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Review Article

Aging and Immune Receptor Signaling: Molecular Mechanism Investigation to Pharmacological Intervention

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ABSTRACT

Immunological receptor signaling maintains homeostasis and prevents infections. Significant immune system changes like immunosenescence decrease innate and adaptive immunity. This lowers resistance to cancer, autoimmune illnesses, and infections. Dysregulation of crucial immunological receptors, such as BCRs, TLRs, and TCRs, and disruptions in signaling pathways, such as NF-κB, MAPKs, and JAK-STAT, in senescent immune cells, worsen immunosenescence. Targeting immune receptor signaling with drugs may reduce these effects. TNF-α and IL-6 inhibitors substantially reduce chronic inflammation. Cancer treatment with immune checkpoint inhibitors and T cell activation may revive the immune system. In older persons and others with weak immune systems, many artificial medications have been studied to boost immunity. These drugs reduce inflammation, modify immune receptor signaling, and boost innate and adaptive immune responses. These include imiquimod, IL-2 analogs, interferons, and rapamycin. Synthetic immune-boosting drugs are included. New pharmaceutical medicines may help elderly people fight immunosenescence and boost immunological resilience.

Keywords: Immunosenescence, Inflammation, Immune surveillance, Immune checkpoint inhibitors, Natural and synthetic drugs used as immunity boosters aging.

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INTRODUCTION

Cell signalling cascades produce immunological responses (Yousefpour *et al.*, 2023 and Lukácsi *et al.*, 2020). Immunity-boosting synthetics in immunocompromised or elderly patients, several synthetic medications and pharmacological substances have been tested for immunity-boosting properties.

Multiple infections share proteins produced and receptors on innate immune system cells (Cerny and Striz *et al.*, 2019). After identification, these receptors activate signaling pathways by transcribed inflammation-related genes and antimicrobial defenses (Figure 1).

RECEPTOR ENGAGEMENT

Antigens or Pathogen-Associated Molecular Patterns (PAMPs) are recognized and bound by immune receptors. T cells have TCRs, B cells have BCRs, and innate immune cells, including macrophages and dendritic cells have PRRs. (Zhang *et al.*, 2022) By beginning a cascade of intracellular signaling events, these receptors help the immune system recognize and respond to infections (Stogerer and Stager *et al.*, 2020; Dominguez *et al.*, 2023).

Initiation of Signalling Cascade

Immune receptors cluster or dimerize, conform, and attract kinases and adaptor proteins when they engage with their ligands, such as antigens or pathogen targets (Li and Wu *et al.*, 2021).

Activation of Intracellular Signalling Pathways

Immune receptor activation activates kinases like ZAP-70 and SYK and phosphatases. Diacylglycerol (DAG), Inositol Trisphosphate (IP3), and Calcium Ions (Ca^{2+}) are released throughout this signaling cascade as second messengers. These chemical intermediates boost signaling, activating immune cells (Sim *et al.*, 2020).

Many biological activities depend on key signaling routes, which are limitless:

NF-κB pathway: Involved in inflammation and immune response gene transcription (Asl *et al.*, 2021).

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MAPK pathway: Controls cell proliferation, differentiation, and survival (Zhang *et al.*, 2021).

PI3K-Akt pathway: Important for cell growth, survival, and metabolism (Liu *et al.*, 2020).

JAK-STAT pathway: Common in cytokine signaling, controlling gene expression (Philips *et al.*, 2022) (Figure 2).

Transcriptional Activation

Intracellular signaling pathways promote immune response gene transcription by translocating transcription factors like NF-κB, NFAT, and AP-1 into the nucleus (Figure 3). Genes encode Cytokines (IL-2, TNF-α), Chemokines (CXCL8), surface proteins (CD40L on T cells), and antibodies (B cells) (Zhang *et al.*, 2020; Gulow *et al.*, 2024).

Effector Functions

Signaling proliferates and differentiates regulatory, cytotoxic, and helper T cells. Encourages B cells to mature into antibody-secreting plasma cells. Pathogen-infected or cancerous cells are targeted by NK cells (Tang *et al.*, 2021 and Goodier *et al.*, 2020).

Signal Termination and Regulation

Phosphate recruitment (SHP-1/2) dephosphorylates key signaling molecules via detrimental feedback mechanisms that strictly control immune receptor signalling (Laletin *et al.*, 2023). To prevent excessive immune activation and autoimmunity, checkpoint molecules like PD-1 and CTLA-4 limit ubiquitin-mediated signaling component degradation (Hu *et al.*, 2021).

AGING AND IMMUNE RECEPTOR SIGNALLING (IMMUNOSENESCENCE)

Immunosenescence-a reduction in innate and adaptive immunity-occurs as people age. It modulates immune receptor signaling as follows:

T-Cell Receptor (TCR) Signalling

Age-related T-Cell Receptor (TCR) signaling changes reduce T cell antigen sensitivity (Zhang *et al.*, 2021). Lck and ZAP-70, which initiate TCR signaling, can be affected. Aged T cells have decreased calcium signaling, NF-κB, and NFAT transcription factor translocation, affecting their fundamental function (Ono *et al.*, 2020).

B-Cell Receptor (BCR) Signalling

Seniors' B cells produce fewer high-affinity antibodies (de Mol *et al.*, 2021) Impaired B Cell Receptor (BCR) signaling decreases downstream pathway activity, such as the PI3K and MAPK pathways, and alters critical signaling molecule expression, including SYK (Liu *et al.*, 2020).

Innate Immune Receptor Signalling

Pattern Recognition Receptors (PRRs), like Toll-Like Receptors (TLRs), lose signaling capacity with age (Connors *et al.*, 2022). Reduced pathogen detection and pro-inflammatory cytokine production. During aging, low-level inflammation called "inflammaging" fuels age-related diseases (Yue *et al.*, 2021).

Protein constancy and proteostatistic mechanisms throughout aging are discussed (Figure 4). Abnormal protein ROS buildup, ubiquitin-proteasome pathway failure, chaperone overload, and autophagy degeneration all contribute to protein homeostasis and functional decrease in senior age. Recent research highlights the importance of BAG 3 sesquestosome and HDAC6 in aggresome

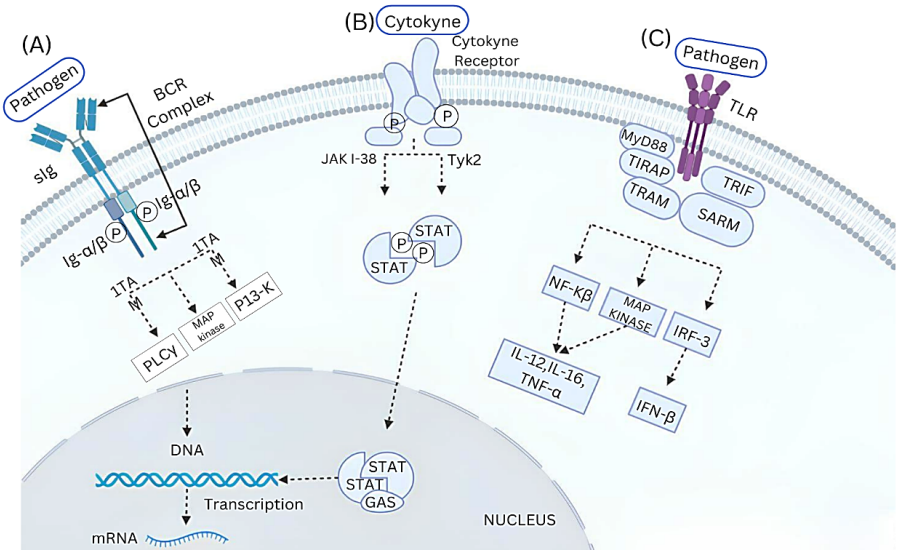


Figure 1: Immune cell signaling. A: Antigen receptor signaling; B: Cytokine receptor signaling; C: TLR-signalling.

formation, modulating HDAC 6, histone deacetylase 6 (Gray and Gibbs *et al.*, 2022).

PHARMACOLOGICAL INTERVENTIONS TARGETING IMMUNE RECEPTOR SIGNALLING IN AGING

Multiple pharmaceutical approaches are being investigated to reverse aging-related immune receptor signaling decrease. These include:

Immune Modulators: PD-1 inhibitor nivolumab activates T-cells in elderly adults. Antibiotic and cancer inhibitors may strengthen older people's immune systems (Federico *et al.*, 2020).

mTOR Inhibitors

Cell growth and immune responses are mediated by mTOR. Rapamycin (Figure 5) boosts vaccination responses, age-related inflammation, and T-cell function. It may restore youthful immunology by balancing immune receptor signalling (Bjedov and Rallis *et al.*, 2020).

Palmitoyl-cysteine

Palmitoyl-cysteine (Figure 5) thioester attaches a 16-carbon fatty acid, palmitate, to a protein's cysteine residue, "anchoring" it to a cell membrane by making it more hydrophobic. Palmitoyl Acyltransferases (PATs) "ping-pong" the palmitate group from

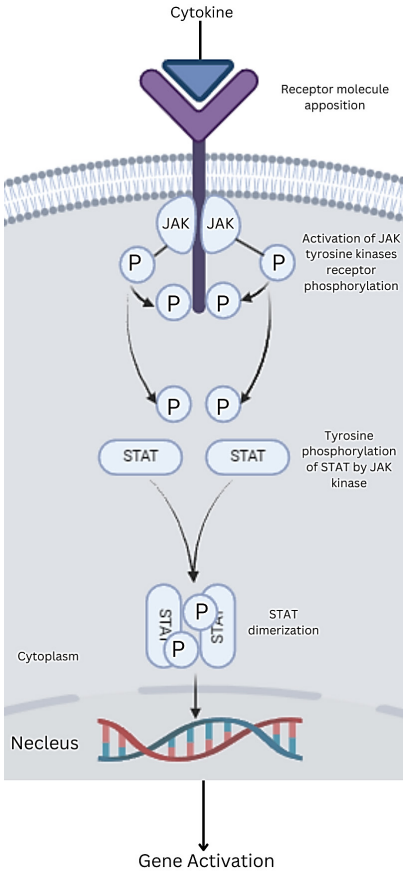


Figure 2: Cytokine Signalling Pathway.

Table 1: Anti-PD1 Checkpoint inhibitors.

Name	Initial US Approved	Manufacturer	References
Pembrolizumab (Keytruda)	2014	Merck and Co	(Hassel *et al.*, 2017)
Nivolumab (Opdivo)	2014	Bristol-Myers Squibb	
Cemiplimab (Libtayo)	2018	Regeneron	
Dostarlimab (Jemperli)	2021	GlaxoSmithKline (GSK)	
Retifanlimab (Zynyz)	2023	Incyte Corporation	
Toripalimab (Loqtorzi)	2023	Coherus BioSciences	
Tislelizumab (Tevimbra)	2024	BeiGene	

Table 2: Deferent action of Immunostimulants.

Name of immunostimulants	Action	Reference
Recombinant cytokines	An immunostimulant that acts on the immune system.	(Namdeo, *et al.*, 2021)
Monoclonal antibody cytokine antagonists.	An immunostimulant that acts on the immune system.	
Monoclonal antibodies	An immunostimulant that prevents cancer cells from evading the immune system.	
Bacterial vaccines, Colony stimulating factors, Interferons, Interleukins, Vaccine combinations, Therapeutic vaccines, Viral vaccines.	An immunostimulant	

palmitoyl-CoA to the target protein's cysteine residue to influence protein localization and function in the cell (Federico *et al.*, 2020).

Senolytics

These compounds selectively release inflammatory molecules and kill non-proliferating senescent cells. Dasatinib and quercetin (Figure 5) can reduce chronic inflammation and improve immunological function in older persons by suppressing senescent cell pro-inflammatory signals (Zhang *et al.*, 2022).

Cytokine Therapies

Increase immunity, cytokine treatments are being explored because aging damages immune receptor signaling pathways. IL-7 may increase older people's T-cell responses by maintaining homeostasis (Pereira *et al.*, 2020).

Antioxidants and Anti-inflammatory Drugs

NSAIDs and TNF-α inhibitors can reduce chronic inflammation caused by immune receptor modifications. Despite reducing inflammation, their extensive immune modulation effects require caution (Stromsnes *et al.*, 2021).

Anti-PD-1 Checkpoint Inhibitors

Anti-PD-1 checkpoint medicines or other immunotherapies that block the PD1/PDL1 immune checkpoint proteins can destroy cancer cells. Many PD1 and PDL1 checkpoint inhibitors have been launched recently. Table 1 lists class essential medications. Programmed Death-1 (PD-1) on T-cells controls immune tolerance and prevents autoimmunity. Malignant cells avoid immune recognition by overexpressing PD-L1, which causes T-cell fatigue and immunological suppression. The immune system's ability to fight cancer is boosted by anti-PD-1 checkpoint inhibitors, which block PD-1. T cells can destroy tumor cells when PD-1 attaches to PD-L1, a protein in some normal or cancerous cells. This protein tells the T cell to leave the other cell alone by preventing PD-L1 from connecting to PD-1 (Figure 6).

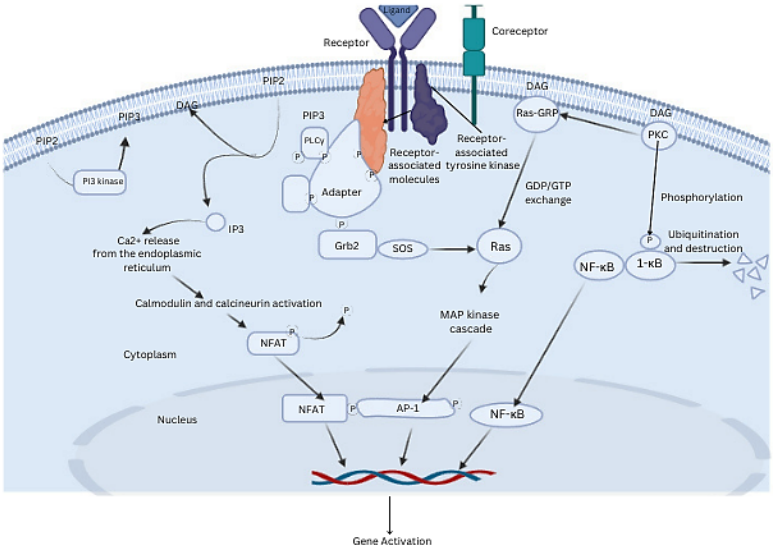


Figure 3: Lymphocyte Signalling.

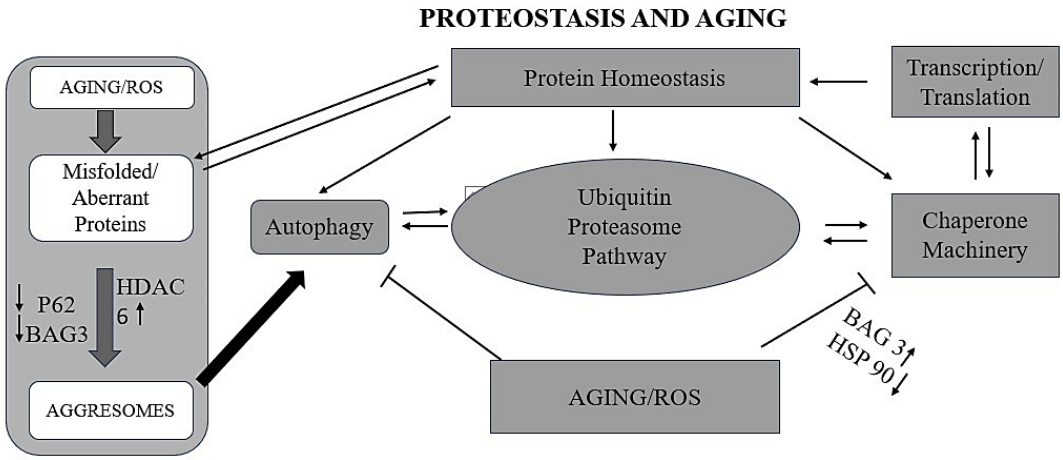


Figure 4: Mechanisms to modulate proteostatistic during aging.

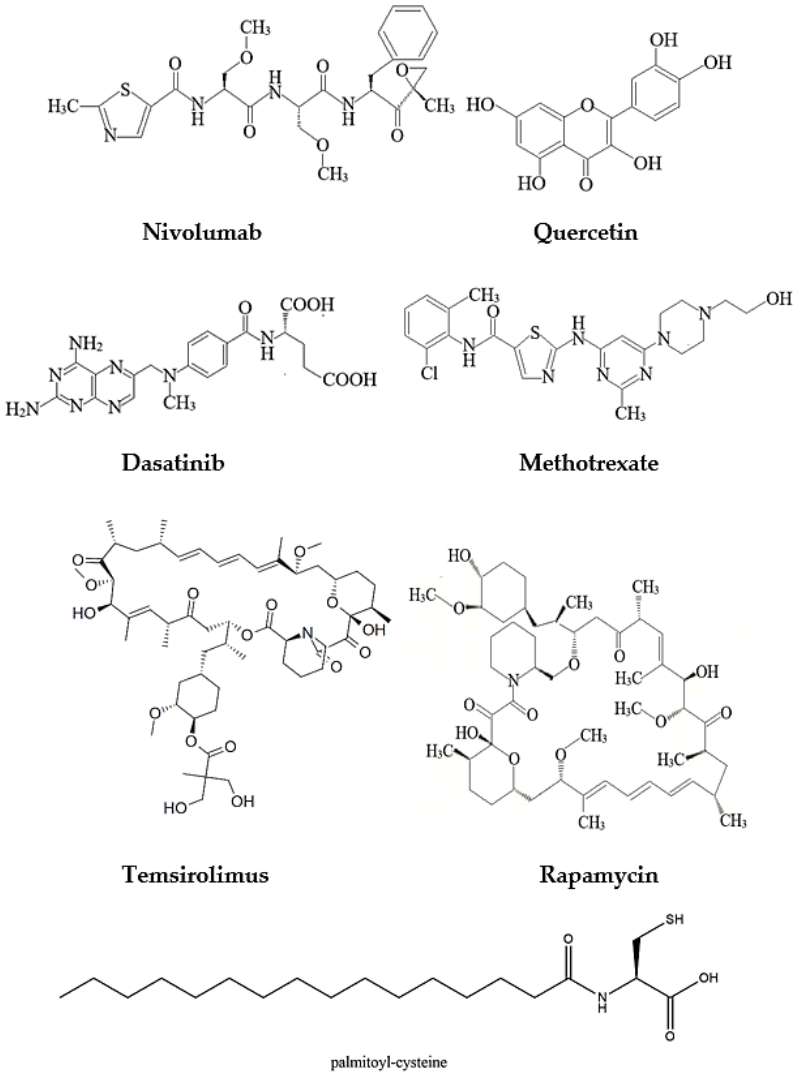


Figure 5: Chemical structure of various drugs.

Immunity booster: Immunostimulants, which can be chemically or naturally created, boost biological defences. Some immunostimulants are:

Acute lung infections and COPD may be treated with immunostimulants. *Ex vivo* immune cell modification for *in vivo* use and protein design for logical immune system modification have been studied extensively. Table 2 lists some synthetic immunostimulants and their mechanisms and uses.

Synthetic drugs used as an immunity booster

Pharmacological and synthetic drugs have been researched for immune enhancement, especially in elderly or immunocompromised patients. These drugs reduce chronic inflammation, boost innate and adaptive immune responses, or modify immune receptor signaling. Table 3 covers many crucial synthetic immunity-boosting drugs.

AGING-RELATED CHANGES IN DRUG METABOLISM AND PHARMACODYNAMICS

In older adults, immune receptor signaling drugs must be processed differently due to aging.

Altered Pharmacokinetics: Aging-related liver and renal function changes can affect drug metabolism and clearance, requiring dose adjustments. Methotrexate, an immunologic receptor, regulates immune responses in autoimmune diseases. A cell membrane usually contains this receptor (Sameer and Nissar *et al.*, 2021).

Types of receptors

The main immune system receptors are PRRs, TLRs, Killer-Activated and Killer Inhibitor Receptors (KARs and KIRs), complement receptors, Fc receptors, B cell receptors, and T cell receptors. The receptor targets and their functions are listed in Table 4 (Weinan *et al.*, 2021 and Alexander *et al.*, 2021).

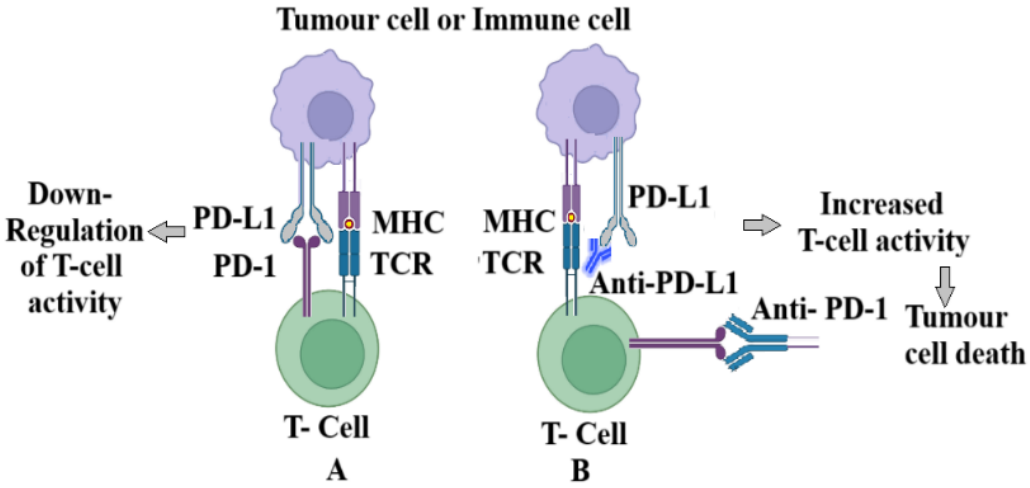
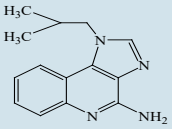
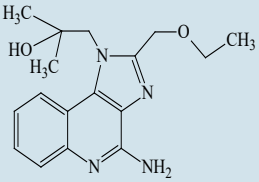
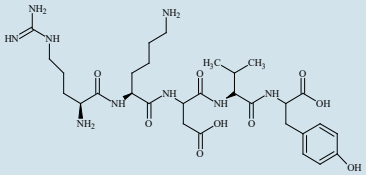
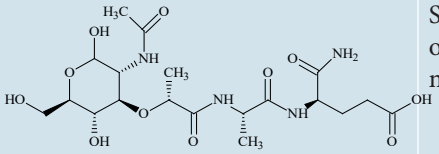
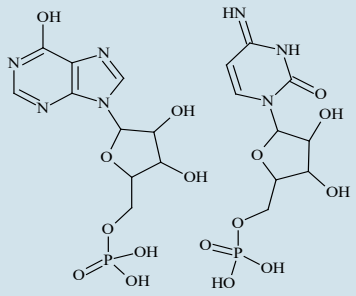


Figure 6: PD1 and anti-PDL1 T-cell activity mechanisms. Activated T-cells in secondary lymphoid tumor tissue (A) increase PD-1 expression. PD-1 binding to its ligands inhibits TCR signaling and controls T-cell activity. (B)Antibody-exhausted T-cells targeting PD-1 or PD-L-1 at the tumor site increase activity and T-cell-mediated tumor cell death.

Table 3: Synthetic drugs used as an immunity booster.

Drug name	Structure	Mechanism	Application	References
Imiquimod ($C_{14}H_{16}N_4$)		Activating toll-like receptor7 on immune cells stimulates cytokine production (TFN- α, IL).	Treat skin conditions (Keratosis) and basal carcinoma.	(Geering and Fussenegger *et al.*, 2015)
Resiquimod ($C_{17}H_{22}N_4O_2$)		Activating toll-like receptor7 and 8 enhancing immune responses by stimulating the production of pro-inflammatory cytokines like IFN-α and TNF-α.	Skin cancers, viral infections, adjuvant vaccines.	
Thymopentin ($C_{33}H_{50}N_{10}O_9$)		Stimulates T-cell activity and increases IL-2 production.	Autoimmune disease disease, adjuvant in cancer therapy.	
Muramyl Dipeptide (MDP) ($C_{19}H_{30}N_4O_{12}P_2$)		Stimulates the production of cytokines and activates macrophages.	Cancer treatment, infectious disease, and autoimmune disease.	
Poly ICLC ($C_{10}H_{13}N_4O_6P$)n		Stimulates interferon production and activates natural killer cells.	Cancer immunotherapy, antiviral immunity.	

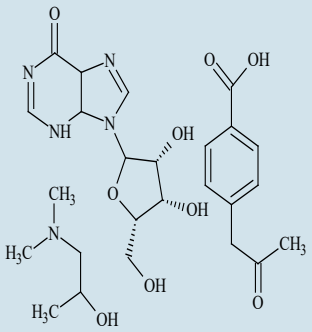
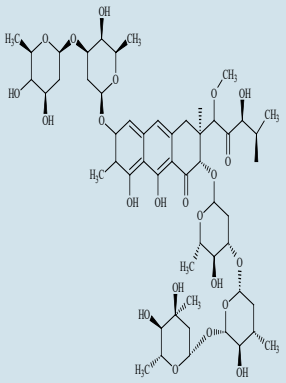
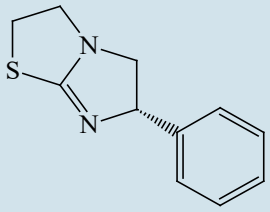
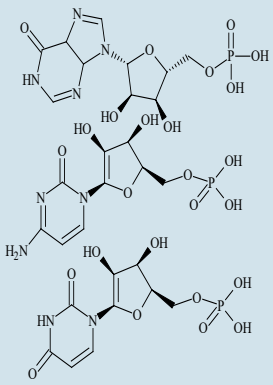
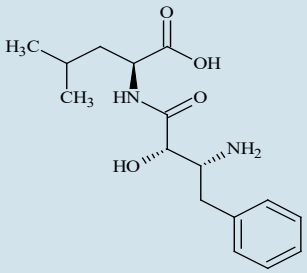
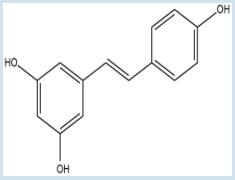
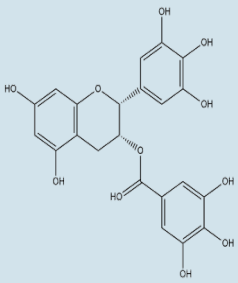
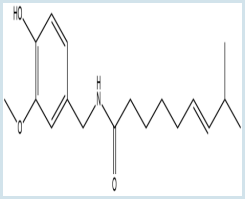
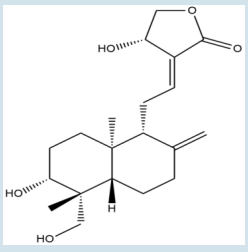
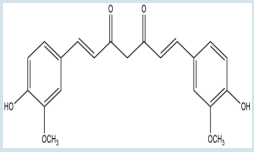
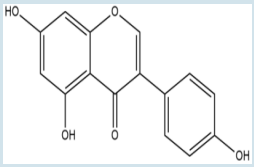
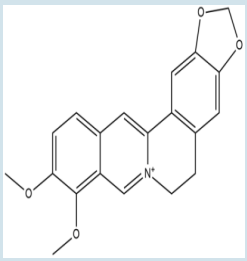
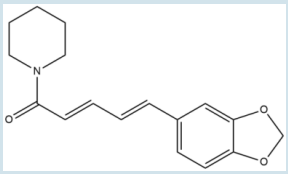
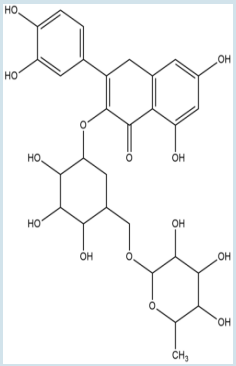
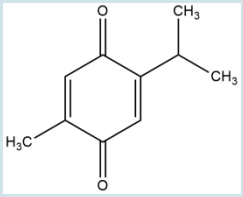
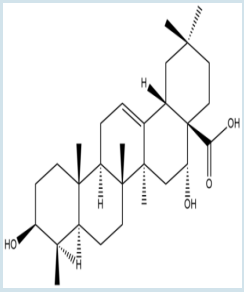
Isoprinosine ($C_{17}H_{25}N_5O_3$)		Activates natural killer cells and macrophages.	Viral infection, immunodeficiency disorders.	
Mithramycin ($C_{52}H_{76}O_{24}$)		Stimulates the production of cytokines and activates macrophages.	Cancer treatment, infectious disease, and autoimmune disease.	
Levamisole ($C_{11}H_{12}N_2S$)		Stimulates T-cell and macrophage activity.	Immunomodulator, parasitic worm infection, adjuvant in cancer therapy.	
Poly A: U $(C_{10}H_{12}N_5O_6P)_n$	----------	Stimulates the production of interferons and activates natural killer cells.	Cancer treatment, infectious disease, and autoimmune disease.	
Ampligen $(C_{10}H_{12}N_5O_6P)_n$		Stimulates the production of interferons and activates natural killer cells.	Cancer treatment, infectious disease, and autoimmune disease.	
Bestatin ($C_{16}H_{24}N_4O_5$)		Stimulates the production of cytokines and activates macrophages.	Cancer treatment, infectious disease, and autoimmune disease.	

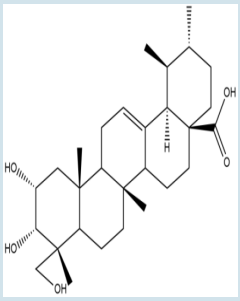
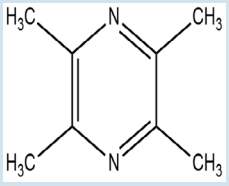
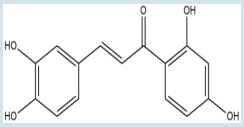
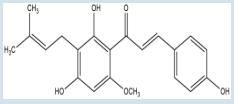
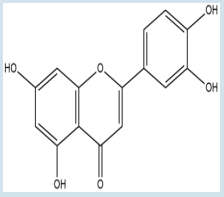
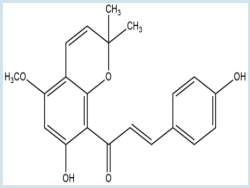
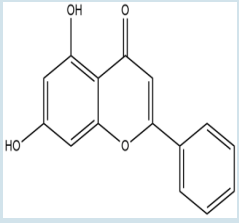
Table 4: Comparison of different receptor targets and associated functions.

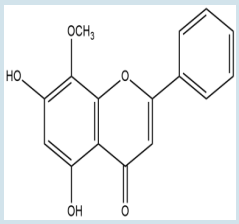
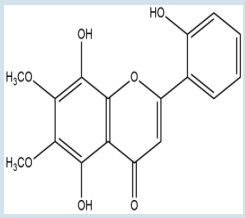
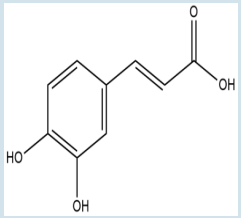
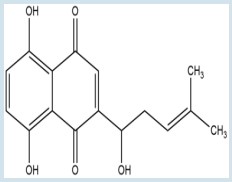
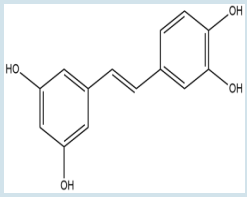
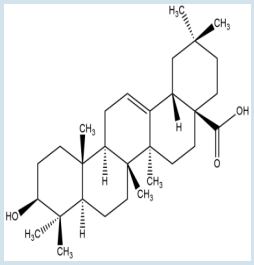
Receptor	Bind to	Function	References
Pattern recognition receptors (PRRs) (TLRs, NLRs)	Pathogen-Associated Molecular Patterns (PAMP).	Mediate cytokine production →inflammation →destroyingpathogen	(Bull SC and Doig *et al.*, 2015)
Killer-activated and killer inhibitor receptors (KARs and KIRs)	----------	It enablesNK cells to identify abnormal host cells (KAR) or inhibit inappropriate host cell destruction (KIR).	
Complement receptors	Complement proteins on microbes	Allow phagocytic and B cells to recognize microbes and immune complexes.	
Fc receptors	Epitope-antibody complexes	Stimulate phagocytosis	
B cell receptors	Epitopes	B cell differentiation intoplasma cells and proliferation.	
T cell receptors	Linear epitopes bound to MHC	Activate T cells	
Cytokine receptors	Cytokines	Regulation and coordination of immune responses.	

Table 5: Natural immunomodulator and immunostimulator.

Plant Name	Drug Name	Structure	Mechanism	Application	References
Grape	Resveratrol		By blocking NF-**κB** in LPS and PMA and blocking COX-2	Anti-inflammatory, anticancer	(Kleiser S and Nystrom *et al.*, 2020, Okcu *et al.*, 2024, Abdel-Tawwab *et al.*, 2022 and Mezosi-Csaplr *et al.*, 2022)
Green Tea	Epigallocatechin-3-gallate		By blocking NF-**κB** in LPS and PMA and blocking COX-2	Anti-inflammatory, anticancer	
Chill Paper	Capsaicin		Inhibits activation and migration of neutrophils to sites of inflammation	Treat the familial Mediterranean fever and acute gout flares (FAD approved)	
Green Chiretta	Andrographolide		Inhibits cancer cell growth by immunomodulatory effect and anti-inflammatory	Treat cancer	

Turmeric	Curcumin		Increase WBC count	Antiproliferative, anticancer, proapoptotic, antiangiogenic, and antioxidant	
soybean	Genistein		Produce NO and PGE2, increase insulin resistance	Treat diabetes	
Huanglian	Berberine		Down -regulate T-helper cells cytokines Th 1 and Th 2 production.	Treat diarrhea and wound infection.	
Long Pepper	Piperine		Reduce proinflammatory cytokines IL-1β, IL-6 and TNF- α	Analgesic, carminatives, immunostimulant, and to treat asthma, insomnia, diabetes, epilepsy	
Rue	Rutin		Inhibit leukocyte migration, suppress production of TNF-α and IL-6, and Inhibit activation of NF-κ B and extracellular regulated kinases.	Rheumatism, dermatitis, analgesic etc.	
Black Caraway	Thymoquinone		Inhibited LPS-induced fibroblast proliferation and H_2O_2-induced 4-hydroxynonenal generation.	Anti-inflammatory, antioxidant, anticancer properties.	
Sponge gourd	Echinocystic acid		Enhance phagocytic index of macrophages in humoral and cell-mediated immune responses.	Rheumatism, chest pain, back ache, orchitis.	

Madecassol	Asiaticoside		Decrease NO production	Wound healing, treating trauma, improving cognitive function	
Szechuan lovage	Tetramethylpyra-zine		Inhibit pro-inflammatory cytokines and reactive oxygen species production. Inhibit macrophage chemotaxis, neutrophile infiltration, and nitric oxide synthase activity. Block the phosphorylation of p38 mitogen-activated protein kinase.	Kidney injury, cancer, cardiovascular disease.	
Oriental cashew	Butlin		Suppress NO production by attenuating iNOS expression. Inhibit translocation of NF-**κB**.	Anticancer, anti-inflammatory, and antioxidant properties.	
Japanese hop	Xanthohumol		Inhibit NO production, which LPS and INF-γ induce.	Anticancer, antimicrobial properties.	
Japanese honeysuckle	Luteolin		Decreased secretion of inflammatory mediators (INF-γ, IL-6) reduced COX-2, ICAM-1 expression.	Cancer, pain, and brain disease.	
Mandarin or Tangor	Nobiletin		Inhibit pro-inflammatory mediators, COX-2, and iNOS expression by blocking NF-**κB** and MAPK signaling pathways.	Nti cancer, liver disease, antiviral, liver disease, osteoporosis, metabolic syndrome.	
Baikal Skullcap	Oroxylin A		Inhibit NO production and iNOS and COX-2 protein expression via inhibiting nuclear factor-**κB** pathway.	Cancer therapy, anti-inflammatory activity, metabolic regulation, neuroprotective effect, etc.	

Baikal Skullcap	Wogonin		Inhibit adhesion and migration of leukocytes by inhibiting cell adhesion molecule expression. Reduces allergic airway inflammation by inducing eosinophil apoptosis through activation of caspase-3	Treating cancer, inflammation, and neurodegenerative diseases.	
Somerset Skullcap	Baicalein		Inhibit mRNA expression of iNOS, COX-2, and TNF-α. Inhibit production of NO and inflammatory cytokine regulating NF-**κB** and ER-dependent pathway.	Anti-inflammatory, antioxidant, and antibacterial properties.	
Curry plant	Arzanol		Reduce eicosanoids generation by inhibiting lipooxygenase and cyclooxygenase activity in the arachidonic acid metabolism pathway.	Anti-inflammatory and anti-allergic properties.	
Purple/red Gromwell	Shikonin		Inhibit NF-**κB** activity, inhibit Th1 cytokines expression, and induce Th2 cytokines.	Antiviral and biological activities.	
Japanese Knotweed	Piceatannol		Decrease iNOS expression. Inhibit transcription factors activation such as NF-kB, ERK, and STAT3.	Antioxidant, antiviral, antibacterial, anti-inflammatory and anticancer properties.	
Sponge gourd	Oleanolic acid		Reduce the level of IL-1α, IL-6, and TNF-α, as well as their effect on the complement pathway through inhibiting C3 convertase. Inhibits adenosine deaminase activity.	Rheumatism, chest pain, orchitis, backache, haemorrhage etc.	

Natural immunomodulator and immunostimulator

Chemical drugs have negative effects, thus natural immunomodulators may substitute them (Table 4) (Shariatinia *et al.*, 2019). Most R&D efforts focus on biochemicals, biologics, or single molecules that target disease targets. It's difficult to create single-molecule medicines with low toxicity, high selectivity, and efficacy for molecular/cellular targets and diseases.

Natural Immunomodulators and Immunostimulators

Naturomodulators and immunostimulators from fungus, plants, and other sources control and stimulate immune responses. They boost or suppress immunity depending on biological needs. Table 5 lists its key categories and instances.

Signaling Through Immune System Receptors

Cells can interact with their surroundings via cell-surface receptors that bind extracellular chemicals (Ruckert and Romagnani *et al.*, 2024). Since T and B lymphocytes respond to antigens, their antigen receptors are the most important and well-studied. The present work will focus on intracellular signals from antigens binding to these receptors that change cell behaviour (Muntjewerff *et al.*, 2020).

CONCLUSION

Immune receptor signaling, aging, and pharmacology ends with immunology, aging biology, and drug development. Desenescence affects innate and adaptive immunity. Age reduces the efficiency or dysregulation of immunological receptor signaling, such as TCRs, PPRs, and cytokine receptors. Immune system changes weaken it, making it more prone to infections, cancer, and inflammatory disease, and poor vaccination response. Age-related alterations may be reversed by immune receptor signaling medications. They boost immune surveillance, resolve chronic inflammation, and restore immunological function. Older individuals' immune systems are being examined with immune checkpoint inhibitors, cytokine modulators, senolytics, and mTOR inhibitors. This review includes immune receptor signaling, aging, and immunological senescence pharmacological treatments, but the subject is evolving. Researchers are discovering the complex link between immune receptor networks and age-related immunological decline. Investigating innovative routes and medicinal methods to understand immune-senescence and its regulation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

mTOR: Mammalian Target of Rapamycin; **NK:** Natural Killer; **PAMPs:** Pathogen-Associated Molecular Patterns; **TCRs:** T-Cell Receptors; **BCRs:** B-Cell Receptors; **PRRs:** Pattern Recognition Receptors; **DGA:** Diacylglycerol; **IP3:** Inositol Trisphosphate; **JAK-STAT:** Janus Kinase (JAK) Signal Transducer and Activator of Transcription (STAT); **NFAT:** Nuclear Factor of Activated T Cells; **TNF-α:** Tumor Necrosis Factor-Alpha; **CXCL8:** C-X-C Motif Chemokine Ligand 8; **CD40L:** Cluster of Differentiation 40 Ligand; **SHP-1/2:** SRC Homology Region Two Domain-Containing Phosphatases 1 and 2; **CTLA-4:** Cytotoxic T-Lymphocyte-Associated Protein 4; **ZAP-70:** Zeta-Chain-Associated Protein Kinase 70; **TLRs:** Toll-Like Receptors; **UPP:** Ubiquitin Proteasome Pathway; **ROS:** Reactive Oxygen Species; **BAG 3:** Bcl2-Associated Athanogene 3: **HDAC6:** Histone Deacetylase 6; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **TLRs:** Toll-Like Receptors; **KARs:** Killer-Activated; **KIRs:** Killer Inhibitor Receptors; **MHC:** Major Histocompatibility Complex; **NO:** Nitric Oxide; **LPS:** lipopolysaccharide; **NF-κB:** Nuclear Factor Kappa B; **IL:** Interleukin; **Th1:** T helper 1; **Th2:** T Helper 2; **PGE2:** Prostaglandin E2; **WBC:** White Blood Cell; **COX:** Cyclooxygenase; **PMA:** Phorbol 12-Myristate 13-Acetate; **TCR:** T Cell Receptor; **MCH:** Mean Corpuscular Haemoglobin; **Inos:** Inducible Nitric Oxide Synthase; **MCP-1:** Monocyte Chemoattractant Protein-1; **IL-1β:** Interleukin-1-Beta; **INF-γ:** Interferon Gamma; **ICAM-1:** Intercellular Adhesion Molecule-1; **mRNA:** Messenger Ribonucleic Acid; **NADPH:** Nicotinamide Adenine Dinucleotide Phosphate; **CD4+:** A cluster of differentiation four positive; **CD8+T:** Cytotoxic T cells that have a Cluster of Differentiation Eight Proteins on their Surface; **ERK:** Extracellular Signal-Regulated Kinase.

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