vaccines

Review

Plant-Based Vaccines in Combat against Coronavirus Diseases

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Abstract: Coronavirus (CoV) diseases, including Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) have gained in importance worldwide, especially with the current COVID-19 pandemic caused by SARS-CoV-2. Due to the huge global demand, various types of vaccines have been developed, such as more traditional attenuated or inactivated viruses, subunit and VLP-based vaccines, as well as novel DNA and RNA vaccines. Nonetheless, emerging new COVID-19 variants are necessitating continuous research on vaccines, including these produced in plants, either via stable expression in transgenic or transplastomic plants or transient expression using viral vectors or agroinfection. Plant systems provide low cost, high scalability, safety and capacity to produce multimeric or glycosylated proteins. To date, from among CoVs antigens, spike and capsid proteins have been produced in plants, mostly using transient expression systems, at the additional advantage of rapid production. Immunogenicity of plant-produced CoVs proteins was positively evaluated after injection of purified antigens. However, this review indicates that plant-produced CoVs proteins or their carrier-fused immunodominant epitopes can be potentially applied also as mucosal vaccines, either after purification to be administered to particular membranes (nasal, bronchus mucosa) associated with the respiratory system, or as oral vaccines obtained from partly processed plant tissue.

Keywords: coronaviruses; COVID-19; MERS-CoV; SARS-CoV; biopharming; plant-based vaccines

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1. Introduction

Coronaviruses (CoVs) are clinically relevant pathogens that infect humans, livestock, mice, birds and many other wild animals [1]. They cause localized infections in the respiratory and/or intestinal tracts, in the liver and the central nervous system of their hosts [2]. They belong to the order *Nidovirales*, the family *Coronaviridae*. Based on phylogenetic analysis, CoVs are divided into four genera: the alpha, beta, gamma, and delta coronaviruses [2]. This family of viruses has gained in clinical relevance since 2003, when a new human coronavirus (SARS-CoV-1) was responsible for Severe Acute Respiratory Syndrome (SARS). Later in 2012, a new outbreak of another coronavirus (MERS-CoV) emerged in Saudi Arabia, causing Middle East Respiratory Syndrome (MERS) [3,4]. Most recently, in December 2019 in Wuhan, the Hubei Province, China, the pathogen responsible for a mysterious pneumonia was identified as SARS-CoV-2 and defined as the causal agent of Coronavirus Disease 2019 (COVID-19) [5]. Due to the rapid spread of the virus around the world, COVID-19 was declared to be a pandemic by the World Health Organization (WHO) in March 2020. The origin of this outbreak was associated with the Wuhan Wholesale Seafood Market, where not only seafood is traded, but also exotic fauna [6]. Due to the fact that the greatest diversity of CoVs has been found in bats [7], the hypothesis has been proposed that more recent CoV introductions to humans were originally bat viruses that propagate to an intermediate host (e.g., the Himalayan palm civet for SARS-CoV-1 and the dromedary camel for MERS-CoV), which then exposed humans to the viruses. According to the WHO, the SARS-CoV-1 pandemic affected 8096 people while the MERS pandemic affected 2494 people, with a fatality rate of 9.19% and 34.4%, respectively [8]. Until November 2021, Virus) L1 protein [99–101]. However, in recent years VLPs derived from plant viruses such as e.g., TMV, CMV or PapMV, (Papaya Mosaic Virus) or PVX, are more and more extensively investigated both as epitope carriers and for other biopharming and nanotechnology purposes [102,103]. Moreover, such VLPs can be safely produced in substantial quantities, due to capacity of massive propagation of plant viruses in suitable hosts [70]. Considerable potential as an epitope carrier is also reported to exist for the oligomeric proteins LTB (heat-labile enterotoxin) and CTB (cholera toxin B), which at the same time act as mucosal adjuvants, as confirmed also in the case of plant-expressed LTB and CTB [104]. The use of carrier platforms may facilitate rapid development of new vaccine variants in response to emerging virus mutants. All these VLPs or oligomers can be used for injection after purification, but prospectively also as vaccines delivered through mucosa, i.e., as intranasal, inhaled or sublingual vaccines (Figure 3).

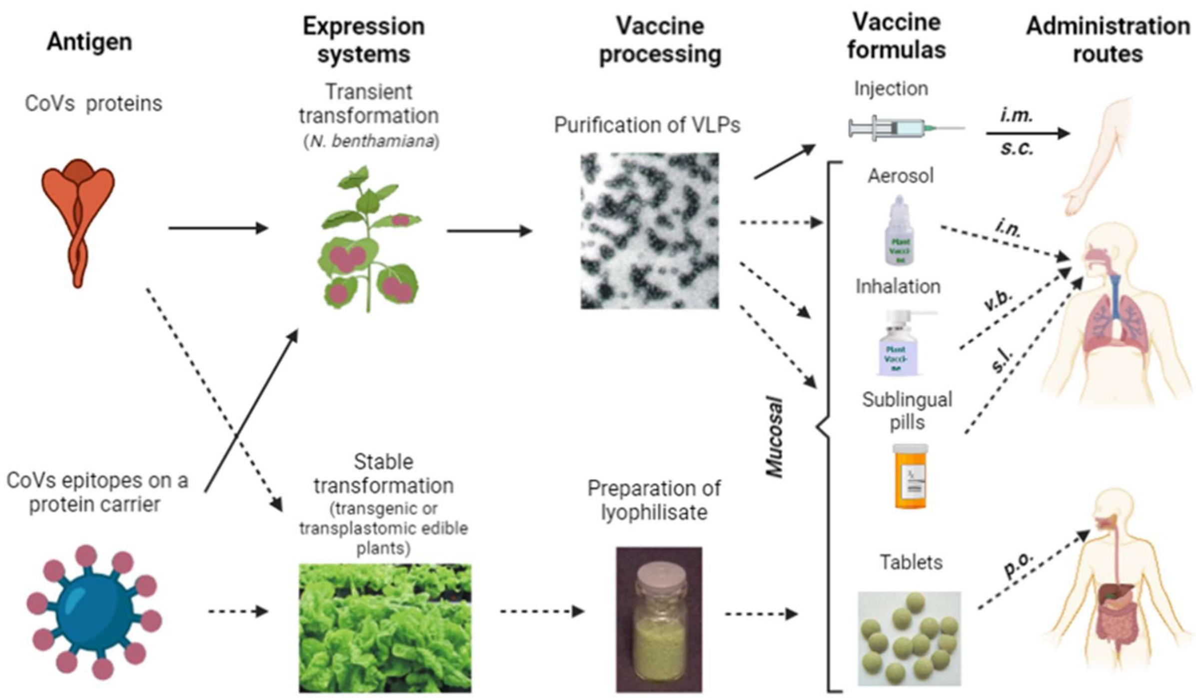

Figure 3. Summary of currently exploited (full arrows) and potential future (dotted arrows) approaches to manufacturing and application of various types of plant-based vaccines against CoVs. Administration routes: *i.m.*—intramuscular, *s.c.*—subcutaneous, *i.n.*—intranasal, *v.b.*—via bronchi, *s.l.*—sublingual, *p.o.*—per os.

Furthermore, since the function of particular parts of MALT such as e.g., NALT or BALT share analogous functioning mechanisms to GALT and they interact with each other, it can be assumed that oral vaccination against SARS-CoV-2 and other coronaviruses would also be developed over time [105,106]. Production of oral vaccines is based on stable antigen expression in transgenic or transplastomic plants and requires only partial tissue processing, usually involving lyophilization [107]. However, development of an appropriate oral administration regime is particularly important. Antigen dosage, frequency of delivery and adjuvants have to be meticulously adjusted to induce efficacious mucosal and systemic responses instead of oral tolerance acquisition [106,108]. Nevertheless, plant-derived oral vaccines were demonstrated to be fully efficacious when applied as boosting doses [109]. Therefore, even in that form they may still be useful at the post-pandemic stage, especially if the SARS-CoV-2 virus becomes a seasonal pathogen. A low-cost plant-derived vaccine would be an advantageous alternative, particularly in developing countries (Figure 3).