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Suppressive effects of medicinal plants and their derivatives on inflammasome complex: a systematic review

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Abstract: Inflammasome activation is mediated by (NOD)-like receptors (NLR) proteins that respond to stimuli. Among NLRs, NACHT- LRR and PYD domains-containing protein 3 (NLRP3) senses the widest array of stimuli. NLRP3 inflammasome has an important role in the development of many inflammation disorders. Regarding the significance of inflammatory diseases, and the necessity of preventing and treating these diseases, the aim of this review article is to report medicinal plants and their nature-based derivatives that are effective on suppression of inflammasome complex. Web of Science and PubMed databases were searched using the Endnote software for the publications about the role herbal medicine in inflammasome activation pathways from 2000 to February 2016. *Sophora flavescens*, *Lycium barbarum*, *Impatiens textori* Miq., *Syneilesis palmata* (Thunb.), *Aloe vera*, citral (3,7-dimethyl-2,6-octadienal), celastrol, sulforaphane, schisandrin, resveratrol, dehydrodiconiferyl alcohol (DHCA), luteoloside, Pulsatilla decoction, and Wuling San have been reported to suppression function of inflammasome. Medicinal plants and their derivatives can be useful for inflammation related disorders by suppress NLRP3 inflammasome activation. However, they should be investigated in clinical trials to help to prevent and treatment of inflammatory diseases.
Keywords: Inflammasome, Inflammation, Medicinal plants, Phytochemicals, Herbal drugs.

Introduction

Inflammasomes are a group of large caspase-1-activating protein complexes. Inflammasomes response to evocation of innate immunity and production of pro-inflammatory cytokines such as LRP1, NLRP3, NLRC4, AIM2, and NLRP6 [1, 2]. They sense sensepathogen-associated molecular patterns (PAMPs) in the cytosol as well as damage-associated molecular patterns (DAMPs) [3, 4]. The inflammasomes play a role in cellular functions such as apoptosis and pyroptosis [5]. Explanation of inflammasome pathways with understanding of

how they contribute to autoimmune and autoinflammatory disorders alike might open up the horizon for the development of new therapies for these diseases [6]. In inflammasome complex, NLRs are activated by structural changes in them and bonding with ASC through pyrin domains. Furthermore, the adaptor protein ASC bonds with pro-caspase-1 through CARD demines. This big complex, called inflammasome, enables caspase-1 to self-activate. Then, caspase-1 is activated and converts inactive form of IL-1β (pro-IL-1β) or IL-18 into active form to prepare it for secretion and biological activity [7, 8].Furthermore previous studies showed that inflammasome activation is mediated by ROS. Actually blockade of ROS production involving the use of chemical scavengers of ROS, and pharmacological inhibitors of NADPH oxidase inhibit NLRP3 inflammasome activation in response to a wide range of stimuli [9-11]. NLRP3 has been shown to play a central role in the induction of obesity and insulin resistance [12].

Normal activation of NLRP3 inflammasome contributes to host defense, but several studies suggest that excessive activation leads to the development of a number of inflammatory diseases [13]. Mutations of the human NLRP3 gene are associated with autoinflammatory syndrome, which is characterized by recurrent bouts of fever with debilitating local and systemic inflammation [14]. In mice, genetic ablation of NLRP3 or caspase-1 protects against obesity-associated inflammation and insulin resistance with reduced IL-1 in adipose tissue [15-17]. Activation of the NLRP3 inflammasome must be tightly regulated, and identification of anti-inflammatory agents that selectively target it would be very important. In this regards, suppression of NLRP3 inflammasome activation can be a new approach for prevention and treatment of inflammatory diseases.

Recently, medicinal plants have been attracting great attention and researchers have made efforts to discover their effects on cells, animals and human [18-25]. Numerous studies have confirmed the positive impact of medicinal plants and their derivatives, according to both folk and modern medicine, on prevention and treatment of various diseases [26-40].Given the significance of inflammatory diseases, and the necessity of preventing and treating these diseases, the aim of this review article is to report medicinal plants and their nature-based derivatives that are effective on suppression of inflammasome complexes.

In this regards, Web of Science and PubMed databases were searched for the publications about the role of herbal medicine in suppression of inflammasome activation pathways2000 and February 2016 using the EndNote software. The used search terms were inflammasome and medicinal plant or herb or herbal medicine or natural compound or phytochemical or herbal drugs and inflammasome. Each database was searched independently. The articles retrieved from both databases were analyzed once. Abstracts were reviewed based on predefined inclusion and exclusion criteria. When necessary, full texts were retrieved to assess study eligibility. Only the articles directly addressing the effect of the medicinal plants and their derivatives were selected and analyzed.

29 articles had investigated the role of the medicinal plants and their derivatives in regulating inflammasomes. *Sophora flavescens*, *Lycium barbarum*, *Impatiens textori* Miq., *Syneilesis palmata* (Thunb.), *Aloe vera*, citral (3,7-dimethyl-2,6-octadienal), celastrol, sulforaphane, schisandrin, resveratrol, dehydrodiconiferyl alcohol (DHCA), luteoloside, Pulsatilla decoction, and Wuling San have been reported to suppression of the function of inflammasome. Table 1 gives further details.

Sophora flavescens

S. flavescens as atraditional herbal medicine used to reduce inflammation, blocked the phosphorylation of IKKα/β, key upstream kinases involved in the degradation of IκBα, and the cleavage of caspase-1. *S. flavescens* exerts its anti-inflammatory effects by blocking *P. aeruginosa*-mediated NF-κB/inflammasome activation and the subsequent production of IL-1β [41].

***Lycium barbarum* (LBP)**

It has been used as a traditional Chinese medicine to nourish liver, kidneys and the eyes. LBP attenuated ethanol-induced hepatic damages through suppressing the activation of NLRP3 inflammasome in a TXNIP-dependent manner in the BRL-3A in vitro system. These results further supported evidence that inhibition of hepatic TXNIPNLRP3 inflammasome axis contributes to the alleviation of hepatic injury caused by ethanol [42].

***Impatiens textori* Miq.**

*I. textori*as a member of Balsaminaceae family, treated at 25, 50, and 100 µg/mL concentrations suppressed interleukin-1β secretion through the attenuation of NLRP3 inflammasome activation leading to the decreased amount of ASC oligomerization and caspase-1 maturation. It inhibited the NLRP3 expression and cell recruitment at the lung tissue in the ALI mouse model. Anti-inflammatory effects of *I. textori*are via the attenuation of NLRP3 inflammasome activation [43].

Aloe vera

A. vera as an immunomodulatory agent inducing anti inflammatory effects. It mediated strong reduction of IL-1 appears to be the consequence of the reduced expression of both pro-IL-1 as well as NLRP3 inflammasome components via suppressing specific signal transduction pathways. The expression of the ATP sensor P2X7 receptor is also down regulated by Aloe vera that could also contribute to the attenuated IL-1 cytokine secretion. These results may provide a new therapeutic approach to suppression of inflammasome - mediated responses [44].

***Syneilesis palmata* (Thunb.)**

S. palmate from Asteraceae family is a traditional Korean therapeutic herb widely used to treat pain, and arthritis. *S. palmate* inhibited the LPS-stimulated release of proinflammatory mediators, such as nitric oxide and interleukin IL-6 in RAW 264.7 cells. *S. palmate* treatment attenuated IL-1β secretion via the inhibition of NLRP3 inflammasome activation induced by monosodium urate, ATP, and nigericin. Further, *S. palmate* ameliorated the severity of NLRP3 inflammasome-mediated symptoms in LPS-induced endotoxin and E. coli-induced sepsis mouse models. Effects of *S. palmate* are mediated through the regulation of TRIF-dependent signaling and inflammasome activation [45].

Citral (3,7-dimethyl-2,6-octadienal)

Citral is a major active compound in a *Litsea cubeba*. Citral inhibited NLRP3 inflammasome activation and levels of ROS, NAD(P)H oxidase subunit p47phox, or COX-2, and it enhanced the activation of nuclear factor E2-related factor 2(Nrf2). Citral alleviates severe lupus nephritis model via inhibition of the activation of NLRP3 inflammasome and enhanced activation of Nrf2 antioxidant signaling. Generation of reduced ROS by Citral may explain the resultant decreased pro-IL-1β protein levels [46].

Celastrol

Celastrol is a quinonemethide triterpene derived from a plant extract used in herbal medicine. It inhibited the proteasome-dependent degradation of proteins in RAW264.7 cells. It also blocked stimulation of IL-18 processing, indicating that celastrol acted upstream of inflammasome activation. Celastrol as an inhibitor of lethal toxin-mediated macrophage lysis and suggests an inhibitory mechanism involving inhibition of the proteasome pathway [47].

Schisandrin

Schisandrin is a phytochemical compound that can induce cellular antioxidant response. It also can suppress the inflammasome activation. Schisandrin B treatment (2 mmol/kg p.o.) ameliorated the Imject Alum-induced peritonitis, as indicated by suppressions of caspase1 activation and plasma IL-1β level [48].

Resveratrol

Resveratrol as a natural compound found in many types of plants and is one of the most intensely investigated phytochemicals. It can inhibit NLRP3-inflammasome activation via inhibiting the accumulation of acetylated α-tubulin. In addition, resveratrol can inhibit the acetylated-α-tubulin-mediated spatial arrangement of mitochondria and their subsequent contact with the endoplasmic reticulum. Actually, resveratrol targets assembly of NLRP3 and ASC, thus an increasing dose of resveratrol suppress mitochondrial ROS production, and subsequent NLRP3-inflammasome activation [49].

Dehydrodiconiferyl alcohol (DHCA)

DHCA is a lignan compound from *Cucurbita moschata*, reduced the production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β and CCL2 and mediators such as iNOS, COX-2 and ROS. DHCA suppressed activation of inflammasomes by down-regulating the activity of I-κB kinase and DNA binding activity of NF-κB [50].

Luteoloside

Luteoloside is a flavonoid isolated from some plants such as *Gentiana macrophylla*. Luteoloside can significantly decrease the intracellular reactive oxygen species accumulation. The decreased levels of ROS induced by luteoloside were accompanied by decrease in expression of NLRP3 inflammasome resulting in decrease in proteolytic cleavage of caspase-1. Inactivation of caspase-1 through luteoloside resulted in inhibition of IL-1 b. Thus, luteoloside exerts its inhibitory effect through inhibition of NLRP3 inflammasome [51].

Sulforaphane

Sulforaphane, as natural compound in cruciferous vegetables, increased nuclear factor erythroid 2 erelatedfactor 2 (Nrf2) nuclear translocation which results in decrease of IL-1b release and microRNA-146a production. Also effects of sulforaphane were replicated by the tyrosine kinase inhibitor, herbimycin A, and Nrf2 activator. These findings suggest that sulforaphane has a potential application in suppression of inflammasome activation [52].

Pulsatilla decoction

Pulsatilla decoction as a chinese formula is likely to exert their therapeutic effect by activating NLRP3 inflammasome which further promote the formation of the corresponding inflammation factors such as 1L-18 and IL-1beta [53].

Wuling San

Wuling San, a famous prescription in Chinese medicine, is composed of some natural compound such as polyporus (a genus of fungi), poria (a famous home-grown bulk Chinese herb), *Alismatis rhizoma*, *Cinnamomi cortex* and *Atractylodis macrocephalae* rhizome. Wuling San suppressed the activation of TLR4/MyD88 signaling to inhibit NF-κB signaling and mitogen-activated protein kinases activation in the kidney of fructose-fed mice. Additionally, Wuling San decreased NLRP3 inflammasome activation and IL-1 β secretion [54].

Regarding the significance of inflammatory diseases, and the necessity of preventing and treating this diseases, the aim of this review article is to report medicinal plants and their nature-based derivatives that are effective on inflammasome complex. Agents that reduce the production and activity of proinflammatory cytokine are likely to have clinical applications. For this purpose, future studies should examine which components in the extracts are responsible for the anti-inflammatory properties described medicinal plants. Also, further studies are needed to better understand the mechanism by which medicinal plants inhibits inflammasome formation. The formation and activation of inflammasome complex is followed by the release of two cytokines, IL-1 β and IL-18, from cells [55]. Among the inflammasomes, the NLRP3 inflammasome is the most widely studied and is known to be activated by a wide range of PAMPs and DAMPs such as nucleotide ATP, nigericin, and monosodium urate. NLRP3 inflammasome, known to be activated upon cellular 'danger' signs, triggers innate immune defense through the secretion of pro-inflammatory cytokines, such as IL-1 β and IL-18 [3, 56]. Therefore, IL-1 β and inflammasomes have emerged as therapeutic targets for an expanding number of systemic and local inflammatory conditions. NLRP3 was recently identified to form a cytoplasmic complex known as the NLRP3 inflammasome, which potently modulates innate immune function by regulating the maturation and secretion of pro-inflammatory cytokines, such as IL-1 b [57]. IL-1 together with TNF are among the most powerful cytokines that under pathological conditions could cause cell degeneration and cell death resulting in multiple organ dysfunction [58]. Activation of the NLRP3 inflammasome is dependent on the generation of ROS [59, 60]. In fact, all known NLRP3 activators generate ROS and, conversely, inhibitors of ROS block inflammasome activation [61]. Our study demonstrated that some medicinal plants were found to

suppress NLRP3 inflammasome activation. This study was the first review article to show scientific evidence and justify the traditional use medicinal plants in the treatment of inflammation related disordersthrough block inflammasome activation. The strong protective effects exhibited by medicinal plants in both in vitro and in vivo experimental models might be partly mediated by the regulation of key inflammatory mechanisms, such as the TRIF signaling pathway and NLRP3 inflammasome activation, providing a valuable therapeutic or/and prophylactic strategy by controlling inflammation-mediated disorders

Table 1: The effects of medicinal plants and their derivates on inflammasome

Plants or their derivates	***Study design* and dosage**	**Results**	**Ref.**
Sophora flavescens	*In vitro* and *In vivo;* 50 ng/μ	Blocked the phosphorylation of IKKα/β, and the cleavage of caspase-1, a key component of the inflammasome.	[41]
Lycium barbarum	*In vitro;* 50 g/ml	Suppressed the activation of NLRP3 inflammasome in a TXNIP-dependent manner.	[42]
Impatiens textori Miq.	*In vivo;* 25, 50, and 100 μg/mL	Suppressed the interleukin-1 β secretion through the attenuation of NLRP3 inflammasome activation.	[43]
Aloe vera	*In vitro;* 1, 3, and 10 v/v%	Inhibited the expression of pro-IL-1 , Nlrp3, caspase-1 as well as that of the P2X7 receptor.	*[44]*
Syneilesis palmata (Thunb.) Maxim	*In vitro* and *In vivo;* 100 μg/mL	Regulated the TRIF-dependent signaling and inflammasome activation.	[45]
Citral	*In vitro* and *In vivo;* 200 mg/kg	Inhibited the activation signal of NLRP3 and enhanced activation of Nrf2.	[46]
Celastrol	*In vitro;* 10 mM	Blocked the stimulation of IL-18 processing.	[47]
Schisandrin	*In vitro* and *In vivo;* 2 mmol/kg p.o	Suppressed the caspase1 activation and plasma IL-1β level.	[48]
Resveratrol	*In vitro;* low< *5* μM, and higher> 25 μM	Inhibited the acetylated-α-tubulin- causing insufficient assembly of ASC on the mitochondria and NLRP3 on the endoplasmic reticulum.	[49]
Luteoloside	*In vitro* and *In vivo;* 25, and 50 mM	Reduced the intracellular reactive oxygen species (ROS) accumulation.	[51]
Sulforaphane	*In vitro;* 5 mM	Dephosphorylated the STAT-1 and activated the Nrf2/HO-1 cascades.	[52]
Wuling San	*In vitro* and *In vivo;* 987, 1316, 1755 and 2340 mg/kg	Suppressed the TLR4/MyD88 signaling and NLRP3 inflammasome activation to reduce IL-1 β production	[54]

Conclusion

Medicinal plants through their active ingredients have a good therapeutic effect of diseases and disorders (62-112). Medicinal plants and their derivates down regulate pro-inflammatory cytokine production. Because patients with rheumatoid arthritis, septic shock, autoimmune disorders, tumors, Alzheimer's disease, and chronic inflammatory diseases secrete large amounts of IL-1β, the agents that decline the production and activity of this proinflammatory cytokine can have clinical applications. Suppression of inflammasome might be an important therapeutic strategy to improve inflammatory-mediated diseases. Therefore, identifying the compounds that regulate the NLRP3-inflammasome is important to develop therapeutic methods with which infectious and inflammatory diseases are treated.

Conflict of Interests

There is no any conflict of interest.

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