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PLANT DERIVED VACCINES: A SYSTEMATIC REVIEW

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ABSTRACT

Vaccines provide immune protection against many human and animal diseases however unavailability and unaffordability of vaccines have caused a concern worldwide and attracted global attention towards production of more acceptable, cost effective, stable and safer vaccines. This paper aimed to review the potential of plant derived vaccines in making immunization ubiquitous with full acceptability and affordability with challenges in the path of its production and rolling out in immunization programs. This review was done with the help of search engines which included online electronic databases PUBMED/MEDLINE, EMBASE, SCIENCEDIRECT, Google Scholar and sources available in internet pertinent to my topic. On reviewing various papers, the information shared from the existing knowledge are highlighted here. In contrast to majority available vaccines, plants offer a right platform for the production of various vaccines having scalable potential. Plant derived vaccines (PDVs) are the result of novel approaches and advancement in immunology and biotechnology. Since 1992, many PDVs have already undergone different phases of clinical trials successfully. Not only vaccines are in pipeline for infectious agents but also for non-Communicable diseases like Diabetes Mellitus-I. Despite the limitations in its production and use, incessant efforts are being made in order to produce efficient vaccine for many human and animals related diseases owing to its great promises for future. Plants derived vaccine have opened new horizons and is encouraging us to think about the existing human problems and some of the least solved disease mysteries through newer and innovative approaches.

KEYWORDS: Plant derived vaccines, transgenic, immunization.

Main Text

Background

Vaccination is the most powerful tool that we can use to change the health scenario of the world. Over 200 years ago, an English physician Edward Jenner laid the foundation of vaccinology by introducing a vaccine against smallpox.[1, 2] Since then, the field of vaccinology has rapidly evolved and currently, an estimated 2 to 3 million deaths are prevented every year through immunization against 25 vaccine preventable diseases.[3] Thus, vaccines have been through a lot of developments but along with that there has been a continuous emergence of novel biologic threats too that includes not only infectious but also chronic non- infectious disease.[4] The conventional vaccines though being successful in inducing strong systemic immune response have lacked in stimulating the mucosal immune system adequately and it still remains a challenge.[5] Hence today while some of the old plagues are still with us, the new emerging devastating diseases are posing a great threat to human health. To combat these issues there is an immense need of new strategy for vaccine development. Novel approach to this is being made through recent advancement in immunology and bio-technology which in future will not only invigorate immunization but will also change perception that vaccine is for prevention of infectious diseases only.[6] With advances the therapeutic role of vaccine is also anticipated and its role in chronic diseases also is being evaluated.[7] Recently an addition to the success story of immunization is being awaited through discovery of Plant Derived Vaccines (PDVs). These have the ability to directly address the health-related goals, specifically the targeted reductions in incidence of major diseases, and of child mortality due to preventable diseases.[3, 8] The principle behind the production of which is to isolate a specific antigen protein, which is immunogenic, from the virus on the target. Then the plant is infected by the gene from the protein with the help of a vector. The proteins then produced by the plant is used for vaccination.[6, 9] With the production of antigens for vaccine with the help of plants as incubators we are

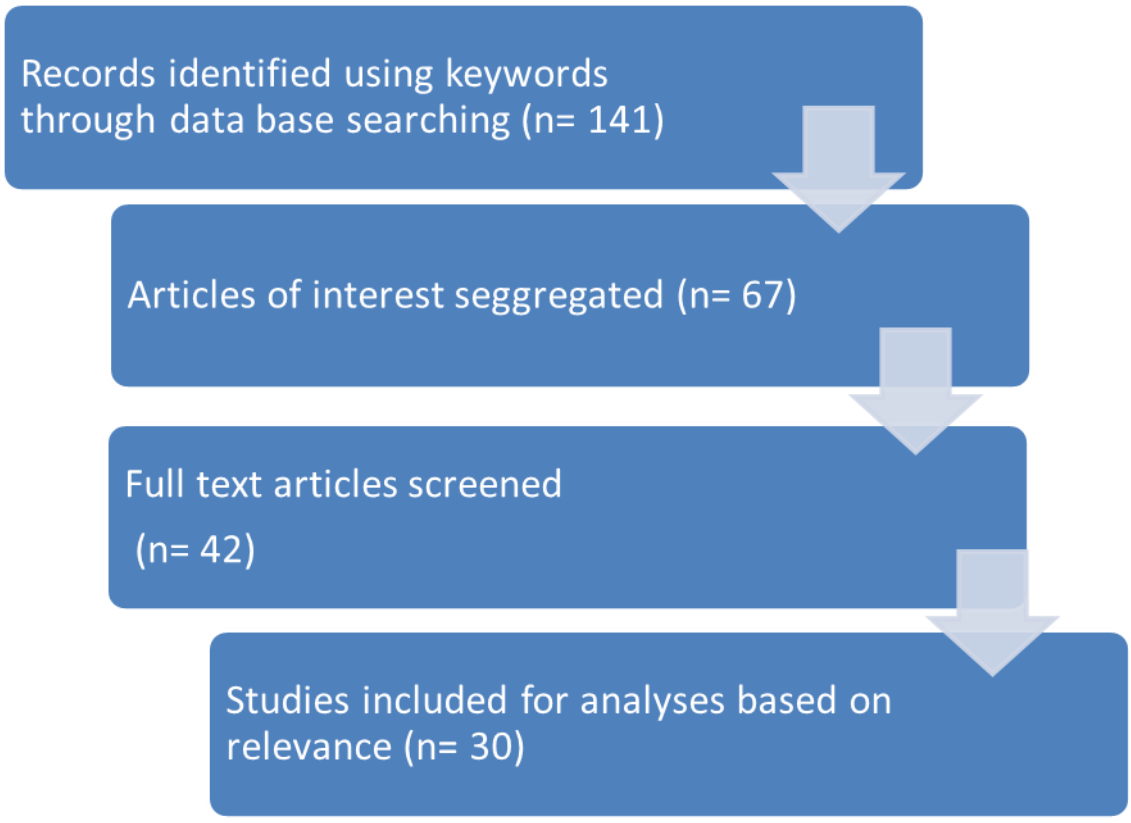
looking at a very near future of a cost-effective, more efficient and rapid vaccine production. Additionally, the ability of plant-production technologies to rapidly produce large quantities of strain-specific vaccine demonstrates their potential use in combating pandemics. So, this paper attempts to review the potential of plant derived vaccines in making immunization ubiquitous with full acceptability and affordability with challenges in the path of its production and rolling out in immunization programs.

METHODOLOGY

This review was done with the help of search engines which included online electronic databases PUBMED/MEDLINE, WHO Global Index Medicus, SCIENCEDIRECT, Google Scholar and sources available in internet pertinent to the topic published after 1990. These databases were searched through May to September 2017. Key words used in the search are: Plant derived vaccines, plant based vaccines, plant made vaccines, transgenic plants and Immunization, newer approaches in immunization. In brief, we used both free text key words and for MEDLINE/PUBMED search also MeSH terms. The papers which were relevant to my topic were segregated using different filters which were reviewed completely. The papers which suited to my interest were included in my review. Relevant references from the bibliographies of identified papers were also searched so as to increase my inclusiveness. And important information from the reviewed papers are aggregated and assimilated so as to provide a perspective towards plant derived vaccines.

RESULT AND DISCUSSION

A total of 67 articles of my interest was sorted out but papers which were available as full article were considered. A total of 30 articles were included on various aspects of PDVs depending on its relevance. On reviewing various papers, the information shared from the existing knowledge are highlighted in various sections such as Sciences behind the PDVs, Thrust in Immunization drive, Status of Plant derived vaccines, Challenges with PDVs and Way forward. Based on the above findings, a PRISMA Flow Chart was mapped which has been shown below.



Science behind the PDVs

Plant derived vaccines need a very specialized laboratory for its processing and production. It undergoes through various steps of genetic engineering. Firstly, the selection of plant for vaccine production is utmost important and many points are kept in mind while doing that. The selected plant should have low number and simple patterns of transgene insertion and transgene line which is stable with regards to its antigen expression. This is done so that gene silencing can be reduced.[5,9] Then the immunogenic antigen is selected from the target virus and a gene from the antigen protein is isolated. This isolated gene is used to genetically modify the plant. It can be done either by trans genetics or by transient

expression system. In trans genetics, the plant micro-organelle preferably chloroplast is introduced with the isolated gene. This process results in stable production units. While in transient expressing system a vector is selected for introduction of the gene into the plant cell which help in production of rapid vaccines but for short time.[10] The produced protein can be given orally or it can be mixed with adjuvants for better systemic effects.

The plants used for vaccine production can be either of the three – plant cell culture, culture of organised plant tissue or whole plant cultivation. In plant cell culture the cells are undifferentiated and individual entities can grow under aseptic conditions in nutrient culture medium. This method ensures continuous supply of product as it is not dependent on seasonal variations. For culture of organised plant tissue hairy roots are taken as its growth is rapid and there is no requirement of external supply of growth factors. They are genetically stable and the genetically engineered cells can be made to secrete the product in the surrounding medium for non-oral administration of vaccine. In cultivation of whole plant as transgene there is an advantage of low cost of production and processing. The modified seeds can be used for storage purposes. The fruits are used as edible vaccines. But the risk of contamination of the environment is always there in this method.[5]

Thrust in Immunization drive

Globally many million lives from infancy to old age are protected from illness through immunization. However 19.4 million infant worldwide are still missing out basic vaccines mostly in developing countries.[3] Many studies have been carried out to find factors responsible for this immunization gap. It is noted that, in spite of both medical and economic benefits of vaccination being well documented, the vaccines continue to be underutilized. Among many reasons some of them are vaccine stock-outs, cold chain problems, fear of injections, lack of resources etc.[11] Continuous effort to overcome these problems has led to an innovative idea of Plant Derived Vaccine. For the growth of these genetically modified plants inexpensive inputs like sunlight, air and water are required leading to low cost of production.[5] Their production is also rapid so mass production is possible.[12] The production may be easily scaled up too as per the requirements.[13] This high yielding property will remove not only a single hurdle but many.

Recent advances in mucosal administration of vaccines is an important approach to the induce protective immune responses against a variety of microbial and other environmental agents.

This will provide a painless delivery of various vaccine antigens used for human immunization. For immunity of mucosal surfaces large amount of vaccine is required which will not be a big issue.[13] The traditional parenteral administration can also be replaced with oral vaccination. This switch from parenteral to oral immunization can increase the acceptability of immunization program by decreasing the fear of injection, side effects and also the need of health staffs beside others. In addition, these can be used in protection against Bio warfare agents like Yersinia pestis [Plague] and its preventive and therapeutic role against some diseases like HIV is under evaluation.[14,15] The landmark step in its journey to a broad spectrum vaccines is the possibility of addition of more than one gene in prokaryotic plastids.[13] Other advantages are that the modified crop can be grown at the site where the vaccine is needed which reduces the cost and making them readily available.[13] Even if storage required, these plants need no special medium for transportation and storage. The risk of environmental contamination, through pollens is also less as the transformation are done in the genes of the chloroplast in contrast to conventional vaccine which pose a risk of passing on of diseases from lower animals to humans and also till date PDV antigens have shown to be more immunogenic than other expression system.[5,16] In recent years, plants have emerged as a commercially attractive system for manufacturing biologics with superior scalability, safety, time and cost-saving benefits, along with significant progress in addressing technical and regulatory issues.[17,18]

Status of Plant Derived Vaccine

Many PDVs have already undergone Phase 1 and Phase 2 of clinical trials successfully and few have entered into Phase 3.[3,5,12,18] Since 1992 a number of antigens have been expressed in plants and its number had reached to 45.[6,12, 14] Many infectious diseases have been taken into target for vaccination by this method. One of the pioneers PDV is edible vaccine against Hepatitis B infection. This vaccine delivery through transgenic raw potato as well as through heat labile toxin sub-unit B of Escherichia coli expressed in corn has been developed by Dr. Arntzen.[14] The transgenic lupin and lettuce plants when fed to mice have shown to produce significant amount of specific antibodies against Hep B. Similar were results in human volunteers.[19,20] Plant derived vaccine has also shown better results in inducing neutralising antibodies against Dengue virus.[16] Another most common viral infection which being vaccine preventable disease still serve to be the topmost cause of mortality among females in the form of cervical cancer is Human Papilloma Virus infection. The reason behind this is highly expensive vaccine which can't be afforded by developing countries.[13] But after the development of plant derived vaccine cost-effective vaccines can be provided to low and middle income countries.[21] In recent years promising development have been made to address AIDS which has rapidly established itself as one of the most fatal illness of the century but none HIV-1 effective candidate has been found so far. With the upcoming concept of plant derived vaccine, there has been studies going on for development of both HIV-1 vaccine as well as antiviral molecule which can be used in a large scale for testing.[15] There has been a successful

creation of edible bananas which is a potential candidate for vaccine against Norwalk Virus infection.[9] Plant-based quadrivalent virus-like particle[QVLP] offers an attractive alternative manufacturing method for producing effective and HA-strain matching seasonal influenza vaccines.[22] But there is an exhaustive list of different diseases against which PDVs have been tried and demonstrated either in the oral or injectable form.

Among the non-infectious disease, one very important disorder tackled by the plant derived vaccine is Diabetes Mellitus. The phase II trials of insulin produced in transgenic safflower [*Carthamustinctorius* L.] has been successfully completed and is still under investigation for further trial phases.[16] For treatment of Gaucher's Disease, *Taliglucerasealfa* produced in stable carrot cell cultures is used. It has been accepted by FDA and is already under the list of prescribed drugs.[16] Therefore the results of on-going clinical trials and studies already show the potential of Plant Derived Vaccines in diagnostic and therapeutic uses.

Vaccines produced in plants have opened up new horizons of innovations in the field of vaccinology. Amidst several types of vaccines, the recombinant vaccine is generally regarded as the most cost-effective and safest type because it is not known to cause diseases and does not require handling of large-scale pathogens. Due to the low cost of their production, PDVs may represent viable and sustainable alternatives for producing subunit vaccines. Genetic engineering of plastids is the advancement in the last three decades and has numerous benefits over nuclear transformation. Oral vaccines produced in transplastomic plants do not have to be purified due to the high level of expression. Hence, they can be consumed directly without any refinement, which reduces the cost of preparation, transportation and handling of the vaccines. Oral vaccination also eliminates the risk of other infections or contaminations, while compartmentation of the plant cell provides an excellent encapsulation to the antigen within the plastid.[23, 24]

Plant Derived Vaccine- the challenges

Great achievements are usually born of many obstacles. Likewise some difficulties are associated with the use of plant derived vaccine too. It was found that the immune response to the plant derived vaccine varies among the individuals. This would lead to non-uniformity in the immunisation process.[25,26] The inherent variability in expression of recombinant proteins in transgenic plants makes it difficult to control the exact dose of antigen delivered by PDV. This can be overcome by food processing techniques such as batch processing and freeze drying which will help standardize the antigen concentration in transgenic plant materials.[5] Common to all vaccines, allergic reaction is a major concern but in case of plant derived vaccine this can be minimised easily by avoiding fruit or vegetables to which the person is allergic and by doing sensitivity test. With advances in genetic engineering the risk of contamination of food chain co-exist. The pollen from transgenic plant can cross react with other food crops. To prevent this strict regulation is given regarding geographical isolation, buffer plants, physical containment in glasshouses, harvest and processing, and transport of the plants and resulting products. Besides FDA and USDA take a 'no tolerance' approach regarding contamination of food crops with genetically modified organisms in which if there is contamination, the entire crop is destroyed.[5] The biggest challenge today is the commercialization and acceptability of plant derived vaccine. Main hurdle in this regard is the need of prerequisite work during production. To avail the benefit of this oral vaccine it is necessary to analyse the characteristics of the target plant (edible, heat stable, long shelf life etc.) and expressed protein in addition to environmental and human risk assessment. Also there is a need of plant expression vector optimization to increase the yield.[27-30]

In 2005, WHO prepared a report on "WHO Informal Consultation on Scientific basis for regulatory evaluation of candidate human vaccines from plants" on 24-25 January in Geneva, Switzerland. This report is constantly revised. It has laid down guidelines for production, processing, acceptability and disposal methods of plant derived vaccines. It also stated the provision for facilities for banking of seeds, its GMP, cultivation and harvesting facilities. It listed probable advantages and problems faced while doing the same.[12]

Conclusion and Way Forward

Worldwide immunisation programs have curtailed the burden of infectious diseases on a global scale. However, there are precincts to the current technology, which often entails expensive infrastructure and long lead times for production. Furthermore, the obligation to keep vaccines within the cold-chain throughout manufacture, transport and storage is often cumbersome and prohibitively expensive in developing nations—the very regions where vaccines are most needed. In contrast, PDVs can be produced at a much lower cost and do not need to be kept within such narrow temperature ranges. This increases the feasibility of developing countries producing vaccines locally at a small-scale to target the specific needs of the region. The Plant Derived Vaccines are certainly a break through discovery in the field of immunisation.

The current trend of development in this field suggests an ever increasing hope that plants will continue to become safe, efficacious and economical platforms for the large-scale production of vaccine and other biopharmaceutical proteins against a wide variety of infectious diseases. With the production of these vaccines a future of global immunisation is foreseen. There is a possibility of prevention of fatal diseases like AIDS and Ebola whose cure has not been found till now. The advantages of plant derived vaccines over classical vaccines are many while the disadvantages are such that

can be overcome with more modifications and clinical studies. The molecular farming and plant biotechnology has a bright future. Plants derived vaccine have opened new horizons and is encouraging us to think about the existing human problems and some of the least solved disease mysteries through newer and an innovative approach. The potential benefits for the world's poor are much too great to ignore and the humanity stands to gain immensely. PDVs are a proven technology that has the prospect to play an imperative role in increasing global health, both in the context of the 2030 Sustainable Development Goals and beyond. The field is exciting but the challenges remain and in the words of Dr. Griffiths, "Be prepared for unanticipated events – expect the unexpected".[14]

Competing interests

The authors declare that they have no competing interests**.**

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Author's contributions

DK conceived and conceptualized the idea. VK has given his important inputs to enrich the manuscript and reviewed extensively. NN did the major literature search in Pubmed and other data bases. EY drafted the manuscript. NK carried out the editing, proofreading and reviewing of the manuscript.

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DISCLAIMER

The views expressed in the paper are solely of authors and should not be attributed to any institutions/organizations they have been affiliated in the past or at present.

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