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REVIEW ARTICLE

Inhibiting toll-like receptors: a comprehensive review of emerging strategies and potential therapeutic implications

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ABSTRACT

Toll-like receptors (TLRs) mediate the inflammatory response by synthesizing and activating various pro-inflammatory mediators through innate immunity. Irrationally TLRs over activation disrupt homeostasis that in turn overproduces cytotoxic cytokines. All such events subsequently enhance the progression of numerous immune system-related disorders. For instance, the overexpression of TLRs is now considered the basis of sepsis, endotoxemia, rheumatoid arthritis, acute kidney injury, acute lung injury, systemic lupus erythematosis, and cardiovascular diseases. The normal physiological pathways of TLRs, as well as some TLR4 inhibitors, are discussed in this review. These drug mixtures range from ordinary small molecular compounds to soothing biologics and nano devices. Specifically, these are either synthesized or obtained from natural resources. Natural TLR4 antagonism has wide therapeutic applications and various synthetic and natural metabolites are under excessively testing involving drug discovery. Nanoparticles are arising as a drug delivery system for powerful TLRs inhibitors of their notable properties for the improvement in bioavailability, supported course, and favored pharmacodynamic and pharmacokinetic profiles. All things considered, these discoveries and continual investigations of TLRs antagonism might change the pharmacological management of various diseases.

Keywords: Toll receptors, signaling pathways, TLR4 receptors antagonist, Natural metabolites.

Introduction

Pattern recognition receptors (PRRs) were initially discovered by scientist Janeway in 1989, who proposed that there are numerous receptors in the human cell that sense specific patterns and were called pattern recognition receptors (PRRs). These receptors can identify specific patterns such as pathogen/ danger-associated molecular patterns (PAMPs/DAMPS).[1] These patterns are specific for each pathogen. These are present on innate immune cells and distinguish self or non-self-structures.[2] These receptors are located at the cell surface as well as on some intracellular compartments of lysosome or endolysosome, endoplasmic reticulum, and endosome.[3] In humans, different classes of PRRs are discovered until now, and toll-like receptors (TLRs) are also included. TLRs family has 11 members from TLR1 to TLR11.[3] Initially recognized by Medzhitov and co-workers in 1997.[4]

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Each TLR has a different recognition pattern, extra- or intracellular localization, and signaling pathway. These type I transmembrane integral receptors for endogenous ligands mediate inflammatory immune responses in the host body.[5]

Signals from PRR binding with the immune cells stimulate pro-inflammatory and microbicidal responses obligatory to eradicate the infectious agents or have a bacteriostatic effect. A signal transduction mechanism is activated that controls cell death through apoptosis.[6]

Among all TLRs, TLR4 is the most studied receptor mainly involved in the aggravation of innate immunity and activation of inflammatory mediators by identifying lipopolysaccharides (LPS) or bacterial endotoxins. TLR4 over activation leading to sepsis, end toxemia, acute lung injury, cardiovascular diseases, and rheumatoid arthritis such as LR2, TLR7 over activation is involved in systemic lupus erythematosis.[7] Furthermore, TLR7/8 dysregulation is linked to autoimmune disorders, cancer, and some other inflammatory disorders.[8] To halt the progression of these diseases, various TLRs antagonists are needed with the ability to down regulate these receptors and for such purpose,

different molecules are under clinical trials.[9] The normal signaling pathway along with the signal transduction mechanism of TLR4 inhibitors is explained in the current review. Furthermore, the possible pathways through which TLR4 inhibitors may possibly bind to their receptors are also discussed.

1. STRUCTURE OF TLRS PROTEIN

TLR is a transmembrane protein having three distinct parts, intracellular Toll/IL-1 receptor domain (TIR), a leucine-rich repeat domain (LRR), and a transmembrane domain.[10] Furthermore, there are different adaptor proteins are also there.[11] Figure-1 represents the generalized structure of the toll like receptor.[12,13]

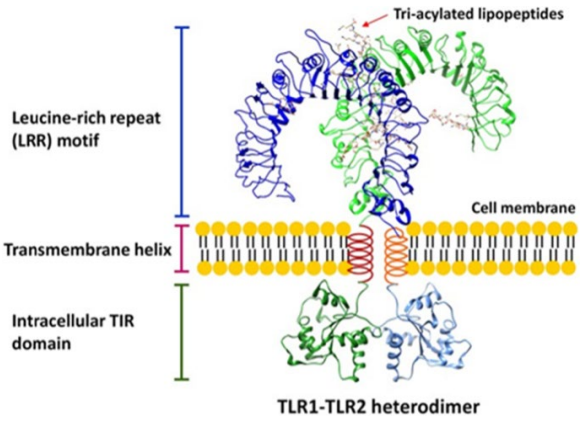

Figure 1: Structure of Toll-Like receptor protein.[12]

Table 1: Types of TLRs as per location

TLRs family	TLRs recognize components	Present of ligands
TLR 1, 2 4 and 6	Lipids and lipopeptides	Granulocytes, macrophages, Monocytes, regulatory T cells, Myeloid dendritic cells (mDC)
TLR5 and mouse TLR11	Proteins	Regulatory T cells, Epithelial cells
TLR3, 7, 8 and 9	Nucleic acids	Dendritic Cells(DCs), Natural Killer cells(NK), macrophages

2. DISTRIBUTION OF RECEPTORS

The cellular distribution of TLRs expresses diversification with many receptors being present on cell surfaces while others are inside the cell. It has been found that TLRs 1,2,4,5 and 6 are present at cell surface whereas TLRs 3, 7, 8, and 9 are present at endosomes intracellularly. Moreover, some TLRs family members are supposed to form homodimers with their respective ligands for signaling such as TLRs 3, 4, 5, 7, and 9 while TLR2 dimerizes heterogeneously with TLR1 and TLR6. In contrast, TLR4 binds with MD2 besides its ligand for its functioning.[14]

3. ADAPTOR PROTEINS

There are 5 diverse adaptor proteins that might be engaged in signaling by the TIR domain of TLRs receptor. These are Myeloid differentiation protein 88 (MyD88), TRIF-related adaptor molecule (TRAM), TIR domain-containing adaptor protein inducing IFN-β (TRIF), MyD88 adapter like or TIR domain-containing adaptor protein (MAL or TIRAP), and Sterile α- and armadillo-motif-containing protein (SARM).[15]

4. PHYSIOLOGICAL TLRs SIGNALLING PATHWAYS:

TLRs mainly identify plasma membrane components of microbes such as lipoproteins, lipids, and proteins.[16] Other than that, TLR4 also recognizes bacterial lipopolysaccharide (LPS) and initiation of secondary mechanism.[17] TLR2 additionally to TLR1 and TLR6 also identifies several PAMPs such as peptidoglycans, lipoproteins etc. Whereas TLR3, 4, 7, 8, and TLR9 receptors result in antiviral responses by inducing IFNb and multiple IFNa. Each TLR differentially activates members of a set of TIR domain-containing adaptors which are proteinous in associated with toll receptors, they include MyD88, TIRAP/MAL, TRAM or TRIF and others,.[3] Figure 2 represents the steps of binding of legends to TLR3 receptors that initiate cascade after dimerization of receptor leading to activation of secondary signaling pathway.[18]

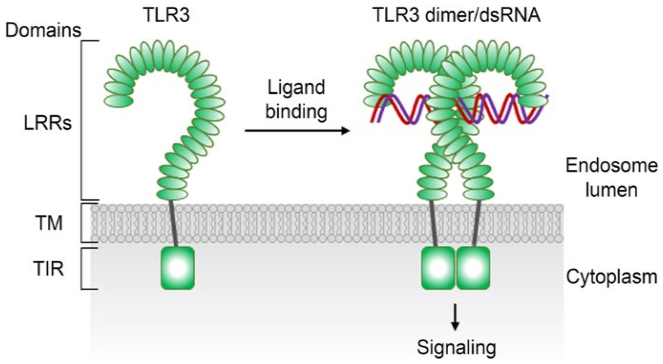

Figure 2: Binding of legend to TLR3 receptors [18]

4.1 MyD88 DEPENDENT PATHWAY

MyD88 is a gene that makes available protein for signaling within immune cells. It acts as an adapter. It promotes and uses each TLRs and in turn, stimulates MAPKs (mitogen-activated protein kinase) and NF-κB (Nuclear factor-kappa B) to activate the genes responsible to produce inflammatory cytokines. As a result of engagement of TLRs, MyD88 creates a complex with IRAK (Interleukin Receptor-Associated Kinase) family members, which further activates two different pathways such as NF-κB and MAPKs which induces inflammatory responses.[3] Many of the signaling events that IL-1 uses are identical to those that IL-18 uses. Myeloid differentiation appears to be used by both adapter molecules. MyD88 (primary response gene 88), interleukin 1 (IL-1).[19] TNF receptor-associated kinase (IRAK) and TNF receptor-associated factor 6 (TRAF 6). There is evidence that IL-1 and IL18 activate c-Jun N-terminal kinases (JNK) and p38 mitogen-activated proteins kinase (MAPK), although there is contradictory evidence whether IL-18 is a prominent NF-kB activator.[20].JNK SIGNALLING pathway is involved in stress regulation, cell regulation such as apoptosis, and Alzheimer disease.[21]

4.2 TRIF-DEPENDENT PATHWAY:

It is the most important adapter protein against viral infections. TRIF interact with TRAF6 (Tumor necrosis factor receptor–associated factor 6) and TRAF3 (Tumor necrosis factor receptor-associated factor 3). The activation of TRAF6 initiates the kinase RIP-1. Kinase RIP-1 further activates the TAK1 complex which triggers MAPKs and NF-κB thereby initiating the inflammatory response.[3]

4.3 TIRAP/Mal DEPENDENT PATHWAY:

Another essential junction important for these receptors are TIRAP (Toll-interleukin-1 Receptor adaptor protein) sometimes also referred to as Mal (MYD88 adapter like). One of the main specificities of this pathway is the interaction between the TIRAP/Mal with TLR4 which is again responsible for one more pathway which is known as TLR4-mediated MyD88-independent signaling pathway. It was also observed that the JNK and NF-B showed retard activation which are functions of TIRAP/Mal macrophages which are alike MyD88 macrophages and both are knockout macrophages.[14]

4.4 INTRACELLULAR SIGNALLING PATHWAY:

When pathogens are recognized, the TLRs initiate the intracellular pathways which results in the initiation of inflammatory cytokines, IFN and chemokines. Furthermore, TLRs signaling initiate the upregulation of co-stimulatory molecules on specialized Antigen presenting cells (APCs) called dendritic cells and this process is known as DC maturation which is important for the initiation of APCs adaptive immune response and indicates the TLRs link innate and adaptive immunity. TLRs activate a common signaling pathway that comes to a head of initiation of inflammatory cytokines like TNF α, IL-1b, IL-6 and IL-12 or other alternating pathways that initiate effector responses against several different types of pathogens.[22] In short, Ligand binding to TLRs stimulates specific downstream intracellular signaling cascades that trigger host defense responses. [23]

In this way, pro-inflammatory cytokines and type 1 interferon are produced by the interactions between PAMP-PRR that direct immune responses to microbes.[24]TLRs signaling depends on the nature of the stimulus, the activated TLR and the downstream adapter molecule. TLR signaling comprises at least two distinct pathways as shown in Fig. 3 [25] MyD88-dependent pathway used by all TLRs except TLR3, leading to the production of inflammatory cytokines.[2] The TRIF-dependent pathway used by TLR3 and 4 and associated with interferon type 1 stimulation.[22-26]

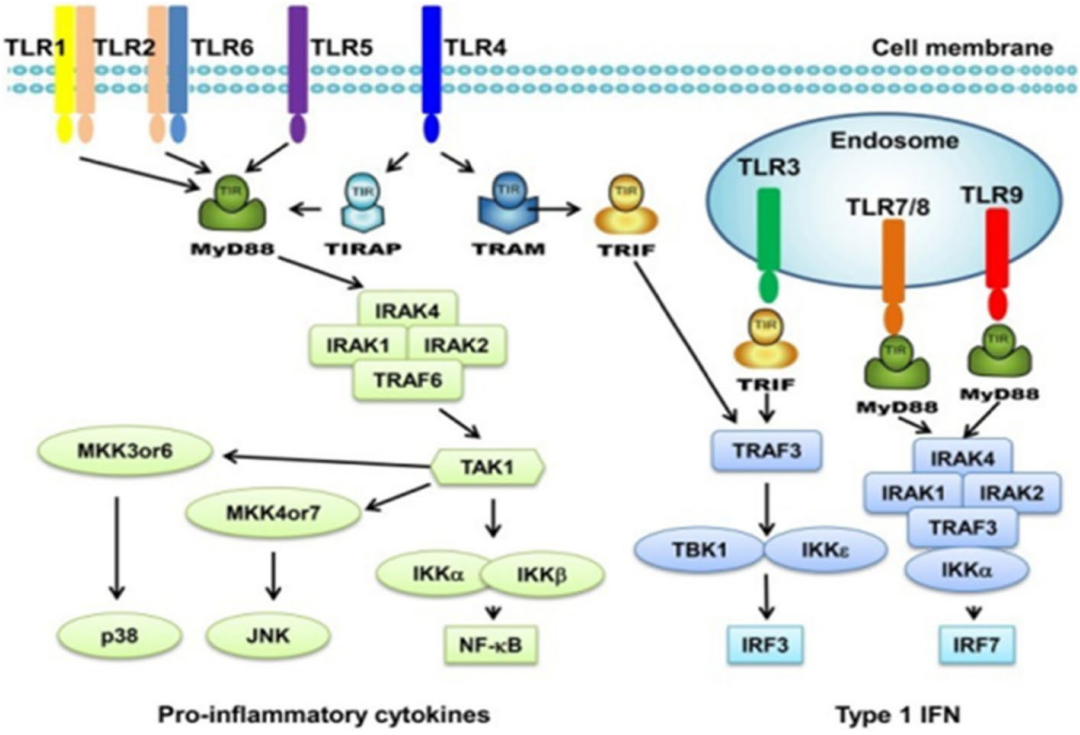

Figure: 3 Signaling pathway of TLRs adapted from [26]

5. DISORDERS LINKED WITH OVERACTIVITY OF TLRS

Abnormal activation of the TLR4 signaling pathway can trigger many medical states, such as infection[27], acute kidney injury (AKI) [28], acute lung injury (ALI) [29], intestinal inflammation[30], rheumatoid arthritis (RA) [31], cardiac diseases[32, 33], diabetes [34] and Blood pressure [35]pregnancy-related disorders, in abuse of drug and COVID-19[36].

As far as the similarity in action due to the structure of these complexes is concerned that it has been reported that the Arg241, Tyr102, Ser120, residues of TLR4, and Lys122 residues of MD2 are among those which takes part in the interaction of antagonistic ligand to the TLR4/ MD2 which can lead to the formation of new designs based on knowledge of structure-based TLR4 inhibitor.[1, 38]

5.1 INFECTIONS AND COVID

Viruses possess nucleic acids such as DNA or RNA in their structure which activate the immune system. The activated immune system leads to the production of certain mediators such as interferon (IFN) that are responsible for the development of resistance against viral infection.[39] Different components of viral RNA that are activated in late endosomal-lysosomal phases are identified by TLRs 3, 7 and 8.[40] During the life cycle of virus, many enveloped viruses infiltrate the cell via interaction with them.

Moreover it is also revealed in an in silico study that the S1 subunit seen on the spike protein of SARSCoV2 binds tightly to the TLR[41] and that such binding may increase the expression of ACE2 on the surface of cells thereby enabling the entry of the virus into cells.[42] Although not much popular, TLR4 may be considered a possible molecule that facilitates SARSCoV2 in gaining entry into cells.[43] Keeping that in mind, several initiators and antagonists of TLR4 are undergoing through clinical trials against SARSCoV2 such as resveratrol, quercetin, berberine and curcumin.[44]

5.2 INFLAMMATION

Inflammation of the gastrointestinal tract is a feature of several common disorders, including ulcerative colitis and chemotherapy-induced mucositis. The activation of TLR4 has been anticipated to have a significant impact on the intestinal inflammatory signaling pathways. TLR4 inhibition has been proposed as an effective treatment for intestinal inflammation.[30]

The development of Rheumatoid Arthritis (RA) can be slowed by inhibiting TLRs activation. In an in vivo study using rats, it was revealed that TAK-242 shows

an anti-arthritic effect in Adjuvant-induced arthritis rats , the effect that led to this inhibition was the stimulation of NF-κB and AP-1. But It is not promising that these effects seen on arthritis rats can be extended to human studies. Different inhibitors of TLR4 need to be examined as a newer therapeutic approach to control RA.[45]

5.3 ACUTE KIDNEY INJURY (AKI)

There are various causes of AKI. Among them, drug induced AKI is now a focal problem. Several nephrotoxic drugs show overactivated TLR4 signaling suggesting their role in the induction and progression of AKI.[46, 47] For instance, it has been suggested as a possible target against paracetamol-induced organ failure. Thus, inhibition of TLR4 with TAK242 found to reduce the kidney damage and improved the kidney function.[48] The connection of TLR4 in hepatorenal syndrome has also been ruled out in different experimental models, in which augmented renal expression of TLR4, mainly in renal tubular cells were found associated with renal damage has been described.[49] TLRS overexpression has also been found in cirrhotic patients developing AKI.[50] Astaxanthin (ATX), a marine antioxidant exerts various biological effects in AKI. A study revealed that ATX has anti-inflammatory effects which protect from early postburn AKI. Tissue inflammation and oxidative stress progress to AKI afterburning through initiation of the MyD88-dependent TLR4/NF-κB pathway. ATX and other TLRS4 inhibitors decrease burn-induced renal inflammation and AKI initiation.[51] Further studies in humans are obligatory to authenticate the promising effects of TLR4 inhibition against AKI.

5.4 ACUTE LUNG INJURY

Because the lung is constantly exposed to a variety of pathogens, antigens, and other danger signals derived from the host, myeloid and stromal cells express a collection of TLRs. This is followed by recognition of endogenously derived DAMPs as well as PAMPs that activate TLRs-associated signaling mechanisms required for host defense.[52] Consequently, TLRs are an integral part of host defense in certain chest infections as well as other conditions such as asthma, chronic obstructive pulmonary disease (COPD), acute lung damage or interstitial lung disease.[53] They are also useful in the treatment of lung cancer. Directing the research towards TLRs signaling system might open the way for the development of more dependable and successful vaccinations against infectious pathogens and as well as the control of lethal illnesses.[54]

5.5 SYSTEMIC LUPUS ERYTHEMATOUS (SLE)

The presence of abundant autoantigens and subsequent failure of self-tolerance against such antigens are the basis of many autoimmune disorders such as SLE which is genetic variant. A literature survey revealed that TLRs are involved in the initiation of pathology of SLE.[55] SLE patients experience the symptoms of lupus nephritis. The SLE management also have connections with various other strategies like protection to cell death, abstain drugs that cause hypomethylation of endogenous nucleic acids, for example, dihydralazine, scavenging nucleic acid waste[56], using TLRS inhibitors such as chloroquine, or blocking interferon-1 signaling.[57,58] Furthermore, other endogenous TLRs were also found triggered i.e. TLR3 in mesangial cells or TLR2 and TLR4 on endothelial cells and podocytes at the glomerular filtration activations are also involved in the disease progression of SLE .[57]

5.6 CARDIOVASCULAR DISEASES

These TLRs have also shown promising effects on cardiovascular diseases. Especially the involvement of TLR2, TLR4 or MyD88. The cardiovascular disease like ischemic injury shows positive response after lessening of myocardial inflammation. While the involvement of TLRs in hypercholesterolemia-induced arterial injury is also explained by many researchers. Among TLRs the TLR3 was noticed to be part of the integrity of the blood vessel wall.[59]

5.7 OBESITY-ASSOCIATED INSULIN RESISTANCE AND INFLAMMATION

It has been found that in obesity, elevated levels of free fatty acids are associated with the activation of certain proinflammatory mediators that promote the insulin resistance. The elevated levels of circulating free fatty acids enhance visceral obesity and encourage fat accumulation in liver and skeletal muscle which contribute to insulin resistance.[60] Saturated fatty acids enhance the TLRs signaling therefore promoting inflammatory reactions.[61] In one study, it was concluded that chronic exposure to saturated fatty acids and glucose increase the levels of various mediators involved in inflammation like IL-6 and TNF α.[62]

5.8 CANCER

The position of the TLR in carcinogenesis has become increasingly important. Certain TLRs were found to help in the carcinogenic process by inducing inflammation.[63,64] In normal physiology of the body, it

has been observed that various immune cells express anticancer activities that inhibit the growth of tumor, but various studies suggest that the presence of activated TLR4 in cancer cells decrease the antitumor activity of host immune cells.[65,66] A study reported that mice deficient in TLR4 were unable to develop colitis-induced tumors.[67]Various studies report that the MyD88 pathway supports the carcinogenesis.[68,69]

5.9 PREGNANCY

Opioid receptor agonists besides the activation of their receptors in the CNS, also activate the TLR4 network, NF-κB activated B cells expression as well as IL-6, TNF-α, and IL-1β. Whereas opioid receptor agonists block the TLR4 signaling pathway (LPS-induced) in peripheral immune cells. These agonists stimulate the MAPK pathway and cause pro-inflammatory effects in the CNS via MAPK[70].

In condition like "fetal inflammatory response syndrome which has its many factors like accompany preterm birth, affects normal fetal development, and predisposes the fetus to morbidity is also mediated by proinflammatory mediators. The other conditions which can be controlled by the TLR4 inhibitors which include drugs like nonopioid receptor antagonists; naloxone and naltrexone have shown promising results in animal models in controlling preterm birth induced by heat-killed Escherichia coli, bacterial mimetic LPS, or the TLR4dependent proinflammatory lipid, platelet-activating factor (PAF). The targeting of TLR4 as a principal regulator of inflammation in fetal and gestational tissues might be the new direction for TLR4 antagonists to prevent and treat preterm delivery and fetal inflammatory injury.[36]

5.10CNS DISORDERS

In mammalian brains, there is no evidence that TLRs interact with neurotrophic factor. However, TLR activation by DAMPs or PAMPs, modulates neurogenesis, neuronal differentiation, and maturation.[71,72] TLR loss cause typical mouse response which specifically related to behaviors and includes learning and memory impairments, as well as symptoms of neurodevelopmental pathologies. It should also be put into consideration that the involvement in the immunological activation of TLRs particularly in the developmental phase may damage neuronal development which can in turn increases the chances of producing neuropsychiatric abnormalities such as schizophrenia and autism spectrum disorders.[73, 74]

Although peripheral cytokines (IL-6 and IL-17) were previously believed to be important for immune activation-induced abnormalities in brain development and neuropsychiatric disorders.[75, 76] Findings suggest that TLRs activation in neurons of the brain may also affect the morphology of neurons and modify brain function. As a result, both PAMPs and DAMPs are expected to alter neuron morphology.[18]

6. TLRS INHIBITORS

TLR4 inhibitors may be used as medicines to treat certain disorders invented as a new class of drugs. There are three basic approaches to correct exaggerated TLR4 signaling pathway i.e., controlling the expressions of the relevant TLR4, as these connects to other major complexes which prohibit TLR4 activity like TLR4 or TLR4/MD2 complex and lastly binding directly to MD2 to inhibit TLR4 signaling pathway binding directly to MD2 to inhibit TLR4 signaling pathway. MD2 is a mandatory secondary protein for the activation of TLR4. This review encompasses the understanding of the TLR4 inhibitors that can bind directly to TLR4 or the TLR4/MD2 complex. The review also includes the drugs that can downregulate TLR4 expression. There are more than 66 compounds that are considered TRLs inhibitors that are under testing.[28] Some TLRs inhibitors are currently under trial. Eritoran is an LPS analog that binds to the TLR4/MD2 complex and antagonizes its activity [77] Tetra-acylated Lipid A, an intermediate produced during lipid A biosynthesis in E. coli, acts as an antagonist of human TLR4 but as an agonist of mouse TLR4 [77]. FP13-17 was rationally designed as a carboxylate-based lipid A by Cochet et al.[79]

7. TLRS INHIBITORS OF NATURAL ORIGIN

There are different natural sources of TLRs antagonists i.e., gram-negative bacteria, cyanobacteria, fungi, plants, etc. In cyanobacteria and microorganisms, molecules with TLR4 antagonists had been structurally Lipo-polysaccharides (LPS) or Lipo-oligosaccharides (LOS) whereas in plants, they have been shown by low molecular weight molecules that are unrelated with LPS structurally. Table 2 shows the phytochemicals with well-expressed TLR antagonist activity.

Table: 2 Natural TLR inhibitors

S#	TLRSs inhibitors	Source	Effects reported in the literature	References
1.	Antrodia cinnamomea	Fungus	Anti-inflammatory in psoriasis	(80)
2.	Asiatic acid (triterpene)	*Extracted from Centella asiatica (L.) Urban*	Anti-inflammatory in acute lung injury	(81)
3.	Atractylenolide I	*Isolated from Atractylodes macrocephala*	Anti-inflammatory in acute lung injury	(82)
4.	Bearberry leaves	*Arctostaphylos uva-ursi*	Anti-inflammatory	(83, 84)
5.	Berberine (isoquinoline alkaloid)	*Rhizoma Coptidis*	Anti-bacterial	(85)
6.	Bilberries	*Vaccinium myrtillus*	Anti-inflammatory	(84)
7.	Caffeic acid phenethyl ester (CAPE, 16,)	Derived from honeybee propolis	anti-inflammatory, anti-viral, anti-tumor, and other activities	(86)
8.	Celastrol (pentacyclic triterpenoid)	*Tripterygium wilfordii Hook F*	Anti-inflammatory	(87)
9.	Chichoric acid	*Echinacea pupurea*	Anti-inflammatory and antioxidant in Alcohol induced liver steatosis	(88)
10.	Cinchona bark	*Cinchona pubescens*	Anti-inflammatory	(84)
11.	Cinnamon bark	*Cinnamomum verum*	Anti-inflammatory	(84)
12.	Common lady's mantle	*Alchemilla vulgaris*	Anti-inflammatory, anti-viral, antioxidant	(84, 89, 90)
13.	Corilagin (polyphenol)	*Arctostaphylos uvaursi*	Anti-inflammatory and antibacterial	(91)
14.	Curcumin	*Curcuma longa*	Anti-inflammatory, effective in brain injury	(92)
15.	Fermented soyabean	*Glycine max*	Anti-inflammatory	(93)
16.	Ferulic acid (phenolic compound)	Fruits and vegetables	Anti-inflammatory and antioxidant	(94)
17.	Iberin (analogue of SFN)	*Brassica oleraceaCabbage*	Anti-inflammatory	(95)
18.	Lipo-oligosaccharides (LOS)	*Bartonella quintana*	Anti-inflammatory	(96)
19.	Lipo-polysaccharide (cyanobacterial product)	*Oscillatoria Planktothrix FP1*	Suppress gene transcription, anti-inflammtory, anti-epileptic and other activities	(97)
20.	LPS and lipid A (Less immunogenic as compared to pathologic strains)	Rhodobacter sphaeroides, Oscillatoria Planktothrix FP1, commensal gut bacteria-derived LPS	As an anti-inflammatory in Inflammatory Bowel Disease	(98)
21.	Naringenin (flavonoid)	Grapefruit and other citrus fruits	Anti-inflammatory and antioxidant in atherosclerosis, arthritis and metabolic syndrome	(99)
22.	Papiliocin (insect cecropin)	Derived from the larvae of the swallowtail butterfly	Antibacterial and antiseptic	(100)
23.	Parthenolide (sesquiterpene lactone)	*Tanacetum parthenium*	Anti-inflammatory, anti-cancer	(101)
24.	Platycodin D (triterpene saponin)	*Platycodon grandiflorum*	Anti-inflammatory	(102, 103)
25.	Probiotics (Golden bifid)	–	Anti-inflammatory	(104)
26.	Sinapis Alba Linn (mustard seed)	*Cruciferae Brassica*	Anti-inflammatory in psoriasis	(105)
27.	Sparstolonin B	*Spaganium stoloniferum*	Anti-inflammatory	(106)
28.	Sulforaphane (SFN)	*Cruciferous vegetables*	Anti-inflammatory	(107)
29.	Sweet chestnut	*Castanea sativa*	Anti-inflammatory, antioxidant, anti-microbial	(84, 108-110)
30.	Total glucosides of paeony	*Paeonia lactiflora*	Anti-inflammatory in diabetic nephropathy	(111)
31.	White willow bark	*Salix alba*	Anti-inflammatory	(84)
32.	Xanthohumol (calchone type flavonoid)	*Humulus lupulus*	Anti-inflammatory	(112)
33.	Ω-3 polyunsaturated fatty acids	Fish, oil and nuts	Anti-inflammatory in traumatic patients	(113)

Conclusion

TLRs are type I integral transmembrane receptors that help the immune system recognize and transmit infections. These receptors can be found either inside the cells on endosomes or on the surface of cells. They are activated by a specific ligand, which causes cytokines to be released via a signal transduction pathway. Excessive synthesis of these cytokines causes immunological homeostasis to be disrupted. From their roles in Infections, Inflammation, Acute Kidney Injury (AKI), SLE and Cancer, TLRs are governing the world of human biology. A plethora of natural inhibitors of TLRs are being investigated in number of studies to control the overproduction of inflammatory mediators. Moreover, these natural TLRs inhibitors also possess other important biological properties such as antibacterial, antiviral, antioxidant etc. Nonetheless, ongoing research in the field of TLRs offers a lot of potential for uncovering natural TLR4 inhibitors.

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