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The third generation edible green vaccine: a state of art for promising platform in vaccination

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Abstract Edible vaccine, synonymously designated food vaccine, green vaccine, subunit vaccine, and plant-based vaccines, is an emerging trend in vaccinology since1990 (s). It has been considered a good biotechnological solution to help avoid the serious side effects, on animal and human health, encountered in traditional vaccines. In this context, the literature of review contains a plethora of reports addressing the past and the ongoing research pertaining to the development of numerous edible green vaccines against various infectious animal and human diseases. Infectious diseases are posing serious health threats to the life of both animal and human around the world. Vaccines are one of the strategies employed to prevent the spread of the infectious illnesses from a prophylactic side. The safety concern associated with the edible green vaccination has caught the interest of numerous researchers in laboratories all around the world. At the time being, edible green vaccines are being developed for human and veterinary purposes. Additionally, this sort of vaccine has come under scrutiny due to the drastically lowered costs connected with the industrialization and marketing of edible green vaccines. Before a vaccine is transferred from the lab to the medical market, it is customary for it to undergo extensive clinical studies. Because of this, the majority of edible green vaccines discussed in various papers are still in the academic zone and haven't moved into the industrial zone unless they can effectively overcome the clinical trials bottleneck. We have gathered information in this minireview about the idea of edible green vaccines, transgenic food plants as renewable therapeutic factories, paradigms of edible green vaccines, current state, pros, cons, and future prospectives.

Keywords: edible green vaccines, transgenic plants, infectious diseases, vaccine medical markets, industrialization state

Introduction Vaccines are defined as biological preparations that are capable to provide an acquired immunity against pathogens (viral or bacterial entities) or malignant and autoimmune diseases. Prophylactic vaccines help ameliorate or prevent the adverse effects of infection by a contagious agent mostly bacteria or viruses (1). However, therapeutic vaccines could fight an illness that has actually happened like cancer and autoimmune diseases (2). Production of vaccines in plant cell lines or plants (using plant molecular farming tools and technologies) as expression platforms is nominated green vaccines or edible vaccines or plant-based vaccines or subunit vaccines. Other definition of edible vaccines is the production of vaccines in green bioreactors, plants, instead of the conventional bioproduction systems. There are three main platforms addressing the production and development of edible vaccines: the first generation, the second generation, and the third generation. The first generation of edible vaccines focuses on the expression of a whole organism or a single antigen from a single pathogen in a plant (3). The second generation of edible vaccines addresses the production of multiple antigens originating from different pathogens in the same plant (4). However, the third generation of edible vaccines utilize the nucleic acids like DNA or RNA encoding the desired antigens to be transcribed and expressed in the plant (5). Plant-based vaccines: Historical background

Traditional vaccines bear certain limitations such has the high expenditure in industrialization step, indispensable need for skilled medical personnel for administrative purposes, inefficiency in eliciting potent mucosal immune response, and storing the administrating vaccines particularly in developing countries (3). The above-mentioned pitfalls of conventional vaccines triggered the attention of Hiatt and co-workers in 1989 1989 to develop antibodies in tobacco plants aiming to elicit passive immunization (6). As a consequence, in1990, the surface Streptococcal surface protein from Streptococcus mutans was expressed successfully in the tobacco leaf for the first time ever and this work was published as a patency under the international patent cooperation treaty. The conceptualization of edible vaccines had been conceived by Arntzen and co-workers in 1997. To settle the conceptualization of edible (green) vaccine in eliciting mucosal immune response, (7) was attempted the optimized expression of HBsAg protein in potato tubers. Since this date, research into green vaccine has developed rapidly to reduce the burden posed by several fatal infectious diseases and a huge effort is done by scientists to improve the output of green vaccine.

Conceptualization of Transgenic plants

Modifying the natural genetic makeup of a given plant, by insertion of a single foreign gene or a combination of foreign genes, would result in getting what is called a transgenic plant. In 1983, the first transgenic plant was reported. The transferred gene (s) are designated transgenes. The artificial insertion of foreign gene (s), from the closely related plant species or from distally related plant species such as mammalian and microbial species, to the recipient plant would introduce new traits to this recipient. Among the possibly acquired traits in transgenic plants are pest resistance, tolerance to extremes in climatic alterations, drought resistance, production of proteins with pharmaceutical potentials like vaccines, proteins, and antibodies (8). The transgenic plants employed in production of vaccines is the topic of the current review.

Molecular plant farming: an approach towards production of edible vaccine

The molecular plant farming (PMF) approach focuses on the unconventional products like vaccines, antibodies (plantibodies), and products with pharmaceutical values like human hormones. Conventional vaccines are normally produced in cell-based expression systems, like bacterial or yeast cultures, mammalian cell lines, and insect cell lines. However, producing of vaccines using plant cells or plant as expression platforms is called edible vaccines, that is a rapidly emerging and growing trend in vaccinology with promising prospectives (9). The review of literature displays a plethora of reports highlighting the usage of plant molecular farming approach in production of edible vaccines. Examples of these edible vaccines are those against influenza virus, Hepatitis B virus, Escherichia coli thermolabile B toxin, rota virus, Ebola virus, foot -mouth disease virus, Plasmodium falciparum, norwalkvirus, dengue virus, and SARS-CoV-2 (10-19). Medicago, Inc, iBio, Inc, and Kentucky BioProcessing, Inc are three companies, that are producing the edible vaccines against influenza virus and SARS-CoV-2.

Paradigms of plants that can be used as edible vaccines models

Currently, there are a list of plants species that can be used for the production of edible vaccines. The most commonly used plant species in this context are banana (Musa Sapientum) (20, 21), rice (Oryza sativa) (22-25), lettuce (Lactuca sativa) (26, 27) , potatoes (Solanum tuberosum) (28-32), tomatoes (Solanum lycopersicum) (25; 33), corn (Zea maize L.) (26), pea (Pisum sativum) (34, 35), tobacco (Nicotiana tabacum) (36, 37), carrot (Daucus carota), neem (Azadirachta Indicia) (38) and Aloe vera (Aloe barbadensis) (39, 40).

Omics and edible vaccines

Omics field attempts to merge information from different fields such as genomics, metagenomics, transcriptomics, metabolomics in order to create biotechnological approaches at all levels of biotechnology. Omics-based technologies with high throughput always target the expansion of research in the agricultural biotechnology field in certain zones such as food, health, energy, etc., (41). Omics -based high throughput technologies aim to develop vaccines particularly edible vaccines.

In the last ten years, several whole genome sequencing projects have been launched by NCBI (National Center for Biotechnology Information) and have aimed the full annotation of the whole genome sequences from a variety of microbial species (bacteria and fungi). This helps identify microbial antigens. Moreover, the completion of whole genome sequencing of the plant Arabidopsis thialana has opened the avenue to modify the plant genome by introducing a specific gene or knocking down a gene with RNAi technology. Hence, genomics has

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contributed in the development of targeted vaccines of biopharmaceutical value. As a rule of thumb, the genome of nay given cell is considered a fixed entity excluding the possible alternations due to the mutational events. On the contrary, transcriptomics is dynamic as it represents only the portion of the DNA that is subjected to the transcription process under certain circumstances particularly biotic and abiotic stress factors. Thanks to the high throughput technologies of sequencing the functional elements in the genome of a given cell of a given species could easily deciphered (42)

Numerous cellular processes in plants are made possible by proteins. Proteomics can control mRNA expression, which leads to protein production and explains how genes work. The texture, yield, flavour, and nutritional value of almost all food products are significantly influenced by a range of proteins found in plants (43). With the aid of expression profiling, proteins may be located at a given period and their functions can be clarified (44). A further development of proteomics from expression to functional, structural, translation, and the manifestation of desired features is called translational plant proteomics.

Edible vaccines: Pros and cons

The plant -based vaccines offer some advantages over the traditional-based vaccines methods. Of most importance are cost-effectiveness, subunit vaccines (not attenuated vaccines), no liability for contamination with bacterial toxins like traditional vaccines, lack of reverse virulence, correct folding of recombinant protein antigens produced in higher plants, non-cumbersome purification, no need for sterilized production facilities, easiness for expansion on a large scale, and feasibility of storage at room temperature without strict refrigerated circumstances, lack of necessity for cold chain transport, easiness of storage of seeds of edible vaccines with accessibility in time of need, simplicity tools of administration compared to those employed in traditional vaccines, lack of medical personnel and sterilization conditions during the administration, simultaneous supply source of food with a combating diseases, edible administration route, absence of need for adjuvants or other elements to elicit the immune response like conventional vaccines, triggering mucosal and systemic immune response, and reduction risk for raising anaphylactic side effects reactions, enhanced compliance particularly for children, delivery of multiple antigens, appropriateness with less common illnesses such as dengue fever and rabies, and transfer of the maternal antibodies to the fetus through placenta or breast milk (45-49).

Nevertheless, plant-based vaccines have some problems and hurdles that could delimit their usage on a large scale and put them in the infancy zone so far. These pitfalls could be summarized in the following lines. Of paramount magnitude are undetermined and variable plant dosage bearing the antigen, undetermined time of how long edible vaccines should last in the body, difficulty in standardizing the exact concentration of the antigen in the plant tissue, possible variation in antigen concentration from fruit to fruit, from plant generation to generation, from lot to lot, underestimated antigen dosage with unsatisfactory immune response, overestimated antigen dosage with undesirable immune tolerance to the vaccine, unknown long-term effects, likelihood of developing negative consequences resulting from pesticides-herbicides and mycotoxins on both the plant vaccines and the consumer, cooked plants with weakened or destroyed antigenic proteins, possible destruction of the plant -based vaccines by gastric enzymes prior activating the immune response, some raising concerns regarding the vaccine behavior as long the glycosylation pattern is different between human and plants, a concern about the undetermined risks of using genetically modified crops on human health, lack of comfortability with ingesting foreign DNA of viral and bacterial origin, and a concern about the likelihood of damaging the environment by the transgenic plants (50-51) There are numerous remarkable benefits for plant-derived vaccines, synonymously called edible vaccines. Plants are easily to be cultivated through basic agricultural methods without need for fermentation facilities or sophisticated cell culturing systems. In addition, culturing of plants is scalable, enabling cumulative mass production to satisfy the global demands, especially in pandemics circumstances. Plants are considered the most ever safe expression hosts for vaccines production as they don't harbor human or animal pathogens, which minimizes the likely risk for contamination. Plant-derived vaccines are more preferable regarding storage and distribution compared to other host for vaccines production, as they have prolonged shelf-life time and do not necessitate strict cold conditions. Oral delivery, as route of administration, is considered one of the privileges encountered in plant-derived vaccines, eliminating the indispensable needs for needles and well-trained personnel. The broad genetic flexibility window, a criterion of plant-derived vaccines, is one the most attractive properties that would enable multiple vaccines synthesis in the same plant host. Lastly, edible vaccines are preferable regarding ethical and environmental sustainability considerations compared to animal-based vaccines production systems (52).

Laboratory strategies toward developing green bioreactors

Developing green bioreactors, plants, that are capable of edible vaccines biosynthesis has the state of art. To generate a green bioreactor, researchers should select which gene delivery method and which transformation method could be employed. Currently, there exists two strategies for gene delivery for the development of green bioreactors: direct gene delivery and indirect gene delivery. However, there exists two transformation procedures: stable transformation and transient transformation system (53,54,55). In the direct gene delivery method synonymously called gene gun or micro-projectile bombardment or biolistic method, the target gene encoding for the antigen should be introduced directly to the plant cell without any vehicle (56; 57; 58). Shortly, the DNA encoding the antigen protein should be coated with gold. After that, the coated DNA would be put in the gene gun, that is under high pressure will be injected into the plant cell (59;60). The other protocol of nuclear transformation of the gene addresses the gene transfer to the plant cell nucleus through non-homologous recombination procedure Paradigms of edible vaccines synthesized by bombardment methods are canine parvovirus, tetanus, plague, anthrax, cholera, and rotavirus (61).

The alternative protocol is called indirect gene delivery synonymously called vector dependent method. Where the recipient plant should be firstly infected with plant or viral bacterial pathogen (63). The most commonly used protocol is the one using Agrobacterium mediated gene transfer method. There are two species of the genus Agrobacterium that can be used in this regard: A. tumefaciens and A. rhizogenes. The first bacterial species harbors Ti-tumor inducing plasmid and the second bacterial species harbors the root inducing plasmid Ri. Firstly, the auxin and cytokines in Ti and Ri plasmids should be removed (62).

Conclusion

Edible vaccines are a promising type of vaccines in the vaccination field both on the therapeutic and prophylactic level. As a novel approach, it still encounters some limitations that would necessitate the unveiling of the nature and dynamics of edible vaccines. Additionally, a through efforts from the scientists' side should be done to answer several questions arisen regarding the edible vaccines.

Ethical Approval

Not Applicable

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Conflicts of interest

The authors declare no conflict of interest

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