Lentinus Edodes

Bioactive Compounds

Shiitake Mushroom

Polysaccharide: (1→3)-β-D-glucan – Lentinan

Lentinan is a high molecular weight polysaccharide extracted from cell walls of fruiting bodies in a triple helix structure containing only glucose molecules with mostly β (1-3)-glucose linkages in the regularly branched backbone, and β (1-6)- glucose side chains. The configuration of the glucose molecule in a helix structure is considered important for biological and pharmacological activity.

1. Recognition by Immune Cells:

- **Dectin-1 Receptor:** The primary mechanism of action involves the (1→3)-β-D-glucans interacting with a specific receptor on immune cells called **Dectin-1**.
- **Pattern Recognition Receptor (PRR):** Dectin-1 is a type of PRR, a protein on the surface of immune cells that recognizes specific patterns on pathogens.

2. Immune Cell Activation:

- **Signal Transduction:** When (1→3)-β-D-glucan binds to Dectin-1, it triggers a cascade of signaling events within the immune cell.
- **Cytokine Production:** This signaling leads to the increased production and release of various cytokines, including:
    - **Interleukin-1β (IL-1β):** A potent pro-inflammatory cytokine.
    - **Tumor Necrosis Factor-alpha (TNF-α):** An important pro-inflammatory cytokine.
    - **Interleukin-6 (IL-6):** Involved in inflammation and immune responses.

3. Enhanced Immune Response:

- **Macrophage Activation:** The released cytokines, particularly IL-1β and TNF-α, activate macrophages, a type of white blood cell playing a crucial role in engulfing and destroying pathogens.
- **Increased Phagocytosis:** Activated macrophages exhibit enhanced phagocytic activity, meaning they are more efficient at engulfing and destroying foreign invaders like bacteria and fungi.
- **Improved Antigen Presentation:** Macrophages also play a crucial role in antigen presentation, which is the process of displaying fragments of pathogens to other immune cells, such as T cells, to initiate an adaptive immune response.

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Polysaccharide: Branched (1→3), (1→6)-β-D-glucan

1. Enhanced Immune Cell Activation:

- **Dectin-1 Interaction:** While the primary receptor for (1→3)-β-D-glucans is Dectin-1, the branching in (1→3), (1→6)-β-D-glucans can influence how they interact with this receptor.
- **Increased Signaling:** The branching may enhance the binding of these glucans to Dectin-1, leading to stronger activation of immune cells.
- **Synergistic Effects:** The branches may interact with other immune receptors, potentially creating synergistic effects with Dectin-1 signaling.

2. Modulation of Cytokine Production:

- **Broader Cytokine Response:** Branched (1→3), (1→6)-β-D-glucans may induce a broader range of cytokines compared to linear (1→3)-β-D-glucans.
- **Th1/Th2 Balance:** They may influence the balance between different types of immune responses (Th1 and Th2), which is crucial for a well-regulated immune system.
- **Improved Phagocytosis:**
    - **Enhanced Macrophage Activity:** Branched (1→3), (1→6)-β-D-glucans may further enhance the phagocytic activity of macrophages, leading to more efficient clearance of pathogens.

3. Fuel for Gut Microbiota:

- **Polysaccharides serve as food for beneficial bacteria** in the gut, promoting their growth and diversity. A healthy gut microbiome is essential for digestion, immune function, and overall health.
- **Short-Chain Fatty Acid Production:** As gut bacteria ferment polysaccharides, they produce short-chain fatty acids (SCFAs), such as butyrate. SCFAs have various beneficial effects on gut health, including reducing inflammation and strengthening the gut barrier.

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Polysaccharide: KS-2-α- Mannan Peptide

1. Immune Modulation

- Toll-Like Receptor (TLR) Activation:
    - KS-2-α-Mannan Peptide can interact with TLRs, particularly TLR4. This interaction triggers signaling pathways within immune cells.
    - TLR4 activation is important because it leads to cytokine production essential for coordinating immune responses.

2. Cytokine Modulation

- This peptide can influence the production of various cytokines, including:
    - Interleukin-1 (IL-1): Involved in inflammation and immune cell activation.
    - Interleukin-6 (IL-6): Plays a role in inflammation and acute-phase responses.
    - Tumor Necrosis Factor-alpha (TNF-α): A key mediator of inflammation and immune responses.
- By modulating cytokine production, KS-2-α-Mannan Peptide can fine-tune the immune response, enhancing its effectiveness against pathogens or abnormal cells.

3. Enhanced Macrophage Activity

- Macrophages are crucial for engulfing and destroying pathogens and cellular debris. KS-2-α-Mannan Peptide can enhance macrophage activity, leading to:
    - Increased phagocytosis (engulfment of particles).
    - Increased production of reactive oxygen species (ROS), which help to kill pathogens.
    - increased production of nitric oxide (NO) also with antimicrobial properties.

4. Natural Killer (NK) Cell Activation

- NK cells are important for killing infected or cancerous cells. KS-2-α-Mannan Peptide can stimulate NK cell activity, enhancing their ability to eliminate target cells.

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5. Influence on Adaptive Immunity

- Promoting the maturation and activation of dendritic cells, antigen-presenting cells critical in initiating adaptive immune responses.
- indirectly by the modulation of the cytokine environment.

6. Gut Health Promotion

- **Prebiotic Effects**:
    - Selective Fermentation:
        - Mannan oligosaccharides (MOS) are non-digestible carbohydrates that reach the large intestine intact.
        - Here, they serve as a food source for beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium* species.
        - These bacteria selectively ferment MOS, producing short-chain fatty acids (SCFAs) as byproducts.
    - Increased Beneficial Bacteria Population:
        - By promoting the growth of beneficial bacteria, MOS help maintain a healthy balance within the gut microbiome.
        - A thriving population of beneficial bacteria can outcompete pathogenic bacteria for resources and space.
    - Production of Short-Chain Fatty Acids (SCFAs):
        - SCFAs, such as acetate, propionate, and butyrate, have numerous beneficial effects on gut health:
            - Energy Source for Colonocytes: Butyrate, in particular, is a primary energy source for colonocytes, the cells lining the colon, promoting their health and integrity.
            - Lowering pH: SCFAs lower the pH of the colon, creating an unfavorable environment for many pathogenic bacteria.
            - Enhanced Gut Barrier Function: SCFAs can strengthen the gut barrier by promoting the production of mucin and tight junction proteins, which help to prevent the leakage of harmful substances from the gut into the bloodstream.
            - Immune Modulation: SCFAs can also modulate immune responses in the gut, helping to maintain a balanced immune environment.

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- **Pathogen Binding and Exclusion:**
    - Competitive Binding:
        - MOS have structural similarities to the binding sites on the gut lining that pathogenic bacteria use to adhere to the intestinal wall.
        - Pathogenic bacteria, such as *E. coli* and *Salmonella*, can bind to MOS instead of the gut lining, preventing them from colonizing the intestine.
    - Agglutination and Excretion:
        - Once pathogenic bacteria bind to MOS, they can be agglutinated (clumped together) and subsequently excreted in the feces.
        - This reduces the number of pathogenic bacteria in the gut and minimizes their potential to cause infection.
    - Reduced Pathogen Adhesion:
        - By blocking the adhesion of pathogens, MOS reduce the likelihood of intestinal inflammation and infection.
- **Modulation of Gut Immunity:**
    - Enhanced Gut-Associated Lymphoid Tissue (GALT) Function:
        - The GALT is a crucial part of the gut's immune system.
        - MOS can influence GALT function, promoting the production of secretory IgA (sIgA), an antibody that helps to neutralize pathogens in the gut lumen.
    - Reduced Inflammation:
        - By promoting a healthy gut microbiome and preventing pathogen colonization, MOS can help to reduce chronic inflammation in the gut.

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Fatty Acid: Eritadenine

1. Cholesterol Reduction:

- **Modification of Hepatic Phospholipid Metabolism:**
  - Eritadenine appears to influence how the liver processes phospholipids. This can affect the composition of lipoproteins, which are responsible for transporting cholesterol through the bloodstream.
  - Specifically, it has been shown to alter the phosphatidylcholine (PC)/phosphatidylethanolamine (PE) ratio in liver microsomes.
- **Increased Cholesterol Excretion:**
  - Some studies suggest that eritadenine may promote cholesterol uptake by the liver leading to increased cholesterol excretion from the body.
  - Research has shown that eritadenine can increase the expression of CYP7A1, an enzyme involved in converting cholesterol to bile acids. Bile acids are then excreted, thus removing cholesterol from the body.
- **Influence on Fatty Acid Metabolism:**
  - Eritadenine has also been observed to affect fatty acid metabolism, potentially by suppressing the conversion of linoleic acid to arachidonic acid. These changes in fatty acid metabolism may contribute to its cholesterol-lowering effects.
- **Inhibition of S-adenosylhomocysteine hydrolase:**
  - Eritadenine is a very potent inhibitor of the enzyme S-adenosyl-L-homocysteine hydrolase in rat liver cells. This causes an increase in the S-adenosylhomocysteine concentration. The increase in S-adenosylhomocysteine concentration, in turn, inhibits the PE N-methylation, thus increasing the PE content in liver microsomes.

2. Cardiovascular Health:

- By reducing cholesterol, eritadenine improves cardiovascular health, potentially lowering the risk of heart disease.

Sterols:

- **Ergosterol:** Upon exposure to ultraviolet (UV) light, ergosterol undergoes photoconversion into vitamin D2 (ergocalciferol).

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Phenolics:

Gallic Acid:

- **Antioxidant:**
  - **Free radical scavenging:** A very effective scavenger of various free radicals, including hydroxyl radicals and superoxide.
  - **Metal chelation:** Strong metal chelating ability, reducing the availability of metal ions that can catalyze oxidative damage.

- **Anti-inflammatory:**
  - **Inhibition of inflammatory mediators:** Can inhibit the production of pro-inflammatory cytokines and enzymes.
  - **Antimicrobial:** Exhibits antimicrobial activity against a range of microorganisms.

Caffeic acid:

- **Antioxidant Activity:**
  - **Free Radical Scavenging:** Caffeic acid acts as a direct antioxidant by donating hydrogen atoms to free radicals, neutralizing them and preventing oxidative damage. It can scavenge various reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, and peroxyl radicals.
  - **Metal Chelation:** It can chelate metal ions, such as iron and copper, which can catalyze the formation of free radicals. By binding to these metal ions, caffeic acid prevents them from participating in redox reactions that generate ROS.
  - **Increased Endogenous Antioxidant Enzymes:** Caffeic acid can enhance the activity of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), which further protect cells from oxidative stress.
- **Anti-inflammatory Effects:**
  - **Inhibition of Pro-inflammatory Mediators:** Caffeic acid can suppress the production of pro-inflammatory mediators, such as:
    - Cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) enzymes, which are involved in the synthesis of prostaglandins and leukotrienes.
    - Nitric oxide (NO) and inducible nitric oxide synthase (iNOS).

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- Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6).

- **Modulation of NF-κB Signaling:** It can interfere with the nuclear factor-kappa B (NF-κB) signaling pathway, a key regulator of inflammation. By inhibiting NF-κB activation, caffeic acid reduces the expression of pro-inflammatory genes.

- **Anticarcinogenic Effects:**
  - **Inhibition of Cell Proliferation:** Caffeic acid can inhibit the proliferation of cancer cells by interfering with cell cycle progression.
  - **Induction of Apoptosis:** It can induce apoptosis (programmed cell death) in cancer cells by activating caspase enzymes and disrupting mitochondrial function.
  - **Anti-angiogenesis:** It can inhibit angiogenesis, the formation of new blood vessels that supply tumors with nutrients and oxygen.
  - **Modulation of Detoxification Enzymes:** Caffeic acid can modulate the activity of detoxification enzymes, such as glutathione S-transferase (GST), which help to eliminate carcinogens from the body.
- **Other Mechanisms:**
  - **Neuroprotective Effects:** Caffeic acid has shown potential neuroprotective effects by reducing oxidative stress and inflammation in the brain.
  - **Antiviral Activity:** Some studies suggest that caffeic acid may have antiviral activity against certain viruses.
  - **Cardiovascular Protection:** By reducing oxidative stress and inflammation, caffeic acid may contribute to cardiovascular protection.

<u>p-Coumaric acid:</u>

- **Antioxidant Activity:**
  - **Free Radical Scavenging:**
    - p-Coumaric acid can directly neutralize free radicals, which are unstable molecules that can cause cellular damage. This contributes to its protective effects against oxidative stress.
  - **Enhancement of Antioxidant Enzymes:**
    - It may also enhance the activity of endogenous antioxidant enzymes, further boosting the body's defense against oxidative damage.

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- **Anti-inflammatory Effects:**
  - **Inhibition of Inflammatory Mediators:**
    - p-Coumaric acid has been shown to inhibit the production of pro-inflammatory mediators, such as:
      - Cyclooxygenase-2 (COX-2)
      - Nitric oxide (NO)
      - Various cytokines.
  - **Modulation of Signaling Pathways:**
    - It can influence signaling pathways involved in inflammation, contributing to its anti-inflammatory effects.
- **Antimicrobial Activity:**
  - **Disruption of Cell Membranes:**
    - Studies indicate that p-coumaric acid can disrupt bacterial cell membranes, leading to leakage of cellular contents and ultimately cell death.
  - **Interaction with DNA:**
    - It may also interact with bacterial DNA, interfering with essential cellular processes like replication and transcription.
- **Anticancer Potential:**
  - **Inhibition of Cell Proliferation:**
    - p-Coumaric acid has demonstrated the ability to inhibit the proliferation of cancer cells.
  - **Induction of Apoptosis:**
    - It may also induce apoptosis, or programmed cell death, in cancer cells.
- **Other Activities:**
  - **Tyrosinase Inhibition:**
    - p-Coumaric acid has shown to be a tyrosinase inhibitor, which is important in the regulation of melanin synthesis. This is very important in the cosmetic industry.

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Ferulic acid:

- **Antioxidant Activity:**
  - **Free Radical Scavenging:**
    - Ferulic acid directly scavenges various free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby protecting cells from oxidative damage.
  - **Enhancement of Antioxidant Enzymes:**
    - It can increase the activity of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), further bolstering cellular antioxidant defenses.
  - **Synergistic Effects:**
    - Ferulic acid often works synergistically with other antioxidants, such as vitamin C and vitamin E, enhancing their protective effects.
- **Anti-inflammatory Effects:**
  - **Inhibition of Inflammatory Mediators:**
    - It can suppress the production of pro-inflammatory mediators, including:
      - Cyclooxygenase-2 (COX-2)
      - Lipoxygenase (LOX)
      - Nitric oxide (NO)
      - Pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6)
  - **Modulation of Signaling Pathways:**
    - Ferulic acid can interfere with key signaling pathways involved in inflammation, such as the NF-κB pathway.

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- **Neuroprotective Effects:**
  - **Protection Against Oxidative Stress:**
    - By reducing oxidative stress, ferulic acid can protect neurons from damage.
  - **Inhibition of Neuroinflammation:**
    - Its anti-inflammatory properties contribute to neuroprotection by reducing neuroinflammation.
  - **Enhancement of Neurotrophic Factors:**
    - Some studies suggest that ferulic acid may enhance the production of neurotrophic factors, which support neuronal survival and function.
- **Anticancer Potential:**
  - **Inhibition of Cell Proliferation:**
    - Ferulic acid can inhibit the growth of cancer cells.
  - **Induction of Apoptosis:**
    - It can trigger apoptosis (programmed cell death) in cancer cells.
  - **Anti-angiogenesis:**
    - It may inhibit angiogenesis, the formation of new blood vessels that supply tumors.
- **Photoprotective Effects:**
  - **UV Absorption:**
    - Ferulic acid absorbs UV radiation, protecting the skin from UV-induced damage.
  - **Antioxidant Activity:**
    - It also reduces the oxidative stress caused by UV exposure.
- **Other Activities:**
  - **Cholesterol-lowering effects:**
    - Ferulic acid has shown some potential in lowering cholesterol levels.
  - **Antidiabetic effects:**
    - Some studies suggest potential benefits in regulating blood sugar.

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<u>Protocatechuic Acid:</u>

- **Antioxidant:**
  - **Free radical scavenging:** Directly neutralizes reactive oxygen species (ROS) such as superoxide, hydroxyl, and peroxyl radicals.
  - **Chelating metal ions:** Can chelate metal ions like iron and copper, which can catalyze the formation of harmful free radicals.

- **Anti-inflammatory:**
  - **Inhibition of inflammatory mediators:** Can inhibit the production of pro-inflammatory cytokines (like TNF-α, IL-1β) and enzymes (like cyclooxygenase and lipoxygenase).
  - **Modulation of pathways:** Interferes signaling pathways involved in inflammation.