Polyethylene glycol (PEG): The nature, immunogenicity, and role in the hypersensitivity of PEGylated products

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Abstract

Polyethylene glycol (PEG) is a versatile polymer that is widely used as an additive in foods and cosmetics, and as a carrier in PEGylated therapeutics. Even though PEG is thought to be less immunogenic, or perhaps even non-immunogenic, with a variety of physicochemical properties, there is mounting evidence that PEG causes immunogenic responses when conjugated with other materials such as proteins and nanocarriers. Under these conditions, PEG with other materials can result in the production of anti-PEG antibodies after administration. The antibodies that are induced seem to have a deleterious impact on the therapeutic efficacy of subsequently administered PEGylated formulations. In addition, hypersensitivity to PEGylated formulations could be a significant barrier to the utility of PEGylated products. Several reports have linked the presence of anti-PEG antibodies to incidences of complement activation-related pseudoallergy (CARPA) following the administration of PEGylated formulations. The use of COVID-19 mRNA vaccines, which are composed mainly of PEGylated lipid nanoparticles (LNPs), has recently gained wide acceptance, although many cases of post-vaccination hypersensitivity have been documented. Therefore, our review focuses not only on the importance of PEGs and its great role in improving the therapeutic efficacy of various medications, but also on the hypersensitivity reactions attributed to the use of PEGylated products that include PEG-based mRNA COVID-19 vaccines.

Key words:

Polyethylene glycol (PEG); anti-PEG antibodies; Hypersensitivity; COVID-19 mRNA vaccines; complement activation-related pseudoallergy (CARPA)

1. Introduction

Polyethylene glycol (PEG) is a synthesized polymer that is widely used in many industries and pharmaceutical formulations due to its well established safety and versatile physicochemical properties [1]. It is noteworthy that PEGs and their derivatives are widely employed in pharmaceutical products as a component, in non-pharmaceutical products as additives [2], and in cosmetics as emulsifiers, lubricants and humectants [3, 4]. PEGs were first used as a lubricant for medical equipment in the 1950s, and they have since been used as anti-freeze agents, food additives, and as a vehicle to carry additives in tablets and in dermatological formulations [3, 5]. PEGs with a high molecular weight are usually used in cosmetics as skin conditioners, surfactants, and as a cleansing agent, in addition to use in other topical preparations such as hair-care products, lotions, creams, lipsticks, and toothpaste [6]. PEGs are also used as a suppository base due to approved hydrophilicity, which allows rapid miscibility with rectal mucosal fluids and a rapid release of drug molecules [7]. PEG 400 is used as a co-solvent in the preparation of Nifedipine soft gelatine capsules to improve oral absorption [8]. In addition, Abuchowski and colleagues pioneered the use of PEGs in the delivery of proteins in a technique known as PEGylation [9]. PEGylation is considered a breakthrough in the field of drug delivery with dozens of applications. PEGylation enhances the biological half-lives of biopharmaceuticals while reducing toxicity and improving stability [10, 11]. Despite the great importance of PEGylation, several limitations have been connected to the use of PEGylation in pharmaceutical formulations; there is growing evidence of the immunogenicity of PEG when conjugated with large molecules such as proteins, and when used as nanocarriers for liposomes and other drug molecules [11-13].

Over the past few decades, PEG has been considered a non-immunogenic molecule that can be safely used as an excipient in medications, cosmetics, and as a food additive [12, 14]. Recently, however, a growing number of reports have suggested that PEG is an immunogenic molecule; therefore, care should be taken when these molecules are used in pharmaceutical formulations, particularly with proteins, lipid nanoparticles, and liposomes [15, 16]. Anti-PEG antibodies could compromise the therapeutic efficacy of subsequently administered PEGylated products both in patients who have received PEGylated products and in healthy individuals. These antibodies tend to affect the distribution and enhance the clearance of PEGylated products, which is the so-called accelerated blood clearance (ABC) phenomenon [17]. Our group and

others have demonstrated how the first dose of PEGylated products could enhance the clearance of a second dose injected between 5 and 7 days later, which in turn affects the therapeutic efficacy of administered PEGylated products [18-21]. Unfortunately, these antibodies not only affect the therapeutic efficacy of PEGylated products but also cause immediate hypersensitivity reactions upon administration of PEGylated products. The PEGylated liposomal formulation doxorubicin (Doxil®) is known to cause immediate hypersensitivity reactions that cannot be explained based on the conventional hypothesis of IgE-mediated type I hypersensitivity. Szebeni *et al.* suggested a rationale and supplied empirical evidence for the concept that these responses represent a novel type of drug-induced hypersensitivity, which is referred to as complement activated-related pseudoallergy (CARPA) [22]. Also, several cases of hypersensitivity have been reported following the use of Oncaspar® (Pegaspargase), which is PEGylated L-asparaginase that has been approved for the treatment of Acute Lymphoblastic Leukemia (ALL). Reports of hypersensitivity reactions to Oncaspar® have also been attributed to anti-PEG antibodies that develop CARPA [23-25].

Due to the rapid spread of the recent COVID-19 pandemic, public health officials now look to the development of treatments or vaccines to limit the spread of diseases. Pharmaceutical companies successfully developed mRNA vaccines such as Pfizer/BioNTech (BNT162b2) [26] and Moderna (mRNA-1273) [27] COVID-19, which can help in limiting the spread of COVID-19, decrease the symptoms, and decrease the mortality rate [28-30]. Unfortunately, despite the success and approved efficacy of the mRNA COVID-19 vaccines, cases of allergies to these vaccines have been reported [31-33]. Thus far, the main causes and exact mechanisms of hypersensitivity to mRNA COVID-19 vaccines have not been fully elucidated, but reports of hypersensitivity reactions have focused on the role of the PEG polymer that is used in the preparation of these vaccines [34-37]. These reports studied the previous history of these cases and pointed out that all these cases received PEG-containing medications such as Depo-Provera, esomeprazole, Naproxen, or osmotic laxative. The formulations resemble shaving foam with low and high molecular weights of PEG and PEG-containing cosmetics [31, 32, 35]. Accordingly, in this review we have attempted to provide insight into the importance of the use of PEG in various areas of life including therapeutic and non-therapeutic applications. In addition, we explain the potential role of PEG in the reports of the immunogenicity and hypersensitivity that has been encountered post-mRNA COVID-19 vaccination.

2. Polyethylene glycols (PEGs)

2.1. PEG properties

PEG, also known as polyoxyethylene (POE) or polyethylene oxide (PEO), is a bio-inert, biocompatible polymer. It is a synthetic hydrophilic polymer composed of repeated units of ethylene oxide, as illustrated in **Figure 1**. Macrogol, Polikol, Polygol, Polyox, Polyoxirane, poly(oxy-1,2-ethanediyl), and Carbowax^{TM} are some of the PEG-based compounds on the market. PEGs are classified using two nomenclature systems: one is based on the Chemical Abstract Service (CAS), and the other is based on the Cosmetics, Toiletry and Fragrance Association (CTFA)/International Nomenclature Cosmetic Ingredients (INCI). In cosmetics, the suffix number to PEG denotes the number of repeating oxyethylene units; for example, PEG 50 denotes the presence of 50 oxyethylene subunits in this particular PEG polymer [6, 38]. PEG 50 is widely used in pharmaceutical applications due to its aqueous solubility, biocompatibility, and safety [39]. The amphiphilic nature of PEGs makes them soluble in a wide range of organic solvents, including chloroform, ethanol, acetonitrile, and acetone in addition to a high level of water solubility [10]. PEGs are thermally stable and electrically neutral at different levels of pH, and they have highly active multifunctional terminal groups. The terminal hydroxyl group (-OH) can bind with different molecules through covalent or hydrogen bonding interaction. For example, PEG-Intron®, a mono-PEGylated INF-α_2b, is synthesized using a succinimidyl carbonate PEG reagent (12-kDa mPEG SC). The mPEG SC reagent forms a covalent carbamate and/or urethane linker with amine groups on the protein [40]. Also, every molecule of PEG 3,350 has the ability to attach to 100 molecules of water through hydrogen bonding [41]. Therefore, PEG polymer is widely used as a hydrophobic drug carrier to promote aqueous solubility and dissolution. In addition, the terminal end of PEGs has a great ability to attach to various bioactive functional groups for a variety of applications [42].

PEGs can be synthesized in a wide range of molecular weights with a variety of properties. Commercially available PEGs have molecular weights ranging from 200 to 35,000 Da and come in a variety of forms and degrees of branching [43]. Low molecular weight PEGs are usually synthesized through the addition of an ethylene oxide subunit together with hydroxyl group donors such as water or any diols in the presence of alkaline catalysts. High molecular weight PEGs, on the other hand, are usually prepared using suspension polymerization in order to achieve large-scale production. They also can be prepared through the anionic polymerization of

ethylene oxide in an inert solvent or through anionic ring-opening polymerization of epoxides [44, 45]. According to their degree of polymerization and molecular weights, PEGs have distinct states and melting temperatures. PEGs with low molecular weights (100-700 Da) are viscous, colorless liquids, while those with molecular weights that range from 1,000 to 2,000 Da are soft solids, and those with higher molecular weights (>2,000 Da) are solid, waxy, and white in color, with melting points proportional to their molecular weights [46, 47]. Penetration of PEG molecules depends mainly on their molecular weight, except in the case of compromised skin, which PEG molecules can penetrate irrespective of their molecular weight — as in the case of burns [48]. Poor penetration of PEGs could be attributed to their hydrophilicity [49]. On the other hand, PEG derivatives can be used as penetration enhancers. For example, PEG stearate has a low molecular weight that enhances the penetration of other drug molecules by decreasing the skin surface tension and conditioning the stratum corneum [4].

2.2. Pharmacokinetics and the fate of PEG in the body

The gastrointestinal absorption and skin penetration of PEG molecules depends mainly on their molecular weight. Chadwick *et al.* reported that PEG 400 is well absorbed from the gastrointestinal tract after oral administration and half of administered doses is excreted mainly through the kidney within 24 h in humans [50]. PEGs are believed to be barely absorbed via intact skin, however, and studies have shown that those with higher molecular weights (4,000 Da or more) may not be absorbed at all [51]. On the other hand, as observed by Herold *et al.* [48] and Tsai *et al.* [52], the presence of injury or damage in the epidermal layers may accelerate the penetration of PEG molecules regardless of their molecular weight. After reaching systemic circulation, PEG is metabolized via slow oxidation of their hydroxyl group to form carboxylic acid, diacids, and hydroxy acid metabolites, which are catalysed by the alcohol dehydrogenase enzyme [53] and some other oxidase enzymes such as cytochrome P-450 [54]. PEG molecules (20,000 Da) are excreted mainly via the renal route, whereas PEGs with molecular weights between 20,000-50,000 Da are primarily excreted via the biliary route rather than the renal route, while PEG with molecular weights larger than 50,000 Da are primarily engulfed by liver macrophages [55, 56].

2.3. Pharmaceutical applications of PEGs

2.3.1. Solubility enhancing agent

Drugs with poor aqueous solubility exhibit poor bioavailability, particularly drugs belonging to biopharmaceutical classification system (BCS) classes 2 and 4 [57]. PEGs are employed as a solubility enhancer because of their strong polarity and solubility in a variety of aqueous and organic solvents, which allows them to interact more effectively with hydrophobic drug molecules [58]. In parenteral and oral preparations, liquid PEGs (up to 1,000 Da) are commonly utilized as water-miscible solubilizing agents. In parenteral and oral preparations, liquid PEGs (up to 1,000 Da) are commonly utilized as water-miscible solubilizing agents. PEGs with high molecular weight (1,000-6,000 Da) are mostly employed to improve the aqueous solubility of microencapsulated hydrophobic medicines where solubilization occurs at higher concentrations than the critical micelle concentration (CMC) of PEG derivatives. Paclitaxel is a potent chemotherapeutic agent that has been approved by the Food and Drug Administration (FDA) for breast and ovarian cancer treatment. PEGylation of Paclitaxel improves its water solubility, and this reflects its liposomal encapsulation efficiency and physical stability. Also, the bioavailability of PEGylated paclitaxel was 3.9-fold higher than conventional non-PEGylated paclitaxel. The increased bioavailability of PEGylated paclitaxel might have resulted from the physicochemical properties of the PEGylated paclitaxel, which is a water-soluble compound and can easily permeate through the gastrointestinal mucosa than non-PEGylated paclitaxel which leads to increase the concentration of paclitaxel in the plasma and subsequently improve the bioavailability than the parent drug [59].

2.3.2. Drug passive targeting

Uneven biodistribution of pharmaceuticals as well as their rapid clearance represent the main challenges in systemic drug administration, which can be alleviated by PEGylation. PEGylation is used to cover the drug surface with a protective hydrophilic coat, which results in an increase in drug particle size, reducing its glomerular filtration. Furthermore, the PEG coat protects drug molecules from enzymes and plasma protein adsorption, resulting in improved in vivo stability and extended circulation time, allowing for enhanced passive drug targeting [60]. The effect of PEGylation on the formulation's stability and passive drug targeting is summarized in **Figure 2**.

PEGylation is thought to be a useful approach for delivering anti-cancer drugs encapsulated in nanocarrier systems. PEGylation is a procedure that involves covalently grafting PEG chains onto the surfaces of other molecules to form nanocarrier systems. PEGylation is

known to improve the stability and plasma half-life of various medications [61, 62]. PEGylation is suggested to prolong the half-life of drug plasma by reducing the protein opsonin adsorption on the surface of nanocarrier systems, which prevents their uptake by the cells of the mononuclear phagocyte system (MPS) (the Stealth effect) [10, 63]. The potential of long-circulating PEGylated nanocarrier systems to pass through leaky blood vessels and accumulate within tumors via enhanced permeability and retention (EPR) [64, 65] is the proposed mechanism for passive drug targeting of tumors [66].

Fukuda *et al.* reported that PEGylated liposomes of doxorubicin (Doxil®) improved the pharmacokinetics and minimized the toxicity of doxorubicin by improving the biodistribution and enhancing the accumulation of doxorubicin in tumor tissues. They also reported, however, that although the use of non-PEGylated liposomes of doxorubicin, as Myocet®, reduced doxorubicin cardiotoxicity and gastrotoxicity; the drug was released more rapidly and had a short plasma circulation time [67]. Park *et al.* reported that encapsulation of doxorubicin into PEGylated nanoparticles maximized therapeutic efficacy while decreasing dose-related cardiotoxicity, and found that using PEG to make nanoparticles allowed for effective and safe doxorubicin administration [68]. Also, a report by O'Shaughnessy *et al.* associated a formulation of doxorubicin in the form of a PEGylated liposomal system with increasing the therapeutic index of conventional doxorubicin. They have also reported that PEGylated liposomal doxorubicin improves drug targeting efficacy without many of the side effects usually reported with the use of conventional doxorubicin therapy such as nausea, vomiting, alopecia, myelosuppression, and cardiac toxicity [69]. In the same manner, Safara *et al.* reported that Doxil® can reduce the risk of cardiomyopathy incidence in patients with solid tumors compared with those receiving free doxorubicin [70]

Some medications' short plasma half-lives may limit their therapeutic use. The cells of MPS are capable of engulfing hydrophobic materials, liposomes, peptides, and genes from systemic circulation [71]. The physicochemical features of drug molecules, such as particle size, hydrophilicity, and surface charge have a significant impact on the recognition of drug molecules by MPS and subsequently on the fate of drug molecules in the body [72, 73]. PEGylation could reduce the clearance of drug molecules by increasing the particle size and preventing the interaction with MPS cells.

The first approved application for the PEGylation method was ADAGEN® (pegademase bovine), which was first approved by the FDA in 1990 for treating severe combined immunodeficiency disease [74]. Doxil® also can ensure effective drug distribution with reduced toxicity [75, 76]. PEGylation of peptides, such as Pegasys® (peginterferon alfa-2a), a clinically approved PEGylated protein for the treatment of hepatitis B and C [40, 77], can also help protect peptides against enzyme hydrolysis, which improves the therapeutic results and stability of particular peptides. In the same manner, in 2004 Macugen® was the first approved PEGylated aptamer for the treatment of neovascular age-related macular degeneration [78]. Examples of clinically approved PEGylated products on the market with improved pharmacokinetics are summarized in **Table 1**.

Table 1. Examples of clinically approved PEGylated products

Marketed product	PEGylated entity	Type of PEG	Half-life Before PEGylation	Half-life After PEGylation	Therapeutic use	Year	Ref.
Adagen®	Adenosine deaminase	5 kDa PEG	11-22 h	72-144 h	Severe Combined Immunodeficiency Disease (SCID)	1990	[79]
Doxil®	PEGylated liposomal Doxorubicin	2 kDa PEG	17.3 h	69.3 h	Ovarian cancer, Breast cancer, Kaposi's sarcoma	1995	[80]
PEG-Intron®	Interferon-alfa-2b	12 kDa PEG	12 h	48-72 h	hepatitis C	2001	[81]
Pegasys®	Interferon-alfa-2a	40 kDa bis-monomethoxy PEG	3-8 h	65 h	Hepatitis C	2002	[82]
Somavert®	Human growth hormone	5 kDa PEG	24-36 h	144 h	Acromegaly	2003	[83]
Macugen®	Anti-Vascular endothelial growth factor (anti-VEGF)	40 kDa mPEG	9 h	240 h	Age-related muscular degeneration	2004	[84]
Mircera®	Erythropoietin	30 kDa Methoxy polyethylene glycol	7-20 h	134-139 h	Anaemia related to kidney disorders	2007	[85, 86]
Cimzia®	Anti-tumor necrosis factor antibody	20 kDa PEG	4.6 h	313 h	Rheumatoid arthritis	2008	[87]
Krystexxa®	Recombinant uricase	10 kDa mPEG	4 h	154-331 h	Chronic gout	2010	[88]
Rebinyn®	Recombinant coagulation factor lX	40 kDa PEG	19.34 h	92.76 h	Haemophilia B	2017	[89]

Jivi®	Recombinant antihemophilic factor VIII	30 kDa PEG	13 h	17-21 h	Haemophilia A	2017	[90]
Asparlas®	L-asparaginase	31-93* 5 kDa	31.2 h	384 h	Leukemia	2018	[91, 92]
Palynziq®	Recombinant phenylalanine ammonia lyase	20 kDa PEG	21 h	60 h	Phenylketonuria	2018	[93]
Esperoct®	Recombinant antihemophilic factor VIII	40 kDa PEG	11.8 h	17-22 h	Haemophilia A	2019	[94]
Ziextenzo®	Granulocyte colony stimulating factor (G-CSF)	20 kDa PEG	3-4 h	15-80 h	Infection during chemotherapy	2019	[95]
Udenyca®	G-CSF	20 kDa PEG	3-4 h	15-80 h	Neutropenia	2019	[96]
Nyvepria®	G-CSF	20 kDa PEG	3-4 h	15-80 h	Neutropenia associated chemotherapy	2020	[97]
Besremi®	Interferon	40 kDa PEG	2-3 h	60-70 h	Polycythaemia vera	2021	[98, 99]
Skytrofa®	Human growth hormone	40 kDa PEG	2-4 h	25 h	Growth hormone deficiency	2021	[100]
Empaveli®	Pentadecapeptide	40 kDa PEG	4 h	192 h	Paroxysmal Nocturnal Hemoglobinuria (PNH)	2021	[101]

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2.4. Immunogenicity of PEGs

2.4.1. Immunogenicity of free PEG

Many studies have been published concerning how the immunogenicity of PEGs could jeopardize the efficacy and safety of PEGylated products [102, 103]. Over the past few decades PEG has generally been recognized as safe and as such is commonly used as a food additive and in pharmaceutical formulations. However, much recent evidence has suggested the presence of pre-existing anti-PEG antibodies in healthy people [104-106]. Anti-PEG antibodies have been found in the blood of about 25% of healthy blood donors, as reported by Garay *et al.* [14]. Similarly, Yang *et al.* reported that substantial levels of anti-PEG antibodies were found in a large percentage of people (> 42%) who had never received PEGylated pharmaceuticals [107].

The presence of anti-PEG antibodies in individuals who never received PEGylated pharmaceuticals may be attributed to their frequent usage of PEG-containing products such as in cosmetics where PEG is a commonly used ingredient. Yang and Lai have also provided a possible explanation for the occurrence of anti-PEG antibodies in healthy people, claiming that any irritation, injury, or abrasion in the skin triggers local inflammatory reactions. Upon frequent use of commonly used cleaning or cosmetic products containing PEG molecules, these molecules can penetrate a site of inflammation and come into contact with inflammatory cells, which would trigger the formation of anti-PEG antibodies [107]. In the same manner, Jakasa *et al.* reported that depending on their molecular weight, PEGs could penetrate the stratum corneum and reach systemic circulation. They also reported that the condition of the skin may represent a critical factor in determining PEG skin permeability. The presence of any defect in the skin barrier, as in the case of atopic dermatitis (AD), could enhance the penetration of PEG molecules of different molecular weights. They also reported that the permeation coefficient of PEG molecules was doubled in cases of compromised skin compared with the rate for normally intact skin [108].

2.4.2. Immunogenicity of PEGylated products

Immunogenicity can be induced not only by free PEG molecules but also by PEGylated products. Numerous researchers have observed rapid clearances of a second dose of PEGylated products compared with the first doses when those products were repeatedly injected within one week [17, 19]. This effect is attributed to the formation of anti-PEG antibodies upon administration of a first dose of PEGylated products [109]. Immunogenicity of PEGylated

products was first described by Richter and Akerblom in 1983, when they found that anti-PEG antibodies could develop in rabbits following the intramuscular or subcutaneous administration of various PEG-modified proteins in Complete Freund's Adjuvant [110]. Our research group previously reported that intravenous administration of PEGylated liposome induces anti-PEG IgM production in both rats and mice [111]. We found that PEGylated liposomes act as T-cell independent antigens during anti-PEG antibody production [103]. We also observed that intravenous administration of PEGylated ovalbumin (OVA) or PEGylated bovine serum albumin (BSA) elicited anti-PEG antibodies similar to PEGylated liposomes [112]. Recently, several reports have described the effect of pre-existing or induced anti-PEG antibodies in humans and the effect this exerts on the therapeutic efficacy of PEGylated products in patients [113-116].

2.5. Accelerated blood clearance (ABC) of PEGylated products

The ABC phenomenon was introduced by Dams *et al.* in 2000. With ABC the first dose of PEGylated liposomes injected into rhesus monkeys or rats led to the enhanced clearance of a second dose of PEGylated liposomes injected within one week [19]. This phenomenon may limit the use of different types of PEGylated products in the future because the treatment with PEGylated products, which would induce anti-PEG antibodies, might affect the clearance as well as the therapeutic efficacy of subsequently administered PEGylated products.

Our research group has reported that an intravenous (i.v.) injection of PEGylated liposomes enhances the clearance of a second dose injected a few days later [20]. We gave a tentative explanation for this ABC phenomenon (**Figure 3**), where the initial dosage of PEGylated liposomes primes the immune system to produce anti-PEG IgM, which selectively interacts with PEG molecules in the second dose of PEGylated liposomes, and results in a complement activation and increased engulfment of the second dose of PEGylated liposomes by Kupffer cells in the liver [117, 118]. We recently reported that i.v. injection of PEGylated lipid nanoparticles (LNP) induces the production of anti-PEG IgM, which then triggers the ABC phenomenon [119]. We also reported that the anti-PEG IgM induced either by i.v. injection of PEGylated OVA or by the subcutaneous (s.c.) administration of Pegasys® effectively enhances the rapid clearance of subsequent Pegasys® doses [21]. We also found a similar phenomenon with repeated doses of pegfilgrastim (PEG-G-CSF), a clinically approved treatment for neutropenia [120]. Similarly, we found that i.v. injection of PEGylated exosomes induces the

production of anti-PEG IgM, which enhances the clearance of a second dosage of PEGylated exosomes or PEGylated liposomes administered via i.v. a few days after the initial dose [121].

Furthermore, anti-PEG antibodies may compromise the therapeutic efficacy of PEGylated therapeutics and/or develop undesirable adverse drug reactions. Pre-existing anti-PEG antibodies are known to enhance the clearance of an initial dose of PEGylated products, which may negatively affect the therapeutic efficacy of these drugs. We previously reported that pre-existing anti-PEG antibodies affect the i*n vivo* fate of PEGylated liposomes. We found that pre-existing anti-PEG IgM induced via the intraperitoneal inoculation of anti-PEG IgM-producing hybridoma cells (HIK-M09 and HIK-M11) decreases the tumor accumulation level of subsequently administered PEGylated liposomes and accelerates liposome clearance by enhancing its accumulation in the liver and spleen [122]. Similarly, Hsieh *et al.* reported that pre-existing anti-PEG antibodies alter the pharmacokinetics and decrease the tumor accumulation and therapeutic efficacy of LipoDox. They reported that the therapeutic efficacy of LipoDox was significantly diminished in a mouse model bearing anti-PEG antibodies compared with a naïve model [104]. Other research groups have reported that these antibodies may be a potential source of hypersensitive reactions following the administration of PEGylated therapeutics [13, 17, 123].

3. Toxicity of PEG in PEGylated products

Although PEG and its derivatives are considered inert and almost non-toxic molecules, some safety-related problems of free PEG or PEG conjugated with nanoparticles and proteins with different molecular weights have been noticed by some researchers. Smyth *et al.* reported a case of chronic oral toxicity in rats upon oral administration of PEG oligomer with a low molecular weight [124]. In the same manner, undesirable toxicity has been reported in monkeys [125]. Thiele *et al.* have been reported that mice intraperitoneally injected with PEG 200 at a dose of 8 mL/kg did not tolerate PEG 200 well, and half of the animals had to be euthanized. The results demonstrate that although PEG 200 is generally considered to be harmless, it can be toxic when it is intraperitonially injected and is painful for the recipient mice [126]. In the same manner, Liu *et al.* have reported that PEG-based monomers including poly (ethylene glycol) methyl ether acrylate (mPEGA) and poly (ethylene glycol) methyl ether methacrylate (mPEGMA) showed obvious cytotoxicity. They reported that PEG-400 and PEG-2000 seem to be non-cytotoxic in their research. PEG-1000, PEG-4000, and mPEGMA-950 showed moderate cytotoxicity, especially at high concentrations. Triethylene glycol (TEG) and mPEGMA-500

showed significant cytotoxicity, and mPEGA-480 showed acute cytotoxicity [127]. Shiraishi *et al.* have been studied the toxicity associated with the use of polymeric micelles composed of poly (ethylene glycol)-*b*-poly(aspartate) block copolymers using Donryu strain rats. They reported that intravenous injection five times with either a low dose (20 mg/kg) or a high dose (200 mg/kg) leads to an increase in the number of foamy cells in the lungs and lymph nodes in micelle-injected rats at the low dose. At the high dose, they observed a significant increase in the number of foamy cells in the spleen. Also, they observed a marked increase in the CD68-positive macrophages in the spleen, liver, and lungs of treated rats, which may confirm the toxicity of PEGylated polymeric micelles [128]. On the other hand, Turecek *et al.* studied the toxicological effects of PEGylated proteins and reported that there was a significant cellular vacuolation was observed in 5 of the 11 approved PEG-protein conjugates and 10 of the 17 PEG-protein conjugates, which may also represent another sign of toxicity of PEGylated products [40].

4. Hypersensitivity reaction (HSR) to PEG or PEGylated products

4.1. Background

Hypersensitivity is a group of undesirable reactions caused by the immune system. The severity of these reactions' ranges from mild to life-threatening. Hypersensitivity is classified into four types (I-IV) according to the onset and the immunological mechanism involved in these reactions [129]. Type I hypersensitivity is also referred to as an immediate type and is mediated by IgE specific for allergens. This is a mast cell-mediated hypersensitivity with examples that include asthma, urticaria, allergic rhinitis, and angioedema. It is noteworthy that some disorders occur via IgE-independent and non-specific activation of mast cells, which are considered sub-types of type I hypersensitivity such as systemic reactions to iodinated contrast reagents, some biological drugs, and opiates [130]. Type II hypersensitivity refers to an antibody-mediated cytotoxic reaction where IgG and IgM antibodies bind to allergens and help eliminate them via different mechanisms. Type II hypersensitivity is further classified into type IIa, which are antibody-mediated cytotoxic reactions characterized by the cytolytic destruction of targeted cells. Type IIb refers to antibody-mediated cell-stimulating reactions such as Graves' disease and chronic idiopathic urticaria [131]. Type III hypersensitivity is an immune complex-mediated reaction where IgG and IgM antibodies bind to antigens and form immune complexes. These complexes activate a complement system, which after several cascades ends with engulfment

and damage of antigens. Type IV hypersensitivity is characterized by delayed reactions, and T cells are the main effector cells in this type. Type IV hypersensitivity is further classified into 4 types as follows. Type IVa is characterized by Th1 cell-mediated reactions and macrophage activation as seen in type 1 diabetes and contact dermatitis. Type IVb refers to Th2 cell–mediated reactions with eosinophilic inflammation such as persistent asthma and allergic rhinitis. Type IVc is made up of cytotoxic T cell-mediated diseases such as Stevens-Johnson syndrome. Type IVd is T-cell-mediated neutrophilic inflammation such as that seen in acute generalized exanthemata's pustulosis and Behcet disease [132].

The administration of PEGylated nanocarriers can interact with the immune system and result in undesirable HSRs. These reactions are also known as CARPA or infusion reactions [133-135]. CARPA is classified as a non-IgE-mediated allergy because it occurs after a single exposure to PEGylated nanocarriers with no past history of exposure to PEGylated nanostructures. This is opposed to type I hypersensitivity, which requires prior allergen sensitization [136]. Symptoms associated with PEG hypersensitivity are characterized by a rapid onset with different degrees of severity. Common manifestations are pruritus, flushing, angioedema, hypotension, and even bronchospasm, which may lead to respiratory failure and death [38]. The role of complement activation in HSRs was first reported in the 1970s by Lang *et al.*, where complement activation was considered to be a marker of allergies caused by radiocontrast media [137]. This role of the complement system in HSRs was verified by Szebeni *et al.* in 2004 [138]. The factors that affect the incidence and the severity of HSRs will be discussed later.

4.2. HSRs to free PEG

Despite the notion that PEG is a biologically inert polymer, there have been reports of a relationship between PEG and the occurrence of HSRs. Bordere *et al.* reported a case of anaphylaxis, which is a life-threatening allergic reaction, caused by PEG 3,350, with symptoms of itching, erythema, and hypotension following the intra-articular administration of Depo-Medrol Lidocaine®, which contains methylprednisolone acetate as an active constituent in addition to PEG 3,350 and other excipients [139]. In addition, Gachoka *et al.* reported symptoms of allergic reactions such as urticaria, angioedema, and anaphylaxis after the administration of a barium enema containing PEG to empty the bowels before an X-ray examination of the colon [140].

Hyry *et al.* reported two cases of anaphylaxis after administration of medications containing macrogol (PEG 6,000), namely V-Pen MEGA® tablets (for tonsillitis treatment) and Fludent® lozenges (for caries prevention). The reported cases had shown short episodes of urticaria, dizziness, and tachycardia within minutes after receiving the medications. Positive skin prick tests to PEG 6,000 in the reported cases confirmed the potential role of PEG 6,000 in HSRs [141]. Reported cases of free PEG-associated hypersensetivity are summarized in **Table 3.**

4.3. HSRs to PEGylated products

Several reports have elucidated the role of the interaction between PEGylated pharmaceuticals (PEGylated proteins, PEGylated liposomes, and PEGylated lipid nanoparticles) and the immune system and the development of hypersensitivity reactions, which is the so-called CARPA, or infusion reaction. This type of hypersensitivity is classified as a non-IgE-mediated pseudoallergy and is initiated by activating the complement system [136, 142-144]. CARPA mainly affects the cardiopulmonary system with various symptoms such as arrythmia, angioedema, bronchospasm, hyperventilation, cardiogenic shock, and myocardial infarction [133]. PEGylation is a commonly used approach to enhance the stability of therapeutic proteins, enzymes and aptamers. A typical example of CARPA is JIVI® (Factor VIII PEGylated protein used in the treatment of Haemophilia A patients) where reports have stated that patients treated with JIVI® for severe haemophilia A developed anti-PEG antibodies and experienced hypersensitivity reactions [145, 146]. Also, anti-PEG antibody-mediated infusion reactions have been reported in the treatment of gout using Krystexxa® (Pegloticase) [147]. In addition, 8.7–23.5% of patients treated with Oncaspar® (pegaspargase) have developed HSRs due to the induction of anti-PEG antibodies [148, 149]. A previous study reported that about 96% of 261 patients with phenylketonuria developed anti-PEG antibodies and experienced hypersensitivity reactions after receiving subcutaneous injections of pegvaliase [150]. In the same manner, severe immediate allergic reactions were reported following treatment with Pegnivacogin (Modified 31-nucleotide RNA aptamer). Pegnivacogin is a PEGylated aptamer prepared by conjugation with 40-kD branched PEG polymer and is used to inhibit factor IXa in coronary artery disease patients. Povsic *et al.* reported that acute allergic reactions to Pegnivacogin occurred in patients with pre-existing anti-PEG antibodies, which might be associated with complement activation due to the interaction between anti-PEG antibodies and PEG in PEGylated aptamer [151].

It is noteworthy that not only PEGylated proteins, but also PEGylated nanoparticles are known to cause hypersensitivity reactions. As many as 45% of cancer patients are known to have developed HSRs upon receiving Doxil® without premedication with antihistaminic and steroids, but this percentage was decreased to between 4.0 and 7.1% in patients premedicated with antihistaminic [152-154]. Likewise, PEGylated liposomes encapsulating oligonucleotides or plasmid DNA generate anti-PEG antibodies in mice, which has led to severe hypersensitivity reactions including facial puffing, vasodilatation, and anaphylactic shock following a second dose of liposomes [155, 156]. Moreover, infusion-related reactions (IRRs) have also been reported following treatment with Onpattro®, which is an siRNA drug (Patisiran) encapsulated within PEGylated LNP. Onpattro® received approval in 2018 for the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis. Its long-term safety studies demonstrated a high incidence of flushing and IRRs (22% each) [157]. Reported cases of PEGylated products-associated hypersensetivity are summarized in **Table 4.**

Recently, Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273 vaccines were approved for the prevention of SARS-CoV-2 infection. Both are mRNA-based vaccines encoding SARS-CoV-2 spike protein delivered by PEGylated LNP (a full list of the components of both vaccines appears in **Table 2**) [158-160]. On December 8th 2020, the National Health System (NHS) in UK started a vaccination campaign for high-risk people. One day later, the healthcare workers reported two cases of allergic reactions after vaccine administration. As a result, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) advised healthcare workers not to provide BNT162b2 vaccines to anyone who had a history of allergic reactions [161]. In North America, the Vaccine Adverse Event Reporting System (VAERS) created by the Centers for Disease Control (CDC) reported severe allergic reactions in 6 cases out of 272,001 vaccinations up to December 19th 2020 [162], which increased to 3,942 cases of allergic reactions among 483,847,837 doses (of both BNT162b2 and mRNA-1273) in the US by December 24th 2021 [163]. This represents one case of allergic reactions in every 122,742 doses, which is about 8.15 times higher than the expected rate of one case per million. Interestingly, there are numerous reports regarding allergic reactions to COVID-19 mRNA vaccines, and the majority of them link allergic reactions to the presence of PEG in vaccine components. Wolfson *et al.* reported that among 65 patients with immediate allergic reactions to a first dose of mRNA vaccines, a total of 14 patients had a positive skin test for PEG (5 cases) and/or polysorbate 80

(12 cases) [164]. Another case reported by Sellaturay *et al.* showed a 52-year-old woman who suffered from an immediate severe allergic reaction to Pfizer/BioNTech COVID-19 vaccine. The woman had a history of allergic reactions to a PEG-containing medication in addition to some cosmetic products. Surprisingly, she developed systemic anaphylaxis after only a skin prick test with 1% PEG 4,000. PEG allergy was confirmed as the reason for the woman's allergic reaction to the Pfizer/BioNTech COVID-19 vaccine [165].

Furthermore, a search of the VAERS database for incidences of allergic reactions to COVID-19 mRNA vaccines BNT162b2 and mRNA-1273 revealed 3,942 cases where symptoms appeared within one day following injection. After further refinement of the results to identify the cases related to PEG allergy, 25 cases with either a positive PEG/polysorbate allergy test or a previous history of PEG/polysorbate allergy were identified (cases are summarized in **Table 5**). The reported symptoms varied from hives to severe life-threatening anaphylactic reactions.

4.4. Mechanism of PEG-associated hypersensitivity

Although the exact mechanism of PEG-induced hypersensitivity has not been fully elucidated, a growing body of evidence suggests that complement activation plays a role in the development of HSRs. Complement activation plays a vital role in the innate immune defense mechanism against foreign antigens [166]. Complement activation is normally controlled by a collection of cell-surface proteins to prevent auto harm to normal tissues. If, however, the complement is hyperactive, as it is in autoimmune diseases, it can cause serious damage to a variety of organs [167].

In this model, the complement system contributes to the occurrence of HSRs by releasing anaphylatoxins C3a and C5a in response to complement activation via the three known activation pathways: classical, alternative and lectin. The released anaphylatoxins bind to their receptors C3aR and C5aR, respectively, causing inflammatory cells such as macrophages, basophiles, and mast cells to become activated. Activated inflammatory cells secrete a group of inflammatory mediators as histamine, leukotrienes, platelet activating factor (PAF), and tryptase. The cardiopulmonary symptoms associated with HSRs generated by PEGylated products are caused by the action of these mediators on their specific receptors [133, 168]. Recent results have highlighted the role of anti-PEG antibodies in PEG-induced CARPA via the classical pathway in the case of PEGylated liposomes and PEG-G-CSF [120, 134]. **Figure 4** represents a simple demonstration for the mechanism of PEG-induced anaphylactic reactions.

Hugli *et al.* investigated the function and structure of anaphylatoxins, concluding that C3a, C4a, and C5a are genetically related and are the key regulators of cardiopulmonary function. They also found that complement activation and the resultant HSRs are linked to the overexpression of anaphylatoxins, particularly C3a and C5a [169].

The double-hit theory is another hypothesis that explains the mechanism of PEG-induced HSRs mainly in the case of pre-existing anti-PEG IgMs in circulation. Anaphylactic reactions, according to this theory, are caused by two hits on immune modulatory cells such as mast cells, basophils, and macrophages; the first is an anaphylatoxin signal, and the second is a direct engagement of drugs or particles with these cells via surface receptors. Interaction with these receptors stimulates a signal transduction network that mediates the secretory response [133]. Binding of the secreted anaphylatoxins to their specific receptors on mast cells or basophiles causes a release of vasoactive inflammatory mediators, which are responsible for HSR symptoms. PEG is believed to act on the same hypothesis, in which PEG on the surface of PEGylated nanocarriers binds to macrophages and mast cells via specific surface receptors to stimulate a secretory response [13, 170].

4.5. Factors affecting PEG-associated hypersensitivity

Several factors could affect the incidence and the severity of PEG hypersensitivity; these are summarized in the following section.

4.5.1. Factors affecting free PEG-induced hypersensitivity

4.5.1.1. PEG molecular weight

Because of the diversity in polymer properties that occurs when the molecular weight of the polymer changes, a wide range of PEG molecular weights are commercially available for use in pharmaceutical formulations, cosmetics, or as food additives. PEG molecular weight is known to have a significant effect on the onset of the severity of the HSRs. Shah *et al.* reported that PEGs with a lower molecular weight can permeate the skin and mucosa more effectively than those of a larger molecular weight, which increases the risk of sensitization. They also reported that PEGs with a high molecular weight can trigger HSRs at low concentrations upon sensitization by comparison with low molecular weight PEGs [171].

Among the various molecular weights (from 300 to 20,000 Da), PEGs with molecular weights of 3,350 and 4,000 Da make up the majority of reported cases of HSRs [38]. Stone *et al.* showed that the serum of patients who reacted clinically to PEG 3,350, was more reactive

towards PEG with a higher molecular weight, indicating that a high molecular weight of PEG is an important factor in PEG-related HSRs. Although PEGs with a high molecular weight are frequently associated with positive PEG skin prick tests (SPT) [172, 173], both low and high molecular weight PEGs can induce HSRs [171, 174].

4.5.1.2. Reaction threshold dose

Not only the molecular weight of PEG but also the dosage of PEG may play a crucial role in the development of PEG hypersensitivity. To investigate the effect of PEG dosage on the development of PEG allergies, Sohy *et al.* used different concentrations of oral PEG 4,000 (starting from 1 mg and increasing the dose every 30 minutes). The results showed that a positive allergic response was observed 30 minutes following the administration of 7.1 mg of PEG 4,000, while lower dosages showed no significant allergic responses [175]. According to Bommarito *et al.*, PEG 4,000 and PEG 6,000 at low concentrations (0.0001%) showed a positive response in the basophile activation test, whereas PEG 400 at various concentrations showed no response [172]. These findings point to the need for a particular test for various PEGs in order to investigate the possibility of PEG hypersensitivity. Furthermore, PEGs with different molecular weights, particularly the lower molecular weight versions, gave false SPT results since the measured dose was insufficient to surpass the patient's reactivity-threshold dose. As a result, each patient should be individually checked against the dose and molecular weight.

4.5.2. Factors affecting PEGylated product-induced hypersensitivity

4.5.2.1. Morphological properties of PEGylated nanocarriers

PEGs are commonly used for surface decoration of nanocarriers such as liposomes, nanoparticles, and exosomes to improve the circulation half-life and stability. The external shape of nanostructures is reported to have a significant impact on complement activation and on the development of PEG allergic reactions. Nanostructures with irregular, oval, or elongated external surfaces generally activate C5 convertases, which are responsible for complement activation [176].

Pedersen *et al.* have reported that the structure curvature has a significant impact on the binding of human IgM antibodies to antigen surfaces. They demonstrated that the presence of curvature in peptidoglycan (PGN) fragments allows for an efficient interaction with IgM, which results in activation of a strong classical pathway complement [177]. According to Szebeni *et al.*, the reactogenicity and increase in the SC5b-9 formation after Doxil® administration compared

with that of free doxorubicin may be attributed to the surface modification of PEGylated liposomes. This reactogenicity may be due to the presence of elongated crystals of doxorubicin and/or to the irregular liposome surface, which causes an ovaliform transition of spherical vesicles followed by an increase in the ratio of flat surfaces to curved areas, and this results in a build-up of multimolecular complexes and complement activation [176].

4.5.2.2. Surface charge and composition of PEGylated nanocarriers

The surface charge of PEGylated products is known to have a significant impact on the extent of complement activation and HSR development. Cationic nanocarriers increase complement activation *in vitro* in human serum analysis, which could be attributed to the efficient binding ability of positively charged molecules with serum and plasma proteins [178]. Gao *et al.* reported that negatively charged plasma proteins such as opsonin protein, which is responsible for exogenous molecule opsonization and then phagocytic engulfment, can efficiently bind positively charged nanoparticles [179]. Similarly, Yallapu *et al.* reported that the interaction of curcumin nanoformulations with plasma proteins is primarily influenced by the surface charge of the nanoformulations with cationic ones enhancing binding with negatively charged physiological membranes and plasma proteins [180]. In addition, large multilamellar vesicles prepared with negatively charged phospholipids are known to have a greater vasoactive effect than those prepared with neutral phospholipids, indicating that charged vesicles can stimulate the immune system via complement activation to a greater extent than uncharged vesicles [181].

Furthermore, the composition of PEGylated formulations has a significant impact on HSR induction. According to Baranyi *et al.*, i.v. injection of multilamellar vesicles with high cholesterol content (71%) can cause pulmonary and myocardial manifestations as a result of complement activation [182]. Szebeni *et al.* reported that the pulmonary hypertensive effect of liposomal administration is directly proportional to cholesterol content [183]. Excess cholesterol content can aggregate and accumulate on the surface of nanocarriers, which makes them available to interact with naturally existing anti-cholesterol antibodies in blood circulation [183, 184]. Caracciolo *et al.* used neutral lipids in the preparation of liposomes to investigate the impact on their interaction with plasma proteins. They prepared neutral dioleoyl phosphatidylethanolamine (DOPE)-based liposomes instead of cationic 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP)-based liposomes. They reported that positively charged

cationic liposomes interact substantially with negatively charged plasma proteins, boosting complement activation, whereas neutral lipids have a poor affinity for plasma protein interaction. They also discovered that employing high cholesterol levels in liposome synthesis can induce interactions of liposomes with complement proteins and immunoglobulins [185].

4.5.2.3. Size and homogeneity of PEGylated formulations

The degree and intensity of complement activation is largely determined by the affinity of antibodies for foreign substances. The binding of anti-PEG, anti-cholesterol, or anti-phospholipid antibodies to PEGylated-lipidic nanocarriers is dependent on their size. This impact can be explained by the fact that increasing the size of an antigen increases the surface area that is accessible for antibody-specific antigen interaction [186]. Highly homogenous unilamellar vesicles are considered highly safe with no vasoactive properties. Increasing the diameters of PEGylated nanovesicles, as in large multilamellar vesicles (LMV), could assure efficient antibody binding, which would trigger higher levels of complement activation and HSRs [187, 188].

Szebeni *et al.* proposed another explanation for the effect of surface area on complement activation, based on the fact that complement activation requires a specific threshold dose of antibodies to be initiated, and that increasing the surface area allows for an optimal arrangement of antibodies on the molecule surface, allowing for a large amount of antibody to bind to the molecule surface, which could be sufficient to initiate complement activation [183]. The same assumption can be extended to PEGylated proteins, since Zang *et al.* proved the importance of particle size in determining the efficacy of anti-PEG antibodies in accelerating the clearance of PEGylated particles [189]. They reported that a particle size greater than 40 nm is required for anti-PEG antibody binding and complement activation, and that the presence of aggregated PEG-uricase increased the particle size of PEG-uricase (around 38 nm) to greater than 60 nm, facilitating antibody binding and the ABC phenomenon. This could also explain why second-dose PEG-OVA and PEG-G-CSF (10 nm) failed to induce the ABC phenomenon in the presence of anti-PEG IgM but not PEGylated liposomes (100 nm) [120].

4.5.2.4. Route and rate of administration

Oral, intravenous (i.v.), intramuscular, intravaginal, and intraarticular administration of PEG-containing products, as well as topical application of PEG-containing products, have all been linked to PEG-induced hypersensitivity [171-173, 190-192]. In terms of the i.v. route, slow

i.v. infusion of PEGylated nanocarriers was found to have a pulmonary hypertensive effect that was lower than that of bolus i.v. injection. The pulmonary hypertensive impact is attributed to an increase in the generation of anaphylatoxins after complement activation [193]. The level of anaphylatoxins in blood is controlled by two main rates: the first is the rate of production (complement activation), and the second is the rate of clearance. Because the rate of clearance is relatively consistent and unaffected by the route of administration, the degree of complement activation is the main contributor to the level of anaphylatoxins. As a result, the route of administration has a significant impact on the level of anaphylatoxins, which is higher in the case of bolus i.v. injection compared with slow i.v. infusion, which allows for substantial complement activation and the generation of anaphylatoxins [13, 194].

The amount of PEG available for absorption affects the development and severity of HSRs when PEG-containing products are applied topically. Low molecular weight PEGs have limited absorption through healthy skin. High molecular weight PEGs (more than 4,000 Da) have difficulty being absorbed through intact skin, which is why PEGs with high molecular weights are favored in cosmetic preparations [4]. On the other hand, the presence of injury or damage in the skin or in the gastrointestinal mucosa allows enough PEGs to be absorbed and subsequently stimulate complement activation. Symptoms of urticaria, pruritus, and oedema have been reported after using oral and topical PEG-containing products in cases with compromised skin or intestinal mucosa [192, 195, 196].

Conclusions

PEGs are widely used synthetic polymers with different molecular weights and different properties. PEGs have promising characteristics such as low toxicity, biocompatibility, and inert nature. Therefore, PEGs have been frequently used in foods, cosmetics and pharmaceutical products as solubility enhancing agents and stabilizing agents. PEGylation can stabilize nanoparticles and protein drugs in vials during storage by preventing their aggregation. PEGylation also improves circulation properties of nanoparticles and protein drugs by preventing adsorption of plasma proteins (opsonisation) and recognition by the cells of MPS. The long circulating effect provided by PEGylation is the main mediator for drug passive targeting in highly perfused tissues such as solid tumors. Despite the widespread usage of PEGs, immunological reactions to PEGs themselves, PEG-containing products and PEGylated products are recognized. The administration of PEGylated products induces production of anti-PEG

antibodies. The presence of pre-existing anti-PEG antibodies, presumably due to extensive use of PEGs in foods and cosmetics, increases the risk of the accelerated blood clearance (ABC) phenomenon, which could lessen the therapeutic efficacy of PEGylated products in clinical settings, as well as, increases the risk of Hypersensitivity reaction (HSR). HSR is currently being reported in many cases following mRNA-based COVID-19 vaccination. Although the mechanism behind HSR induced by mRNA-based COVID-19 vaccines is still uncertain, understanding the mechanism and exchanging the knowledge between the nanomedicine and vaccine field are important since PEGylated lipid nanoparticles are used for all mRNA-based COVID-19 vaccines as delivery vehicles. With widespread use of PEG household items and PEGylated therapeutics, an increase in the incidence of HSR is predictable. The role of PEGs in induction of anti-PEG antibodies and PEG-induced HSRs and the mechanism behind these immunological reactions should be further elucidated to unearth more facts, attaining more effective preventive measures.

Conflicts of interest

There is no conflict of interest for any of the authors.

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Table 2. Components of BNT162b2 and mRNA-1273 vaccines

Vaccine	**mRNA encoded**	**Lipids**				**Other additives**	**Ref.**
		Ionizable lipid	Helper lipid	Cholesterol	PEG-lipid		
Pfizer/BioNTech BNT162b2	Nucleoside-modified mRNA encoding SARS-CoV-2 spike (S) glycoprotein	ALC-0315 = ((4-hydroxybutyl) azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	DSPC = 1,2-Distearoyl-sn-glycero-3-phosphocholine	Cholesterol (plant derived)	ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide	Dibasic sodium phosphate dihydrate Monobasic potassium phosphate Potassium chloride Sodium chloride Sucrose	[197]
Moderna mRNA-1273	Nucleoside-modified mRNA encoding SARS-CoV-2 spike (S) glycoprotein	SM-102 = heptadecane-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate	DSPC = 1,2-Distearoyl-sn-glycero-3-phosphocholine	BotaniChol® (non-animal origin cholesterol)	PEG2000-DMG = 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol	Sodium acetate Sucrose Tromethamine Tromethamine hydrochloride Acetic acid	[198]

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Table 3. Cases with PEG-related allergic reactions to free PEG [31]

PEG-containing product	Active constituent	Type of PEG	Allergic symptoms	Previous history of allergy
- Depo-Provera®	- Medroxyprogesterone PEG-3350	- PEG-3350	Sneezing, rhinorrhoea, urticaria, ocular irritation, hypotension, chest tightness, Biphasic urticaria.	None
- MoviPrep®	- Osmotic laxative PEG-3350	- PEG-3350	Urticaria, Pruritus, urticaria, angioedema, swelling of hands and feet, hypotension, Contact urticaria.	None
- Vimovo® - Effervescent vitamin C®	- Esomeprazole, naproxen. - Effervescent vitamin C: HMW-PEG	- PEG-8000	Urticaria, angioedema, syncope, presyncope. Generalized pruritus.	None
- Klean Prep® - Phosphate Sando®	- Osmotic laxative, PEG-3350 - Effervescent phosphate, PEG-4000.	- PEG-3350 - PEG-4000.	Dyspnea, angioedema, visual disturbance, syncope, presyncope.	None
- Motilium Suppository® - Nurofen®	- Domperidone, PEG-400 and 1000. -Ibuprofen, PEG-6000.	- PEG-400 and 1000. - PEG-6000.	Angioedema, throat tightness, paraesthesia, throat tightness.	Chronic Spontaneous Urticaria (CSU)
- Betadine® - Voltorol Oral®	- Povidone-iodine, PEG-400, 6000 - Diclofenac PEG-8000	- PEG-400, 6000 - PEG-8000	Urticaria, angioedema, presyncope, hypotension, respiratory distress, Contact urticaria.	CSU

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Table 4. Cases with PEG-related allergic reactions to PEGylated products

Commercial product	PEGylated entity	Type of PEG	Allergic symptoms	Previous history of allergy	Ref.
JIVI®	Recombinant antihemophilic factor VIII	30 kDa PEG	Urticaria, angioedema, dyspnea.	None	[145]
Neulasta®	Pegfilgrastim	10 kDa PEG	Minimal rash on her arms and abdomen as well as a sore throat, pruritis, erythematous, lip swelling	None	[199]
Cimzia®	Certolizumab pegol	40 kDa mPEG	Erythema, urticarial rash, dyspnoea, wheeze, and a sensation of presyncope.	Movicol® (PEG 3350) allergy	[200]
Oncaspar®	Pegaspargase	5 kDa PEG	Transient flushing or rash, urticaria, dyspnea, symptomatic bronchospasm, angioedema, hypotension, anaphylaxis.	None	[201]
Palynziq®	Pegvaliase	40 kDa PEG	lip swelling, flushing, dyspnoea.	allergic rhinitis	[202]
Doxil®	PEGylated liposomal Doxorubicin	2 kDa PEG	Shortness of breath, flushing, feeling warm and dizziness	None	[203]
Macugen®	Pegaptanib	40 kDa mPEG	Tongue oedema, lip swelling, prolonged urticarial rash.	None	[204]
Pegnivacogin®	RNA aptamer	40 kDa mPEG	Angioedema, flushing, difficulty of breathing.	None	[205]
Onpattro®	Patisiran	PEG_{2000}-DMG	Flushing, peripheral oedema, muscle spasm, dyspnoea.	None	[157]

Table 5. Cases with PEG-related allergic reactions to mRNA COVID-19 vaccines according to the CDC [163]

Vaccine	Anaphylaxis	Symptoms	Onset	Current illness	Adverse events prior vaccinations	Current medications	Allergy test	History of allergies	VAERS ID
Moderna	Yes	Massive bloody diarrhea, one large vomitus, hives, tongue swelling, difficult to speak and swallow.	Within 9 h	None.	None.	None.	Polysorbate allergy: Negative PEG allergy: positive	Seasonal Trees avocado	1020162-1
Moderna	No	Tachycardia, tingling, dizziness, hives	Within minutes	None.	None.	None.	Polysorbate 80 allergy: positive	Acyclovir, tree pollens, grass pollen, and dogs.	1285640-1
Pfizer/BioN Tech	No	Hives; face flushing	Within 5 minutes	None.	None.	None.	BNT162B2 allergy: positive PEG allergy: positive Polysorbate 80 allergy: positive	Meat allergy	1405639-1

Moderna	No	Cognitive issues; headaches; sleep disturbance; vertigo; fatigue; Red inflammation in vein of right foot; swollen lymph nodes; skin felt like crawling; Hands tremoring; legs and hands weakness; freezing; Arm was very sore and little achy; rapid heartbeat; Feet tingling; blood pressure elevated; dizziness; strange taste in mouth; foggy	Within the first day	None	None.	None.	Polysorbate 80 allergy: positive	Allergic to dogs; Drug allergy (allergic to acyclovir); Food allergy (poly sorbate 80); Pollen allergy (allergic to grass pollen.)	1614213-1

Pfizer/BioN Tech	Yes	Felt 'impending doom', heart racing, tunnel vision, chest pressure, throat constriction fatigue, SOB, and nausea, chills, fever.	Within 15 minutes	Reflux	None.	Prevacid	PEG 3350 allergy: positive	Allergic reaction to sushi	1853854-1
Moderna	No	Pressure on the front of throat, high heart rate, weakness, insomnia, stomach pain, arm swelling, headache, difficult breathing, numbness and pinching on left side.	Within 1.5 h	Fibromyalgia and pre-diabetic	Reaction to flu vaccine in 2012.	Vitamin D and multivitamin.	PEG allergy: positive	Amoxicillin, penicillin, I'm sensitive to azithromycin, allergic to melons	1396793-1
Moderna	No	Itchy arms and legs, allergic dermatitis	Within minutes	None	None.	Claritin	N/A	PEG, colophony, thimerosal, gold	0924196-1

Moderna	Yes	Cough, difficult breathing.	Within 15 minutes	None.	None.	Centrum Women's, Zyrtec, Climentadine, vitamin B12, and D, Levothyroxine, Cinopril, Lexapro	PEG allergy: positive Polysorbate allergy: positive	Penicillin, Sugars (sucrose), Nickel, Shellfish, MSG, Perfumes, Makeups, Cleaning, Tree nuts	1036813-1
Pfizer/BioN Tech	Yes	Gasping for air; Tongue swelling; Swollen lips; Throat closing; tickle in the throat; Headache; Dizzy; Confusion; weak; fatigued; full tongue affecting talking; tingling in lips	Within seconds	Hashimoto's disease; Undifferentiated connective tissue disease	None.	None.	N/A	Amlodipine which has PEG and Lisinopril	1150913-1

Moderna	No	Arm swelling, Sense of taste lost, metallic taste, Fingertips and throat swollen, itching all over.	Within 2 h	None.	None.	N/A	N/A	Aspirin, codeine, penicillins, PEG, and possibly more per patient. Patient reported allergy to Benadryl (contains PEG)	1709669-1
Pfizer/BioN Tech	No	Sharp chest pain, shortness of breath, headache, and nausea.	Within 8 h	None.	None.	None.	N/A	PEG, PCN, ibuprofen	1865357-1
Pfizer/BioN Tech	Yes	Tingling, tightness in throat, tongue swelling, difficulty swallowing, Hyperventilating, difficult breathing.	Within 3 h	None.	None.	5mg loratadine Ritual Prenatal Vitamin 1000mg turmeric Probiotic	N/A	Hashimoto's, Asthma, Gluten Intolerance, Chronic Hives, patient reported severe eczema after application of eye cream containing PEG	1139132-1

Pfizer/BioN Tech	No	Throat closing; Shortness of breath; Swollen throat; Dizziness/ Lightheaded; Wheezing.	Within the first day	None.	None.	Metoprolol tartrate; ativan; lexapro	N/A	Patient previously had a reaction to Miralax (contains PEG)	1332760-1
Moderna	No	Blurred vision, high blood pressure, flushing, dizziness, back of head/neck soreness, arthralgia, and fatigue.	Within the first day	None.	None.	None.	N/A	Propofol which contains polysorbate, Demerol	1581247-1

Pfizer/BioN Tech	Yes	Mid-back pain; coughing; wheezing; SOB; severe pain in chest; flushing and itching.	Within 5-10 minutes	None.	None.	Zyrtec; topamax; spironolactone; vitamin D; benadryl	N/A	Cephalasporins, oral Diflucan, clindamycin, PEG, Polysorbate, Propylene glycol, sulfa, Levaquin The patient had known allergies to polysorbate, polyethylene glycol, and propylene glycol	1645678-1

Pfizer/BioN Tech	No	Itching; Allergic reactions; Tachycardia; Numbness and tingling in her mouth; Feeling of congestion in the back of her throat; was not able to swallow; Patient cannot talk in complete sentences.	Within 20 minutes	None.	None.	Benadryl; claritin [clarithromycin]; zyrtec [cetirizine hydrochloride]; prednisone	N/A	Patient reported PEG sensitivity	1648915-1
Moderna	Yes	Lip swelling; Tongue Swelling; Chest tightness; dizziness; irregular heart rate.	Within 15 minutes	None.	None.	Fish oil; vitamin D; probiotics	N/A	Atenolol, Sensitivity to petroleum type products, Egg allergy. Patient reported PEG allergy	1691526-1

Pfizer/BioN Tech	No	Swelling up the injection site; redness; lots of soreness; 4x4 discoloration area; The lymph nodes under arm became rock hard and was the size of palm.	Within the first day	None.	None.	None.	PEG allergy: Negative.	Patient reported polysorbate allergy	1823560-1
Pfizer/BioN Tech	No	Allergic reaction to the shot; Rash; Itching	Within 15 minutes	None.	None.	None.	N/A	Sulfonamide allergy, influenza vaccine and polysorbate 80	1903830-1
Moderna	No	Nausea, tachycardia, rash on face and neck, tongue swelling	Within 15 minutes	None.	None.	Zyrtec Vyvanse birth control	Polysorbate 20/80 allergy: positive PEG 3350 allergy: positive.	Seasonal Trees avocado	1030771-1
Pfizer/BioN Tech	No	Hives	Within the first day	Fever 3days before vaccinatio n, asthma	None.	Multivitami ns	Polysorbate 80 allergy: positive	None	1959413-1

Pfizer/BioN Tech	Yes	Rash and itching	Within 10 minutes	None.	Anaphylaxis; age 12; MMR vaccine. Anaphylaxis; age 29; flu vaccine.	Adderall, Lopressor, Seasonique, Ventolin, Flovent, Seravent, Fioricet	N/A	Latex, pineapple. Sensitivities to PEG and polysorbate.	1205076-1
Pfizer/BioN Tech	No	Abnormal breathing patterns, lightheaded, cold, clammy, respiratory/acute distress/breathing difficulty, swelling of entire face and sinuses.	Within the first day	Chronic daily migraine, hypothyroid, hypertension	None.	N/A	N/A	PEG/PG, eggs, wheat, dairy, peanut	1675204-1
Pfizer/BioN Tech	Yes	Dizziness, tongue swelling and sensation of throat closing.	Within the first day	None.	None.	None.	N/A	Depo-provera, PEG	1749850-1

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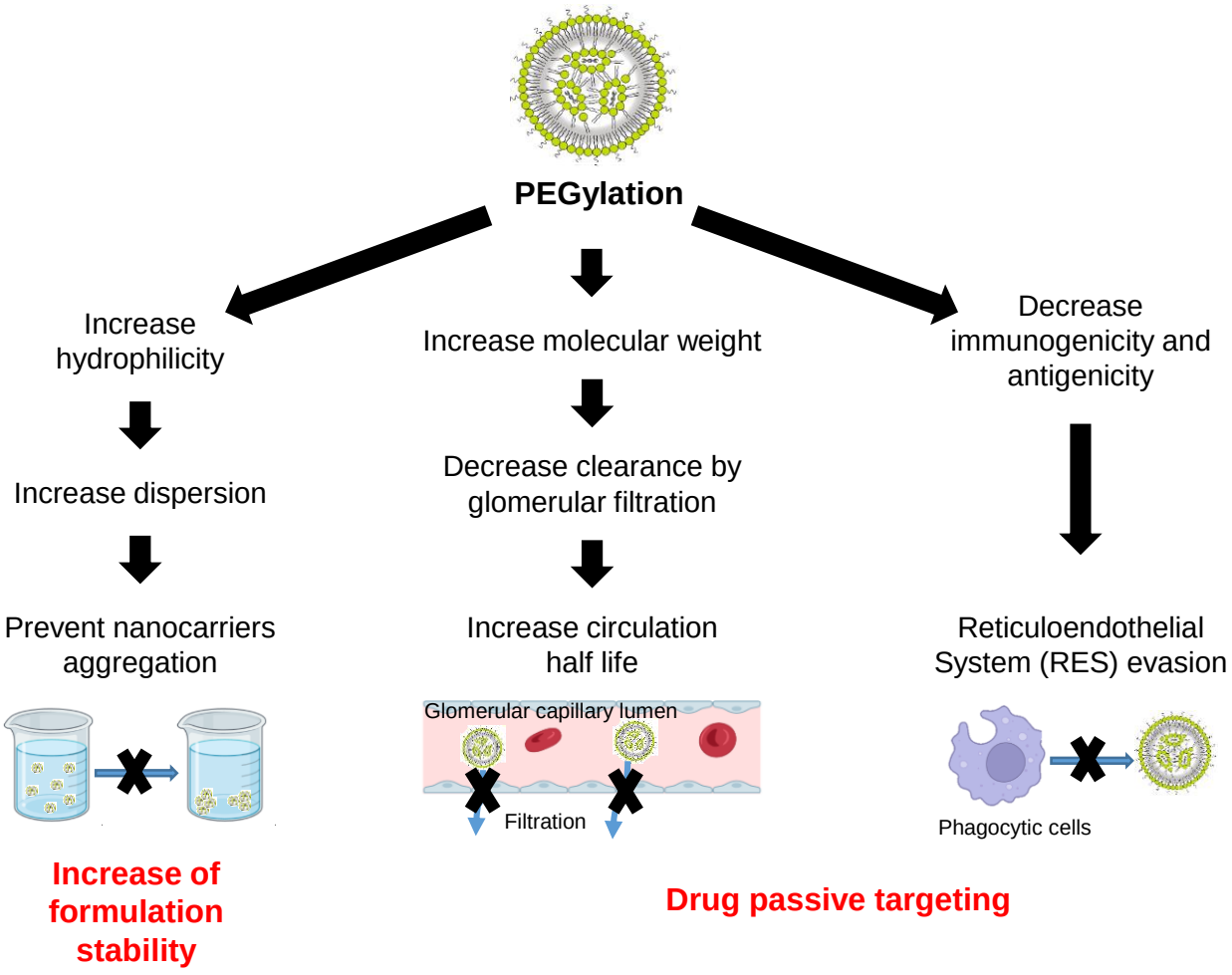
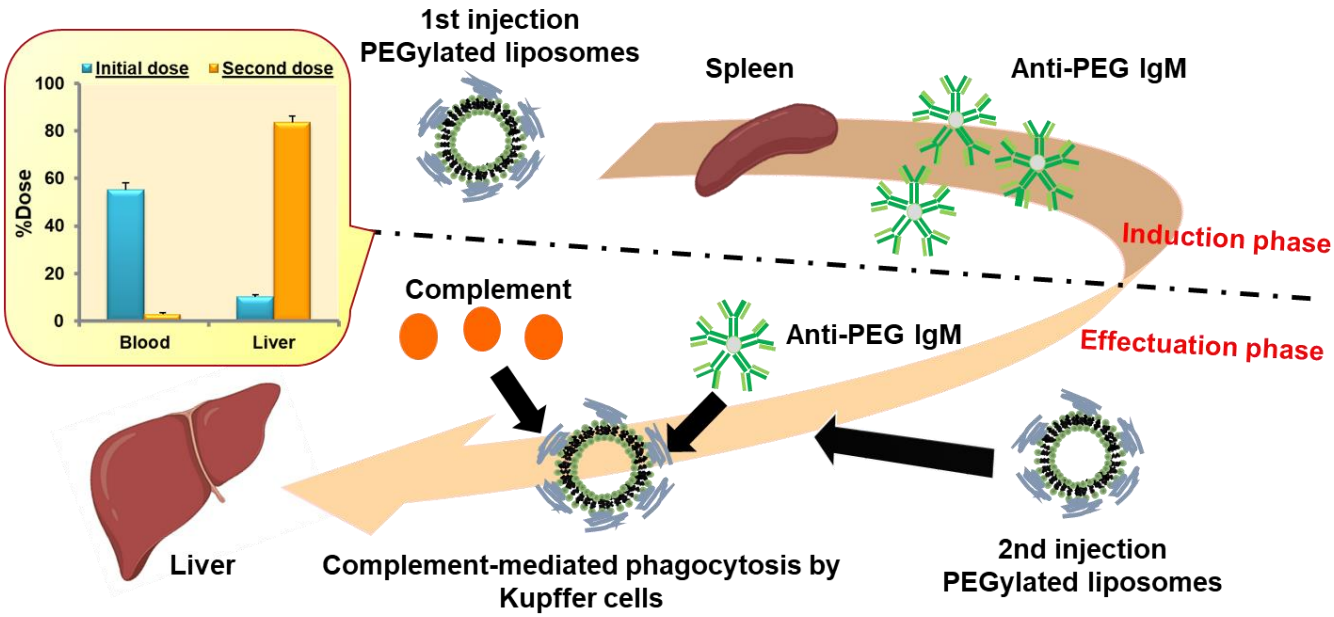
Figures Legends

Ibrahim et al., Figure 1

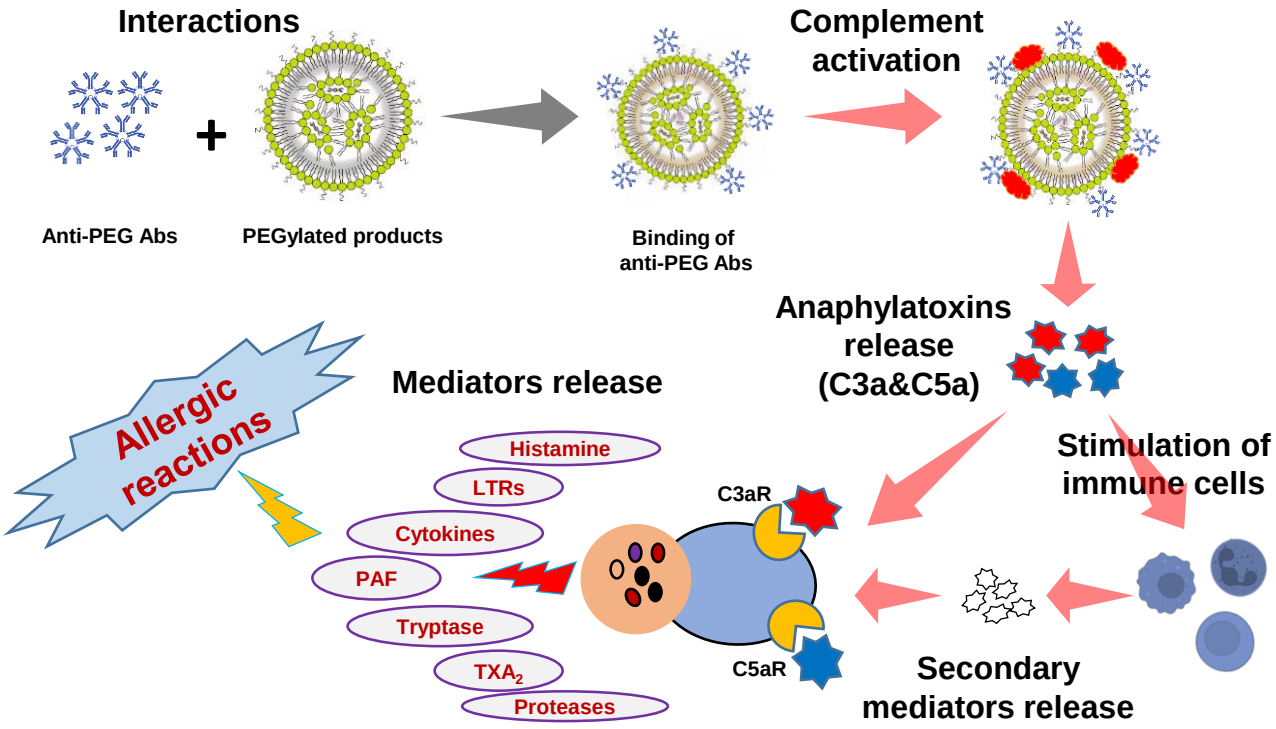
Ibrahim et al., Figure 2

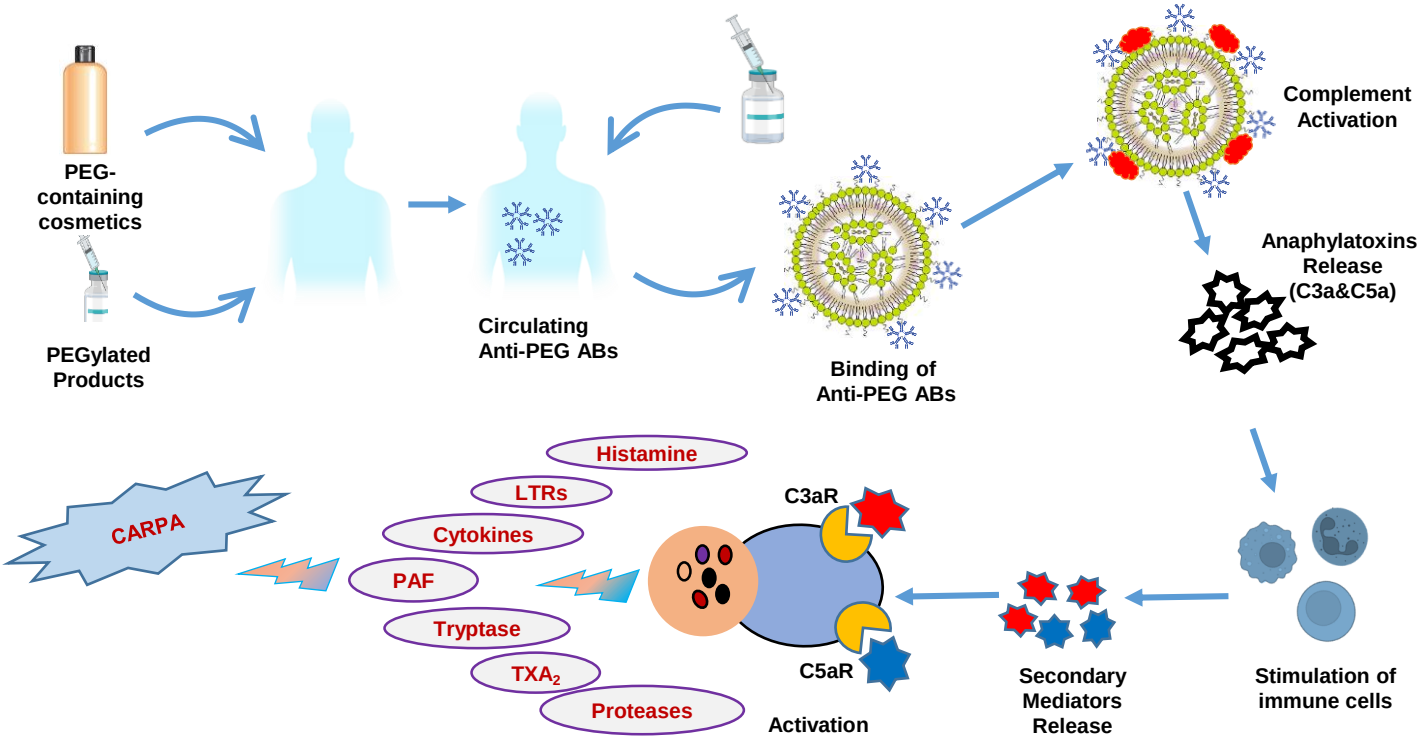


Ibrahim et al., Figure 3



Ibrahim et al., Figure 4





Abbreviations: ABs, Antibodies; C3a and C5a, complement fragments; C3a R and C5a R, complement fragments receptors; LTRs, Leukotrienes; PAF, Platelet activating factor; TXA2, Thromboxane A2; CARPA, complement activation-related pseudoallergy.