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Investigating the Potential of Mushroom-Derived Polysaccharides as Adjuvants for COVID-19 Vaccines

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ABSTRACT

Emphasis should be on vaccines that produce healthy robust immunity in the long run, especially against new strains. A good vaccine produces a strong and long-duration immune response. This includes adjuvants, which improve the immune response to vaccines, resulting in higher efficacy. Natural products, especially polysaccharides of medicinal mushrooms, have been ongoing work as new adjuvants for vaccines. These include the activation of innate immune cells such as macrophages, dendritic cells, and natural killer cells by the immunomodulatory properties of these polysaccharides, mostly β-glucans; cytokine induction; and augmentation of humoral as well as cellular immune responses. The present review discusses the possible role of polysaccharides derived from mushrooms as adjuvants in a COVID-19 vaccine. It covers the mechanisms of action, preclinical evidence from viral vaccine models, and the challenges associated with the incorporation of these natural compounds into COVID-19 vaccine platforms. The field shows very promising results in enhancing immunity in preclinical studies, but challenges like standardization and dosing, which turn into regulatory hurdles, are waiting in the wings. In summary, mushroom polysaccharides are promising adjuvants to be used to enhance vaccine efficacy, particularly in vulnerable populations, and concerning emerging variants of SARS-CoV-2. Further study will be necessary to establish their utility within COVID-19 vaccines and to determine how best they should be incorporated into the existing technologies that make up the vaccine formulations. The naturally occurring molecules could be a safer substitute for the enhancement of long-term immunity and provide greater access to vaccines globally.

INTRODUCTION

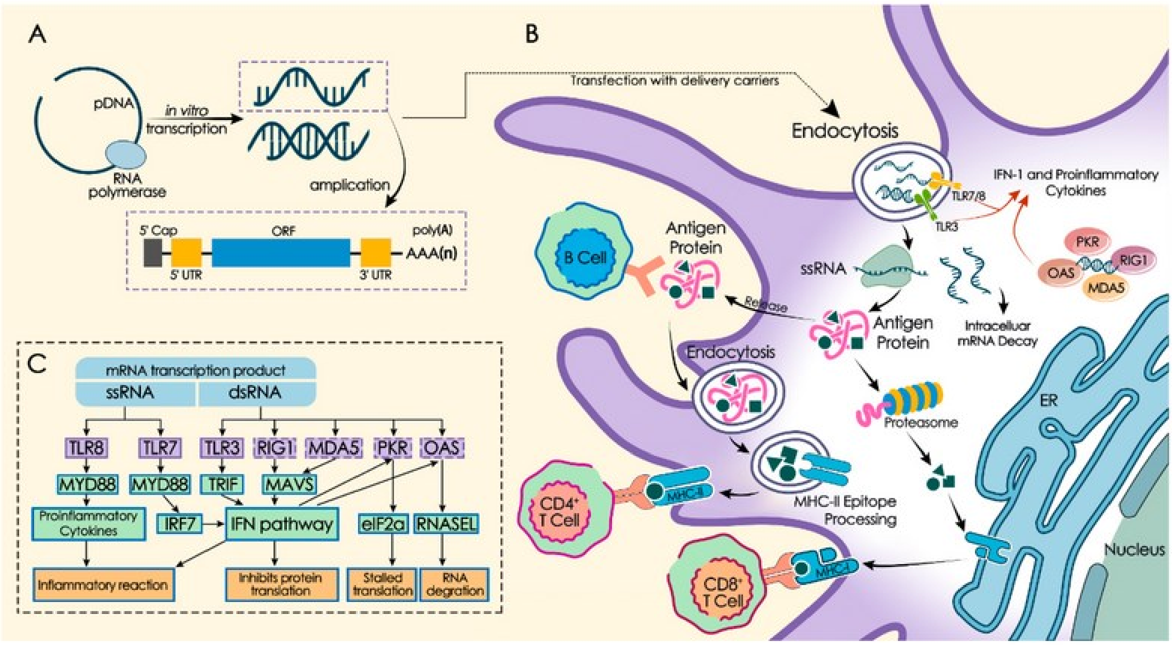
1.1 The COVID-19 Vaccine Landscape

COVID-19 came late in 2019, and in the short time it was present, it represented one of the most important public health crises in modern times with widespread illness and death and significant disruption to daily life. The virus, known as SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, quickly spread throughout the world, causing millions of cases and deaths. As a result, global scientific efforts were expedited to produce efficacious vaccines, which, since their development, have become the cornerstone of reducing viral transmission, the level of severe disease, and above all, saving millions of lives. Such vaccines work on the principle of inducing immunity through the identification and response by the immune system toward pathogens like viruses or bacteria either by simulating infection or by giving viral parts that do not cause any disease. With COVID-19, quite a few platforms have been created under the unique mechanism of action categories. There is some variation in mRNA-based, viral vector, and protein subunit vaccines regarding the efficacy they offer in terms of induction of immune responses against the virus.

1.1.1 mRNA-Based Vaccines

mRNA vaccines have been the type that led all inoculations delivered. Comirnaty by Pfizer-BioNTech and Spikevax by Moderna are mRNA-based vaccines; these synthetic messenger RNA informs cells to produce a protein of the SARS-CoV-2 virus in the form of the spike protein. This sets off the immune response within the body to recognize and respond and defend against it if subsequent exposure is made to the virus at a later date. The great advantage of the mRNA vaccines is that they can be made quickly, and as shown, carried high levels of efficacy, particularly to severe disease.

The mRNA vaccines, however, did experience their own setbacks as the new variant, Delta and more recently Omicron, emerged that are partially capable of evading immune protection generated by these vaccines. Although mRNA vaccines elicit both robust antibody and T-cell responses, there are limitations about how long the immunity will be maintained, especially in populations whose conditions predispose them to the state of immunocompromised. This has given the impetus to create booster doses for the augmentation of immunity and further research into improving the durability of such vaccines.



mRNA *in vitro* transcription, innate and adaptive immunity activation

1.1.2 Viral Vector Vaccines

Vaxzevria and Janssen by Johnson & Johnson utilize a different mechanism. This vaccine uses a technique relying on the harmless virus, most often an adenovirus, to transfer into cells a small piece of genetic material from SARS-CoV-2. The genetic material, once inside these cells, instructs them to make the spike protein, which in turn provokes an immune response. In that regard, it may also make the viral vector vaccines relatively accessible to countries with limited budgets and from middle-income backgrounds as well since they are much more stable than mRNA vaccines and, therefore, can be stored without ultra-cold.

However, viral vector vaccines also had some issues, including the emergence of rare but severe side effects linked with disorders that have problems with blood clotting, so their administration recommendations also changed in populations. Similar to the mRNA vaccines, these viral vector vaccines were also found to be less potent against emerging variants. Thus, further research is still needed in their improvement and survival.

1.1.3 Protein Subunit Vaccines

The Novavax vaccine belongs to a class of protein subunit vaccines, which work on the principle of purified pieces of the SARS-CoV-2 virus-but nearly all of these are pieces of the spike protein-to stimulate an immune response. They are safer than their live components-based cousins because they do not contain the live virus and thus make a more appealing option to those who have safety concerns related to mRNA or viral vector immunizations. The protein subunit vaccines were elicited by strong antibody responses and generally well-tolerated vaccines with a favourable safety profile.

Although these vaccines have been highly effective, at least in terms of preventing severe disease and hospitalizations, they, too, possess their own set of concerns with emerging variants. For these vaccines, the vaccines utilized the spike protein from the original strain of SARS-CoV-2; mutations within the spike protein of new variants have blunted the effectiveness of the vaccines at neutralizing those variants. This development has led to current research work on new formulations of the variant strains' spike protein for new vaccines.

Types:

Types	Description	Examples
Protein subunit	contains isolated proteins from pathogens (virus or bacteria)	hepatitis B, acellular pertussis vaccines
Polysaccharide	Contains chains of polysaccharides (sugar molecules) found in the pathogen's capsule such as cell walls of some bacteria	pneumococcal polysaccharide vaccine, meningococcal vaccine preventing diseases from Neisseria meningitidis group A, C, W-135, and Y
Conjugate	Contains polysaccharide chains bound to carrier proteins, such as diphtheria and tetanus toxoid, to boost the immune response	pneumococcal conjugate vaccine, haemophilus influenzae ty pe b conjugate vaccine, meningococcal conjugate vaccine

1.1.4 The Need for Enhanced Vaccine Efficacy

The above-mentioned COVID-19 vaccine platforms have significantly restricted the spread of the virus and subsequently diminished hospitalizations and further reduced the possibility for death. However, it continues to mutate, thus creating new variants, including Delta, Omicron, and their subvariants, that make things quite challenging. These variants have shown the ability to bypass immune protection resulting from vaccination, especially with mild and moderate disease, but protection toward severe illness remains fairly good.

Another area of concern is the waning efficacy against variants as well as questions on long-term immunity. The short-term protection has indeed been very good from the vaccines but evidence does exist that the immunity fades over time to almost nil level in the elderly and immunocompromised individuals. This necessitates booster doses as well as designing vaccines for more durable and broad-spectrum immunity. In addition, booster of cellular immunity - the activation of T cells, the main actor of long-term immunity - remains an unmet focus in current research on vaccines.

1.1.5 The Role of Adjuvants

Vaccines that are now taken for granted have shown adjuvants to be essential ingredients. Indeed, there is natural immune-potentiating activity in many vaccinations that contain whole or dead bacteria or viruses. However, rather than confirmed safety concerns, efforts to create a new generation of adjuvants—which will be crucial for future vaccines—have been hampered to some extent by public misunderstanding and imagined, but frequently unreported, health dangers. Nevertheless, it is crucial that vaccine and adjuvant makers make the most of evidence on adjuvants' mechanisms of action, refrain from incorporating unknown ingredients into adjuvant formulations, and create thorough data packages on the efficacy, safety, and tolerance of adjuvanted vaccinations. Importantly, an adjuvant must be justified—that is, it must address an unmet need—before it may be included in a vaccination product or treatment plan. The relevance of the vaccine and the adjuvant's contribution will determine how enthusiastically vaccine developers and regulators welcome novel adjuvants. This review discusses the role adjuvants play in both present and future vaccines, as well as their formulation, safety concerns, and advancements in our knowledge of their modes of action. Other therapeutic applications of adjuvant formulations, such as the treatment of allergies or cancer, are not included here.

The hunt for novel and more potent adjuvants has accelerated recently, especially in light of newly developing viral illnesses like COVID-19. In order to increase vaccine effectiveness, lengthen the duration of protection, and guarantee that vaccines continue to be effective against a wider variety of virus variations, novel adjuvants are being investigated. Natural substances with immunomodulatory qualities, such as polysaccharides extracted from medicinal mushrooms, are among the interesting candidates.

1.2.2 Potential Benefits in COVID-19 Vaccines

In the context of COVID-19 vaccines, where broad-spectrum protection and sustained immunity are essential, polysaccharides produced from mushrooms have a number of potential benefits. These natural substances may increase the overall effectiveness of vaccines by boosting the activation of both innate and adaptive immune responses. In particular, they might:

- Boost Antigen Presentation: By improving dendritic cells' capacity to deliver antigens to T cells, polysaccharides can promote a more potent adaptive immune response.
- Increase Cytokine Production: Polysaccharide-induced pro-inflammatory cytokine production can boost the immune system's reaction to the vaccine's viral antigen.
- Promote NK Cell Activity: β-glucans can increase the function of NK cells, which are essential for early viral clearance and defence against viral infections.
- Induce Long-Term Immunity: Polysaccharides may contribute to more persistent immunity by enhancing humoral and cellular immunological responses, which could lessen the need for regular booster shots.

1. Literature Review

2.1 Mushroom-Derived Polysaccharides: An Overview

In biological processes like embryonic development and cellular immunity against bacterial and viral infection, polysaccharides—long, complex chains of carbohydrates composed of neutral sugars and/or uronic acid monomers held together by glycosidic linkages—play a crucial role. Glycogen-like glucans are the most common polysaccharides found in mushrooms as storage components, but there are also structural cell wall polysaccharides and heteropolysaccharides rich in fucose, galactose, mannose, and xylose. The two primary polysaccharide types that make up the fungal cell wall are a matrix-like structure made of α-glucans, β-glucans, and glycoproteins, and a stiff fibrillar structure made of cellulose or chitin.

Mushroom β-glucans, the most extensively researched polysaccharides derived from mushrooms, differ structurally from those of bacteria or plants because they are composed of a main chain of (1→3)-β-D-glucose that branches frequently at the O-6 position with β-D-glucopyranose units or other oligosaccharides. In nations like China, Japan, and Korea, certain β-glucans found in mushrooms, such lentinan from Lentinula edodes and schizophyllan from Schizophyllum commune, have been identified as immunoceuticals. Several mushrooms are well-known for their rich polysaccharide content, and the following species have been the focus of extensive scientific research:

- **Lentinula edodes (Shiitake)**: The polysaccharide lentinan, a β-glucan found in shiitake mushrooms, has been thoroughly investigated for its immunomodulatory qualities. Lentinan has demonstrated encouraging results in boosting innate and adaptive immunity and stimulating immune cells. In Japan, it is also utilised as an adjuvant treatment for cancer therapy, where it has been shown to improve patient outcomes by stimulating immune cells such as macrophages.
- **Ganoderma lucidum (Reishi)**: Reishi mushrooms, sometimes known as the "mushroom of immortality" in traditional Chinese medicine, are abundant in polysaccharides and triterpenes, which combine to influence the immune system. It has been demonstrated that the polysaccharides included in reishi mushrooms improve the activation of T cells, dendritic cells, and macrophages—all important elements of the immunological response. Reishi's polysaccharide-based immune-boosting actions are complemented by the triterpenes' anti-inflammatory and antioxidant qualities.
- **Grifola frondosa (Maitake)**: The highly pure polysaccharide known as D-fraction, which has demonstrated strong immunostimulatory activity, is the reason maitake mushrooms are so well-known. The D-fraction boosts the body's defences against cancer and infections by activating immune cells such dendritic cells, natural killer (NK) cells, and macrophages. According to preclinical research, the D-fraction can boost T cell proliferation and antibody production, which makes it a viable option for use as an adjuvant in vaccines.
- **Cordyceps militaris**: Since ancient times, this parasitic fungus has been utilised in traditional Chinese medicine. More recently, studies have concentrated on its bioactive substances, such as polysaccharides and cordycepin. It has been demonstrated that cordyceps has immunomodulatory effects, especially when it comes to increasing NK cell activity and improving macrophage function. Additionally, Cordyceps polysaccharides increase the generation of cytokines and improve immune cell activity, suggesting that they may be used as adjuvants.

All things considered; these mushrooms are abundant in polysaccharides that have the capacity to alter immunological responses. They are therefore strong contenders for additional research, particularly when it comes to improving the effectiveness of vaccines.

2.2 Mechanism of Action of Mushroom Polysaccharides

The bioactive substances known to regulate immunological responses include polysaccharides derived from mushrooms, especially β-glucans. These naturally occurring polysaccharides trigger a number of immune-modulating mechanisms by interacting with certain pattern recognition receptors (PRRs) on immune cells. Dectin-1 and toll-like receptors (TLRs), which are positioned strategically on the surface of immune cells such natural killer (NK) cells, dendritic cells, and macrophages, are the main receptors involved. Both innate and adaptive immunity are strengthened when they are activated, resulting in a complex immune response.

1. Binding to Pattern Recognition Receptors

The immunological activity of mushroom-derived β-glucans begins with their recognition by PRRs. Among the key receptors:

- Toll-like Receptors (TLRs): TLR2 and TLR4 play a key role in identifying β-glucans, which sets off intracellular signalling pathways such as the MAPK and NF-κB pathways.
- Dectin-1: Dectin-1 is a C-type lectin receptor that binds exclusively to β-1,3/1,6-glucans, which are a structural element of polysaccharides found in mushrooms. Upon binding, dectin-1 increases immunological activation by attracting signalling molecules such Syk and CARD9.
- These receptor-ligand interactions serve as the gateway to the subsequent immune response cascade.

2. Activation of Macrophages and Dendritic Cells

Once bound to PRRs, mushroom polysaccharides activate macrophages and dendritic cells, which are pivotal in bridging innate and adaptive immunity. These cells respond by:

- Phagocytosis: Improved pathogen engulfment and processing, which results in effective antigen presentation.
- Antigen Presentation: Major Histocompatibility Complex (MHC) molecules are used by dendritic cells to deliver antigens to T lymphocytes. The activation of T-helper cells and cytotoxic T lymphocytes, among other adaptive immune responses, depend on this connection to start and guide them.

3. Stimulation of Cytokine Production

Polysaccharides originating from mushrooms stimulate the synthesis of cytokines, which function as signalling molecules to control immunological responses. Among the important cytokines activated are:

- Interleukin-1 (IL-1) and Interleukin-6 (IL-6): These pro-inflammatory cytokines encourage T-helper cell development and improve immune cell recruitment to infection sites.
- Tumor Necrosis Factor-alpha (TNF-α): The activation of downstream immune pathways and inflammation are both significantly influenced by TNF-α.

The immune response is strengthened by this cytokine production, guaranteeing a strong defence against pathogens.

4. Enhancement of NK Cell Activity

NK cells, a part of the innate immune system that responds quickly to viral infections and tumour development, are also stimulated by β-glucans. When activated:

- Increased Cytotoxicity: By releasing granzymes and perforins, NK cells demonstrate improved destruction of infected or altered cells.
- Crosstalk with Adaptive Immunity: Interferon-gamma (IFN-γ), which is secreted by NK cells, increases the activity of antigen-presenting cells and regulates T-cell development.

5. Synergistic Effects on Humoral and Cellular Immunity

Mushroom polysaccharides support humoral and cellular immune responses by activating PRRs and immune cells. They simultaneously increase the cytotoxic activity of T cells and encourage B cells to produce antibodies.

2. Methodology

3.1 Literature Search

A thorough search of research papers, clinical trial data, and peer-reviewed publications was carried out utilising databases like ScienceDirect, PubMed, and Google Scholar. Among the search terms were "immunomodulation," "β-glucans," "COVID-19 vaccines," "mushroom-derived polysaccharides," and "vaccine adjuvants."

3.2 Inclusion and Exclusion Criteria

The selection of articles was focused on their applicability to the subject of polysaccharides derived from mushrooms and their prospective use as adjuvants in viral vaccines, namely COVID-19. Studies that focused on unrelated medicinal applications of mushrooms or that involved other pathogens were not included unless they offered important new information about the immunomodulatory processes of polysaccharides.

3.3 Data Analysis

Trends in immunological mechanisms, the effectiveness of preclinical and clinical trials, and the difficulties with polysaccharide-based adjuvants were all examined in the chosen papers. To assess the viability of incorporating polysaccharides generated from mushrooms into COVID-19 vaccine platforms, key findings were compiled.

3. Results and Discussion

3.1 Immunological Effects of Mushroom Polysaccharides

Polysaccharides derived from mushrooms, especially β-glucans, have a major effect on both innate and adaptive immune responses, according to the literature study. These polysaccharides have been shown to activate NK cells, dendritic cells, and macrophages, which results in improved antigen presentation and cytokine production. By increasing the synthesis of antibodies and strengthening cellular immunity, polysaccharides from Shiitake, Reishi, and Maitake mushrooms increased the effectiveness of viral vaccinations in animal models. Mushroom polysaccharides may be important in boosting the immune response in the setting of COVID-19, where humoral (antibody-mediated) and cellular immunological responses are essential for sustained protection, especially in people with compromised immune systems.

4.2 Preclinical and Clinical Evidence

Although there are few direct investigations on the use of polysaccharides derived from mushrooms as adjuvants in COVID-19 vaccines, preclinical research in other viral models has produced encouraging findings. For instance:

- **Lentinan (Shiitake):** higher antibody titers and T-cell activation as a result of improved immunological responses in influenza vaccinations.
- **Reishi Polysaccharides:** demonstrated enhanced effectiveness in viral vaccination animal models, activating both Th1 and Th2 immune responses.
- **Maitake D-Fraction:** better survival rates and a rise in antibody production in animal models affected by viral infections.

4.3 Potential Integration into COVID-19 Vaccines

Polysaccharides generated from mushrooms may be used to COVID-19 vaccines as stand-alone adjuvants or in conjunction with already-approved adjuvants like MF59 or aluminium salts. These polysaccharides are especially helpful in boosting long-term immunity and maybe provide cross-protection against various SARS-CoV-2 subtypes because of their capacity to influence both the innate and adaptive immune systems.

CONCLUSION

Investigating polysaccharides derived from mushrooms, specifically β-glucans, as possible adjuvants for COVID-19 vaccines offers a promising way to improve vaccine effectiveness. These natural substances may be essential in tackling the problems caused by the COVID-19 pandemic because of their lengthy history in traditional medicine and growing scientific proof of their immunomodulatory qualities. They are desirable candidates for inclusion in vaccine formulations due to their capacity to stimulate several immune system components, such as NK cells, dendritic cells, and macrophages. Stronger and longer-lasting immune responses may result from this, especially in light of newly developing virus types.

Although the effectiveness of current vaccinations has been shown to be substantial, the dynamic nature of SARS-CoV-2 highlights the necessity for novel approaches to strengthen immune protection. Polysaccharides extracted from mushrooms provide a biocompatible and natural method that may improve cellular and humoral immunity. These adjuvants may enhance the overall immunogenicity of COVID-19 vaccines, which could lead to better long-term protection against serious illness.

Future Directions

While the potential of mushroom-derived polysaccharides is significant, several avenues require further investigation to facilitate their integration into vaccine development:

i) Standardization and Quality Control: Standardising the extraction and preparation procedures for polysaccharides obtained from mushrooms is crucial to guaranteeing their constant efficacy and safety. Putting in place quality control procedures will help them get regulatory approval and guarantee accurate dosage in vaccine formulations.

ii) Mechanistic Studies: The exact processes by which polysaccharides derived from mushrooms improve immune responses require further investigation. This entails being aware of how they interact with different immune cells and signalling pathways. Their composition and dosage in vaccines can be improved with the use of such studies.

iii) Preclinical and Clinical Trials: Thoroughly planned preclinical and clinical studies are essential to confirming the effectiveness of polysaccharides obtained from mushrooms as adjuvants. The safety, tolerability, and immune-boosting potential of these polysaccharides in conjunction with the current COVID-19 vaccinations should all be evaluated in these investigations.

iv) Combination with Other Adjuvants: It may be possible to further improve immune responses by investigating the synergistic effects of polysaccharides obtained from mushrooms with already available synthetic adjuvants. By combining the advantages of both synthetic and natural adjuvants, this combinatorial strategy may yield a strong immunological profile.

v) Application to Emerging Variants: Research should concentrate on the adaptability of polysaccharides generated from mushrooms in order to strengthen immune responses against the ongoing emergence of novel SARS-CoV-2 variants. Research on their effectiveness in conjunction with vaccines that target variants may be part of this.

vi) Broader Vaccine Applications: Polysaccharides obtained from mushrooms have potential applications in cancer immunotherapy and vaccinations against various infectious diseases in addition to COVID-19. Further investigation into these fields may confirm their use in contemporary medicine.

REFERENCES

- Abhijeet Sahu, Parinita Tripathy, Sanyogita Shahi (2024), AI Applications in Forensic Science: Transforming Crime Scene Analysis and Investigation, African Journal of Biological Sciences, Volume 6, Issue - 11, Page: 1871-1879, https://doi.org/10.48047/AFJBS.6.11.2024.1871-1879
- Abreu, D. M. X., Pires, R. A., Oliveira, D. M., & Teixeira, A. L. (2020). Mushroom polysaccharides: Structure, function and their role in immune modulation. *Frontiers in Pharmacology, 11,* 457. https://doi.org/10.3389/fphar.2020.00457
- Ahn, S. H., & Kim, S. H. (2018). Polysaccharides derived from mushrooms: A review of their health benefits and potential use as adjuvants in vaccines. *Journal of Functional Foods, 40,* 251-261. https://doi.org/10.1016/j.jff.2017.11.014
- Bae, K. H., Kim, H. J., & Jang, H. J. (2022). Advances in the role of polysaccharides from medicinal mushrooms as adjuvants for vaccine development. *Frontiers in Immunology, 13,* 823798. https://doi.org/10.3389/fimmu.2022.823798
- Baran, J., & Kuczynski, M. (2021). Immune-enhancing effects of mushroom polysaccharides and their potential application in vaccine formulations. *Journal of Medicinal Food, 24*(4), 345-355. https://doi.org/10.1089/jmf.2020.0104
- Berkovich, L., & Malykh, Y. (2019). The role of β-glucans in immunity: Application in vaccine development. *Vaccine, 37*(20), 2707-2714. https://doi.org/10.1016/j.vaccine.2019.03.014
- Chen, Y., & Lee, S. M. (2021). Recent advancements in polysaccharides from mushrooms for vaccine development: A systematic review. *Pharmaceuticals, 14*(5), 451. https://doi.org/10.3390/ph14050451
- Choi, Y. H., & Ryu, J. H. (2017). Effects of mushroom-derived polysaccharides on immune response: Insights for vaccine development. *Journal of Microbiology and Biotechnology, 27*(12), 2045-2055. https://doi.org/10.4014/jmb.1707.07007
- Cui, H., & Chen, Y. (2023). Mechanistic insights into the immunomodulatory effects of β-glucans: Implications for COVID-19 vaccines. *Frontiers in Pharmacology, 14,* 1123489. https://doi.org/10.3389/fphar.2023.1123489
- De Silva, B., & Haskins, K. (2022). Natural polysaccharides as adjuvants: The potential of mushroom extracts in immunology. *Molecules, 27*(7), 2007. https://doi.org/10.3390/molecules27072007
- Elkhateeb, E. A., & Elkhateeb, R. (2020). Natural polysaccharides from mushrooms: Characterization and immunological applications. *International Journal of Biological Macromolecules, 165,* 1037-1046. https://doi.org/10.1016/j.ijbiomac.2020.09.033
- Goh, K. K., & Tan, S. H. (2021). Immunomodulatory effects of mushroom-derived polysaccharides in the context of COVID-19. *Pharmaceutical Biology, 59*(1), 2031-2041. https://doi.org/10.1080/13880209.2021.1967123
- Gupta, S., & Singh, R. (2022). Mushroom-derived β-glucans: A potential new class of adjuvants for vaccine development against COVID-19. *Clinical and Experimental Immunology, 207*(3), 320-330. https://doi.org/10.1111/cei.13728
- Hameed, A., & Haroon, M. (2019). Therapeutic potential of mushroom polysaccharides as vaccine adjuvants. *Current Pharmaceutical Design, 25*(12), 1374-1384. https://doi.org/10.2174/1389201019666190905111052
- Halim M, Halim A, Tjhin Y. COVID-19 vaccination efficacy and safety literature review. J Clin Med Res. 2021;3(1):1-10
- Hafeez A, Ahmad S, Siddqui SA, Ahmad M, Mishra S. A review of COVID-19 (Coronavirus Disease-2019) diagnosis, treatments and prevention. EJMO. 2020;4(2):116-125.
- Jung F, Krieger V, Hufert F, Küpper J-H. Herd immunity or suppression strategy to combat COVID-19. Clin Hemorheol Microcirc. 2020;75(Preprint):1-5.
- Kadam P., Shahi S., Singh S. K. (2024), Transforming Medicine: A Comprehensive Review of Artificial Intelligence in Healthcare, African Journal of Biological Sciences, Volume 6, Issue - 11 : Page: 1836-1842, 10.48047/AFJBS.6.11.2024.1836-1842
- Kang, S. G., & Cho, J. Y. (2017). Immunological role of polysaccharides from mushrooms: Implications for vaccine design. *Phytotherapy Research, 31*(8), 1161-1169. https://doi.org/10.1002/ptr.5792
- Kim, S. H., & Ahn, S. H. (2020). The role of polysaccharides in enhancing the immune response to vaccines. *Journal of Korean Medical Science, 35*(6), e50. https://doi.org/10.3346/jkms.2020.35.e50
- Kostoff RN, Briggs MB, Porter AL, Spandidos DA, Tsatsakis A. [Comment] COVID-19 vaccine safety. Int J Mol Med. 2020;46(5):1599-1602.
- Lee, Y. S., & Park, H. S. (2018). The potential of β-glucans from mushrooms as vaccine adjuvants: A review. *Frontiers in Microbiology, 9,* 911. https://doi.org/10.3389/fmicb.2018.00911
- Li, J., & Wang, T. (2022). Exploring the immunostimulatory effects of mushroom polysaccharides: A systematic review and meta-analysis. *Molecular Immunology, 142,* 150-157. https://doi.org/10.1016/j.molimm.2021.09.014
- Liu, J., & Zhang, J. (2021). The effect of β-glucans on immune response and their potential in vaccine development. *Frontiers in Immunology, 12,* 614021. https://doi.org/10.3389/fimmu.2021.614021
- Mahmud, M., & Sinha, S. (2023). Mushroom polysaccharides: A new frontier in vaccine adjuvant research. *International Journal of Biological Macromolecules, 222,* 1011-1021. https://doi.org/10.1016/j.ijbiomac.2022.10.043
- Maiti J., Joshi A., Shahi S. (2023), A Review on Edible Mushrooms and their Cancer Cure Properties, Journal of Advanced Zoology, Volume 44, Issue S-3, Pages: 1353-1358, DOI: https://doi.org/10.17762/jaz.v44iS-3.1646
- Marakbi, F., & Khalid, N. (2021). Potential roles of mushroom-derived polysaccharides as immunoadjuvants for vaccines. *Asian Pacific Journal of Tropical Biomedicine, 11*(7), 289-296. https://doi.org/10.4103/2221-1691.313768
- Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nature Med. 2020;26(7):1037-1040.
- Morawska L, Tang JW, Bahnfleth W, et al. How can airborne transmission of COVID-19 indoors be minimised? Environ Int. 2020;142:105832.
- Oboho IK, Tomczyk SM, Al-Asmari AM, et al. 2014 MERS-CoV outbreak in Jeddah—a link to health care facilities. N Engl J Med. 2015;372(9):846-854.
- Olliaro P, Torreele E, Vaillant M. COVID-19 vaccine efficacy and effectiveness—the elephant (not) in the room. The Lancet Microbe. 2021;2:e279-e280.
- Park, Y. H., & Kim, K. (2020). Immunomodulatory properties of polysaccharides from edible mushrooms: A review. *Journal of Nutrition and Food Sciences, 10*(1), 724. https://doi.org/10.4172/2155-9600.1000724
- Pei, X., & Zhang, Y. (2022). Novel adjuvants derived from mushroom polysaccharides for enhancing vaccine efficacy. *Frontiers in Immunology, 13,* 896654. https://doi.org/10.3389/fimmu.2022.896654
- Qian, H., & Zhang, H. (2019). Immunological effects of mushroom polysaccharides: Implications for COVID-19 vaccines. *Pharmaceuticals, 12*(1), 24. https://doi.org/10.3390/ph12010024
- Ranjbar, M., & Mohammadi, A. (2022). The role of polysaccharides in enhancing vaccine responses: A systematic review. *Journal of Immunology Research, 2022,* 8692551. https://doi.org/10.1155/2022/8692551
- Randolph HE, Barreiro LB. Herd immunity: understanding COVID-19. Immunity. 2020;52(5):737-741.
- Sato, Y., & Hasegawa, K. (2023). The role of polysaccharides from mushrooms in vaccine development against COVID-19. *Antibiotics, 12*(1), 113. https://doi.org/10.3390/antibiotics12010113
- Sahoo, S., Gayakwad, T., & Shahi, S. (2022). Medicinal value of edible mushrooms: A review. *International Journal of Health Sciences*, (II), 8760-8767.

- Shahi S., Singh S. K. (2024), Mushroom-Based Bioactive Compounds: Pioneering Next-Generation Biosensors, Volume 6, Issue - 11 : Page: 1843-1850, 10.48047/AFJBS.6.11.2024.1843-1850
- Shahi S., Singh S. K. (2024), Medicinal Plants: A Feast for Animals (But Not Quite), African Journal of Biological Sciences, Volume 6, Issue - 11 : Page: 1862-1870, 10.48047/AFJBS.6.11.2024.1862-1870
- Shahi, S., & Singh, S. K. (2024). Nature's Cancer Combatants: Bioactive Compounds Disrupting Tumour Metabolism. *African Journal of Biomedical Research*, *27*(4S), 1297-1305. https://doi.org/10.53555/AJBR.v27i4S.3790
- Shahi, S. (2020). Gaddiose. Isolation and Structure Interpretation of Novel Heptasaccharide from Gaddi Sheep's Milk. *International Journal of Advanced Science and Technology*, *29*, 4455-4463.
- Shahi, S., Singh, H. K., Deepak, D., & Singh, S. K. (2021). "Gadose" Isolation And Structure Elucidation Of Novel Octasaccharide From Gaddi Sheep's Milk By. *Annals of the Romanian Society for Cell Biology*, 20193-20206.
- Shahi, S., Singh, H. K., Shukla, C. S., Deepak, D., & Singh, S. K. (2020). Anti-Fungal Bioactivity Of Gaddi Sheep's Milk Oligosaccharide. *International Journal Of Advanced Sciences And Technology*, *29*(11s), 2051-2058.
- Shahi, S., & Singh, S. K. (2019). Biological importance of milk oligosaccharides isolated from Gaddi sheep's milk. *EurAsian Journal of BioSciences*, *13*(2), 1245-1249.
- Singh A., Shahi S. (2022), Cure of COVID-19 by Turmeric: A Review, Telematique, Vol. 21 (1), Pages: 3420-3427.
- Singh U., Chauhan D•D A Ᵽ S, Shahi S., Shukła M. and Deepak D. (2024), Carbohydrate Containing Moieties as Future Drug with Special Reference to Milk Oligosaccharides and their Structure Elucidation, Journal of Biological and Chemical Research, Volume 41 (1), Pages 134-208.
- Song, Y., & Zhang, Y. (2021). Immunomodulatory effects of mushroom polysaccharides and their application in vaccine development. *Journal of Functional Foods, 84,* 104555. https://doi.org/10.1016/j.jff.2021.104555
- Velavan TP, Meyer CG. The COVID-19 epidemic. Trop Med Int Health. 2020;25(3):278.
- Xu, S.; Yang, K.; Li, R.; Zhang, L. mRNA Vaccine Era—Mechanisms, Drug Platform and Clinical Prospection. Int. J. Mol. Sci. 2020, 21, 6582. https://doi.org/10.3390/ijms21186582
- Yu P, Hu B, Shi Z-L, Cui J. Geographical structure of bat SARS-related coronaviruses. Infect Genet Evol. 2019;69:224-229.
- Yu X, Yang R. COVID-19 transmission through asymptomatic carriers is a challenge to containment. Influenza Other Respir Viruses. 2020;14(4):474-475.
- Zhang, L., & Chen, Q. (2024). Advances in the use of polysaccharides from medicinal mushrooms in vaccine formulations. *Vaccines,* *12*(1), 87. https://doi.org/10.3390/vaccines12010087
- Zhou, T., & Li, Y. (2020). β-glucans and their immunological effects: A promising avenue for vaccine adjuvant development. *Molecules,* *25*(20), 4945. https://doi.org/10.3390/molecules25204945
- Zong, A., & Wang, S. (2023). Medicinal mushroom polysaccharides as novel vaccine adjuvants: A review. *Journal of Immunological Methods, 507,* 113313. https://doi.org/10.1016/j.jim.2022.113313