Acta Scientific Women's Health (ISSN: 2582-3205)

Volume 3 Issue 10 October 2021

Review Article

Plant-based Vaccines for SARS-CoV-2 Novel Corona Virus - A Review

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Received: August 21,2021

Published: September 20, 2021

Abstract

Introduction: The novel SARS CoV2 coronavirus is believed to have emerged from bats in Wuhan in 2019 last yearAs of July 8, 2021, 20 vaccines worldwide have been licensed; 96 vaccines are in human clinical trials, 32 of which have entered the final stage of testing. VLP proved to be a promising alternative to soluble antigens. Because they have the conformation and composition of natural viruses, their shape, size, repeated antigen structure and geometry will trigger stronger humoral and cellular immune responses. Plants have a complex mechanism for eukaryotic protein production and also support the amplification of a large number of plant-specific viruses.

Method: 35 articles from Medline, Embase, Google Scholar, Scopus. PubMed were reviewed using the key words SARS CoV-2 plant-based vaccines.

Review: Virus-like particles (VLPs) are self-assembling structures derived from viral antigens, which mimic the natural structure of viruses but lack the viral genome. VLPs are similar in size and shape to real coronaviruses, but they lack nucleic acid and are therefore not infectious. The Phase 1 trial of Medicago's plant virus-like particles started in July 2020, involving 180 healthy volunteers aged 1855. All preparations are well tolerated, and adverse events after vaccination are usually mild to moderate. British American Tobacco, through its US biotechnology subsidiary Kentucky Bioprocessing (KBP), is developing a potential COVID19 vaccine and is currently undergoing preclinical testing. Using its plant-based Fast Pharming® system, iBio, a biotechnology innovator and biologics contract manufacturing organization, reported on its progress in the development of the second-generation vaccine candidate subunit IBIO202, which aims to prevent SARSCoV2 infection.

Conclusion: Now is the time to explore the true potential of plant-based vaccines, proven technologies that have the potential to play an important role in promoting global health.

Keywords: SARS-CoV-2; Pandemic; Plant-Based Vaccines; Virus Like Particles; Covid-19

Abbreviations

SARS-CoV-2; MERS-CoV; WHO; ACE2; VLP

Introduction

The new SARSCoV2 beta coronavirus is believed to have emerged in Wuhan in Bats last year. Crossing the species barrier, it enters humans through human-to-human transmission and infection. In the past 20 years, β-coronavirus has jumped between species and caused three outbreaks of zoonotic diseases, namely SARS CoV (2002-03), MERSCoV (2012) and SARSCoV-2 (2019 to present).

Since its emergence in November 2019, although WHO and governments have made meticulous efforts to control the infection, it has spread to 188 countries and 25 regions around the world, mainly due to the highly contagious nature of the virus. As of May 22, 2021, a total of 175,733,110 cases have been reported globally, with 3,791,245 deaths. (World Health Organization, 2020) [1-3].

Since the beginning of the pandemic, efforts have been made across the world to develop vaccines. As of July 8, 2021, 20 vaccines worldwide have been licensed; 96 vaccines are in human clinical trials, 32 of which have entered the final stage of testing. At least 77 animal preclinical vaccines are under active research.

Most of the COVID19 vaccine candidates administered with viral antigens or viral gene sequences are designed to induce neutralizing antibodies against the viral pico protein (S), avoiding uptake through the human ACE2 receptor, thereby blocking infection [4].

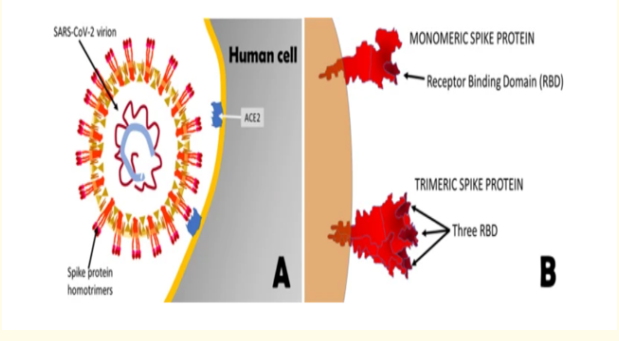

Figure 1

Vaccines and candidate vaccines are not only notable for their number, but also for their diversity, including traditional (such as inactivated virus particles, live attenuated vaccines, and protein + adjuvants) and new types (such as replicating mRNA, DNA, and adjuvants), vira vectors and non-replicating platform [5-7].

S.no	Vaccine	Type of vaccine	Manufacturer
1	RBD-Dimer (ZF2001)	Protein subunit	Anhui Zhifei Longcom
2	Covaxin (BBV152)	Inactivated	Bharat Biotech
3	Ad5-nCoV (Convidecia)	Non replicating viral vector	CanSino
4	Kovivac	Inactivated	Chumakov Center
5	EpiVacCorona	Protein subunit	FBRI
6	Sputnik V (Gram-Covid-Vac)	Non replicating viral vector	Gamaleya
7	Janssen (Ad26COVS1, JNJ-78436735)	Non replicating viral vector	Johnson and Johnson
8	QazVac (QazCovid-in)	Inactivated	Kazakhstan RIBSP
9	SARS-CoV-2 Vaccine (Vero Cells)	Inactivated	Minhai Biotechnology Co
10	Moderna: mRNA-1273	RNA	US biotech company
11	Oxford/AstraZeneca: AZD1222 (Vaxzevria)	Non replicating viral vector	Oxford Vaccine Group and AstraZeneca
12	BNT162b2 (Tozinameran, Comirnaty)	RNA	Pfizer/BioNTech
13	Covishield	Non replicating viral vector	Serum Institute of India
14	BBIBP-CorV	Inactivated	Sinopharm (Beijing)
15	Inactivated (Vero Cells)	Inactivated	Sinopharm (Wuhan)
16	Sinovac-Coronavac	Inactivated	Sinovac/ China National Pharmaceutical Group
17	TAK-919	RNA	Takeda Pharmaceutical Company

Table 1: Vaccines approved for emergency use for COVID 19 in various countries.

Aims and Objectives

To review plant derived vaccines under trial for SARS-CoV-2.

Materials and Methods

Databases included - Medline, Embase, Google Scholar, Scopus. PubMed. Around 35 articles were reviewed using the key words SARS CoV-2 plant-based vaccines.

Summary of work done by the contributors

Selection of topic, interdepartmental discussions, discussions on database collections, aims & objectives for the review analysis, criteria to search the database, searching the databases selectively, finalizing the findings and writing them briefly.

Results and Discussion

Plant based virus like particles COVID 19 vaccines

Virus-like particles (VLP) are self-assembled structures derived from viral antigens, which mimic the natural structure of viruses but lack the viral genome. Due to its safety, immunogenicity and manufacturing advantages, VLP has become the premier vaccine platform. The particle nature and high-density presentation of viral framework proteins on its surface also make VLP an attractive carrier for displaying foreign epitopes. Due to its safety, immunogenicity and manufacturing advantages, VLP has become the premier vaccine platform.

VLP proved to be a promising alternative to soluble antigens. Because they have the conformation and composition of natural viruses, their shape, size, repeated antigen structure and geometry will trigger stronger humoral and cellular immune responses [8-10]. Plant viruses are non-enveloped particles composed of simple proteins, which can be produced in complex forms in various ways. Therefore, plant cells can efficiently produce protein viruses with very precise 3D structures, including VLPs. As a result, several VLP-based vaccines have been approved for human use and have achieved significant clinical and economic success. Initial attempts were made to produce vaccines using tobacco plants to express antibodies. The United States Department of Agriculture (USDA) approved the world's first plant-based vaccine for poultry against Newcastle disease virus (NDV) [11,12]. It has been proven to provide more than 90% protection for chickens. The only authorized plant-derived product is a single-chain fragment variable monoclonal antibody (scFv mAb) made from plants, which is used to produce a recombinant vaccine against hepatitis B virus (HBV) in Cuba [13,14].

The herbal vaccine against COVID19 was developed by expressing the antigenic components of SARSCoV2 to induce active immunity or expressing antibodies against the virus to provide passive protection. Part of the SARSCoV2 virus that causes COVID19 is replicated and inserted into plants for rapid reproduction. These plants are then harvested to remove the inactive virus "lumps" and chemically attach them to microscopic nanoparticles as carriers or carriers to form vaccine antigens that stimulate the immune response in the body [15,16].

Canadian biopharmaceutical company Medicago successfully developed virus-like particles (VLPs) of the coronavirus 20 days after obtaining the SARSCoV2 gene sequence. The gene sequence encoding the COVID 19 spike protein was introduced into Agrobacterium, a common soil bacterium. The resulting plant produces a virus-like particle composed of a plant lipid membrane and the COVID19 spike protein. Medicago is using Nicotiana benthamiana, a close relative of the tobacco plant, to produce VLPs for the SARSCoV2 virus. VLP is similar to the real coronavirus in size and shape, but it lacks nucleic acid, so it is not infectious [16-18].

The first phase of Medicago's plant virus-like particles began in July 2020, involving 180 healthy volunteers aged 1855. The vaccine is administered in two intramuscular injection doses of 3.75 μg, 7.5 μg or 15 μg, with an interval of 21 days, with each injection of CpG1018 adjuvant, AS03 or no adjuvant. CpG 1018 and AS03 are compounds commonly added to vaccines to induce a stronger immune response in the body. All preparations are well tolerated, and adverse events after vaccination are usually mild to moderate. According to their results, in addition to ASO3, a two-dose regimen with a concentration of 3.75 μg showed the best results, and these results have been in phase 2/3 trials in Canada and the United States [19].

British American Tobacco, through its US biotechnology subsidiary Kentucky Bioprocessing (KBP), is developing a potential COVID19 vaccine and is currently undergoing preclinical testing. KBP experts cloned part of the SARSCoV2 gene sequence, and they used it to develop a potential antigen that was inserted into the tobacco plant for production. The vaccine passed the preclinical test and the immune response was positive, and it is about to enter the human phase 1 clinical trial. In this study, a total of 180 healthy volunteers were recruited, divided into two age groups, 1849 years old and 5070 years old. Then each group will be subdivided into low-dose and high-dose treatment groups (N ~ 45) and randomly receive a low dose (15 μg KBPCOVID19 vaccine + 0.5 mg adjuvant) or placebo, or a high dose (45 μg KBPCOVID19) vaccine + 0.5 mg adjuvant) or placebo. The results of the study are expected to be obtained in mid-2021. If the results are positive, they will be allowed to proceed to the second phase of regulatory approval [20,21].

Using its plant-based Fast Pharming® system, iBio, a biotechnology innovator and biologics contract manufacturing organiza-

tion, reported on its progress in the development of the second-generation vaccine candidate subunit IBIO202, which aims to prevent SARSCoV2 infection. IBIO201 is the company's vaccine candidate. It combines an antigen derived from the spike protein ("Protein S") with iBio's proprietary LicKM ™ enhancement molecule, and recently completed an IND activation toxicology study. These studies did not find low-dose or high-dose adverse reactions. The company also reported the development of IBIO202, a vaccine candidate subunit for the nucleocapsid protein ("N protein") of SARSCoV2. The N protein of many coronaviruses is highly immunogenic and is expressed in large quantities during infection. iBio has successfully expressed the protein N antigen and initiated intramuscular and intranasal preclinical studies to determine a favorable combination of antigen adjuvants. Results are expected early in the first quarter of fiscal 2022. Immunization with more conservative sequences (such as the N protein) is expected to produce T cells, which can kill spike protein variant viruses in addition to the parent virus. The IBIO202 protein N strategy is a complement to the existing first generation protein S targeted vaccine and may be suitable as a more general coronavirus vaccine [22].

Akdeniz University in southern Turkey's Antalya province has developed a drug and vaccine candidate that can also be used as a protective spray against the new coronavirus. The protein produced by the "transient plant expression system" in the leaves of a tobacco plant called "Nicotiana benthamiana" is used as the basis of medicine. According to a study, the reduction of angiotensin converting enzyme 2 (ACE 2) in the body blocked by the COVID19 virus can cause serious human health problems, noting that most intensive care patients have a small amount of this enzyme unit. With the help of a transient plant expression system, the researchers achieved a high yield of this enzyme. These proteins that we produce from plants can be used in spray and injection treatment forms. The research is still in the preclinical stage [22].

Two other drug candidates from the University of Shiraz (Iran) and the Baiya Phytopharm/Chula Vaccine Research Center (Thailand) are in the preclinical stage and use the plant as an expression system and are in the preclinical stage.

Vaccine	Vaccine Platform Description	Manufacturers	Transformation Method	Expression System	Clinical trials	Dose
COVID-19 VPL Vaccine (CoVLP)	Virus-like particle (VLP)/Spike protein	MedicagoInc. (Québec, Canada)	VLPExpress™ system (Agro-infiltration)	*Nicotiana benthamiana*	Phase 2/3	2 dose, IM, 21 days apart
COVID-19 Subunit Vaccine (KBP-201)	Protein Subunit	Kentucky Bioprocessing,Inc. (KBP)	Agro-infiltration	*Nicotiana benthamiana*	Phase 1	2 dose, IM, 21 days apart
COVID-19 Subunit Vaccine (IBIO-201)	Protein Subunit/ Spike protein	iBio, Inc. (NY, USA)	Fast Pharming™ system (Agro-infiltration)	*Arabidopsis thaliana*	Pre-clinical	NA
COVID-19 Subunit Vaccine	Development of recombinant protein based S1 and S2 (Spike) and nucleocapsid subunits vaccines using a plant expression vector.	Akdeniz University (Turkey)	Agro-infiltration	*Nicotiana benthamiana*	Pre-clinical	NA
COVID-19 VLP	Virus-like particle/ Spike protein	ShirazUniversity (Iran)	Agro-infiltration	*Nicotiana benthamiana*	Pre-clinical	NA
COVID-19 Subunit Vaccine	Plant-based subunit (RBD-Fc + Adjuvant)/Spike protein	Baiya Phytopharm/ Chula Vaccine Research Center (Thailand)	Agro-infiltration	*Nicotiana benthamiana*	Pre-clinical	NA

Table 2: Plant based COVID vaccines under trials.

Conclusion

Plant-derived VLP vaccines have several advantages over traditional vaccines, including cost-effectiveness and the ideal choice for large-scale production, as well as the stability of antigens in long-term storage. Plant-produced vaccines have been shown to elicit strong immune responses in humans and animals. However, there are few risk factors associated with herbal vaccines. Allergic; Compared to natural plant pathogens, genetically modified products can undergo different post-translational modifications. This can cause a new allergic reaction in the host during vaccination. At the same time, the use of adjuvants can induce hypersensitivity reactions. Inconsistent doses: Insufficient amounts of antigen may not produce the necessary immune response needed to prevent fatal diseases. The wrong frequency or the wrong dose can lead to tolerance and reduce the effectiveness of certain vaccine candidates. With advances in technology and sufficient preclinical and clinical trials, these limitations can be overcome. The approved plant-based influenza vaccine brings hope to the potential of the plant-based COVID19 vaccine. Plant-derived virus particle vaccines have been proven effective against SARS-CoV-1. Therefore, plant-derived VLP vaccine is an effective method against SARS-CoV-2. It takes five to six weeks to produce vaccines through chicken embryo technology and is widely used by many vaccine manufacturers. This duration may be limited by herbal vaccines that only require five to six weeks. Now is the time to explore the true potential of herbal vaccines, as they are a proven technology that has the potential to play an important role in promoting global health. However, it is expected that you will receive a cost-effective vaccine with little or no side effects and at least more than 85% protective levels.

Acknowledgements

I thank my honorable Chief Executive Director Sir for motivating us to write on interesting studies done by various authors

Conflict of Interest

No conflict of interest exists.

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