

Overview for Immune-related Efficacies and their Mechanisms of Ginseng

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Objective : Ginseng is one of the most popular Oriental medicinal plants considered as a tonic worldwide. This study aimed to produce comprehensive understanding for immune-related pharmaceutical activities of Ginseng.

Methods: We surveyed all literatures, 168 of immunity-focused papers with Ginseng in Pub-med, and analyzed pharmaceutical characters according to immune elements and Ginseng' components.

Results : The main functions of Ginseng have been associated with modulation of immunity. Whole body of Ginseng or its ingredients differently show the effects on both cellular and humoral elements of immune system. Ginseng enhances the activities of T and B lymphocytes, NK cells, macrophages and dendritic cells whileas suppresses mast cell-associated allergy and release of histamine.

Conclusion : These results will provide Korean doctors or scientists an immune-related overview of Ginseng, and help them in clinical applications and developments of Korean Ginseng as a global competitive drug in world market.

Key Words : Ginseng, Immunity, Oriental Medicine

Introduction

Ginseng is a one of the most popular herbal plants and has been used to restore and enhance vital energy in Asian countries for thousands years¹⁾. Ginseng has been accepted by doctors and patients as a beneficial drug based on long clinical experiences and Oriental pharmaceutical theory. Numerous scientific researches have been performed on ginseng, which 1,600 studies about ginseng are reported so far²⁾.

Main researches for ginseng' effects are focussed on reduction of physical and biological stress^{3,4)}, anti-cancer^{5,6)}, protection of nerve system^{7,8)} and helping blood environments^{9,10)}. In particular, immune-related activity of ginseng was emphasized in accordance with its known clinical applications increasing

general vitality and protection against pathogenic environments^{11,12)}.

On the other hand, Korea has taken a position of priority of ginseng, and ginseng was a representative product of Korea for a long time. However, there is concerning for loss of global competitive power of Korean ginseng. An aging society is rapidly progressing, thus not only conventional therapeutic medicine but also remedies for preventive purpose for quality of life (QOL) are required. Ginseng is one of the most important herbal drug in these fields, and many efforts are given to develop ginseng as novel drug or supplement^{13,14)}.

In these days, every physiologic/pathologic phenomena and Oriental medicine including herbal drugs could be explained by immunologic aspects. One of the most well known functions of ginseng is imm-

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une modulation, but it is likely to be complicated to clearly characterize its action due to complexity of the data.

This study herein purposed to provide a overview of immune-related activity of ginseng via review all papers experimentally reported by Jun 2008.

Methods

1. Study design

To build the overview of Ginseng' effects on immune system, every papers related to ginseng-immunity were selected from database of PubMed. Then, we analyzed the activities and mechanisms according to the composition of ginseng and immune system.

2. Data collection

First, 1,879 of papers were collected using “ginseng” as search-keyword under limit of “Title and Abstract” from PubMed database, reported from 1991 to June 2008. Next, we finally selected 168 of immune-focussed papers after reading abstract of each paper. Then, the immune-related effects and its mechanisms were classified through reviewing every papers.

Results

1. General feature of ginseng-related researches

First, we analyzed total 1,879 papers for ginseng

studies according to their subjects (Fig. 1). The cancer-focussed papers had the highest number of 210. Studies for central nervous system, immunity, blood vessel or blood pressure and physiologic activity were main subjects as 196, 168, 109 and 100 respectively. In addition, ginseng has been a important research resource for various subject such as antioxidant activity, diabetes mellitus, cardiac disease, renal disease and nutritional supplement.

2. General feature for immune-related researches using ginseng

As the result shown above, immune-focussed papers had the third large number of 168 papers. Next, we classified those papers according to sub-subjects of immune study (Fig. 2 left). Among them, around 45% (76 papers) of papers were for immunomodulation. Studies about infection, inflammation, allergy, AIDS and cancer immunity followed them.

On the other hand, those papers were classified into three by study-methods, then majority was belonged in “*in vitro*” 50 % and clinical study was the smallest only 9 % (Fig. 2 right).

3. Immunologic functions of ginseng according to its components

Next, we searched about the connection between ginseng and immune functions. Many immune-focussed studies had been performed using ginseng extract itself, fractionated parts or individual active

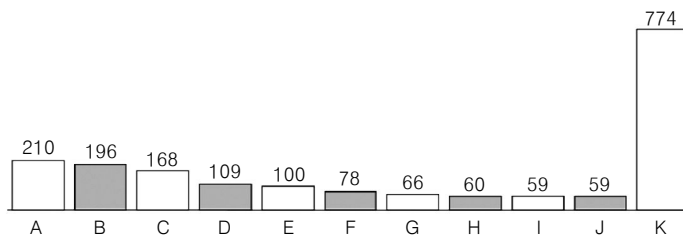


Fig. 1. Gross pattern of ginseng-related researches according to subjects.

A, Cancer; B, Central nervous system; C, Immunity; D, Blood vessel or blood pressure; E, Physiologic activity; F, Antioxidant; G, Diabetes mellitus; H, Cardiac disease; I, Renal disease; J, Nutritional supplement; K, Others.

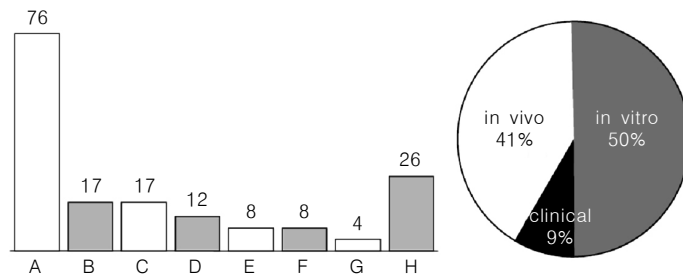


Fig. 2. Immune-related researches according to subject (left) and methods (right) using ginseng. A, Immunomodulation; B, Infection; C, Inflammation; D, Allergy; E, AIDS; F, Cancer immunity; G, Review; H, Others.

compounds. Majority of the studies were done using active compounds. Ginsenoside Rb1 and Rg1 were most frequently used among them.

Ginseng extract activates Th1 type through IL-12

gene expression¹⁵⁻¹⁷), and do macrophage via toll-like receptor 4 expression during physical stress¹⁸). Ginseng extract also showed anti-fungal activity, inhibition of COX-2 enzyme and stimulation of TNF-alpha

Table 1. Immune-related functions and mechanisms of ginseng components

Components	Effects and Mechanisms
Ginseng extract	Increase Th1 via IL-12 expression ^{15,16} , Enhance both Th1(IL-2, IFN-gamma) and Th2(IL-4, IL-10) cytokine production ¹⁷ , TLR-4 expression of macrophage ¹⁸ . Anti-fungal activity ¹⁹ , Inhibit COX-2 ^{20,21} , TNF-alpha production by alveolar macrophages ²²
Total saponin	Production of iNOS of macrophage ²³ , Stimulate phagocytic capacity of canine peripheral blood phagocytes ²⁴ . Enhance GM-CSF expression ²⁵
Protopanaxadiol	Inhibition of LPS-induced iNOS expression via inactivation of NF-kB ²⁶
G-Rb1	Activate macrophage phagocyte ²⁷), CD4+/CD8+ lymphocyte proliferation ²⁸ , Balance Th1/Th2 ²⁹ , VEGF production ³⁰ , GM-progenitor cells ³¹ , Inhibit mast cell activation ³² , TNF-alpha production ³³
G-Rb2	Inhibit CD4+/CD8+ lymphocyte proliferation ²⁸), TNF-alpha production ³³
G-Rd	Induction of COX-2 via CCAAT/enhancer binding protein and CREB ³⁴
G-Rg1	Induction IL-2 of old-aged rats ³⁵ , Enhance CD4 T-cell activity and Th2 ³⁶ , GM-progenitor cells ³¹ , Macrophage activation ³⁷ , Inhibit LPS-induced NO production ³⁸
G-Rf	Rf1 enhance Th2 cytokines via expression of IL-4 whereas Rf3 enhance the IFN-gamma but decreased IL-4 ^{39,40}
20(S) G-Rg3	Prevent endothelial cell apoptosis via inhibition of a mitochondrial caspase pathway ⁴¹ , Inhibit COX-2 expression and NF-kB activation ⁴²
G-Rh	Rh1 and Rh2 inhibit NO production ⁴³ . Rh1 and Rh2 possess anti-allergic activities ⁴⁴ . Rh2 inhibit PCA induced by IgE and contact dermatitis ⁴⁵
G-M1, G-M4	Maturation of dendritic cells and polarization into Th1 ⁴⁶
G-Ro	Enhance Th2 cytokine IL-4 and decrease Th1 cytokine IFN-gamma ⁴⁷
Polysaccharide	Produce interleukin-2 by PBMC ⁴⁸ , NO production ⁴⁹ , Induction of IL-8 ⁵⁰

Table 2. Immune-activities of ginseng according to immune components

Components	Effects and Mechanisms
T and B cells	Ginseng extract exhibits Th1-like immune response or augments both Th1 and Th2 cytokine production ¹⁵⁻¹⁷ . Rb1 and Re enhance T lymphocyte proliferation ²⁸ , Rb1 balances Th1 and Th2 immune response ²⁹ . G-M polarizes into Th1 but G-Ro exhibits Th2 type ^{46,47}
NK cells	Protopanaxatriol and G-Rh2 enhance NK cell activity ^{51,52}
Dendritic cell	G-M1 and G-M4 mature dendritic cells and polarize into Th1 ⁴⁶
Macrophage	Ginseng extract enhances anti-candida activity via macrophage ⁵³ , and innate immunity by production of proinflammatory cytokines via macrophage TLR-4 ¹⁸
Mast cells	Ginseng extract inhibits histamine releases ⁵⁴ , Ginsenoside inhibits mediator release of mast cells ³²
Cytokines	Ginseng extract increases IL-12, IL-2, IFN-gamma as well as IL-4, IL-10 cytokine production ¹⁵⁻¹⁷ . G-Rf1 increases IL-4 whereas Rf3 increases IFN-gamma ^{39,40} . G-Ro increases IL-4 and decreases IFN-gamma ⁴⁷
Complement	Ginseng saponins exhibits anti-complement activity ⁵⁵

production¹⁹⁻²²). Ginseng total saponin has pharmaceutical properties such as enhancing activity of macrophage, phagocytic capacity of peripheral blood phagocytes and GM-CSF expression²³⁻²⁵. The representative results with important findings are summarized in table 1.

4. Immunologic functions of ginseng according to elements of immunity

Lastly, pharmaceutical actions of ginseng for each element of immune-system were searched. The studies of T cell activation and modulation of Th1/Th2 were most frequently investigated. Ginseng can drive T cell into Th1 or Th2 or both types²³⁻²⁵. T cell proliferation could be activated by Rb1 and Re²⁶. NK cell activity is augmented by protopanaxatriol or Rh2^{51,52}. Macrophage cell activity are also enhanced by ginseng to kill microorganisms⁵³ while mast cells are inhibited by ginseng⁵⁴. In addition, ginseng saponins exhibits anti-complement activity⁵⁵. Immune mediators, cytokines, could be induced as many differential patterns according to ginseng components. These results are summarized in table 2.

Discussion and Conclusion

Ginseng is a typical medicinal herb used as a

tonic, and many of its pharmacological actions are attributed to the ginsenosides⁵⁶. In current aging society, the botanical supplement market is rapidly growing in accordance with a medical need for maintaining good health. So, ginseng market reached at 90 billion won in Korea and 20 trillion won in the world².

There are plenty of ginseng-associated researches such as about functional studies or compositional investigations. Among total 1,879 papers, 168 of studies had focussed on immune functions. The effects of ginseng have covered all around of immune system including various cellular compartments and humoral immunity.

Ginseng-derived immunologic effects has various patterns according to the resource of ginseng such as ginseng extract, total saponin or individual component of ginsenoside. Ginseng enhances innate immunity through activation of macrophage and NK cells⁵¹⁻⁵³, and shows anti-complement effect. Additionally, ginseng is like to drive lymphocytes into Th1 direction^{15,16}. However, there is another evidence that ginseng could enhance both Th1 and Th2 immune directions simultaneously. Ginseng produced Th1-representable cytokines, IL-2 and IFN-gamma as well as Th2 cytokines, IL-4, IL-10¹⁷. This result is familiar with the fact that ginseng has been

believed to work on whole body and whole immune system in Oriental medical theory.

On the other hand, individual active compound of ginseng saponin showed a specific immune response. For example, ginsenoside Rg1, Rf1, Ro activated Th2 type of response whereas Rf1 did Th1 type direction^{36,39,40,46}. Interestingly, Rb1 showed the balanced-response between Th1 and Th2²⁹.

Recently, ginseng is considered as an immunoregulator rather than a purely immunopotentiating agent. One study showed that Rg1 induced proliferation of T cells and IL-2 expression in only old-aged rats but not in young rats³⁵. Accordingly, anti-candida and anti-fungal activity of ginseng could be optimally applicable to immune compromised subjects or aged people^{19,53}. Ginseng has a wide range of pharmaceutical efficacy as same as the name "panax" meaning a panacea. Especially, many data supported the usefulness of ginseng for allergic disease^{32,54} which became a abundant medical problem in developed counties.

Ginseng contains complex repertoires of effects and multi-mixed active compounds, which sometimes give us the difficulty for comprehensive understanding on ginseng. This study tried to provide a clarified feature of ginseng about immune-related effects. We hope that this could be helpful for clinical application of ginseng or ginseng-derived drug development.

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