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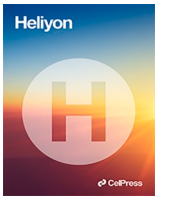

Review article

From inflammation to immune regulation: The dual nature of dietary lectins in health and disease

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ABSTRACT

Beans, vegetables, fruits, and mushrooms offer a delightful array of fragrances and an abundance of nutrients, including essential vitamins, minerals, protein rich in vital amino acids, and omega-3 fatty acids. However, they may also contain lectins, carbohydrate-binding proteins with potential health risks. While some lectins exhibit stability and resistance to digestion, posing threats to gastrointestinal integrity and immune function, others, such as those from butterfly peas and pink bauhinia, show immunomodulatory properties that could bolster immune responses. While some lectins, such as phytohemagglutinin, have been associated with inflammatory responses and autoimmune disorders, others, such as wheat lectin, have shown potential benefits in nutrient absorption. Additionally, mushroom lectins, while generally nontoxic, exhibit immunomodulatory properties with implications for immune health. Despite their potential benefits, challenges remain in understanding lectin dosages, administration routes, and mechanisms of action. Further research is needed to elucidate the intricate roles of dietary lectins in immune function and autoimmune disorders. This review surveys the immunomodulatory effects of dietary lectins from plants and mushrooms, shedding light on their mechanisms of action. From inflammation modulation to potential autoimmune implications, the diverse roles of dietary lectins have been explored, highlighting avenues for future investigations and therapeutic exploration.

1. Introduction

When tissues are hampered by bacteria, trauma, toxins, heat, or any other cause, an inflammatory reaction (inflammation) occurs. Histamine, bradykinin, and prostaglandins are chemicals released by wounded cells. Blood vessels leak fluid into tissues due to these toxins, creating swelling. Conversely, the property of reducing inflammation or swelling is anti-inflammatory [1]. Since ancient times, humans have relied on medicinal plants and herbs to heal various ailments. The selection of an appropriate plant remains a question of trial, error, and experience. Polyphenols, carotenoids, phytosterols, and polysaccharides are compound phytochemicals in fruits and vegetables that are responsible for their therapeutic qualities [2]. Plant-based diets are considered beneficial to human health because they contain various essential nutrients and health-promoting constituents, such as antioxidants, phenolic compounds, fibre, vitamins, minerals, three specific fatty acids, and other products that help lower blood pressure and cholesterol. Because of their high nutritional

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and functional content, plant-based diets help treat acute and chronic ailments [3]. Several varieties of edible mushrooms, macrofungi, are also appreciated for their dietary and pharmacological value [4]. Currently, scientific frontiers in dietary studies are striving to produce a food formula to lower the risk of infection in animal models and immunocompromised hosts [5]. Although dietary plants and mushroom products have substantial nutritional benefits, they also contain antinutritional agents that decrease nutrient absorption. Toxic factors include lectins, tannins, saponins, protease inhibitors, phytic acid, gossypol, and amylase inhibitors. Lectins are carbohydrate-binding proteins in various edible beans, cereals, and vegetables. Certain plant lectins, particularly those present in legumes such as kidney beans and lentils, function as antinutritional agents by resisting digestion when consumed raw or undercooked [6]. This resistance leads to gastrointestinal disturbances such as nausea and stomach upset [7,8]. Although some lectins are antinutritional, dietary lectins have significant physiological and immunological ramifications [9]. In general, plant lectin may have anticancer [10], antimicrobial [11], antiulcer, and immunomodulatory properties [12,13]. Lectins may trigger autoimmune disorders by binding to the gut lining or tissues such as pancreatic islet cells, inducing immune responses that contribute to conditions such as type 1 diabetes and rheumatoid arthritis. Proper cooking methods are essential to minimize the adverse effects of these lectins and reduce the risk of autoimmune diseases [14]. Jacalin, derived from jackfruit seeds, plays an intriguing immunomodulatory role by stimulating peripheral blood mononuclear cells (PBMCs) and promoting their proliferation and cytokine production. Initially, it triggers the expression of pro-inflammatory cytokines such as IFN-γ, but prolonged exposure to IFN-γ elevates the levels of anti-inflammatory cytokines, primarily TGF-β. While initially impeding tumor growth by polarizing PBMCs, prolonged jacalin exposure fosters an immunosuppressive tumor microenvironment, facilitating tumor progression. These dual effects underscore the potential of jacalin in modulating immune responses, offering insights into cancer immunotherapy and immune-related conditions [15,16]. These lectins exert their effects primarily through their distinct carbohydrate-binding sites. When these sites are blocked by a haptenic sugar, the observed effects are neutralized. For instance, WGA, a lectin originating from wheat germ (*Triticum aestivum*), binds specifically to N-acetylglucosamine and sialic acid residues found on the surfaces of cell glycoproteins and glycolipids. WGA has been demonstrated to modulate immune responses by engaging with various immune cells, including macrophages and T lymphocytes. It has the capacity to stimulate cytokine production and initiate signaling pathways associated with inflammation and the activation of immune cells [17].

This review seeks to elucidate the immunomodulatory effects of dietary lectins from plants and mushrooms, with a particular emphasis on their mechanisms of action. Additionally, it explores the varied roles these lectins play, from modulating inflammation to their potential involvement in autoimmune disorders, while highlighting opportunities for future research and therapeutic development.

2. Methodology

2.1. Literature search strategy and data selection

We embarked on a comprehensive literature search across PubMed, Google Scholar, and relevant academic journals utilizing keywords associated with lectins, inflammation, immune regulation, autoimmune diseases, dietary effects, and health implications. Recent articles deemed relevant to our topic were prioritized during the selection process.

2.2. Data extraction and analysis

Pertinent information was meticulously extracted from the chosen literature, focusing on the research findings, methods employed, and overarching conclusions. Recurring themes were identified, and the data were categorized according to lectin type, source, mechanism, and observed effect.

2.3. Critical evaluation of the literature

A critical analysis of the literature was conducted to assess quality and reliability. Conflicting findings were scrutinized, and study limitations were acknowledged. Interpretations concerning the role of dietary lectins in modulating inflammation and immune responses have been formulated.

2.4. Structuring the review article

The review article is divided into distinct sections: Introduction, Beans/Vegetables/Fruits Lectins, Mushroom Lectins, Lectins' Role in Autoimmune Disorders, Dietary Lectins as and Anti-inflammatory and Immunity Boosting Agents, Limitations and Challenges Restricting the Future of Dietary Lectins, etc. In each section, concise summaries of findings are provided, and visual aids are incorporated to enhance clarity and comprehension.

2.5. Identification of research gaps and future directions

Gaps in the current understanding of the health effects of dietary lectins were identified, and future research directions were proposed to address these gaps. The potential implications of further research on the immunomodulatory effects of dietary lectins on human health are highlighted.

3. Beans, vegetables, and fruit lectins

Lectins are present in most plant parts, types, and families and are often considered one of the negative components of various plant-based diets. However, the accuracy of these claims has been debated. Phytohemagglutinin (PHA), an "anti-nutrient lectin," has garnered significant attention as a potential contributor to chronic inflammation and autoimmune diseases.

Lectins are abundant, especially in uncooked legumes such as kidney beans (*Phaseolus vulgaris*). When taken raw or semicooked, they defy digestion and go beyond the gut mucosa to adhere to the glycosylated membrane of the cell lining in the digestive tract [18]. They damage the epithelial lumen and hamper food absorption processes, causing nausea, vomiting, stomach disturbance, and bloating. Moreover, it may alter hormonal and immunological cascades, leading to autoimmune illnesses whose development mechanisms are unresolved [19,20]. However, researchers increasingly recognize molecular mimicry as a possible cause of many autoimmune disorders caused by dietary components [21]. Nevertheless, luckily, not all lectins that traverse the GIT unbroken lead to problems. Most plant lectins in the human diet are present in minute amounts and might become beneficial and assist with food transportation across the GIT barrier [22]. For instance, wheat lectin (*Triticum vulgaris*) has been proven to aid in the absorption of nutritional factors such as flavonoids and calcium [23]. Lectins may adhere to a broad spectrum of target tissues, comprising connective tissue, the liver, pancreas, thyroid, heart muscle, prostate gland, breast tissue, and the brain. It has been demonstrated that lectins bind to glycoconjugate receptors in tissues, eliciting cellular and humoral reactions against the lectin and the tissue. For example, dietary lectins may attach to pancreatic islet cells, activating an autoimmune reaction against these cells and contributing to the development of type 1 diabetes and β-cell destruction [24]. Lectins can also attach to glycosaminoglycans and proteoglycans in synovial fluid in joints, potentially causing autoimmune rheumatic inflammatory diseases [25]. The garlic lectins ASA I and ASA II are found in numerous human blood samples and can cross the gastrointestinal barrier and be detected by the immune system. Although these lectins resisted peptic digestion, they had a lower hemagglutination capability [26]. When treated with murine thymocytes at 0.01 μg/well, *Allium cepa* (Onion) agglutinin, a mannose-specific lectin, was found to be comparable to concanavalin A (ConA), which is used as a positive control, at the same dose (0.01 μg/well). The proliferation of 421 thymocytes increased 4- and 3.5-fold, respectively. Furthermore, incubation of a macrophage line (RAW264.7) with pure onion lectin was demonstrated to stimulate nitric oxide production in macrophage lines [27]. Venkatesh's group also conducted another study with onion lectin (*Allium cepa* agglutinin, "ACA"). However, in experimental animals, cyclophosphamide (CP) induces immunosuppression. They concluded that administering ACA to immunocompromised CP-treated mice could elicit innate and adaptive immune responses. The levels of TNF-α and other inflammatory mediators, particularly IL-10, were also elevated. NO and COX-2 production were also increased, indicating that macrophages were activated [28]. Animal studies have shown that providing rats with onion extract enhances their immunological response by increasing the number of immune-reacting cells and triggering the release of pro-inflammatory cytokines [29]. Tarin, also known as *Colocasia esculenta* lectin, has long been used as a medicinal plant to improve health by fortifying the immune system. The cytokine-mimetic properties of Tarin have been established by its ability to stimulate hematopoietic cell proliferation. B220+ spleen cells alter the myeloid population, specifically granulocytes, in the bone marrow and circulation. This action aids animal recovery by lowering leukopenia and genotoxicity in immunocompromised mice [30,31]. The lectin specific to *N*-acetyl-D-glucosamine found in *Araucaria angustifolia* seeds, historically consumed by humans since pre-Columbian times [32], has been shown to inhibit carrageenan-induced neutrophil migration and significantly reduce inflammatory paw edema, particularly at a dosage of 1 mg/kg. Carrageenan induces the secretion of pro-inflammatory and immunomodulatory cytokines, along with various inflammatory mediators including biogenic amines, prostaglandins, and nitric oxide. This investigation suggests that the lectin may disrupt the release of inflammatory mediators, thereby acting as an anti-inflammatory agent [33]. Table 1 includes a compilation of the most recent reports on dietary lectins with pro- and anti-inflammatory effects and information on their plant families, isolation parts, molecular structures, etc.

A few dietary lectins have been shown to boost the immune system through their anti-inflammatory effects, even though their effects have yet to be well documented. BmoLL, a galactose-specific lectin, was isolated from *Bauhinia monandra* leaves. This plant is popularly cooked and consumed locally in several Asian nations, including India [54]. A galactose-specific lectin from *Bauhinia monandra* leaves (BmoLL) significantly decreased leukocyte migration induced by carrageenan injection into the mice's paws. BmoLL also significantly reduced the pain caused by the intraperitoneal injection of acetic acid. This effect is most likely accomplished by inhibiting inflammatory mediators such as histamine, serotonin, and bradykinin, which BmoLL seems to suppress [55]. Similar results were obtained using a purified 60 kDa seed lectin from velvet bean (*Mucuna pruriens*). The discomfort caused by an intraperitoneal injection of acetic acid and formalin was greatly reduced by administration of pure lectin [56]. *Tetracarpidium conophorum*, a member of the Euphorbiaceae family, is usually referred to as the African walnut. This plant is widely grown throughout Africa because of its relatively high nutritional content, which can be found in nuts or seeds. A lactose/galactose-specific lectin (TcSL) with a subunit molecular weight of 34 kDa was purified from the plant seeds. The purified lectin exhibited anti-inflammatory activity by inhibiting carrageenan-induced leukocyte migration into inflammatory sites. Lectin has also shown potent antinociceptive efficacy against the pain-inducing effects of formalin in laboratory animals [57]. In a study by Coriolano et al. the impact of water-soluble Chitin-binding lectin (WSMoL) derived from *Moringa oleifera* [58], a plant known for its traditional medicinal and culinary applications, on human peripheral blood mononuclear cells (PBMCs) was explored. When administered at a concentration of 10 μg/mL for 24, 48, or 72 h, WSMoL promoted the activation of $CD8^+$ T lymphocytes and triggered the release of TNF-α, IL-2, and IL-6, which are commonly associated with pro-inflammatory responses. Moreover, WSMoL induced the secretion of IL-10, an anti-inflammatory cytokine, along with nitric oxide. These observations imply that WSMoL can have both pro-inflammatory and anti-inflammatory effects, contingent upon its concentration and specific immune milieu [59]. Soybean agglutinin (SBA) lectin has dual effects, acting as both an inflammatory agent and an anti-inflammatory agent. SBA injected into rats triggers a dose-dependent inflammatory response characterized

Table 1
Pro-inflammatory and anti-inflammatory plant lectins.

Latin name	Family	Investigated Plant Part	Lectin name	Lectin specificity	Native Mr (kDa)	Subunits Mr kDa	Immunomodulatory Response	Type	Ref
Allium cepa	Liliaceae	Tuber	ACA	Mannose	48	12 (Tetramer)	Induces: NO, TNF-α and IL-1, 2IFN-γ, IL-2	Pro-inflammatory	[27, 28]
Allium sativum L	Alliaceae	Tuber	ASAI	Galactose/mannose	25	11.5 and 12.5 (heterodimer)	Induces: NO, IFN-α	Pro-inflammatory	[34]
			ASAII	Galactose/mannose	24	12 (homodimer)			
Alpinia purpurata	Zingiberaceae	Inflorescences	ApuL	Fetuin, ovalbumin	34	oligomeric	Inducse: IFN-γ, TNF-a, and IL-6, IL-17A, NO, IL-10	Pro-inflammatory, Anti-inflammatory	[35]
Arisaema erubescens	Araceae	tubers	AEL	Asialofetuin	12	NA	Induces: Neutrophil migration, production of NO, prostaglandin, TNF-α	Pro-inflammatory	[36]
Artocarpus heterophyllus	Moraceae	recombinant	ArtinM	Mannose	35	12, 15.4 (heterodimer)	Induces: β-hexosaminidase, TNF-α activation of Mast cell	Pro-inflammatory	[37, 38]
Artocarpus hypargyreus	Moraceae	Fruit	AHL	Galactose	65.2	19 and 15 (heterodimer)	Induces: IFN-γ, TNF-α and IL-6, NO, TNF-α and IL-12	Pro-inflammatory	[39]
Bauhinia bauhinioides	Fabaceae	Seeds	BBL	Galactose	28.3	NA	Induces: TNF-α and IL1-β and inhibit neutrophil migration	Anti-inflammatory	[40]
Canavalia oxyphylla	Fabaceae	Seeds	CoxyL	Mannose/glucose	30	13, 16 (heterodimer)	Induces: Neutrophil migration	Anti-inflammatory	[41]
Centrolobium tomentosum	Fabaceae	Seeds	CTL	Mannose/glucose	27.5	NA	Induces: Neutrophil migration mediated by TNF-α	Pro-inflammatory	[38]
Clitoria fairchildiana	Fabaceae	Seeds	CFAL	Complex sugar		100, 116 (SDS–PAGE)	Induces: Neutrophil migration	Anti-inflammatory	[42]
Colocasia esculenta	Araceae	Tuber	Tarin	Mannose *N*-glycan chain	24.5	11.9 and 12.6 (heterodimer)	B-lymphocytes stimulation, leukopenia	Pro-inflammatory	[31]
Dioclea wilsonii	Fabaceae	Seeds	DwL	Mannose	25.6	12 (Dimer)	Modulation of mast cells	Don't produce pro or anti-inflammatory cytokines	[43]
Fagopyrum tataricum	Polygonaceae	Seeds	TBL	NA	65	NA	Induces: rhTNF-α, IL-10, IL-12, activation of dendritic cells	Pro-inflammatory	[44]
Moringa oleifera	Moringaceae	seeds	WSMoL	Ovalbumin, Azocasein, Asialofetuin	60	30, 20, and 10	Induces: TNF-α, IL-2, IL-6, IL-10, NO and activation of $CD8^+$ T lymphocytes	Pro-inflammatory	[45, 46]
Musa acuminata,	Musaceae	Pulp	BanLec	Glucose/mannose	60	15 (homotetramer)	Induces: IL-10, IL-17 and TNFα, Decrease: IFNγ and IL-6. increase of $CD4^+$ and a decrease of $CD8^+$ T cells	Pro-inflammatory	[47]
Parkia biglobosa	Fabaceae	Seeds	PBL	Mannose/glucose	98	47.5 (Dimer)	Induces: Neutrophil migration and production of cytokines	Pro-inflammatory	[48]
Pinellia ternata	Araceae	tubers	PTL	NA	13	13 (homodimer)	Induces: TNFα, IL-1β, IL-6, ROS	Pro-inflammatory	[49, 50]
Schinus terebinthifolius	Anacardiaceae	Leaves	SteLL	*N*-acetyl-glucosamine	14	14 (monomer)	Reduces: IL-6, MCP-1, TNF-α, and VEGF	Anti-inflammatory	[51]
Vatairea guianensis	Fabaceae	Seeds	VGL	Galactose		32, 30, 18, 15 (tetramer)	Induces: TNF-α	Pro-inflammatory	[52, 53]
zizyphus oenoplia	Rhamnaceae	Seeds	ZOSL	galactose	25	25 Monomer	Anti-allergic, anti-inflammatory	Anti-inflammatory	[45]

by exudation and neutrophil migration. This response can be suppressed by glucocorticoid treatment or coadministration of *N*-acetyl-galactosamine. SBA also attracts human neutrophils and stimulates an immune response, increasing CD4+/CD8-lymphocytes and activating macrophages. Intravenous SBA administration increases the number of circulating neutrophils and inhibits carrageenan-induced neutrophil migration, suggesting an anti-inflammatory effect in the bloodstream [60].

Oral administration of banana lectin (BanLec), a homodimeric mannose-binding protein weighing 15 kDa/unit, to experimental animals and subsequent analysis of serum from the animals for changes in cytokine secretion yielded intriguing findings [61]. The authors' research demonstrated a decrease in IFN-γ with no significant increase in IL-2 levels after *in vivo* challenge of animals with BanLec [47]. However, contradicting these results, Cheung and his colleagues demonstrated increased IFNγ, IL-2 and TNFα and decreased IL-4 and IL-10 [62]. Astonishingly, the genetically engineered BanLec given through the rectal route also provoked the secretion of IFNγ, IL-2 and IL-4. The authors attributed these variabilities to differences in the route of administration of the lectin [47]. Several dietary lectins have been detected in higher titres in the serum of many people who consume them. Anti-banana lectin (BanLec-1) IgG4 antibodies, for example, have been detected in pooled human sera. Secreted IgG4 has been shown to interact strongly with BanLec-1 via a nonlectin sugar-binding site interaction, ruling out any interaction between the sugar-binding site of the lectin and the glycosidic chains on IgG4. Furthermore, mannose did not affect such interactions [63]. This research sheds light on a naturally occurring protein in a widely consumed fruit, suggesting its potential role in influencing immune responses to infections, immune diseases, and cancer [47,64].

Partially purified lectin from *Praecitrullus fistulosus* fruit obtained using phloem exudates was examined for its anti-inflammatory/immunomodulatory effects on a carrageenan-induced mouse model and its ability to inhibit nitric oxide (NO) production. The results demonstrated significant anti-inflammatory effects compared to those in control mice, supported by reductions in myeloperoxidase activity and NO production in paw exudates [65]. Nitric oxide is a key signaling molecule involved in immune regulation and inflammatory processes. When its production is inhibited, it suggests a downregulation of immune activation and inflammatory signaling pathways. Therefore, from an immunological perspective, inhibition of NO production potentially dampens the immune response, leading to reduced inflammation. While a decrease in myeloperoxidase (MPO) production typically signifies decreased neutrophil activity or infiltration, MPO, found in neutrophil granules, serves as an indicator of inflammation severity and presence. This decrease in MPO production signifies a reduction in neutrophil activation and inflammation [66].

4. Mushroom lectins

Mushrooms are low-calorie, high-nutrient foods. They have long been acknowledged as essential to any diet due to their high concentration of health-promoting vitamins, minerals, and antioxidants. Mushrooms cultivated in the sun, for example, are high in vitamin D. As a result, it was recommended that vitamin D be incorporated into communal diet recipes during the COVID-19 pandemic as a powerful tip to boost body immunity [67,68], which is essential for bone and immune health. It is widely accepted that mushrooms boost macrophages in the immune system, strengthening their ability to fight foreign bodies [69]. In addition, the multibioactive chemicals found in edible mushrooms may contain lectins, but not all of these compounds can negatively affect human health. It is crucial to emphasize that mushroom lectins are often nontoxic to humans and do not contribute to mushroom poisoning [70]. Lectin from the fruiting body of *Pleurotus ostreatus* fruiting body, purified from immobilized desialylated hog gastric mucin, is a homodimer of 40 kDa each. Lectin binds to Toll-like receptors on dendrites, which then travel to draining lymph nodes, where they develop and produce cytokines such as IL-12 and TNF. Dendritic cells head to areas where T cells are present and perform antigen presentation. However, because recombinant HBV vaccination is ineffective at eliciting innate cellular immunity in chronic HB patients, the authors proposed *Pleurotus ostreatus* lectin as a prospective therapeutic agent that activates the TLR6 signaling pathway and elicits Tfh responses [71]. Another homodimeric *Phellodon melaleucus* lectin (PML) with a native molecular weight of approximately 85 kDa and high hemagglutinating activity was identified and purified. PML possesses complex sugar specificity, as it was not inhibited by any of the numerous simple polysaccharides employed. The thymus produces T lymphocytes, which are part of the adaptive immune system and provide cellular immunity. The spleen induces macrophages and lymphocytes. B lymphocytes (B cells) are involved in humoral immunity. PML has been demonstrated to be a possible anticancer agent by elevating the levels of numerous cytokines, including IL-10 [72]. An astonishingly thermostable galactose-specific lectin was purified from *Ganoderma capense*. The lectin was thermally stable when exposed to temperatures ranging from 0 to 100 °C, losing essentially no activity when incubated for up to 60 min at 100 °C.

Furthermore, lectin has an extremely high pH stability range of 4–10. Furthermore, it has been demonstrated to have significant mitogenic effects on splenocytes and antiproliferative effects on tumor cells [73]. Despite its intriguing stability and potential to withstand low gastric juice pH and cross the GIT barrier, there has been no evidence thus far on the immunomodulatory function of this interesting protein. *Auricularia polytricha* lectin, with a molecular weight of approximately 13.4 kDa, has the potential to activate murine splenocytes, increase their proliferation, secrete gamma-interferon (IFN-), and produce both nitric oxide (NO) and tumor necrosis factor-alpha (TNF-α) [74]. A partially purified lectin, identified as a galactose-specific agglutinin, was isolated from *Lactarius deliciosus*, a mushroom commonly known as the Delicious Milkcap or Saffron Milkcap. The partially purified lectin significantly enhanced the immunomodulatory effects on the reticuloendothelial system, boosting the phagocytic activity of macrophages and neutrophils [75]. The antitumour lectin from *Pleurotus citrinopileatus* was purified, which is maltose, *O*-nitrophenyl-β-d-galactopyranoside, O/P-nitrophenyl-β-d-glucuronide, and insulin specific. It is a dimeric protein with a molecular weight of 32.4 kDa in its natural state. The lectin was stable at temperatures up to 60 °C and at concentrations of 0.1 M and 0.006 M in NaOH and HCl, respectively. It induced a mitogenic response in mouse splenocytes *in vitro*, with the highest response occurring at a lectin concentration of 2 μM. In response to the pro-inflammatory stimulus lipopolysaccharides, *agaricus bisporus* lectin (ABL) suppressed *in vitro* nitric oxide (NO) generation by mouse peritoneal macrophages. However, it did not affect the activity of arginase (a macrophage

enzyme often thought to induce inflammation), indicating that while ABL inhibits M1 macrophage activation, it does not affect M2 macrophage activation [76]. Notably, macrophage-1 and -2 (M1 and M2) help regulate inflammation, with the former aiding in pro-inflammatory responses and the latter in anti-inflammatory responses [77].

5. Lectins may cause leaky intestinal wall diseases and autoimmune disorders

All nucleated cells and platelets express HLA class I antigens except for central nervous system cells and platelets. In contrast, antigen-presenting cells (APCs), such as B lymphocytes, dendritic cells, macrophages, monocytes, Langerhans cells, endothelial cells, and thyme epithelial cells, express HLA class II antigens [78]. Several inflammatory illnesses, including inflammatory bowel disease, diabetes, rheumatoid arthritis, and celiac disease, are related to plant-derived lectins. However, data to determine the mechanism for these inflammatory pathways still need to be included. Some dietary lectins resistant to low gastric pH and peptic digestion may adhere to the luminal membrane of intestinal cells, impair the capacity of the intestine to produce, protect, or digest food, and ultimately make their way into the bloodstream. Various cells can be bound by such lectins, such as connective tissue, liver, pancreas, thyroid, cardiac muscle, prostate, breast, brain, etc., and thereby induce the expression of class II antigens on these cells, which ordinarily do not do so. Alternatively, if a dietary lectin escapes, it may also cause the release of endotoxins such as lipopolysaccharides (LPSs), which increase gut permeability and release lectins, food antigens, and bacterial toxins into the circulatory system [79]. The LPS released from the gram-negative bacterial wall leaks into the bloodstream to the connective tissues, where it causes systemic inflammation through the inflammasome NLRP3. They also cause cartilage degradation, and high circulatory LPS results from an unbalanced microbiome with too many harmful intestinal invading bacteria [80]. Kharrazian and colleagues, for example, titrated insulin receptor alpha, ZnT8, IA2, GAD-65, and GAD-67 monoclonal and polyclonal antibodies with various dietary proteins. Their findings revealed that some of these proteins have strong to mild immunological interactions with insulin receptors, which elicit antibodies [81]. Caspase-1 is an enzyme that converts the inactive form of the inflammatory cytokines IL1β and IL-18 into their active forms, the primary inflammatory

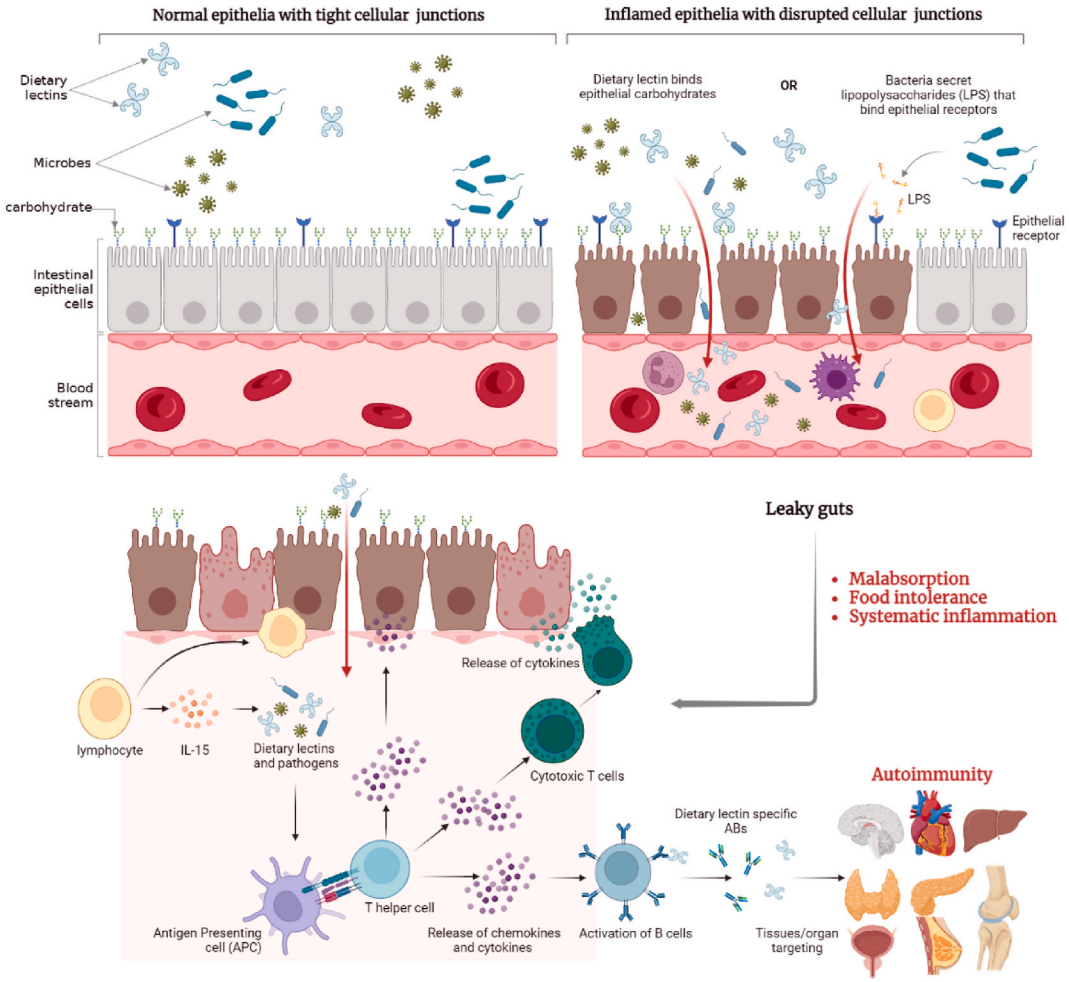

Fig. 1. Effect of dietary lectins, their target organs and plausible mechanisms of action.

mediators driving the host response to infection, injury, and illness [82]. Soyabean and Wheat Germ Agglutinins are thought to activate pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which in turn instruct oligomerization of the NLRP3 inflammasome (multiprotein complex) to activate Caspase-1. As a result, the authors hypothesize that dietary lectins may play a direct role in triggering inflammatory disorders [83]. IgA nephropathy is an autoimmune disorder characterized by the deposition of IgA and complement components in the kidney's glomeruli. These IgA deposits cause inflammation and damage to the glomeruli and nephron sclerosis [84]. Wheat germ agglutinin (WGA), red kidney bean and Soyabean agglutininins have also been proposed to be involved in the etiology of rheumatoid arthritis (RA) [85,86]. In mice, dietary lectin antigens cause the deposition of antigen-antibody IgA complexes in glomerular mesangial cells. People fed lectin-containing diets had greater levels of lectin-binding IgA activity in their blood, suggesting that such lectins may be associated with autoimmune diseases [87]. Scientists have known for decades that many people with gastrointestinal problems might be connected to bowel diseases with joint problems. Researchers have attributed the frequent co-occurrence of intestinal enhanced leakage or permeability with gut infections to this relationship [88]. Despite the attention of numerous scientists on the potential involvement of dietary lectins in initiating autoimmune diseases, conclusive evidence remains elusive (Fig. 1).

6. Plant lectins as proinflammatory and anti-inflammatory agents

Plant lectins can exhibit both pro-inflammatory and anti-inflammatory effects by interacting with various components of the immune system. They can activate immune cells and stimulate the production of cytokines, enhancing the body's defense mechanisms against infections and facilitating tissue repair. Conversely, they can also modulate immune responses to reduce inflammation, suppressing excessive immune activity and promoting the resolution of inflammation. This dual capability makes plant lectins versatile in their impact on immune regulation and inflammation management. Below are the definitions of these terms, as well as a schematic

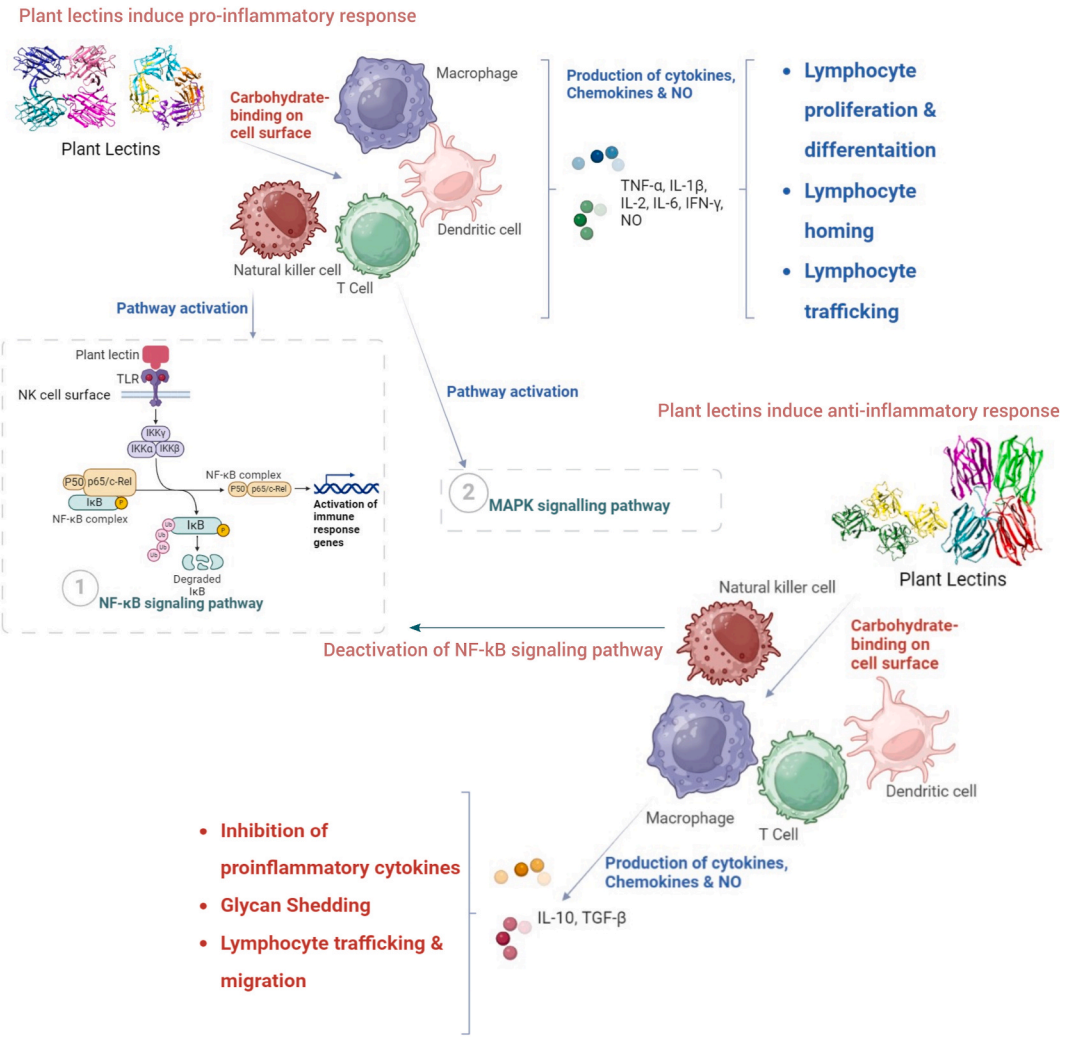

Fig. 2. Summary of plant lectins action as pro- and anti-inflammatory agents.

illustration demonstrating how plant lectins carry out these actions (Fig. 2).

7. Mechanism of proinflammatory action of plant lectins

The pro-inflammatory effect describes the body's immune response, which includes the activation and recruitment of immune cells, the production of cytokines, and various molecular mechanisms aimed at combating infections, repairing tissue, and responding to injuries. While this response is vital for defense and healing, it can sometimes result in chronic inflammation and tissue damage if not properly regulated. Plant lectins are known to induce inflammation through several key mechanisms. Their interactions with immune cells and the activation of inflammatory signaling pathways play a significant role in this process. Here's a brief breakdown of how plant lectins can induce inflammation.

7.1. Binding to glycoproteins and glycolipids

Cell Surface Receptors: Lectins bind specifically to carbohydrate structures on glycoproteins and glycolipids present on the surface of immune cells, such as macrophages, dendritic cells, and T cells. This binding can trigger cellular activation and inflammatory responses [89]. When plant lectins bind to receptors on macrophages and dendritic cells, they can induce the activation of these cells. This activation results in the production and release of pro-inflammatory cytokines such as TNF-α and IL-6 [90].

T Cells: Some lectins, like phytohemagglutinin (PHA), can directly stimulate T cells, leading to their proliferation and the production of inflammatory cytokines such as IFN-γ and IL-2 [91].

7.2. Stimulation of inflammatory signaling pathways

NF-κB Pathway: Plant lectins can activate the NF-κB signaling pathway, a key regulator of the inflammatory response. Activation of NF-κB leads to the transcription of genes encoding pro-inflammatory cytokines, chemokines, and other inflammatory mediators [92].

MAPK Pathway: Lectins can also activate the mitogen-activated protein kinase (MAPK) pathway, which plays a critical role in the production of pro-inflammatory cytokines and the regulation of inflammatory responses [93].

7.3. Cytokine and chemokine production

Pro-inflammatory Cytokines: Lectin-induced activation of immune cells results in the release of various pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IFN-γ. These cytokines amplify the inflammatory response by recruiting additional immune cells and promoting further cytokine production [94].

Chemokines: Lectins can also stimulate the production of chemokines, which are signaling molecules that attract immune cells to the site of inflammation. This recruitment of leukocytes enhances the inflammatory response [95].

7.4. Promotion of cellular adhesion and migration

Adhesion Molecules: Lectins can upregulate the expression of adhesion molecules on endothelial cells and leukocytes. This promotes the adhesion of immune cells to the vascular endothelium and their subsequent migration into tissues where inflammation is occurring [96].

Leukocyte Trafficking: By binding to specific carbohydrate structures, lectins can facilitate the migration of leukocytes to sites of infection or injury, contributing to the inflammatory response [97].

7.5. Induction of reactive oxygen species (ROS) and nitric oxide (NO)

Oxidative Stress: Lectin binding can induce the production of reactive oxygen species (ROS) and nitric oxide (NO) in immune cells. These molecules play a role in killing pathogens but also contribute to tissue damage and inflammation when produced in excess [98].

8. Mechanism of anti-inflammatory action of plant lectins

The anti-inflammatory effect refers to the processes and mechanisms by which the body reduces inflammation and prevents excessive inflammatory responses. This involves the suppression of pro-inflammatory signals, the activation of pathways that resolve inflammation, and the promotion of tissue repair and healing. Anti-inflammatory responses are crucial for maintaining balance in the immune system, preventing chronic inflammation, and avoiding tissue damage. Plant lectins, while often associated with pro-inflammatory activities, can also exert anti-inflammatory effects through various mechanisms. These mechanisms typically involve the modulation of immune responses and signaling pathways that reduce inflammation. Here's a succinct explanation of how plant lectins can exert anti-inflammatory effects.

8.1. Induction of regulatory immune cells

Regulatory T Cells (Tregs): Plant lectins can enhance Tregs, which maintain immune tolerance and suppress excessive inflammation

by producing IL-10 and TGF-β cytokines [99].

M2 Macrophages: Lectins can promote M2 macrophage polarization, associated with anti-inflammatory functions and tissue repair [100].

8.2. Modulation of cytokine production

Increase in Anti-inflammatory Cytokines: Lectins boost anti-inflammatory cytokines like IL-10 and TGF-β, inhibiting pro-inflammatory cytokine production [47].

Decrease in Pro-inflammatory Cytokines: Lectins reduce pro-inflammatory cytokines (TNF-α and IL-1β) by inhibiting related signaling pathways [101].

8.3. Inhibition of pro-inflammatory signaling pathways

NF-κB Pathway: Some lectins inhibit NF-κB activation, reducing the transcription of pro-inflammatory genes [102].

8.4. Glycan shielding

Blocking Pathogen Recognition: Lectins bind to glycans on pathogens, preventing their recognition by immune receptors and reducing inflammation.

Modulation of Cell Surface Glycans: By binding to immune cell glycans, lectins modulate signaling and decrease inflammation [103].

8.5. Antioxidant effects

Reduction of Oxidative Stress: Some lectins have antioxidant properties, reducing oxidative stress and associated inflammation by scavenging ROS [104].

8.6. Modulation of immune cell function

Inhibition of Neutrophil Migration: Certain plant lectins inhibit neutrophil migration and activation, key players in acute inflammation [105].

9. Dietary lectins as anti-cancer and immune booster agents

As discussed, it is anticipated that dietary plant lectins will grow in significance for managing inflammatory diseases in the future [106]. Their capacity to regulate immune responses and target inflammatory pathways suggests their potential as anti-inflammatory agents. These lectins can modulate immune responses and curb excessive inflammation by inhibiting the production of pro-inflammatory cytokines while promoting the generation of anti-inflammatory mediators. This dual action contributes to the resolution of inflammation [107]. Conversely, plant lectins can interact with immune cells such as macrophages, dendritic cells, and lymphocytes, promoting their activation. This activation may lead to the secretion of pro-inflammatory cytokines, chemokines, and other inflammatory mediators [12]. In a recent study focusing on dietary lectin isolated from *Phaseolus vulgaris* (red kidney beans), lectins from both boiled and raw beans were examined. Variations in sugar specificity were observed, with boiled bean lectins exhibiting specificity for *N*-acetylneuraminic acid, while raw bean lectins were specific to the glycoproteins thyroglobulin and fetuin. Both types of lectins displayed antiproliferative effects on cancer cells. Additionally, boiled bean lectins notably suppressed tumor necrosis factor-alpha and interleukin-6 expression. These findings suggest that lectins from boiled kidney beans possess anti-inflammatory and anticancer properties and could serve as chemopreventive agents [106].

In a separate investigation conducted by Ryva and colleagues (Ryva et al., 2019), wheat germ agglutinin (WGA) displayed potent cytotoxic effects against acute myeloid leukemia (AML) cells while preserving normal cells. WGA triggered dose- and time-dependent apoptosis in AML cells, independent of subtype, with minimal impact on normal cells. Its cytotoxic mechanism involved binding to *N*-acetyl-D-glucosamine (GlcNAc) and engaging with sialic acid-containing glycoconjugates. Treatment with neuraminidase, which eliminates sialic acid residues, attenuated WGA-induced cell death in AML cells. Notably, WGA administration exhibited significant *in vivo* efficacy against AML cells in a xenograft mouse model, suggesting its promise as a potential therapy for leukemia [108]. Ryvs's group did not elucidate the immunological mechanism of action that underlies the inhibition of leukemic cells. However, an independent study by da Silva and colleagues (da Silva et al., 2017) demonstrated that ArtinM, a D-mannose-binding lectin derived from jackfruit (*Artocarpus heterophyllus*), activates murine $CD4^+$ and $CD8^+$ T cells. This activation enhances the expression of their activation markers and increases cytokine production. Additionally, ArtinM induces apoptosis in Jurkat T cells, which are immortalized cell lines commonly used to study acute T cell leukemia. The lectin achieves this by recognizing aberrantly glycosylated neoplastic lymphocytes, suggesting its potential as a therapy for lymphocytic leukemia. Importantly, the lectin's mechanism of action depends on its recognition of CD3εγ-chain glycans, which triggers the activation of proinflammatory cytokines and apoptotic pathways in leukemic cells [109]. Conversely, in a separate investigation, ArtinM was observed to engage with *N*-glycosylated receptors on hematopoietic cells, stimulating migration, degranulation, and cytokine release. Furthermore, it was shown to facilitate the induction of reactive oxygen species generation and autophagy. The eventual cell death was attributed to ArtinM's recognition of particular *N*-glycan structures

[110].

10. Delivery methods and limitations in studying plant lectin immunomodulatory effects

When studying dietary lectins' immunomodulatory effects, researchers encounter challenges due to their delivery methods and agglutination properties; although orally administering lectins mimics natural intake, it presents difficulties in experimental control and reproducibility, such as susceptibility to degradation by digestive enzymes, limited absorption across the gastrointestinal tract, and vulnerability to acidic pH environments [111]. Consequently, subcutaneous (s.c.) and intraperitoneal (i.p.) injections are frequently employed in experimental studies.

Subcutaneous (s.c.) Injection: Subcutaneous administration allows for a controlled, slow, and sustained release of lectins into the systemic circulation, maintaining stable lectin levels over extended periods. This method reduces the risk of immediate systemic agglutination and provides better dosage control. However, it bypasses the digestive tract, thereby omitting interactions with gut microbiota and digestive enzymes, which are crucial for understanding the complete immunomodulatory effects of dietary lectins. In a phase I trial, subcutaneous injection of natural mistletoe lectins (nML) in healthy volunteers revealed detectable serum levels, inducing transient fever and flu-like symptoms. While nML showed prolonged detectability compared to intravenous administration, it didn't impact natural killer cell activation [112].

Intraperitoneal (i.p.) Injection: Intraperitoneal injection facilitates rapid absorption and quick onset of action, making it suitable for studies focusing on acute immunological responses. This method also helps mitigate the risk of agglutination by diluting the lectins in the peritoneal fluid. Despite these advantages, i. p. injection also bypasses the digestive tract and may cause stress and site-specific inflammation in experimental animals. In rats and mice, administering plant lectins intraperitoneally led to significant histological changes, particularly evident with wheat germ lectin (WGA) injection. WGA prompted neutrophil migration and alterations in vessel walls. Similar changes, albeit less pronounced, were observed with kidney bean lectin (PHA) injection [113].

Lectin Dosage Regulation and Monitoring: Accurate dosage regulation is critical in these studies to ensure reliable and reproducible results. Researchers select dosages based on preliminary dose-response studies and existing literature to balance efficacy and safety. Typically, lower doses are used to investigate anti-inflammatory effects, while higher doses are necessary to elicit pro-inflammatory responses. Continuous monitoring of lectin levels through biomarkers helps adjust dosages as needed to avoid adverse effects and ensure the validity of the experimental findings. In a study utilizing mistletoe lectin-I (ML-I), a galactose-specific lectin extracted from mistletoe, researchers investigated the impact of different doses of the lectin on human melanoma implanted in mice over a 19-day period. Administering a low dose of ML-I (30 ng kg−1) led to a 35 % reduction in primary tumor weight ($P = 0.03$) and a 55 % decrease in lung metastases ($P = 0.016$). ML-I promoted apoptosis in melanoma cells but not in lung metastases. Furthermore, the low dose of ML-I significantly increased dendritic cell infiltration in tumors ($P < 0.0001$) and protected them from apoptosis, whereas higher doses induced apoptosis in dendritic cells ($P < 0.01$). These findings indicate that low-dose ML-I primarily curbs melanoma growth and metastasis through immunomodulation [114].

11. Limitations and Challenges Restricting the future of dietary lectin therapy

The use of dietary lectins for therapy faces several limitations. Many dietary lectins lack specificity and selectivity, potentially leading to unintended interactions and off-target effects in the body. Additionally, their bioavailability is often limited due to degradation by digestive enzymes and poor absorption in the gastrointestinal tract. Some dietary lectins can also be toxic in high amounts or under certain conditions, necessitating careful consideration of their safety [115]. Furthermore, lectins may elicit immune responses, posing risks of allergic reactions or autoimmune reactions [10]. Determining optimal dosing regimens and addressing interindividual variability in response to lectin therapy present further challenges [116]. Regulatory approval for lectin-based therapies requires rigorous evaluation to demonstrate safety, efficacy, and quality standards. Overcoming these limitations will require collaborative efforts to enhance lectin stability, improve bioavailability, address toxicity concerns, and optimize dosing strategies, ultimately advancing the therapeutic potential of dietary lectins.

12. Conclusion and future research perspectives

This review underscores the dual nature of dietary lectins, which can either exert beneficial immunomodulatory effects or pose risks to health, particularly gastrointestinal integrity and immune function. While some lectins, such as those found in legumes, may induce gastrointestinal disturbances and trigger autoimmune disorders by binding to gut tissues, others exhibit immunomodulatory properties that could enhance immune responses. Notably, jacalin derived from jackfruit seeds exemplifies this dichotomy, initially stimulating immune cell proliferation and cytokine production but potentially leading to an immunosuppressive tumor microenvironment with prolonged exposure. The intricate interplay between dietary lectins and immune responses highlights the importance of understanding their mechanisms of action and dosages to mitigate health risks while harnessing their potential therapeutic benefits.

Further research is warranted to elucidate the precise roles of dietary lectins in immune function and autoimmune disorders. Addressing key questions regarding lectin dosages, administration routes, and mechanisms of action will be crucial in optimizing their therapeutic potential and minimizing adverse effects. Additionally, exploring the immunomodulatory effects of specific lectins from grains, vegetables, and mushrooms offers promising avenues for therapeutic exploration in cancer immunotherapy and immune-related conditions. By deepening our understanding of the impact of dietary lectins on immune responses, we can pave the way for more targeted interventions and personalized approaches to immune health and disease management.

CRediT authorship contribution statement

Emadeldin H.E. Konozy: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Makarim Elfadil M. Osman:** Writing – review & editing, Writing – original draft, Validation, Data curation, Visualization.

Data avaliability statement

All data relevant to this review article are included within the manuscript. There are no additional datasets to be made available.

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