Send Orders for Reprints to reprints@benthamscience.net

Suppression of Inflammatory and Allergic Responses by Pharmacologically Potent Fungus *Ganoderma lucidum*

Neha Bhardwaj[1], Priya Katyal[2] and Anil K. Sharma[1,*]

[1]*Department of Biotechnology, Maharishi Markandeshwar University, Mullana-Ambala-133207, India;* [2]*Department of Microbiology, Punjab Agricultural University, Ludhiana-141004, India*

Received: January 1, 2014; Accepted: June 17, 2014; Revised: June 17, 2014

Abstract: Acute inflammation is the result of a complex signal transduction pathway that protects and heals our body and is necessary for our good health and normal wellbeing. Whereas, chronic inflammation can be correlated well with the onset of a plethora of autoimmune disorders; rheumatoid arthritis, systemic lupus and polymyalgia, rheumatic and other diseases like asthma, inflammatory bowel diseases, cardiovascular disorders, ulcerative colitis and Crohn's disease. Also, it has been reported to be associated with the onset of various cancers. An effective anti-inflammatory drug should be able to inhibit the development of chronic inflammation without interfering in normal homeostasis. A number of herbal drugs have been identified in the past that can target inflammatory cytokines. Among these, *Ganoderma lucidum:* a powerful medicinal mushroom has been found to possess immune-modulating and immune-potentiating capabilities and has been characterized as a wonder herb. This review mainly focuses on the molecular mechanism of anti-inflammatory and anti-allergic action of this mushroom and also sheds light on various patent studies related to its pharmacological action.

Keywords: Anti-allergic, anti-inflammatory, formulations, *Ganoderma lucidum*, immune-modulating, inflammation.

INTRODUCTION

Mushrooms represent a major untapped source of potent pharmaceutical products. Nearly, 10,000 mushroom species are known of which 2000 are safe for humans and about 300 of them possess medicinal properties. *Ganoderma lucidum* has been used in folk medicine in China and Japan for over 2000 years for a wide range of ailments. In China, fruiting bodies of *Ganoderma* have been regarded as a panacea for all types of diseases [1]. Different workers have reported a wide range of pharmacological potential of this wonder herb [2-4].

Inflammation has been recognized as an important symptom or an initial response of the body to injury/infection that resolves with time and leads back to normal homeostasis [5]. An unresolved/chronic inflammation leads to a huge variety of diseases including atherosclerosis, arthritis, diabetes, fatty liver disease, inflammatory bowel disease, neurodegenerative diseases, chronic respiratory diseases, sepsis, tumors, ulcers and cancers [6, 7]. Inflammation is the result of a complex signaling cascade including the inducers, sensors, mediators and the effect of mediators on surrounding tissues. Macrophages, mast cells, endothelial cells and epithelial cells act as sensors and use extracellular and intracellular receptors to sense inducers that are produced by cells under the condition of stress/damage as well as exogenous inducers signaling infection. These receptors are called PRRs (Pattern recognition receptors) that sense both exogenous and endogenous inflammation stimuli [8].

Exogenous inducers include lipids, carbohydrates, peptides and nucleic acid components of bacteria and viruses, while endogenous inducers are ATP, K^+, uric acid, high mobility group proteins, heat shock protein, fatty acids, heparin sulfate and oxidized lipoproteins in metabolically disturbed tissues. Ligand receptor couples to downstream signaling molecules, that regulate the activities of several classes of signal-dependent transcription factors, including nuclear factor (NF-κB) and activator protein 1 (AP-1). These factors recruit multiple transcriptional co-regulators that remodel local nucleosomes to alter the expression of inducible genes coding for inflammatory cytokines, chemokines and MHC complex [9].

The product of these genes acts as mediators (e.g. TNF-α, IL-6, ROS, PGE2, NO), promotes vascular permeability, and up-regulates the expression of cell adhesion molecules on vascular endothelium to allow the access of plasma proteins and leukocytes to extravascular tissue. The recruited neutrophils have enhanced phagocytic abilities and can release RO and RN intermediators and toxic granules to kill the microorganisms. Macrophages can secrete transforming growth

*Address correspondence to this author at the Department of Biotechnology, M. M. University, Mullana (Ambala), Haryana, India-133207; Tel: +91-8059777758; Fax: +91-1731274375;
E-mails: anibiotech18@gmail.com; hod.biotech@mmumullana.org

2212-2710/14 $100.00+.00

Table 1. Anti-inflammatory Activities of Phytochemicals from *Ganoderma lucidum*.

Target Pathway	Effects	References
Anti-oxidative and radical Scavenging activities	Promoting antioxidant enzymes activity	[1,15,16]
	Inhibiting pro-oxidant enzymes activity	
	Prevention of free radical attacks	
	Enhancing endogenous antioxidant molecules	
Modulation of cellular activities of inflammation related cells	Inhibition of enzymes involved in signaling transduction and cell activation processes (T cell, B lymphocyte) or cytokine production	[17-21]
	Inhibition of arachidonic acid release from membrane (degranulation)	
Activation and stimulation of various cytokines	Activation of immune response, Activation of B-lymphocytes, stimulation of IL-1β, IL-6, TNF-α, and IFN-γ production by macrophages and T lymphocytes	[22-24]
Modulation of the production of other Pro-inflammatory molecules	Inhibition of pro-inflammatory cytokines from different sources	[3, 25-28]
Growth inhibition *in vivo*, Antioxidant and cytotoxic property for various cells	Growth inhibition of hepatoma, sarcoma S-180 tumor in mice and reticulocyte sarcoma L-II *in vivo*	[29, 30]
	Inhibition of farnesyl protein transferase, angiogenesis, DNA-polymerase and neutrophil apoptosis	[25, 31]
	Cytotoxic for hepatoma cells sarcoma and lung carcinoma cells	

factor β, growth factors and anti-inflammatory lipid mediators, including lipoxins, resolvins and protectins [10] and thereby resolve inflammation, failure to do so leads to pathological tissue remodeling or fibrosis.

An effective anti-inflammatory drug should be able to inhibit the development of chronic inflammation without altering the homeostasis. A large group of therapeutics, mainly target nuclear receptors but are associated with adverse side effects. Therapeutic approaches that prevent activation of sensors of inflammatory signals, such as biologicals that specifically target inflammatory cytokines such as TNF and IL-1 show delivery constraints, are costly and disease recurrence may occur when treatment ceases [11].

Thus, inhibition of activation of the inflammatory cells appears to be an important therapeutic target for small molecular drugs for the treatment of inflammatory disease [12]. The evaluation of anti-inflammatory effects of various bioactive plant components has gained the widespread attention. One of these herbal medicinal mushrooms is *Ganoderma lucidum*, used commonly in the treatment of several diseases in Asian countries [13, 14]. Table **1** outlines some of the important findings that can be correlated to anti-inflammatory properties of this wonder herb [15-31].

The pharmacological effect of *Ganoderma lucidum* is based on its powerful immune-modulating and immune potentiating capabilities which further support and enhance the overall immune function, due to the presence of more than 400 active elements which can be categorized into water soluble, organic soluble and volatile soluble compounds. The fruiting body, mycelia and spores of *G. lucidum* contain approximately 400 different bioactive compounds which mainly include triterpenoids, polysaccharides, nucleotides, sterols, steroids, fatty acids, proteins (peptides) and trace elements [32]. From the spores of *G lucidum*, 6 highly oxygenated lanostane-type triterpenes have been isolated called ganoderic acid, which is the active ingredient. *G. lucidum* is widely cultivated nowadays and is sold as raw material or lingzhi extracts in many Asian markets and Western health shops [33].

INFLAMMATION AND ITS MOLECULAR MECHANISM

Inflammation is a protective strategy evolved in higher organisms in response to detrimental insults such as microbial infection, tissue injury and other noxious conditions. It is an essential immune response by the host that enables the removal of harmful stimuli as well as the healing of damaged tissues. The entire course of inflammation comes with many different processes involved in its initiation, regulation and resolution. The inflammatory response is regarded as the first of a number of overlapping processes involved

in wound healing. In skin repair, the infiltrating leukocytes are the principal cellular components of the inflammatory response. They are not only effector cells for invading pathogens but are also involved in tissue degradation and tissue formation.

An excessive, reduced influx or activation of infiltrating leukocytes into the damaged tissue may have profound effects on downstream cell migration, proliferation, differentiation and the quality of the healing response. Tissue injury causes the immediate onset of acute inflammation. It has been considered that the inflammatory response is instrumental for supplying growth factors and cytokine signals that leads the cell and tissue movements necessary for repair [34, 35]. In various experimental animal models and human skin wounds, it has been demonstrated that the inflammatory response during normal healing is characterized by spatially and temporally changing patterns of various leukocyte subsets and the well-defined chronology of these events is essential for optimal repair [36, 37].

Inflammatory stimuli are first recognized by the host cells through specific trans-membrane receptors called pattern recognition receptors (PRRs) which are expressed by cells of both innate and adaptive immune systems. PRRs are germline encoded receptors, which are responsible for sensing the presence of infecting microorganisms as well as the incidence of any cellular damage. They do so by recognizing structures conserved in microbes called pathogen associated molecular patterns (PAMPs) as well as endogenous molecules derived from internal injuries called danger associated molecular patterns (DAMPs) [38]. A number of PRRs have been identified with the selective ability to detect PAMPs, DAMPs or both and these include Toll like receptors (TLRs), C-type lectin receptors (CLRs), RIG-1-like receptors (RLRs) and NOD- like receptors (NLRs).

The interactions of these receptors with the appropriate stimuli result in transmitting signals to nucleus where the activation of a selective set of genes takes place via both transcriptional and post transcriptional mechanisms. Inflammatory responses are coordinated by the products of such genes precisely pro-inflammatory cytokines such as TNF, IL-1β and IL-6 which are expressed in response to bacterial infection. Unlike TNF and IL-6, IL-1β is synthesized by a two-step mechanism:

1) In the first step, IL-1β is expressed as IL-1β zymogen, pro-IL-1β which is initiated by the synthesis of its mRNA in a TLR dependent manner [39].

2) The second step involves the maturation of IL-1β by the caspase -1 mediated cleavage of pro-IL-1β a process requiring a 'Caspase-1 activating' high molecular weight complex called inflammasome. Inflammasome is assembled by the oligomerization of scaffold proteins including NLRs. In case of viral infections, type-1 IFNs induce the phosphorylation and nuclear translocation of a complex called IFN-stimulated gene factor 3 (ISGF3), which is composed of signal transducers and activators of transcription 1(STAT 1), STAT 2 and IFN regulatory factor 3 (IRF3). ISGF3 in turn activates the expression of antiviral genes such as protein kinase R (PKR) and 2', 5' oligoadenylate synthase (OAS). The proliferation of virus infected cells is inhibited by PKR where as OAS suppressed viral replication is inhibited by cleaving viral nucleotides [40].

Wide ranges of phytoconstituents are responsible for anti-inflammatory activity. Several mechanisms of action have been proposed to explain the anti-inflammatory actions of phytoconstituents [41], which broadly fall in these categories:

1) Anti-oxidative and radical scavenging activities

2) Modulation of cellular activities of inflammation-related cells (mast cells, macrophages, lymphocytes and neutrophils)

3) Modulation of pro-inflammatory enzyme activities such as phospholipase A2 (PLA2), cyclo-oxygenase (COX), and lipoxygenase (LOX) and the nitric oxide (NO) producing enzyme, nitric oxide synthase (NOS)

4) Modulation of the production of other pro-inflammatory molecules

5) Modulation of pro-inflammatory gene expression

The inflammatory process can be initiated by various inflammatory stimuli including viruses, chemicals and reactive oxygen or nitrogen species, which subsequently increase the synthesis and secretion of pro-inflammatory cytokines. The unchecked activation of NF-κB/AP-1 and the production of TNF-α signaling have provided evidences about the critical role for these factors in coupling inflammation and many chronic diseases. Phytochemicals have been shown to modulate various points in these inflammatory processes [42] by various mechanisms mentioned above. These modulations serve as controlling points where the amplification of the inflammatory processes can be disconnected and thereafter reduce subsequent diseases risk. Several plant products have already passed the clinical tests and are in therapeutic use while others are undergoing extensive phase II and phase III clinical trials [43, 44].

ANTI-INFLAMMATORY PROPERTY

Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation. A brief outline of events involved in anti-inflammatory role of *Ganoderma lucidum* is given in Fig. (**1**). The anti-inflammatory function of *G. lucidum* extract has been reported in HT-29 human colonic carcinoma cells [45]. An ethyl acetate extract rich in ganoderic acid was found to exhibit both systemic and topical anti-inflammatory activities in a croton oil-induced mouse ear inflammation test [46]. Four ganoderic acids isolated from *G. lucidum* were found to inhibit 12-*O*-tetradecanoylphorbol-3acetate-induced inflammation in mice ears [47]. Joseph *et al.* [1], reported anti-inflammatory activity of the chloroform extract of *G. lucidum* in acute and formalin induced chronic inflammatory models in mice. The extract showed remarkable anti-inflammatory activity in

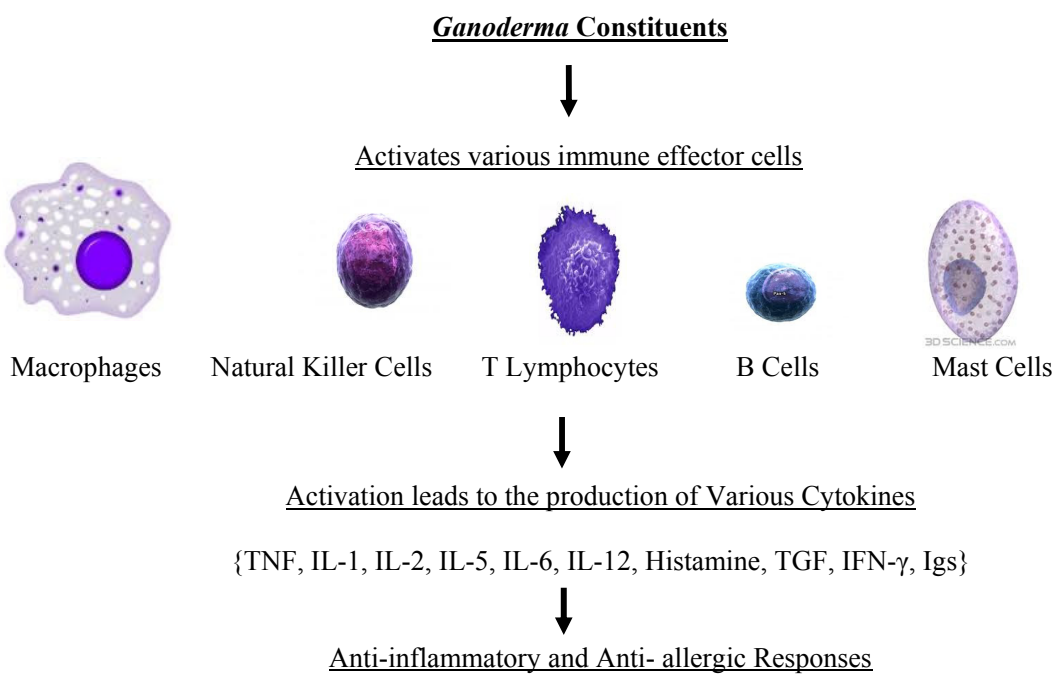

Fig. (1). Overview of anti-inflammatory and anti-allergic action of *Ganoderma lucidum.*

both models. Horng *et al.* [48] studied the anti-inflammatory properties of triterpenoids and steroids from *G. lucidum.* More than 100 different highly oxygenated lanostanoid triterpenes have been identified in reishi mushrooms. The predominant triterpenes are ganoderic acids A-Z. Ganoderic Acid C isolated by fractionation of a non-polar solvent extract of *G. lucidum* was found to account for most of the anti-inflammatory activity determined by *in vitro* tests such as histamine release from mast cells. An ethyl acetate extract rich in ganoderic acids was later found to exhibit both systemic and topical anti-inflammatory activities in standard animal models.

The major effects of active substances derived from *G. lucidum* include mitogenecity and activation of immune effector cells such as T lymphocytes, macrophages and NK cells leading to the production of cytokines including ILs, TNF-α IFNs etc. [49-51]. Other effects like inhibition of mast cells, activation of B lymphocytes and the complement system have also been reported [52,53].

TRITERPENES AS MAJOR *ANTI-INFLAMMATORY* COMPOUNDS OF *G. LUCIDUM*

Triterpenes comprise a broad group involved in the pharmacological action of many medicinally important plant products being used since ages in treatment of immune associated diseases. They have been described as *anti-inflammatory* compounds. Xu [54] made substantial efforts in the development of submerged fermentation as a promising technology for the production of triterpenes of *G. lucidum.* Triterpenes act on chemical mediators released from mast cells, neutrophils and macrophage, and their derivatives have potent concentration dependent inhibitory effects on the release of β-glucuronidase. In many studies, it has been shown that GLT (***G. lucidum* triterpene)** (triterpene extract from the medicinal mushroom *G. lucidum*) suppressed the inflammatory response in lipopolysaccharide (LPS) activated murine macrophages. GLT markedly suppressed the secretion of inflammatory cytokine, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), inflammatory mediator nitric oxide (NO) and prostaglandin E2 (PGE2) from LPS-stimulated murine RAW264.7 cells. GLT also down-regulated LPS-dependent expression of inducible nitric oxide synthase (NOS) and cyclooxygenase 2 (COX-2) in RAW264.7 cells. The anti-inflammatory effects of GLT were mediated by the inhibition of transcription factor NF-κB as demonstrated by decreased NF-κB-DNA binding activity and the suppression of p65 phosphorylation in LPS stimulated macrophages treated with GLT [55, 56].

Macrophages play an important role in both host-defense mechanism and inflammation and the overproduction of inflammatory mediators by macrophages has been implicated in several inflammatory diseases and cancer. GLT also inhibited LPS-dependent induction of NF-κB as well as expression, phosphorylation and nuclear translocation of p65 NF-κB subunit. It suppressed LPS-induced activation of AP-1 and down-regulated expression of AP-1 subunit and also inhibited LPS-dependent phosphorylation of extracellular signal-regulated kinase (ERK1/2) and c-Jun-N-Terminal Kinase (JNK) demonstrating its potency to suppress the key molecules responsible in the inflammatory response [57, 58]. The NF-κB/AP-1 axes are crucial for the inflammatory response leading to the production of TNF-α, IL-6, NO and PGE2 and other inflammatory mediators from activated macrophages, the suppression of NF-κB/AP-1 signaling has a potential therapeutic effect. The inhibition of blood levels of circulating TNF-α and IL-6 in LPS-challenged mice treated with GLT, further suggests the possible therapeutic use of GLT [59].

ADDITIONAL ACTIVITIES ASSOCIATED WITH *G. LUCIDUM* TERPENOIDS AND POLYSACCHARIDES

1. **Aldose Reductase:** Aldose reductase (AR) is the first enzyme that converts glucose into polyols (such as sorbitol) and its inhibition can play a therapeutic role. The accumulation of sorbitol then leads to diabetic complications. For this reason, AR inhibitors have been introduced as a vehicle for the treatment of diabetic complications. Reishi possesses AR inhibitory activity and appears to be one of the most potent mushrooms for this activity [60]. It appears that the carboxyl group on the side-chain is critical for aldose reductase inhibition and double bonds on C20-C22 as well as hydroxyl groups on C3, 7, 11, and 15 increase inhibitions. This ideal molecule is called ganoderic acid C2.

2. 5α Reductase: The triterpenoids in *Ganoderma* possess 5α-reductase inhibitory potential, inhibiting the conversion of testosterone into dihydrotestosterone (DHT). Higher levels of DHT have been reported to be linked to benign prostatic hyperplasia (BPH) or prostatic cancer. Inhibition of 5α Reductase is pharmacologically important for BPH [61].

3. NK cells: Zhuang *et al.* [62] reported that cancer patient who ingested a dietary complex *G. lucidum* for 6 wks showed a decrease of leucopenia and neutropenia, as well as a delay in decrease of NK cell and CD4 lymphocyte count.

4. TLR4: Toll-Like Receptor 4 is a receptor present on many immune cells that can mediate the immune response. *Ganoderma* polysaccharide appears to be a ligand and an activator of these receptors. Many effects seen in dendritic cells can be inhibited via inhibiting the TLR4 receptor, pairing this with the activation of TLR4 and some polysaccharides serves as evidence that this receptor activation is a central mechanism of action. Activation of TLR4 has been noted on macrophages and causes downstream effects that increase macrophage phagocytic capabilities. These effects may be mediated by polysaccharides and proteoglycans. It has been suggested that a polysaccharide fraction F3, which contains fucose binds to TLR4 on macrophages in order to activate proteins such as ERK involved in the regulation of meiosis, mitosis and post mitotic functions as well as JNK and p38, involved in cell proliferation/ differentiation, inflammation and cytokine production [63].

5. NF-kB: NF-κB is a common name for a family of transcription factors consisting of 5 proteins. Three proteins, p65 (RelA), c-Rel and RelB belong to the Rel family (also called NF-κB1), whereas the other two proteins, p50 and p52 and their precursors p105 and p100, respectively, belong to the NF-κB family (also called NF-κB2). In un-stimulated cells, NF-κB complexes are kept inactive in the cytoplasm via non-covalent interaction with an inhibitory protein, called inhibitor of κB (IκB). NF-κB has been reported to be a vital transcription factor in numerous signaling pathways and many biological processes including inflammation, cancer and the immune response. Pro-inflammatory cytokines lead to the phosphorylation of IκB proteins at the two *N*-terminal serine residues by the IκB kinase (IKK) complex leading to ubiquitination and degradation of IκB and translocation of unbound NF-κB, mainly RelA-p50 dimers, from the cytoplasm to the nucleus and then to induction of the transcription of respective NF-κB target genes. Considering the vital role of NF-κB in vascular inflammation, the inhibition of NF-κB activation is a promising approach for disrupting the expression of many proteins that are involved in inflammation. During co-incubation with LPS, activation of NF-κB appears to be suppressed. This is opposite of when *Ganoderma* is incubated without LPS in which macrophages and immune cells expressing TLR4 experience a rise in NF-κB activity. Studies carried out by Batbayar *et al.* [64] suggested that β-glucan of *Ganoderma* (BGG) induces macrophage secretion of inflammatory cytokines, which can be potentiated by the presence of LPS, likely by binding to dectin-1 and TLR-2/6 receptors, which activate NF-κB and prompt the secretion of cytokines.

6. TNF-α (Tumor Necrosis Factor Alpha): Rubel *et al.* [65] reported a rise in IFN-γ concentration and IL-10 production along with a decrease in NO production, TNF-α release and $CD3^+$ and $CD8^+$ T spleen cells count by feeding mice on wheat flour supplemented with *G. lucidum.* These data suggested that *G. lucidum* metabolites can act not only to enhance specific immune response against tumor and pathogen invasion but also mitigate the adverse effects of autoimmune and inflammatory diseases. *Ganoderma lucidum* appears to prevent the increase in TNF-α (with a pro-inflammatory stimulus such as LPS) by reducing nF-κB activity by both suppressing phosphorylation of Akt on Ser473 in a dose dependent manner and preventing degradation of IκB, which also suppresses nF-κB translocation. *Ganoderma lucidum* can act as an anti-inflammatory agent via reducing the inflammatory response. This has been observed *in vivo* after human ingestion of 3g *Ganoderma* spore powder. Conversely, without the pro-inflammatory insult, *Ganoderma lucidum* appears to increase circulating TNF-α levels via activation of macrophages [55, 64].

7. FXR: The Farnesoid X Receptor (FXR), is a nuclear transcription activator having role in the maintenance of bile acid homeostasis such as regulation of glucose and lipid metabolism. Pronounced FXR inducing effect was shown by five triterpenoids from the ethanolic fragment of *G. lucidum* extracts at 100μg/ml were able to induce FXR to 150% the level of the active control, CDCA (chenodeoxycholic acid), whereas the 5 isolated triterpenoids at 10μM were similar in potency to CDCA [33].

8. Cholesterol esterase inhibitor: *Ganoderma* also possesses a non-competitive cholesterol esterase inhibitor, the enzyme that is required to absorb dietary cholesterol.

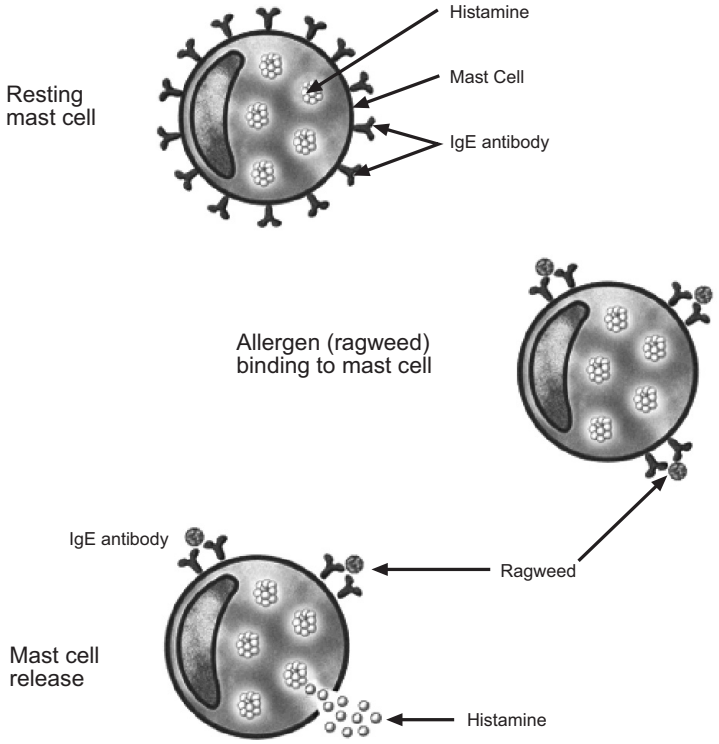

Fig. (2). Activation of mast cells by allergens.

Therefore, cholesterol uptake from the diet can be reduced with increased fecal cholesterol in experimental animals fed on *Ganoderma lucidum* [66]. When tested *in vivo*, three separate studies on rats reported that cholesterol levels can be reduced after consumption of *Ganoderma* polysaccharides; however, these studies were in models of type I diabetes [67]. Various (n = 18) triterpenoids from *Ganoderma lucidum* have been shown to possess acetylcholinesterase inhibitory actions with an IC_{50} value ranging from 9.40μM to 31.03μM [68].

ALLERGY AND ITS MODE OF ACTION

An allergy is a hypersensitivity disorder of the immune system. Allergic reactions occur when a person's immune system reacts to normally harmless substances in the environment. These reactions are acquired, predictable and rapid. Allergy is one of the four forms of hypersensitivity, allergic reactions are distinctive because of excessive activation of certain white blood cells called mast cells and basophils by a type of antibody called Immunoglobulin E, Fig. (**2**).

The allergic process has an important inflammatory component. The reactions can be divided into four types:

Type I: This is called immediate or anaphylactic hypersensitivity mediated by IgE. Mast cells and basophils play a central role in immediate allergic inflammation through releasing chemical mediators such as histamine and cysteinyl leukotrienes, cytokines and chemokines. The reaction may involve skin (eczema), eyes (conjunctivitis), nasopharynx (rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis).

Type II: This is known as antibody-cytotoxicity mediated by antibodies of the IgM or IgG classes and complements. Antibodies directed against cell surface antigens cause cell damage such as hemolytic disease of the newborn (Rh disease) and myasthenia gravis (MG).

Type III: This is known as immune complex hypersensitivity mediated by IgG or IgM classes. The reaction may be general (serum sickness) or may involve individual organs including skin, joints (rheumatoid arthritis) or other organs.

Type IV: This is known as cell mediated or delayed type hypersensitivities. These reactions are mediated by CD4+ T cells and involved in the pathogenesis of many autoimmune diseases (multiple sclerosis). Another form of delayed hypersensitivity is contact dermatitis [41].

Anaphylactic histamine release from the mast cell is triggered by an increased concentration of ionized calcium in the cytosol. This calcium may be derived from intra or extra cellular sources according to the conditions. In the presence of exogenous calcium, the immunological stimulus increases the permeability of the cell membrane to the cation by opening calcium gates in the membrane. Influx of the ion from the external environment then initiates the release process. In the absence of added calcium, the stimulus mobilizes membrane bound stores of the cation. This mobilization may be facilitated by brief pretreatment of the cells with chelating agents. In view of the central role of the ion in the release mechanism, factors which modulate calcium homeostasis

can clearly regulate secretory activity. It has been suggested that a number of anti-allergic drugs may inhibit histamine release by acting directly on the gating mechanism to prevent movement of calcium from the extracellular milieu into the cytosol.

Activation of the mast cell membrane may involve the opening of a gated channel which normally contains appreciable amounts of bound calcium. Extracellular calcium (when present) would then enter the channel, displace the bound ion into the cytosol and so trigger secretion. In the absence of added calcium, the immunological stimulus could displace the ion directly by local perturbation of the cell membranes. However, even if the mechanism is correct, inhibitory compounds would have to prevent efflux of calcium from the channel into the cytosol rather than the gated influx into the channel from the extracellular environment [69].

ANTI-ALLERGIC PROPERTY

Allergy is the example of histamine mediated allergic response. This condition is increasing in frequency and is difficult to target with modern medicine. The modern approach to anti-allergic drug research is target specific and does not consider the natural defense mechanisms of the body or the causative factors that is the shift of cytokine TH1 to a predominantly TH2 cytokine underlying histamine-mediated allergic responses. The fruiting bodies *G. lucidum* have been traditionally used as anti-inflammatory agents for the treatment of asthma or allergy [70].

Ganoderma lucidum as immune-nutraceutical with its unique array of compounds could play a major role in the treatment of histamine-mediated allergic responses. *Ganoderma lucidum* is an effective agent to restore the normal balance between the cytokines TH1 and TH2 immune states in patients with histamine-mediated allergic responses. It has been considered as a potential candidate for biotechnological production of anticancer and immunomodulatory drugs [71]. In the course of a screening test by a group of researchers for the inhibition of histamine release from rat mast cells, it was found for the first time that ganoderic acids C and D inhibited histamine release from rat mast cells [69]. Other than the triterpenoid compounds, cyclo-octasulfur from this fungus also effectively inhibited histamine release from rat peritoneal mast cells and interacted with membrane proteins to inhibit Ca uptake causing a blockade of histamine release [72].

The body is considered to be in a "balanced" immune state when there is a constant movement between TH1 and TH2 immune states in a 24-hour period. These two arms of the immune system are mutually inhibitory and in a balanced state, the body spends 12 hours in a TH1 state (anti-viral, anti-bacterial and anti-parasitic activities) and then 12 hours in a TH2 state (pro-inflammatory activity). Factors such as stress and chemical exposure weaken our body's ability to defend itself, not through impairing the cellular immune response (TH1 - the ability of the body to recognize and destroy foreign bodies) but through leading to a chronic elevation of the humoral immune response (TH2), a pro-inflammatory state, which normally predominates in cases of local wound healing or histamine-mediated allergic response [73].

When a chronic elevation of the humoral immune response is prolonged, this is known as a "TH1 to TH2 Shift". In a TH1 to TH2 Shift, the pattern of cytokines moves from an anti-viral, anti-bacterial and anti-parasitic pattern (TH1) to an inflammatory repairing pattern (TH2) but does not return to a TH1 state within 12 hours. This chronically elevated pro-inflammatory immune response is termed a TH2 immune state. Histamine-mediated allergic responses are prolonged TH1 to TH2 shifts. For this reason, allergies are considered "TH2 conditions". As long as the shift continues, there is little relief from symptoms caused by such "TH2 conditions". Recent clinical studies have established that mushroom nutrition is able to rebalance the TH1 and TH2 immune states, thereby reversing a "TH1 to TH2 shift" [73].

The currently used topical and systemic anti-inflammatory drugs have serious drawbacks such as they can suppress pituitary-adrenal function, dangerously unbalance fluids/electrolytes and cause undesirable changes in skin texture and the salicylic acid-derived prostaglandin inhibitors can result in severe gastric irritation [74]. Hence, the potential use of *Ganoderma lucidum* (Reishi) supplementation could offer a safe and effective alternative for the reduction of histamine-mediated immune responses. Histamine-mediated allergic responses are provoked by chronically elevated pro-inflammatory immune responses. For this reason, allergies are considered "TH2 conditions". As long as the cytokine TH1 to cytokine TH2 shift continues, there is no relief from symptoms caused by allergies.

Medical tools have focused on treating the symptoms of allergies but not the prolonged TH2 condition. Modern approach to drug research is target-specific and does not consider the natural defense mechanisms of the body or the causative factors (cytokine TH1 to cytokine TH2 shift) underlying histamine-mediated allergic response. *Ganoderma lucidum* (Reishi) as immunonutrition with its unique array of compounds working in concert could play a major role in current treatment practices for histamine-mediated allergic response [70, 75]. *Ganoderma lucidum* (Reishi) is an effective agent to restore the normal balance between the TH1 and TH2 immune states in patients with histamine-mediated immune response. Such an approach treats the underlying cause for the TH2 condition see Table **2**, [76-83].

PATENTS BASED ON *GANODERMA* AS AN ACTIVE INGREDIENT

Description about the Patents based on the use of *Ganoderma* as active ingredient for pharmaceutical applications is given in Table **3**, [84-98]. From these extensive studies, one can very well understand the diversity of the pharmaceutical application of this miracle herb and its positive effects while its use in combination with other prescribed drugs makes it a potential candidate for further extensive clinical trials.

Table 2. Anti-Allergic Activities of Phytochemicals.

Target Pathway	Effects	References
Effect on IgE mediated Hypersensitivity (Type I)	Inhibition of chemical mediator release and Cytokine production by mast, basophil or T cells	[21,23,76-80]
	Inhibition of signal transduction and gene expression in mast, basophil or T cells	
	Preventing allergic asthma	
Effect on cell-mediated Hypersensitivity (Type IV)	Preventing contact dermatitis	[79, 81]
Attenuating autoimmune Disorders	Improving multiple sclerosis (MS) Disease	[82, 83]

Table 3. Patents Based on the Use of *Ganoderma* as an Active Ingredient for Pharmaceutical Applications.

S. No.	Patent No.	Title	Physiological/Pharmacological Implications
1.	US20130122035	Herbal composition for treating cancer	Herbal composition was created using the cumulative clinical experience of a medical oncologist which combines Eastern medicine and Western medicine. Due to lack of efficacy, *Scutellaria baicalensis* and *Bulbus fritillariae* were added with extracts of *Ganoderma lucidum* to strengthen its anti-cancer potency [84]
2.	US6893641	*Ganoderma lucidum* spores for treatment of autoimmune diseases	The present invention relates to a method for treating mammals with immunological disorders, particularly autoimmune diseases, and most favourably systemic lupus erythematosus (SLE), by orally administering germination activated *Ganoderma lucidum* spores ("GLSs") to the mammals. The GLSs can be co-administered with a corticosteroid to achieve a better therapeutic effect on treatment of SLE [76]
3.	US5334704	Glycoprotein isolated from *Ganoderma* having immunosuppressive activity	A novel glycoprotein was derived from *Ganoderma mycelia*. The glycoprotein is free of human hemagglutination ability and has immunosuppressive activities and a molecular weight of 16,000-18,000 as measured by SDS gel electrophoresis [85]
4.	US6468542	Germination activated *Ganoderma lucidum* spores and method for producing the same	The present invention describes a method for germination activating spores of *Ganoderma lucidum* to produce bioactive substances which have medicinal effects on patients with immunological disorders, cancer, AIDS, hepatitis, diabetes, and cardiovascular diseases, and can prevent or inhibit free radical oxidation and hepatotoxic effects [86]
5.	EP2604272	Effective fraction from the fruiting bodies of *Ganoderma lucidum*, extraction method, use and preparation thereof	The effective fraction was prepared from the defatted fruiting bodies of *Ganoderma lucidum* by extracting with alkali, dialyzing and drying. The effective fraction has effect of significantly lowering blood sugar [87]

Table (3) contd….

S. No.	Patent No.	Title	Physiological/Pharmacological Implications
6.	US7947283	Compositions and methods for treating psoriasis by *Ganoderma lucidum* (Reishi) polysaccharides	The present invention relates to pharmaceutical compositions containing *Ganoderma lucidum* extract to treat psoriasis. The symptoms of psoriasis are alleviated by providing a pharmaceutical composition containing *Ganoderma lucidum* extract and administering an amount of the composition effective to increase at least one of an IL-10 and IL-1Ra expression [88]
7.	US20090060939	Compositions and methods for treating allergies, auto-immune diseases and improving skin condition by *Ganoderma lucidum* (Reishi) polysaccharides	A method for treating an allergy by providing a pharmaceutical composition containing *Ganoderma lucidum* extract and administering a therapeutically effective amount of the composition to a patient so that symptoms of the allergy are alleviated and administering an amount of the composition effective to decrease at least one of an IgE and IgG2a level [89]
8.	US20130101616	Compositions of botanical extracts for cancer therapy	Compositions comprising therapeutically effective amounts of two or more of an extract of *Ganoderma lucidum*, an extract of *Salvia miltiorrhiza*, an extract of *Scutellaria barbata* and optionally a therapeutically effective amount of an extract of *Hippophae rhamnoides* are used for testing their efficacy against cancer [90]
9.	US20110009597	Recombinant *Ganoderma lucidum* immunomodulatory protein (Rlz-8) and uses thereof	Provided is the use of the recombinant *Ganoderma lucidum* immunomodulatory protein (rLZ-8) for the manufacturing of a medicament for antitumor, increasing leukocyte and inhibiting immunological rejection and the pharmaceutical composition comprise the rLZ-8 protein [91]
10.	US20100104605	Method for preventing and treating influenza	The present invention provides a method for making pressure-induced *Ganoderma* spores, for using the *Ganoderma* spores to ameliorate and prevent influenza in a mammal, and to stimulate the host immune system in a mammal [92]
11.	US8476238	Uses of an immunomodulatory protein (GMI) from *Ganoderma microsporum*	The invention provides a method for inhibiting EGF receptor activity comprising contacting an EGF receptor with an immunomodulatory protein (GMI) from *Ganoderma microsporum*, or a recombinant thereof. It also provides a method for treating invasion and metastasis of cancer cells [93]
12.	US20130184244	Process for preparing delta-7, 9(11) steroids from *Ganoderma lucidum* and analogs thereof	The invention described here pertains to processes for the preparation of delta7, 9(1 1) steroids from *Ganoderma lucidum*, and related compounds and use of the compounds to treat cancer [94]
13.	US6613754	Polysaccharide-based extract from *Ganoderma*, pharmaceutical use thereof and process for preparing the same	The invention describes a process for preparing a polysaccharide-based extract from *Ganoderma*. The polysaccharide-based extract can be used in an orally active medicinal product which has immune-potentiating and anti-tumor effects [95]

Table (3) contd….

S. No.	Patent No.	Title	Physiological/Pharmacological Implications
14.	US7135183	Immuno-modulating antitumor activities of *Ganoderma lucidum* (Reishi) polysaccharides	The present invention provides medicinally active extracts and fractions, and a method for preparing the same by extracting and fractioning constituents from the tissue of plant components of *Ganoderma lucidum*. These active extracts and fractions are useful for inhibiting tumor growth, modulating immune response, and increasing hematopoietic activity [27]
15.	EP2266589	*Ganoderma tsugae* active substance having endothelial cell-protecting and atherosclerosis preventing effects, process for preparing the same and composition containing the same	The object of the invention is to provide *Ganoderma tsugae* active substance having endothelial cell protecting and atherosclerosis preventing effects. Another object of the invention is to provide a process for preparing *Ganoderma tsugae* active substance [96]
16.	EP1398036	*Ganoderma lucidum* spores for treatment of Systemic Lupus Erytrhomatosus (SLE)	The present invention relates to a method for treating mammals with immunological disorders, particularly autoimmune diseases and most favorably systemic lupus erythematosus (SLE) by orally administering germination activated *Ganoderma lucidum* spores ("GLSs") to the mammals. The GLSs can be co-administered with a corticosteroid to achieve a better therapeutic effect on treatment of SLE [97]
17.	EP1449534	*Ganoderma atrum* extract as matrix metalloprotease inhibitor	The present invention relates to a solvent extract of *Ganoderma atrum* having matrix metalloproteinase (MMP) inhibitor activity. More specifically the invention pertains to an MMP inhibitor that has high safety and is expected to have effects on prevention, suppression and symptomatic relief of various activated MMP-causing disorders and diseases, such as metastasis of cancers, ulceration, rheumatoid arthritis, osteoporosis, periodontitis and cosmetic treatment of aging of skin [98]

GANODERMA SUPPLEMENTATION IN VARIOUS OTHER PHARMACEUTICAL PREPARATIONS

Various herbal formulations have been created that combine Eastern medicine and Western medicine for the benefit of mankind. The components of these formulations have been changed several times in order to improve their efficacy, based not only on patients' feedback, but also on research into modern literature for physiological implications associated with the disease symptoms. Several patents include the use of different components of *Ganoderma* as supplements for improving the pharmacological effect of active ingredients derived from other sources. Table **4** summarizes the information on such patents [99-103].

CURRENT & FUTURE DEVELOPMENTS

Enhanced immune surveillance is required to counter diseases like cancer. Ideal chemoprotective agent should have minimal or zero toxicity, and should be convenient to use with proven efficacy. The research on medicinal mushrooms especially *Ganoderma* during the last two decades or so gives us the impression and confidence that its bioactive components have much more to offer to the healthcare needs in future. *Ganoderma* which is non-toxic and without any side effects has the potential to stimulate immune system which could be through natural Killer cells and cytotoxic T-lymphocytes. It is greatly anticipated that *Ganoderma* could successfully complement as an effective nutraceutical where the modern medicine fails to provide a complete remedy, thus augmenting the success of the treatment. The continual efforts will provide new insight into various biological activities of *Ganoderma* and other medicinal mushrooms which may eventually lead to development of new classes of anti-cancer, anti-inflammatory and anti-allergic agents. The trend today is to seek bioactive compounds from such wonder herbs like *Ganoderma* that will serve as leading

Table 4. Active Constituents of *Ganoderma* as Supplement in Pharmaceutical Preparations.

S. No.	Patent No.	Title	Components of formulation	Pharmacological/Physiological Implications
1.	US20130108587	Methods and compositions for enhancing stem cell mobilization	Polysaccharide-rich fraction of *Lycium barbarum* extract, protein-rich fraction of colostrum extract, fucoidan, including an isolated component or compound extracted from an algae, polysaccharide-rich fraction of mushroom extracts, including *Cordyceps sinensis, Ganoderma lucidum, Hericium Erinaceus, spirulina*, including *Arthrospira platensis, Arthrospira maxima*	Affects the migration of stem cells, such as CD34high (CD34+) cells. Decreases the number of bone marrow-derived stem cells and/or hematopoietic stem cells circulating in the peripheral blood. Enhanced expression of CXCR4 on circulating stem cells [99]
2.	WO2013074801	Use of foti to enhance stem cell mobilization and proliferation	Blended composition of plant parts, fruits, mushrooms, microorganisms, maternal fluids, and extracts thereof	Migration of the stem cells to specific sites of maintenance and repair within tissues and/or organs Increased circulation of HSCs and/or BMSCs and migration towards sites of Maintenance [100]
3.	WO2012030137	Pharmaceutical composition for preventing or treating inflammatory diseases, allergic diseases or asthma, containing *Diospyros blancoi* a. Dc. Extract as active ingredient	*Diospyros blancoi* extract as an active ingredient and *Ganoderma lucidum* (0.5 wt parts) used for preparation of Zen food as pharmaceutical preparation	Inhibitory activity against the nuclear translocation of NF-κB, Suppress the production of NO and PGE2, the expression of iNOS and COX-2, and the release of IL-1beta and TNF-alpha Significantly down regulate Th2-mediated IL-4 and IL-13 production. Inhibit the activation of eosinophils in broncho alveolar lavage fluid. Suppress the secretion of immunoglobulins and chemokines in broncho alveolar lavage fluid and blood [101]
4.	EP2617702	Novel biphenyl compound or pharmaceutically acceptable salt thereof, method for preparing novel biphenyl compound or pharmaceutically acceptable salt thereof, and pharmaceutical composition containing same as active ingredient for preventing or treating diabetes complications	*Osteomeles schwerinae* Schneid Extract and Ganoderma lucidum powder (0.5 wt parts) in grain powder preparation	Effective inhibitory effect on AGE formation compared to the known amino guanidine. Changes in occludin, the protein which constitutes the tight junction for protecting eyes, changes in retinal blood vessels a dose-dependent decrease in the angiogenic factor inhibit formation of advanced glycation end products. Hence preventing or treating diabetic complications such as diabetic retinopathy [102]
5.	EP2623108	Composition for preventing or treating atopic dermatitis including galenical extract or lactobacillus fermentation thereof.	Galenical mixture including sophora root, licorice, lonicer a flower, Korean angelica root, Korean aralia root, *Epimedium Koreanum nakai, Ginseng, Lithospermum, Oleoresin, Cnidium, Scorophulariae radix, and Reynoutria* or *Lactobacillus* fermentation of the galenical extract	Reduced scratching, erythema, itchiness and dry skin, edema and hematoma, erosion, and lichenification. Reduces IgE concentration in blood [81]

Table (4) contd….

S. No.	Patent No.	Title	Components of Formulation	Pharmacological/Physiological Implications
6.	US20130244959	Composition containing styrax-lignolide A or the aglycone thereof as an active ingredient for preventing or treating asthma	Styraxlignolide A compound separated from stems and barks of *Styrax japonica* and *Ganoderma Lucidum* powder (0.5 wt parts) in grain powder preparation	Attenuating weight loss and airway hyper responsiveness, Inhibiting the generation of reactive oxygen species in airway Inhibiting generation of IgE, TGF-beta1, and IL-17 in the serum and broncho alveolar lavage fluid Inhibiting endobronchial inflammatory cell infiltration, formation of a mucous plug and sub epithelial fibrosis [80]
7.	WO2013012117	Pharmaceutical compositions for preventing or treating inflammatory diseases, comprising phytosterol compound	*Trachelospermum asiaticum* var. Intermedium's phytosterol fractions	Inhibiting the production of TNF, nitric oxide and the release of inflammatory cytokines [103]
8.	WO2013138871	Immunomodulatory agent and uses thereof	Immunomodulatory agents that are useful for treating or preventing joint damage in RA	Eliciting an antigen specific tolerogenic response to an aggression polypeptide including citrullinated forms thereof to treat or prevent joint damage [22]

compounds for synthetic or semi synthetic development. Further research on *Ganoderma* for validating its usage and in-depth knowledge of the main pharmacologically active component are essentially required in order to standardize procedures for obtaining herbal remedies to replace crude products with modern pharmacological formulations. Such studies need to be carried out on a larger scale with sound assessment in established animal models.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We greatly acknowledge Maharishi Markandeshwar University, Mullana (Ambala) and also appreciate the assistance provided by Rohit Sharma especially in patent search.

REFERENCES

[1] Joseph S, Sabulal B, George V, Smina TP, Janardhanan KK. Antioxidative and anti-inflammatory activities of the chloroform extract of *Ganoderma lucidum* found in South India. Sci Pharm 2009; 77: 111-21.

[2] Sanodiya BS, Thakur GS, Baghel RK, Prasad GBKS, Bisen PS. *Ganoderma lucidum*: A potent pharmacological macrofungus. Curr Pharm Biotechnol 2009; 10: 717-42.

[3] Zengtao X, Xiuping C, Zhangfeng Z, Lidian C, Yitao W. *Ganoderma lucidum* polysaccharides: Immunomodulation and potential anti-tumour activities. Am J Chinese Med 2011; 39: 15-27.

[4] Batra P, Sharma AK, Khajuria R. Probing Lingzhi or Reishi medicinal mushroom *Ganoderma lucidum* (Higher Basidiomycetes): A Bitter Mushroom with Amazing Health Benefits. Int J Med Mush 2013; 15(2): 127-43.

[5] Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454: 428-35.

[6] Okada F, Fujii J. Molecular mechanism of inflammation-induced carcinogenesis. J Clin Biochem Nutr 2006; 39: 103-13.

[7] Gorjao R, Takahashi HK, Pan Ji AN, Hirabara SM. Molecular mechanism involved in inflammation and insulin resistance in chronic diseases and possible interventions. J Biomed Biotechnol 2012; Article ID 841983.

[8] Huang W, Glass CK. Nuclear receptors and inflammation control: Molecular mechanism and pathophysiological relevance. Arterioscler Thromb Vasc Biol 2010; 30: 1542-49.

[9] O'Neil LA, Bowie AG. The family of five: TIR domain-containing adaptors in toll-like receptor signaling. Nat Rev Immunol 2007; 7: 353-64.

[10] Serhan CN, Savill J. Resolution of inflammation: The beginning programs the end. Nat Immunol 2005; 6: 1191-7.

[11] Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov 2003; 2: 473-88.

[12] Nagel A, Hertl M, Eming R. B-cell directed therapy for inflammatory skin diseases. J Invest Dermatol 2009; 129: 289-301.

[13] Chang ST, Buswell JA. *Ganoderma lucidum* (Aphyllophoromycetideae) a mushrooming medicinal mushroom. International J Med Mush 1999; 1(2):139-46.

[14] Galor SW, Yuen J, Buswell JA, Benzie IFF. *Ganoderma lucidum* (Ling zhi or Reishi) A medicinal mushroom. In: Herbal medicine: Biomolecular and clinical aspects (2nd ed.). Edited by Benzie IFF and Galor SW. Boca Raton (FL): CRC Press 2011.

[15] Hanaski Y, Ogawa S, Fukui S. The correlation between active oxygen scavenging and antioxidative effects of flavonoids. Free Radic Biol Med1994; 16: 845-50.

[16] Mau JL, Lin HC, Chen CC. Antioxidant properties of several medicinal mushrooms. J Agric Food Chem 2002; 50(21): 6072-77.

[17] Manna SK. Double-edged sword effect of biochanin to inhibit nuclear factor kappaB: Suppression of serine/threonine and tyrosine kinases. Biochem Pharmacol 2012; 15: 1383-92.

[18] Mizushina Y, Yamaguchi T, Takemura M, Sugawara F, Saneyoshi M, Matsukage A, *et al*. A mushroom fruiting body-inducing substance inhibits activities of replicative DNA polymerases. Biochem Biophys Res Commun 1998; 249(1): 12-22.

[19] An SJ, Pae HO, Oh GS, Choi BM, Jeong S, Jang SI, *et al*. Inhibition of TNF-alpha, IL-1beta, and IL- 6 productions and NF-kappa B activation in lipopolysaccharide-activated RAW 264.7 macrophages by catalposide. Int Immunopharmacol 2002; 2: 1173-81.

[20] Ranjeny, T. Immunomodulatory agent and uses therefor. WO2013138871 (**2013**).

[21] Trevillyan JM, Lu YL, Atluru D, Phillips CA, Bjorndahl JM. Differential inhibition of T cell receptor signal transduction and early activation events by selective inhibitor of protein-tyrosine kinase. J Immunol 1990; 145: 3223-30.

[22] Hua KF, Hsu HY, Chao LK, Chen ST, Yang WB, Hsu J *et al. Ganoderma lucidum* polysaccharides enhance CD14 endocytosis of LPS and promote TLR4 signal transduction of cytokine expression. J Cell Physiol 2007; 212: 537-50.

[23] Wang SY, Hsu ML, Hsu HC, Tzeng CH, Lee SS, Shiao MS, *et al.* The antitumor effect of *Ganoderma lucidum* is mediated by cytokines released from activated macrophages and T lymphocytes. Int J Cancer 1997; 70(6): 699-705.

[24] Zhang J, Tang Q, Zimmerman-Kordmann M, Reutter W, Fan H. Activation of B lymphocytes by GLIS, a bioactive proteoglycans from *Ganoderma lucidum*. Life Sci 2002; 71(6): 623-38.

[25] Wang, Y.Y., Khoo, K.H., Chen, S.T., Lin, C.C., Wong, C.H., Lin, C.H., Chen, H.S., Yow- Tsai, F. Immuno-modulating antitumor activities of *Ganoderma lucidum* (reishi) polysaccharides. US7135183 (**2006**).

[26] Zhou S and Gao Y. The immunomodulating effects of *Ganoderma lucidum*. (Ling-Zhi, reishi mushroom). Int J Med Mushrooms 2002; 4(1): 1-11.

[27] Wang YY, Khoo KH, Chen ST, Lin CC, Wong CH, Lin CH. Studies on the immuno-modulating and antitumor activities of *Ganoderma lucidum* (Reishi) polysaccharides: Functional and proteomic analysis of a fucose-containing glycoprotein fraction responsible for the activities. Bioorg Med Chem 2002; 10(4): 1057-62.

[28] Hong JJ, Jeong TS, Choi JH, Park JH, Lee KY, Seo YJ, *et al*. Hematein inhibits tumor necrotic factor-alpha-induced vascular cell adhesion molecule-1 and NF-kappaB dependent gene expression in human vascular endothelial cells. Biochem Biophys Res Commun 2001; 281: 1127-33.

[29] Liu X, Yuan JP, Chen XJ. Antitumour activity of sporoderm-broken germinating spores of *G. lucidum*. Cancer Lett 2002; 182:155-61.

[30] Wasser SP, Weis AL. Medicinal Mushrooms *Ganoderma lucidum*. Israel: Peledfus Publ House 1997; 39.

[31] Li EK, Tam LS, Wong CK, Li WC, Lam C, Wachtel-Galor S, *et al.* Safety and efficacy of *Ganoderma lucidum* (Lingzhi) and San Miao San supplementation in patients with rheumatoid arthritis: A double-blind, randomized, placebo-controlled pilot trial. Arthritis Rheum 2007; 57(7):1143-50.

[32] Zhu HS, Yang XL, Wang LB, Zhoa DX, Chen L. Effects of extracts from sporoderm-broken spores of *G. lucidum* on HeLa cells. Cell Biol Toxicol 2000; 16: 201-6.

[33] Grienke U, Mihaly-Bison J, Schuster D, Afonyushkin T, Binder M, Guan SH, *et al.* Pharmacophore-based discovery of FXR-agonists. Part II: Identification of bioactive triterpenes from *Ganoderma lucidum*. Bioorg Med Chem 2011; 19: 6779-91.

[34] Simpson DM, Ras R. The neutrophilic leukocyte in wound repair. A study with antineutrophil serum. J Clin Invest 1972; 51: 2009-23.

[35] Leibovich SJ, Ross R. The role of the macrophage in wound repair. Am J Pathol 1975; 78: 71-100.

[36] Martin P. Wound healing-aiming for perfect skin regeneration. Science 1997; 276: 75-81.

[37] Singer AJ, Clark RAF. Cutaneaous wound healing. N Eng J Med 1999; 341: 738-46.

[38] Bianchi ME. DAMPs, PAMPs and alarmins: All we need to know about danger. J Leukoc Biol 2007; 81(1):1-5.

[39] Shichita T, Sakaguchi R, Suzuki M, Yoshimura A. Post-ischemic inflammation in the brain. Front Immun 2012; 3:132.

[40] Chilton PM, Embry CA, Mitchell TC. Effects of differences in lipid A structure on TLR4 pro-inflammatory signalling and inflammasome activation. Front Immun 2012; 3: 154.

[41] Bellik Y, Boukraâ L, Alzahrani HA, Bakhotmah BA, Abdellah F, Hammoudi SM, *et al.* Molecular mechanism underlying anti-inflammatory and anti-allergic activities of phytochemicals: An update. Molecules 2013; 18: 322-53.

[42] Kim HJ, Young PJ. Direct analysis of Curcumin in turmeric by DART-MS. Phytochem Anal 2009; 20(5): 372-77.

[43] Harvey A. Strategies for discovering drugs from previously unexplored natural products. Drug Discov Today 2000; 5: 294-300.

[44] Jachak SM, Saklani A. Challenges and opportunities in drug discovery from plants. Curr Sci 2007; 92:1251-7.

[45] Hong KJ, Dunn DM, Shen CL, Pence BC. Affects of *Ganoderma lucidum* on apoptotic and anti-inflammatory function in HT-29 human colonic carcinoma cells. Phytother Res 2004; 18: 768-70.

[46] Karaman MA, Mimica-Dukic NM, Matavulj MN. Lignicolous fungi as potential natural sources of antioxidants. Arch Biol Sci 2005; 57: 93-100.

[47] Akihisa T, Nakamur Y, Tagata M, Tokuda H, Yasukawa K, Uchiyama E, *et al.* Anti-inflammatory and anti-tumor-promoting effects of triterpene acids and sterols from the fungus *Ganoderma lucidum*. Chem Biodiv 2007; 4: 224-31.

[48] Horng-Huey K, Hung CF, Wang JP, Lin CN. Antiinflammatory triterpenoids and steroids from *Ganoderma lucidum* and *G. tsugae*. Phytochemistry 2008; 69(1): 234-39.

[49] Lull C, Wichers HJ, Savelkoul HFJ. Anti-inflammatory and immunomodulating properties of fungal metabolites. Mediators Inflamm 2005; 2: 63-80.

[50] Hsu HY, Hua KF, Wu WC, Hsu J, Weng ST, Lin TL, *et al*. Reishi immuno-modulation protein induces interleukin-2 expression via protein kinase-dependent signaling pathways within human T cells. J Cell Physiol 2008; 215:15-26.

[51] Yeh CH, Chen HC, Yang JJ, Chuang WI, Shea F. Polysaccharides PS-G and protein LZ-8 from Reishi (*Ganoderma lucidum*) exhibit diverse functions in regulating murine macrophages and T lymphocytes. J Agric Food Chem 2010; 58: 8535-44.

[52] Min BS, Gao JJ, Hattori M, Lee HK, Kim YH. Anticomplement activity of terpenoids from spores of *Ganoderma lucidum*. Planta Med 2001; 67: 811-14.

[53] Seo HW, Hung TM, Na MK, Jung HG, Kim JC, Choi JS, *et al*. Steroids and triterpenes from the fruit bodies of *Ganoderma lucidum* and their anti-complement activity. Arch Pharm Res 2009; 32: 1573-79.

[54] Xu JW, Zhao W, Zhong JJ. Biotechnological production and application of ganoderic acids. Appl Microbiol Biotechnol 2010; 87: 457-66.

[55] Dudhgaonkar S, Thyagarajan A, Sliva D. Suppression of the inflammatory response by triterpenes isolated from the mushroom *Ganoderma lucidum*. Int Immunopharmacol 2009; 9(11):1272-80.

[56] Huang M, Mei X, Zhang S. Mechanism of nitric oxide production in macrophages treated with medicinal mushroom extracts (Review). Int J Med Mush 2011; 13(1): 1-6.

[57] Guha M, Mackman N. LPS induction of gene expression in human monocytes. Cell Signal 2001; 13: 85-94.

[58] Laskin DL, Pendino KJ. Macrophages and inflammatory mediators in tissue injury. Annu Rev Pharmacol Toxicol 1995; 35: 655-77.

[59] Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation and cancer. J Clin Invest 2007; 117: 1175-83.

[60] Fatmawati S, Kuniyoshi S, Kondo R. Ganoderic acid D, a new triterpenoid with aldose reductase inhibitory activity from the fruiting body of *G. lucidum*. Fitoterapia 2010; 81(8): 1033-6.

[61] Liu J, Kurashiki K, Shimizu K, Kondo R. 5α-Reductase inhibitory effect of triterpenoids isolated from *Ganoderma lucidum*. Biol Pharm Bull 2006; 29(2): 392-5.

[62] Zhuang SR, Chen SL, Tsai JH, Huang CC, Wu TC, Liu WS, *et al.* Effect of citronellol and the chinese medical herb complex on cellular immunity of cancer patients receiving chemotherapy/radiotherapy. Phytother Res 2009; 23: 785-90.

[63] Chen HS, Tsai YF, Lin S, Lin CC, Khoo KH, Lin CH, *et al.* Studies on the immuno-modulating and anti-tumor activities of *Ganoderma lucidum* (Reishi) polysaccharides. Bioorg Med Chem 2004; 12: 5595-601.

[64] Batbayar S, Kim MJ, Kim HW. Medicinal mushroom Lingzhi or Reishi, *Ganoderma lucidum* P. Karst., beta-glucan induces Toll-like receptors and fails to induce inflammatory cytokines in NF-kappaB inhibitor-treated macrophages. Int J Med Mushrooms 2011; 13(3): 213-25.

[65] Rubel R, Santa HSD, Bonatto SJR, Bello S, Fernandes LC, Bernardi RD, *et al*. Medicinal Mushroom *Ganoderma lucidum* (Leyss:

Fr) Karst triggers immunomodulatory effects and reduces nitric oxide synthesis in mice. Med Food 2010; 13: 142-8.

[66] Kim SD. Isolation and structure determination of a cholesterol esterase inhibitor from *Ganoderma lucidum*. J Microbiol Biotechnol 2010; 20(11):1521-23.

[67] Teng BS, Wang CD, Zhang D, Wu JS, Pan D, Pan LF, *et al.* Hypoglycemic effect and mechanism of a proteoglycan from *Ganoderma lucidum* on streptozotocin-induced type 2 diabetic rats. Eur Rev Med Pharmacol Sci 2012; 16:166-75.

[68] Lee I, Ahn B, Choi J, Hattori M, Min B, Bae K. Selective cholinesterase inhibition by lanostane triterpenes from fruiting bodies of *Ganoderma lucidum*. Bioorg Med Chem Lett 2011; 21: 6603-7.

[69] White JR, Pearce FL. Effect of anti-allergic compounds on anaphylactic histamine secretion from rat peritoneal mast cells in the presence and absence of exogenous calcium. Immunology 1982; 46(2): 361-7.

[70] Martin P. The Use of *Ganoderma lucidum*. In: The Management of Histamine-Mediated Allergic Responses. Townsend Letter for Doctors and Patients Consolidated Press: Seattle, Washington, 2006; 26-30.

[71] Boh B. *Ganoderma lucidum*: A potential for biotechnological production of anti-cancer and immunomodulatory drugs. Recent Pat Anticancer Drug Discov 2013; 8(3): 255-87.

[72] Kenyon-Dove K. Observational non-controlled study of the use of *Coriolus versicolor* supplementation in 30 cancer patients. Mycology News 2003; 1(8): 2-4.

[73] Prasad AS. Role in immunity, oxidative stress and chronic inflammation. Curr Opin Clin Nutr Metab Care 2009; 12: 646-52.

[74] Calder P. Immunonutrition. BMJ 2003; 327:117-8.

[75] Hsu CC, Lin KY, Wang ZH, Lin WL, Yin MC. Preventive effect of *Ganoderma amboinense* on acetaminophen-induced acute liver injury. Phytomedicine 2008; 15(11): 946-50.

[76] Tong, C.K., Tong, S.K. *Ganoderma lucidum* spores for treatment of autoimmune diseases. US6893641 (**2005**).

[77] Cheong H, Ryu SY, Oak MH, Cheon SH, Yoo GS, Kim KM. Studies of structure activity relationship of flavonoids for the anti-allergic actions. Arch Pharm Res 1998; 21: 478-80.

[78] Fraňova S, Strapkova A, Mokry J, Šutovska M, Joškova M, Sadloňová V, *et al*. Pharmacologic modulation of experimentally induced allergic asthma. Interdiscp Toxicol 2011; 4: 27-32.

[79] Ikarashi N, Sato W, Toda T, Ishii M, Ochiai W, Sugiyama K, *et al*. Inhibitory effect of polyphenol-rich fraction from the bark of *Acacia mearnsii* on itching associated with allergic dermatitis. Evid Based Complement Alternat Med 2012; 2012: Article ID 120389.

[80] Ahn, K.S., Jang, H.Y., Oh, S.R., Lee, H.K., Kwon, O.K., Kim, S., Kim, J.H., Kim, D.Y. Composition containing styraxlignolide A or the aglycone thereof as an active ingredient for preventing or treating asthma. US20130244959 (**2013**).

[81] Jin, Y.M. Composition for preventing or treating atopic dermatitis including galenical extract or lactobacillus fermentation thereof. EP2623108 (**2013**).

[82] Riccio P. The molecular basis of nutritional intervention in multiplesclerosis: A narrative review. Complement Ther Med 2011; 19: 228-37.

[83] Xie L, Li XK, Takahara S. They have bright prospects for the treatment of multiple sclerosis. Int Immunopharmacol 2011; 11: 323-30.

[84] Sheng, Y.H.P. Herbal composition for treating cancer. US20130122035 (**2013**) & EP2707012 (**2014**).

[85] Tsunoo, H., Kino, K., Yamashita, A. Glycoprotein isolated from *Ganoderma* having immunosuppressive activity. US5334704 (**1988**).

[86] Liu, X., Chung, C.K. Germination activated *G. lucidum* spores and method for producing the same. US6468542 (**2002**).

[87] Ping, Z., Yang, H., Teng, B., Wang, C. Effective fraction from the fruiting bodies of *Ganoderma lucidum*, extraction method, use and preparation thereof. EP2604272 (**2013**).

[88] Tu, T.R., Li, C.F., Su, S.H., Wong, C.H., Fan, E. Compositions and methods for treating psoriasis by *Ganoderma lucidum* (Reishi) polysaccharides. US7947283 (**2011**).

[89] Tu, T.R., Li, C.F., Su, S.H., Wong, C.-H., Fan, E. Compositions and methods for treating allergies, auto-immune diseases, and improving skin condition by *Ganoderma lucidum* (reishi) polysaccharides. US20090060939 (**2007**).

[90] Dao, J., Dao, T.C.S., Tong, D.D., Wilson, L., Jordan, M.A., Gerwick, W. Compositions of botanical extracts for cancer therapy. US20130101616 (**2013**).

[91] Fei, S., Xitian, Z. Recombinant *Ganoderma lucidum* immuno modulatory protein (Rlz-8) and uses thereof. USP20110009597 (**2011**).

[92] Chung, C.K., Zuo, L. Method for preventing and treating influenza. US20100104605 (**2010**).

[93] Jiunn-Liang, K., Taichung, H. Uses of an immunomodulatory protein (GMI) from *Ganoderma microsporum*. US8476238 (**2013**).

[94] Robert, M., Erin, K. Process for preparing delta-7, 9(11) steroids from *Ganoderma lucidum* and analogs thereof. US20130184244 (**2013**).

[95] Wu, R.T. Plant extracts obtained by solvent extraction and protein removal, used as immunology potentiators and antitumor agents. US6613754 (**2003**).

[96] Wei, Y.S., Hsieh, C.W., Wung, B.S. *Ganoderma tsugae* active substances having endothelial cell-protecting and atherosclerosis preventing effects, process for preparing the same and composition containing the same. EP2266589 (**2010**).

[97] Chung, C.K., Tong, S.K. *Ganoderma lucidum* spores for treatment of systemic lupus erytrhomatosus (SLE). EP1398036 (**2003**).

[98] Hattori, K., Mizutani, H., Osumi, K. *Ganoderma atrum* extract as matrix metalloprotease inhibitor. EP1449534 (**2011**).

[99] Drapeau, C., Jensen, G.S. Methods and compositions for enhancing stem cell mobilization. US20130108587 (**2013**).

[100] Drapeau, C., Jensen, G.S. Use of foti to enhance stem cell mobilization and proliferation. WO2013074801 (**2013**).

[101] Ahn, K.S. Pharmaceutical composition for preventing or treating inflammatory diseases, allergic diseases or asthma, containing *Diospyros blancoi* a. dc. extract as active ingredient. WO2012030137 (**2012**).

[102] Jin, S.K. Novel biphenyl compound or pharmaceutically acceptable salt thereof, method for preparing novel biphenyl compound or pharmaceutically acceptable salt thereof and pharmaceutical composition containing same as active ingredient for preventing or treating diabetes complications. EP2617702 (**2013**).

[103] Jeong, L., Jung, H. Pharmaceutical compositions for preventing or treating inflammatory diseases, comprising phytosterol compound. WO2013012117 (**2013**).