrition, Hyderabad). Guava is a rich source of Vitamin C, Vitamin A, Vitamin B2, (riboflavin) and minerals like Calcium, Phosphorus and Iron. The Vitamin C contents of the Guava fruit are four to five times higher than those of the citrus fruits. Except Guava no other fruit became available throughout the year. Guava fruit is the best when it became perfectly ripe and was plucked from the trees afresh. It emits a sweet aroma and was pleasantly sweet and refreshingly acidic in its flavour. It was wholly edible along with its skin which was like paper thin and had almost merged with the pulp.

Sodic soil conditions affect almost all crops because of the deterioration of soil physical conditions. Dispersion of soil aggregates in sodic soils decreases soil permeability to water and air, thereby reducing plant growth. Many researchers stated that guava crop is performing well under soil sodicity conditions. Many plants adapt to salt stress by enhanced biosynthesis of secondary metabolites, such as soluble solids, sugars, organic acids, proteins, and amino acids (Ashraf and Harris 2004), which may act as osmolytes or osmoregulators to maintain plant turgor under salt stress. The presence of these metabolites often greatly increases the nutritive quality and marketability of fruits and vegetables. Beneficial effects include increased sugar concentration, increased total soluble solids, improved grain quality and protein content, increase firmness and improve post harvest handling characteristics and reduce pungency. Sodicity may also cause oxidative stress and induce production of reactive oxygen species. The primary defensive plant response to oxidative stress is the biosynthesis of antioxidants. As a result, salt-stressed plants often contain enhanced concentrations of antioxidants, such as flavonoids, ascorbate, tocopherols, carotenoids, and lycopene. With proper management practices, it is likely that economic losses associated with yield reductions due to sodicity may be offset by production of high-quality fruit crops that can be marketed at a premium to meet the changing demands of the market and health conscious consumers.Hence cultivation of guava crop is one among the viable options for sodic soil.

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SEED AND PLANTING MATERIALS TREATMENT IN ORGANIC FARMING

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Seed treatment is an effective method of delivering the desired products / inoculum into plant root zone for pest and disease management; biological nitrogen fixation; nutrient mineralization /solubilization etc. Since many of the plant diseases are seed borne and their inoculum get activated along with the seed germination and later on, develops disease on the plant. Thus, treatment of seeds with proper biological agent will stop / restrict the pathogenic growth through seed and thus prevents the progress of the disease on developing plant. Nitrogen fixing and nutrient solubilizing microbial agents can also be applied through seed treatment for their establishment in root zone and help in biological nitrogen fixation and increased nutrient availability. Following seed treatments methods can be used in organic farming:

Hot water treatment

Generally done at 53°C for 20-30 minutes to inactivate many plant pathogens (bacterial, phytoplasmal and viral pathogens). Extreme care should be taken during treatment because lesser temperature and time may not kill the pathogen and higher range of temperature can cause loss of seed viability.

Cow urine and Beejamrit

Soak 10kg of seeds or seedling roots in solution of cow urine (1litre of cow urine+2litre of water) or Beejamrit (2litre) for about 30 min. and shade dry it before sowing.

Trichoderma*/*Pseudomonas fluorescens:

Suspend 10 gram of bioagent in 500 ml of water and small amount of jaggary in it. Spread suspension over the seed and mix thoroughly. Dry the treated seeds in shade for about 30 min. before sowing. Seed treatment may be done in evening and allow the bioagents to be activated for overnight and sow the seeds in next day morning (**biopriming**).

***Rhizobium* and other nitrogen fixing/nutrient solubilizing bacteria**

Mix 200 gram of formulation in 500 ml of water. Add small amount of jaggary (40-50gram) and dissolve in it. Sprinkle over 10 kg of seeds. Shade dry treated seeds before sowing. When multiple inoculations are needed (treatment with more than one preparation) try to treat the seeds first with antifungal preparations followed by insecticidal preparation and in last, with nitrogen fixing/nutrient solubilizing agents. During multiple seed treatments, strains of biological agents must be compatible with each other.

SCIENCE MUSEUMS AND ECOLOGICAL PARKS: AN IMPORTANT APPROACH TO DISSEMINATE THE APPLICATIONS AND MARVELS OF SCIENCE AND TECHNOLOGY TO THE PUBLIC

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Academics, scientists, researchers and scholars around the planet make substantial contributions to the development of science and technology through their work and research publications. Unfortunately, these important works highlighting the latest progress in science and technology remains restricted to research journals, magazines, newsletters and bulletins; and do not disseminate easily to the general public. In short, the fruits and the marvels of science and technology does not always find the easy transition pathway from lab to land and integrate with general public knowledge domain. So we also need to remember scientific research papers are highly technical and often beyond ability of ordinary citizens to apprehend or appreciate them and understand the basic utilities other than a short fraternity of experts on that particular field.

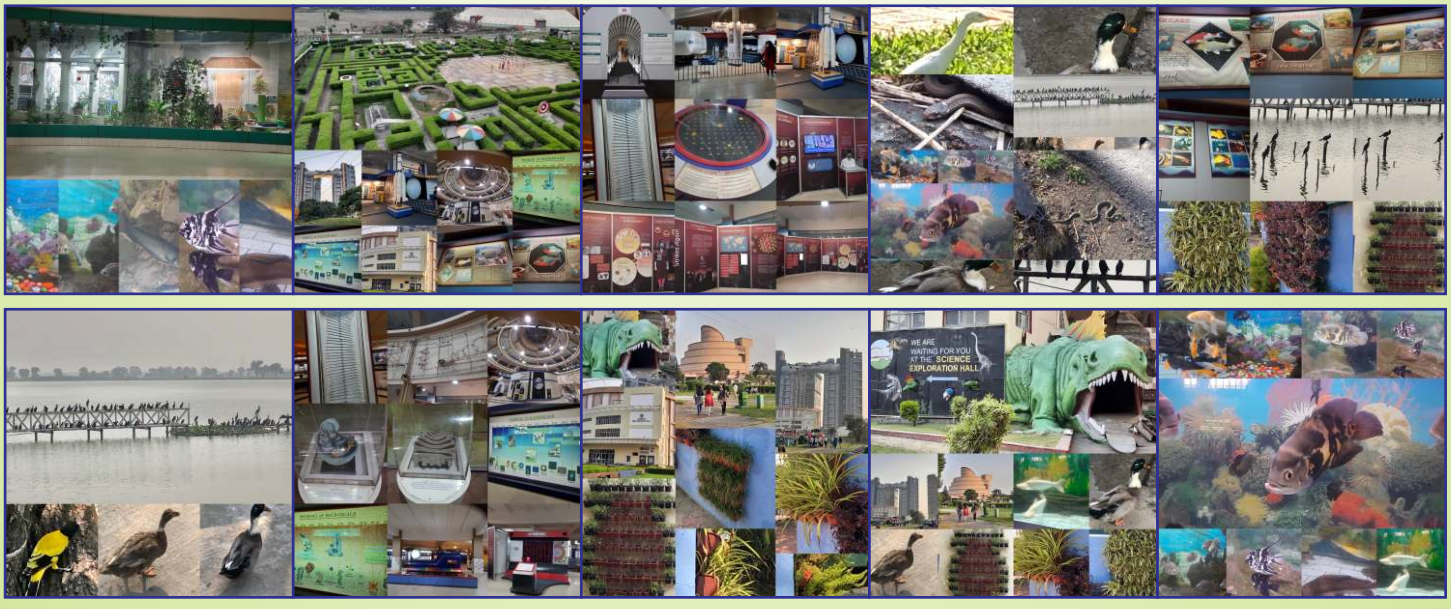
However it is also pretty important to designate the latest development in science and technology and the progress it brings in the domain of ordinary public just beyond the primary, secondary and tertiary levels of education. It is quite unfortunate that proper education or awareness of these important developments in science and technology that are going to change and shape our lives in the not so distant future is actually not reaching the public very easily. This is not the problem of a specific region of the country but this is the scenario around the world. Scientists and researchers are failing to appeal to the general republic and cater to their needs in simple terms and formats. This is a great shortcoming to my mind to have public support for scientific work and development! Hence, we desperately need to look for avenues and platforms to disseminate the marvels and progress made in science and technology easily to the public.

One of the best strategies that is now being used around the world and quite successfully is the establishment of premier science museums, science parks, ecological parks and educational and awareness fairs to disseminate science and technology for the public. India has not been behind in this regard and over the past seventy years has developed good infrastructure in this arena. But compared to the massive population of the country and it's gigantic size they are much less in number compared to the need of the vast populations scattered across this nation.

Furthermore most of this ecological theme parks or science museums or scientific parts are restricted to towns and cities far from the remote corners of the country. Therefore the fruits of disseminating science and technology is not reaching equally to all the sections of the society and to all the geographical regions of the country quite successfully. Much needs to be done in this sector. The Indian education and knowledge industry should not restrict themselves in just developing private schools, colleges and universities as a profit making ventures. They have a responsibility in educating the general public too. If they are sincere enough in investing and seriously developing such ecological parks and science museums in the rural areas; that could make significant differences in the successful dissemination of scientific and technological knowledge to the general public.

Modern science and technology has several disciplines such as engineering sciences, natural sciences, earth, ocean and planetary sciences, medical sciences, life sciences, agricultural sciences, physical and chemical sciences, environmental sciences and even social sciences to that matter. It is therefore important to develop new and innovative theme parks and museums dedicated to various areas of science and technology. This will have long-term positive impacts on our society. It inspires the new generation of students to be dedicated and appreciative of the development in science and technology; and make them interested in opting for science in higher studies. Furthermore, it also provides a platform for our partially educated or uneducated common masses to get an idea of how science is shaping our lives. In a country which is still riddled with superstitions and numerous old age baseless myths, riddles and prejudices; the promotion of science and technology among the public is very important for the progress of the society as well as the nation.

It is quite important to understand that through such theme parks and museum, we could disseminate the progress and the marvels of science and technology to the general public in a very successful manner. Investments in this area will also bring in



From the Editor's

Dear Readers,

I wish my warm wishes!!

December is the last month of the year and marks the beginning of severe winter. Christmas Day is celebrated in December including several other festivals and important days. **World AIDS Day** is observed on 1 December every year to raise awareness and knowledge about HIV and a call to move toward ending the HIV epidemic. It was first celebrated in 1988. The theme of 2019 is "Ending the HIV/AIDS Epidemic: Community by Community". And according to UNAIDS, the theme of this year is "Communities make the difference". **National Pollution Control Day** is celebrated on 2 December to raise awareness about pollution and its hazardous effects. This day is observed in the memory of the people who lost their lives in Bhopal gas calamity and is considered as one of the biggest industrial disasters. Indian Council of Agricultural Research has designated on 3rd December as **Agricultural Education Day** to commemorate the birth anniversary of first President of Independent India and Union Minister of Agriculture, Bharat Ratna, Dr. Rajendra Prasad. **World Soil Day** is observed on 5 December to raise awareness about the importance of soil, healthy ecosystems and human well-being. **International Mountain Day** is celebrated on 11 December every year to educate children and people about the role that mountains play in providing freshwater, clean energy, food, and recreation. The theme of National Energy Conservation Day in 2020 is "Mountain biodiversity". It is observed on 14 December to raise awareness about the need for energy and its conservation in daily life. **Kisan Divas or Farmer's Day** in India or National Farmer's Day is celebrated on 23 December across the country to commemorate the birth anniversary of the former Prime Minister Chaudhary Charan Singh. On this day various events, seminars, functions, and competitions are organised on agriculture and its importance to educate and provide knowledge to the people.

In December issue, we recount the various projects and popular articles. Once again, I express sincere and huge thank to all the persons who shared articles, without which there wouldn't have been this newsletter issue. Please continue sharing such articles and share with your friends also.

I would like to thank President and General Secretary, NESA, New Delhi, and the Editorial team including Print, Designer and Publication committee for their nonstop support and efforts throughout this edition.

Hope this edition makes an interesting read. Please feel free to offer any suggestions for improvement.

Dr. Sushma Tiwari
Associate Editor

Dr. R. S. Tomar
Editor-in-Chief

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revenue in the form of tickets sold per day. It could also become an essential part of social communication as it will attract people from all levels of the society and the region and could serve as a knowledge as well as entertainment platform for passing quality family time at a reasonable rates on holidays and weekends or even on weekdays.

But we need to change the age old vision of having those parks and museums restricted only to the towns and cities; and they need to be spread across the rural sectors of the country. We need to remember that the vast section of the Indian society is restricted to villages. If we cannot cater to the needs of the villagers and educate and make them aware about science and technology and our degrading ecosystems and environment and how to care for them; then we will not be able to see the fruits of mass education for the progress of the nation as we are always restricting and targeting cities only excluding the rural areas unfortunately for decades.

Photo credit: **S. K.Basu**

To,

Vol. 23 Issue - 12 (Monthly) December 2020

From
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