

# CURRENT RESEARCH TOPICS IN PHARMACY: *Pharmacology Debates*

April 19th, 2023 10.00 AM ISTANBUL

FOR REGISTRATION:



**First Session- Moderator: Esra TATAR 10.00-11.30 AM**

Welcome- Prof. Hatice Kübra Elçioğlu  
Marmara University, Istanbul, Türkiye

The roles of cheminformatics in natural product-based drug discovery-Prof.Long Chiau Ming  
School of Medical and Life Sciences, Sunway University, Kuala Lumpur, Malaysia

Applications of machine learning to the lead discovery: Practical approaches – Dr.Said Moshawih  
Universiti Brunei Darussalam, Gadong, Brunei Darussalam

**Second Session – Moderator: Ayşe Nur HAZAR YAVUZ 12:00-13.30 PM**

Can Vitamin C supplements prevent premature rupture of membranes and preterm birth- Assist. Prof. Ana V. Pejčić  
University of Kragujevac, Kragujevac, Serbia

Drugs affecting newborn weight, length and head circumference at birth -Assist.Prof. Milos N. Milosavljevic  
University of Kragujevac, Kragujevac, Serbia

From traditional medicine to brain tumor therapy using Plectranthus diterpenes-Assoc.Prof.Patricia Rijo  
Lusofona University, Lisbon, Portugal

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Third Session- Moderator: Mehmet GÜMÜŞTAŞ 14.00-15.30 PM

Side effects of COVID 19 vaccines and the contribution of graphenes- Assoc.Prof.Beril Anılanmert  
Institute of Forensic Sciences and Legal Medicine, Istanbul University-Cerrahpaşa, Istanbul, Türkiye

Knowledge and behaviour of medical university students about drug store and use-Assist.Prof.Klodiola Dhano  
Aldent University, Tirana, Albania

The advancement of herbal-based treatments for hair loss- Dr.Oğuzhan Aydemir  
Istinye University, Istanbul, Türkiye

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# SIDE EFFECTS OF COVID VACCINES AND THE CONTRIBUTION OF GRAPHENE

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The safety of COVID-19 vaccines became a concern for the masses, after the increasing number of reports of serious cardiac and neurological complications as blood clotting, Bell's palsy, myocarditis, cerebral venous thrombosis, etc., following the administration of specific vaccines. Till February 2022, more than 130 million COVID 19 vaccine doses had been distributed in France. During the first year of vaccination: 128,766 adverse events (AE) were reported. ~40,000 AE reported per year for all drugs in the pre-pandemic years [1].

The majority of a COVID-19 vaccines, work by expressing spike in the cells by infecting the cells with an adenovirus carrying a spike gene (AstraZeneca and Janssen vaccines) or by transfecting them with a spike mRNA (Pfizer and Moderna vaccines) and finally spike is recognized by the immune system as an antigen, triggering an immune response to SARS-CoV-2. However, there are some negative consequences with this mechanism: Spike mediated cell-cell fusion occurs resulting with syncytia [2].TMPRSS2, TMEM16F, phosphatidylserine and cholesterol are the endogenous elements enhancing syncytia. Syncytia are formed by S on infected cells, via interacting with ACE2 on other cells. Antibodies against spike protein S1 have been shown to have a high affinity toward other human tissue proteins, leading to autoimmune tissue damage in susceptible individuals [3]. Inducing IFN1 repeatedly with mRNA vaccines, can lead to depression and cognitive slowing. IFN-I stimulates cytokine storm. Exposure to spike protein can occur by natural infection or in higher amounts by repeated mRNA vaccination [4]. The amount and duration of spike protein exposure, age, cellular autophagy, and activation, function and regulation of p53 affects the formation of neurodegeneration.

The fusion of endothelial cells among themselves or with other cells e.g. platelets, can result in thrombosis, while the fusion of neurons may lead to neurological complications [2]. CD16+ monocytes can generate spike protein for months after vaccination. Presence of mRNA given in stabilized form in the body or reverse

transcribed mRNA to DNA might be responsible for this phenomena [5]. Spike has been optimized as a less fusogenic form in some vaccines when compared with AstraZeneca [6]. The structure of the spike protein was slightly changed during manufacture through two mutations hindering a conformational change induced by binding to ACE2. This decreased cell fusion by several fold. So it is expected that the incidence of adverse effects would decrease. No manufacturer have yet mutated the S2' subunit, which includes the fusion peptide. Spike protein crosses the brain-endothelial cell barrier.

Inactive vaccines as Sinovac would have an intermediate frequency of adverse effects since spike proteins in inactivated viruses can also cause cell fusion and syncytia according to the amount of injected inactive viruses. However, the reported side effects are less than mRNA vaccines. Different nucleotide compositions of RNA in different brands of vaccines have been reported to influence the immunization and reactogenicity of the vaccines at different levels. Additional complications may appear if the dose is not adjusted according to the geriatric and pediatric groups, and pregnant regarding the fetus.

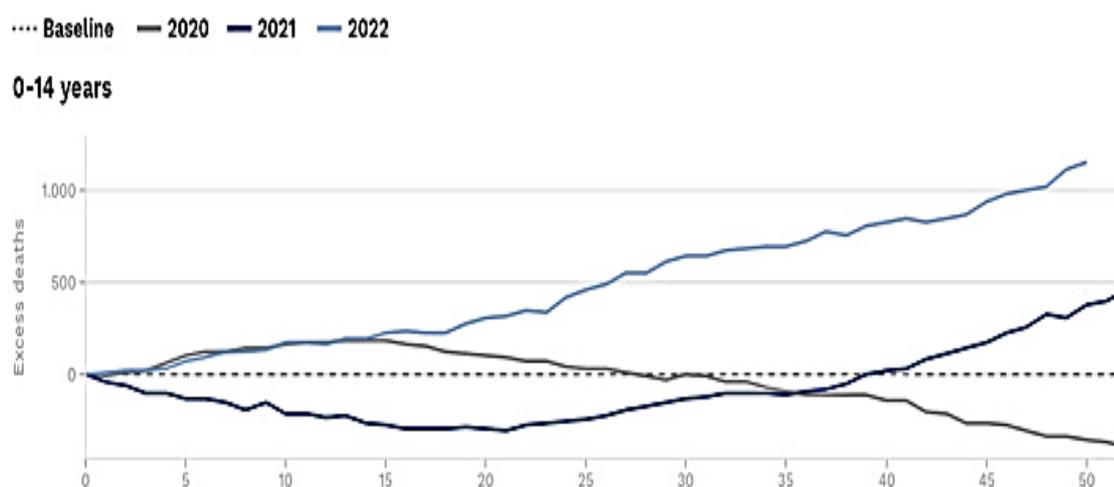
Since the mutations in the gene coding S protein, which is the basic leg of the vaccines lead to new variants [7], serious concerns exist about the reduction in the vaccine efficacy. However, the advantage of VLP as in Turkovac (Turkey) is that the immune responses are produced through some parts of the spike protein (S) and matrix (M), envelope (E), and nucleocapsid (N) proteins. In the studies on Turkovac, no anaphylaxis or any serious side effects were reported except one myocarditis case with a 55 year old individual who was performing heavy sports [8].

Severe side effects as myocarditis, pericarditis, thrombosis, thromboembolism, thrombocytopenia, anaphylaxis, which cause hesitation in the uninfected healthy community have emerged with mostly AstraZeneca and mRNA vaccines as Moderna and Pfizer. Lymphadenopathy, bleeding, arthritis, heartburn, decrease in memory brain fogging/reduced mental clarity/attention, vertigo-like symptoms, paralysis, incoordination, palpitations, heat/cold intolerance are among the symptoms associated with BNT162b2 mRNA vaccine. Since the end of 2021 and throughout 2022, young age excess mortality has substantially increased in many European countries along with the progressing vaccination activities [9]. More deaths were reported in England in 2021 among 15-29 years old individuals, compared with the average of 5 years before the coronavirus pandemic (Table 1). Higher rates of myocarditis and pericarditis were determined in comparison to the rates in unvaccinated individuals [10].

**Table 1.** The ratios of death from the diseases of the circulatory system [11].

Underlying cause of death	2021 Deaths	2021 % of total	2020 Deaths	2020 % of total	2019 Deaths	2019 % of total
All causes	2.125	56,5%	1.214	32,3%	321	8,5%
Diseases of the circulatory system	191	79,3%	44	18,3%	6	2,5%

The excess mortality in the age group 0–14 started to increase significantly after the second half of 2021 and the graph in Figure 1. Figure 1 was constructed with data from 27 participating European countries [9,12].



**Figure 1.** Graph showing the excess mortality in the age group 0–14 until week 2022–51, generated with data from 27 participating European countries [9].

Also, interestingly, regarding the 26 cases of Creutzfeldt-Jacob Disease (diagnosed in 2021), first symptoms emerged in a mean of 11.38 days after vaccination with Pfizer, Moderna, or AstraZeneca. By 2023, only 1 remained alive [3].

Lower peak oxygen-consumption percentage, reduction in the peak-exercise heart rate, and lower ventilation values were noted in the vaccinated individuals. 8-12% of vaccinated individuals with breakthrough infections may develop long COVID [13]. Long COVID is suggested to appear as an initial outburst of antibody production leading to the formation of autoantibodies which attack the body and damage cells. Brain fog, headaches, oscillations in blood pressure were reported.

The association between the COVID-19 vaccine and the development of autoimmune syndromes should be further investigated especially regarding Graves disease, autoimmune liver diseases, immune thrombocytopenic purpura, IgA nephropathy, autoimmune polyarthritis, systemic lupus erythematosus which were reported as the immunological side effects of vaccination [14].

Acute kidney injury was associated especially with Biontech, followed by Moderna and Janssen (ROR = 2.15, 95% confidence interval = 1.97, 2.36)

Pathologies have been demonstrated in animals: hepatitis and pulmonary eosinophilia, T<sub>H</sub>2-type immunopathology with eosinophils, pulmonary eosinophilia, eosinophil-associated T<sub>H</sub>2 immunopotential along with reinfection [16].

Due to the genetic diversity regarding populations, the complications of different vaccines among different populations should be investigated [17]. The prevalence of side effects was higher in overweight individuals (BMI>25) in the AZD-1222 and Covaxin vaccines.

Allergic reactions were reported by 12.7% of the Biontech vaccinees. The magnitude of COVID-19 vaccine adverse effects was comparatively higher in the existence of comorbid conditions. The current evidence suggests a lower frequency of side effects after Sinovac than the Pfizer and Astra-Zeneca vaccines.

The use of graphene has currently being searched for biomedical applications, as drug delivery, adjuvant for vaccines, etc. When chemically reduced, graphene oxide can create graphene which has been described as “the strongest, thinnest and most conductive material on the earth. It binds to peptides and antibodies, enzymes, metals and many molecules in the body including DNA. It is used in signal amplification for other purposes. Toxicities of graphene materials have been demonstrated on reproductive organs, lungs, liver, DNA (mutation), mitochondria, dermal fibroblast cells, T-lymphocytes, esophageal epithelium, renal epithelial cells, intestines (with the loss of microvilli), neurons, human erythrocytes, etc. They elevate ROS, induce immunotoxicity and cause pulmonary edema after injection. Graphene oxide is accumulated in different organs such as the lungs, liver, spleen, and bone marrow. Modified graphene oxide derivatives also used in DNA/RNA transfection, stabilizing RNA before transfection. Graphene derivatives pass through the fetus, studies on the blood-brain barrier.

A series of analyses using phase Contrast Microscopy, Dark Field and Bright Field Optical Microscopy, Transmission Electron Microscopy (TEM), and Energy-Dispersive X-ray spectroscopy (EDS) presented a list of evidence of toxic nano-metallic particles, graphene oxide structures, and parasites (*Tripanosoma kruzi*) in COVID-19 vaccines [18-20]. The investigations with EDS, showed the presence of reduced graphene oxide or graphene hydroxide in the samples along with the other undisclosed ingredients. Luisetti used Transmission Electron Microscopy (TEM)

Energy Dispersive Spectroscopy which gave the chemical nature of the observed micro and nano particulates and their morphology, an organic-inorganic aggregate was identified [19,20].

It is established with some literature studies that mRNA can copy itself to host DNA via endogenous reverse transcriptase [21,22]. This may lead to changes in the DNA and transgenetic effects. It may not do it at the first shot in every individual. To increase the possibility, the vaccines carrying the genetic material RNA should be injected more than one.

DNA can be transferred from vaccinated to unvaccinated: Mother to infant while feeding; mother to fetus; between married partners. We don't know the severity and incidence of these adverse events in the long term, and these types of vaccines should be evaluated more in terms of toxicity and the medical rule that «there is no disease there is patient». We suggest that the most important first step is the natural immunity that must be focused on and supported.

It is not certain or an estimated result that everyone will catch COVID 19 in the pandemic period, however it is certain that mass vaccination has been applied to individuals without knowing if they would catch COVID 19. In most of the literature studies, the vaccinated people were compared with the infected ones who were registered to a hospital. What about the people who were not infected because of working/living in isolated conditions with necessary precautions, or the ones who were mildly infected but not registered and healed on foot? Regardless of this foresight, we cannot comment as if all unvaccinated individuals will be infected with COVID 19 and has more risk of developing myocarditis than vaccinated. So new studies are needed with different universes as “vaccinated” and “unvaccinated” to be statistically evaluated. At that time the results will probably reverse.

**Keywords:** Vaccination for coronavirus infection; Side effects of COVID-19 vaccine; Adverse events; Graphene oxide toxicity; mRNA/vector/VLP based technologies

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