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## Introduction

Pepper (chili or hot pepper) (*Capsicum annum* L.) is the fruit from plant of *Capsicum* that belongs to the Solanaceae, one important plant for homology of food and medicine. In the traditional medicine including Mongolian Medicine, Chinese Medicine, Indian Medicine and Tibetan medicine, etc., pepper has pungent flavor and hot-natured, has been used to treatment of cold syndrome, for example cold syndrome of stomach and pain from rheumatism, etc. [1-5]. In the Western Medicine, pepper exhibit a variety of pharmacological effects, including analgesia, antibiosis, anticancer, anti-radiation, reduce weight and treatment of some skin diseases [6], etc. At present, peppers spread all over the world, 1/4 people world worldwide are often taking peppers and become a dietary habit, and growing number of people eating peppers.

## Research Article

# Often Taking Peppers Change Body Constitution to Allergic Constitution

## Abstract

Pepper (chili or hot pepper) is one important plant for homology of food and medicine. At present, 1/4 people world worldwide are often taking peppers, also 1/4 people world worldwide have allergic constitution. We observed many people who have allergic constitution are often taking peppers in the clinical. However, relation between often taking peppers and allergic constitution are unclear. In the present study, we examined the effects of peppers on immune system in rabbit that was administrated by peppers by means of intragastric administration q.d. for 3 months. Administration of peppers significantly increased contents of interleukin2(IL-2), IL-5, IL-16, leukotriene D4(LTD4), malonaldehyde (MDA), bile acid (BA) and immune cells, especially eosinophile granulocyte (EO) and lymphocyte (LY), significantly decreased activities of superoxide dismutase(SOD), in the serum of rabbits (respectively,  $P < 0.05$  or  $P < 0.01$ ). Our results indicate that often taking peppers could change body constitution to allergi constitution through induce individual immune dysfunction such as enhancement of IL-2, IL-5, IL-16, LTD4, BA, EO and LY in the serum, increased free radicals; and suggest that regular consumption of peppers can become an independent cause of allergic constitution and has harmful actions to health.

However, side or toxic effects of peppers are unclear. A notable problem is growing number of people gating allergic constitution, up to 1/4 people world worldwide are suffer from allergic constitution[6-8]. We observed clinically many people who have allergic constitution are often taking peppers. The relation between often taking peppers and getting allergic constitution are also unclear. Constitution is an important form of human life as well as an integrated, relatively stable trait in the performance of the morphological structure, physiological function based on genetic and acquired. Constitution is closely related to human health and disease [7,9]. Therefore, the research on the relationship between constitution and disease has become an important subject in the Medical Sciences and Life Sciences research. Individual immune function disorder has a crucial role in the formation of allergic constitution. The main characteristics of the immune function disorder of allergic constitution are high level serum immunoglobulin, abnormal in the proportion of Helper T cells 1(Th1) and Helper T cells 2(Th2) class two cells and often Th2 cell dominant, high level serum histamines, leukotriene (LT) and interleukin 16 (IL-16), an allergic asthma related chemokine, etc.. Latest research shows that excessive accumulation of free radicals in the body is closely related to formation of allergic constitution and allergic attack [10-12]. In the present study, therefore, we examined the IgE, IgM, IgG, histamine, Th1-associated cytokines such as interleukin 2 (IL-2),  $\gamma$ -interferon (IFN- $\gamma$ ) and

$\beta$ - tumor necrosis factor(TNF- $\beta$ ), Th2-associated cytokines such as IL-4, IL-5,IL-6 and IL-10, an allergic asthma related chemokine IL-16, and LT, activity of superoxide dismutase (SOD), contents of malonaldehyde (MDA),bile acid (BA) and immune cells in the serum of rabbit that was administrated by peppers; to test whether often taking peppers changes body constitution to allergi constitution.

## Materials and methods

The investigation was conducted in accordance with the rules and regulations of the Institutional Animal Care and Use Committee of Inner Mongolia Medical University.

### Experimental animal

18 Healthy male Japanese white rabbits (2.0 $\pm$ 0.2 kg body weight) were purchased from Xing Long Experimentary Animal Central (Peking, China). Animals were housed in a temperature-controlled environment (22°C) with alternating12-hour light-dark cycles. The 18 rabbits were randomly divided into control group (C), low dose peppers group (LDP) and high dose peppers group (HDP), 6 rabbits in each group.

### Materials

Reagents were purchased from Sigma Chemical Co. (St. Louis, MO) unless otherwise indicated. Peppers (chilli) were purchased from Sichuan Honglin Foods Co; Ltd.in China. Commercially available Kits (ELISA) that using for measuring indexes such as IgE, IgM, IgG, histamine, IL-2, IFN- $\gamma$ , TNF- $\beta$ , IL-4, IL-5,IL-6 IL-10, IL-16, LT, SOD,MDA and BA in the serum of rabbit were purchased from Peking Huan Ya Tai Biomedical Technology Co., Ltd in China.

### Preparing peppers powder and peppers solution

Made of 120 fine powder of peppers by a pulverizer special equipment. 10 min before intragastric administration, make 20% peppers solution (20g peppers: 100 ml double distilled water) for administration of low dose peppers and 40% peppers solution (40g peppers: 100 ml double distilled water) for administration of high dose peppers.

### Intragastric administration of peppers or distilled water

Rabbits in the low and high dose peppers group were administrated by peppers by means of intragastric administration q.d. using a stomach pump for 3 months. The low dose peppers group rabbits were administrated by peppers 1.443 g /kg/rabbit (Equivalent to 5g of adult 70kg body weight, q.d.), the high dose peppers group were administrated by peppers 4.329 g /kg/rabbit (equal to 3 times the low dose). Rabbits in the control group were administrated by only double distilled water with the same volume and stomach pump as the low and high dose peppers group.

### Preparation of serum samples and assessment of the indexes

The end of the experiment (after 3 months administrated peppers), all of rabbits were fasted 12 hours, take 10 ml of venous blood and placed it at room temperature after coagulation, and then Centrifugal the coagulated blood for 10 minutes and take

the serum. The indexes (such as IgE, IgM, IgG, histamine, IL-2, IFN- $\gamma$ , TNF- $\beta$ , IL-4, IL-5, IL-6 IL-10, IL-16, LT, SOD, MDA, BA and immune cells) are determined in strict accordance with the kits (ELISA) and the relevant instructions and procedures.

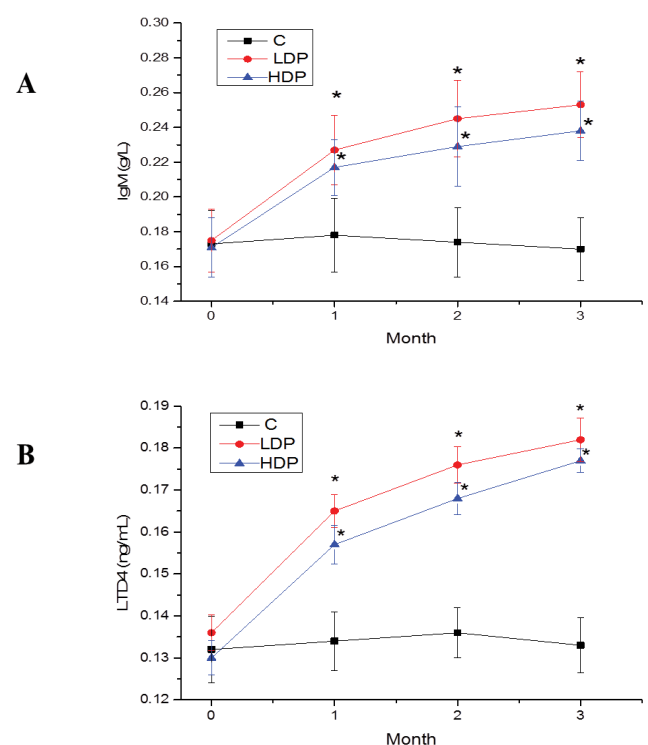
### Statistical analysis

Origin Pro 8.5.1 analysis software was used for Statistical analysis. All data are expressed as mean  $\pm$  SE. The differences between groups were analyzed by Student's t test. Statistical significance was set at P <0.05, very significant difference was set at P <0.01.

## Results

### Effects of pepper on the serum level of IgE, IgM, IgG and histamine

Rabbits were administrated by peppers for 3 months, compared with the control group, the contents of IgM in the serum of rabbits were increased at all of the testing points (end of the first month, second month and third month administrated peppers) in the both of low dose peppers group and high dose peppers group (P <0.05) and more significant in the low dose peppers group, as shown in the Figure 1A; the contents of both IgE and IgG were slightly decreased in the both of low dose peppers group and high dose peppers group, but no significant (P > 0.05); the concentrations of histamine



**Figure 1:** Effects of pepper on the serum level of IgM and LTD4 in rabbits. (A) Represents the change in serum level of IgM in before and after administrated peppers for 3 months. C: control group; LDP: low dose peppers group; HDP: high dose peppers group; data are expressed as means  $\pm$  SE. n = 6 in each group. \*P <0.05; (B) Represents the change in serum level of LTD4 in before and after administrated peppers for 3 months. C: control group; LDP: low dose peppers group; HDP: high dose peppers group; data are expressed as means  $\pm$  SE. n = 6 in each group. \*P <0.05 vs control group.

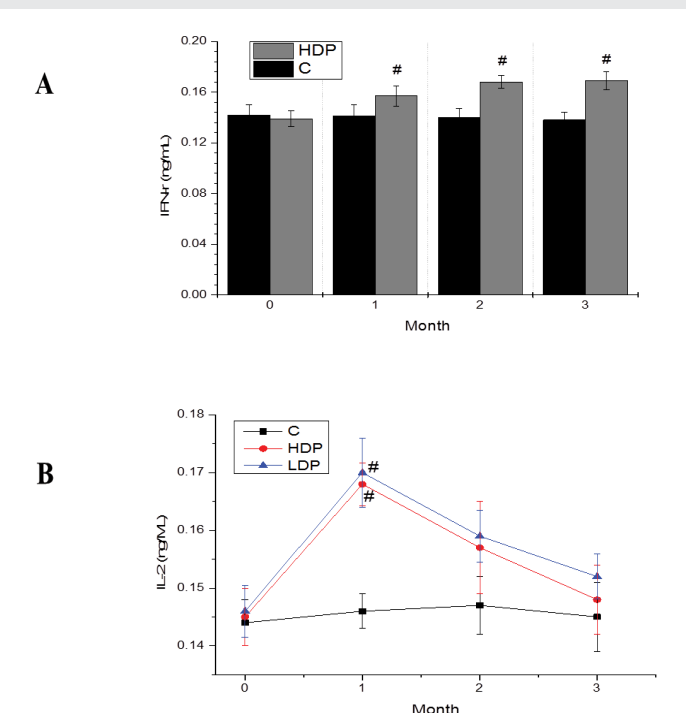
in the serum were not significantly changed in both of the low dose peppers group and high dose peppers group ( $P > 0.05$ ).

### Effects of pepper on the serum level of LTC4, LTD4 and LTE4

As shown in the Figure 1B, compared with the control group, the contents of LTD4 in the serum of rabbits were increased at all of the testing points (end of the first month, second month and third month administrated peppers) in the both of low dose peppers group and high dose peppers group and more significant in the low dose peppers group, ( $P < 0.05$ ); whereas the contents of LTC4 and LTE4 in the serum were not significantly changed in the both of low dose peppers group and high dose peppers group ( $P > 0.05$ ).

### Effects of pepper on the serum level of the Th1-associated cytokines

Compared with the control group, the contents of IFN- $\gamma$  in the serum of rabbits were increased at all of the testing points (end of the first month, second month and third month administrated peppers) in the high dose peppers group ( $P < 0.05$ ), as shown in Figure 2A, no significant change in the low dose peppers group ( $P > 0.05$ ). The contents of IL-2 was significantly increased at end of the first month administrated peppers ( $P < 0.05$ ), than gradually restored at second and third month administrated peppers in both of the low dose peppers group and high dose peppers group, as shown in Figure 2B, whereas the contents of TNF- $\beta$  were not significantly changed



**Figure 2:** Effects of pepper on the serum level of the Th1-associated cytokines in rabbits. (A) Represents the change in serum level of IFN- $\gamma$  in before and after administrated peppers for 3 months. C: control group; HDP: high dose peppers group; data are expressed as means  $\pm$  SE.  $n = 6$  in each group. #  $P < 0.05$  vs control group; (B) Represents the change in serum level of IL-2 in before and after administrated peppers for 3 months. C: control group; LDP: low dose peppers group; HDP: high dose peppers group; data are expressed as means  $\pm$  SE.  $n = 6$  in each group. #  $P < 0.05$  vs control group.

at all of the testing points (end of the first month, second month and third month administrated peppers) in the both of low dose peppers group and high dose peppers group ( $P > 0.05$ ).

### Effects of pepper on the serum level of the Th2-associated cytokines

As shown in Figure 3A, compared with the control group, the contents of IL-5 in the serum of rabbits were increased at all of the testing points (end of the first month, second month and third month administrated peppers) in the low dose peppers group ( $P < 0.05$ ) and no significant change in the high dose peppers group ( $P > 0.05$ ). As shown in Figure 3B, the contents of IL-10 in the serum of rabbits were increased at all of the testing points (end of the first month, second month and third month administrated peppers) in the high dose peppers group ( $P < 0.05$ ), no significant change in the low dose peppers group ( $P > 0.05$ ). There are no significant change in the contents of IL-4 and IL-6 in the serum at all of the testing points (end of the first month, second month and third month administrated peppers) in both of the low dose peppers group and high dose peppers group ( $P > 0.05$ ).

### Effects of pepper on SOD activities and concentrations of MDA in the serum

Compared with the control group, the SOD activities were slightly decreased at the end of first month and significantly decreased at the end of the third month after administrated peppers in both of the low dose peppers group and high dose peppers group ( $P < 0.05$ ) and more significant in the low dose peppers group ( $P < 0.01$ ); whereas the concentrations of MDA in the serum were slightly increased at the end of first month and significantly increased at the end of the third month after administrated peppers in the both of the low dose peppers group and high dose peppers group ( $P < 0.05$ ) and more significant changed in the low dose peppers group ( $P < 0.01$ ), as shown in Figure 4A and Figure 4B.

### Effects of pepper on the serum level of the allergic asthma related chemokine IL-16

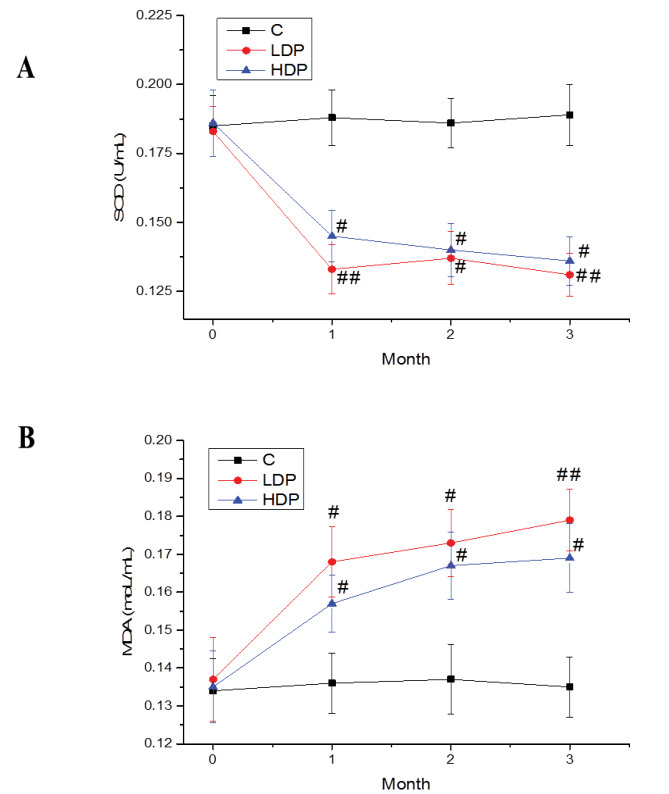
Compared with the control group, the contents of IL-16 in the serum of rabbits were increased at all of the testing points (end of the first month, second month and third month administrated peppers) in both of the low dose peppers group and high dose peppers group ( $P < 0.05$ ) and more significantly changed in the low dose peppers group ( $P < 0.01$ ), as shown in Figure 5A.

### Effects of pepper on concentrations of BA in the serum

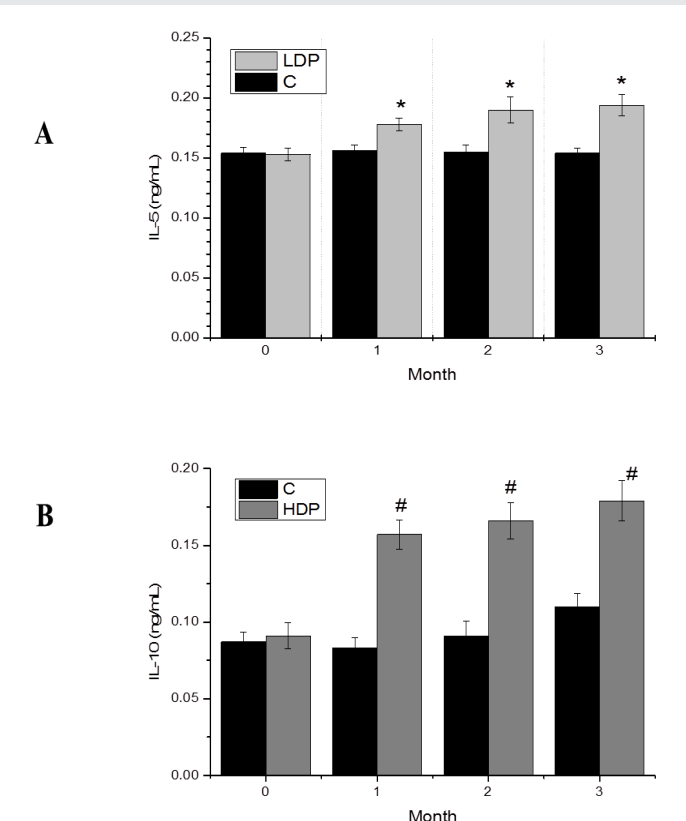
Compared with the control group, the concentrations of BA in the serum of rabbits were significantly increased at all of the testing points (end of the first month, second month and third month administrated peppers) in the both of low dose peppers group and high dose peppers group ( $P < 0.05$ ) and more significant in the low dose peppers group; ( $P < 0.01$ ), as shown in Figure 5B.

### Effects of pepper on immune cells in the serum

As shown in Table 1 and Table 2, compared with the control group, in the serum of rabbits, the white blood cells (WBC), especially the eosinophile granulocyte (EO) were very significantly increased with beyond normal range at all of the testing points (end of the first month, second month and third month administrated peppers) in the both of low dose peppers group and high dose peppers group ( $P < 0.01$ ); the neutrophile granulocytes (NE) were very significantly increased with beyond normal range at the end of the first month ( $P < 0.01$ ), than shows a trends to gradually restore at the end of second and third month administrated peppers in the both of low dose peppers group and high dose peppers group; whereas the lymphocytes (LY) were more significantly increased with beyond normal range at the end of the third month ( $P < 0.01$ ) than that at the end of the first month ( $P < 0.05$ ) in the both of low dose peppers group and high dose peppers group; enhancement of monocytes (MO) in the both of low dose peppers group and high dose peppers group has similar trends to LY. Those effects are more significant in the low dose peppers group. There are no significant change in basophile granulocyte (BA) at all of the testing points (end of the first month, second month and third month administrated peppers) in both of the low dose peppers group and high dose peppers group ( $P > 0.05$ ).



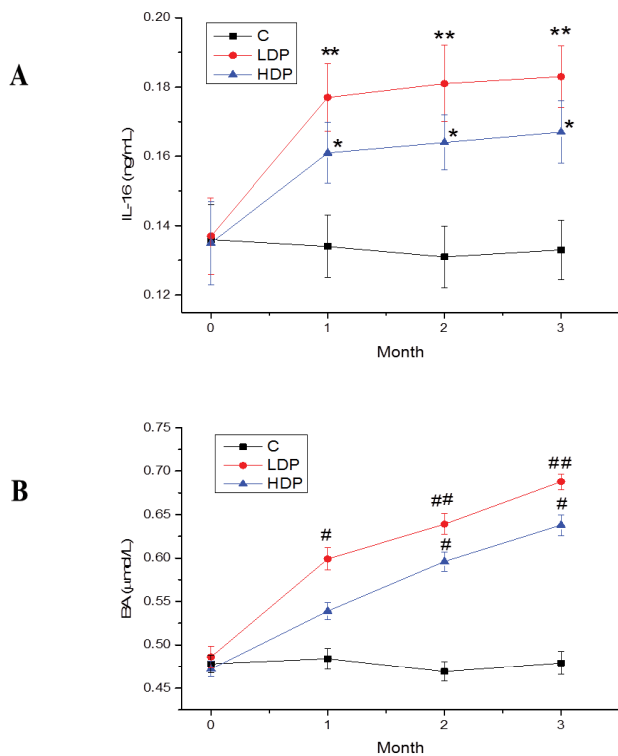
**Figure 4:** Effects of pepper on SOD activities and concentrations of MDA in the serum of rabbits. (A) Represents the change in SOD activities in before and after administrated peppers for 3 months. C: control group; LDP: low dose peppers group; HDP: high dose peppers group; data are expressed as means  $\pm$  SE.  $n = 6$  in each group. #  $P < 0.05$  and ##  $P < 0.01$  vs control group; (B) Represents the concentrations of MDA in before and after administrated peppers for 3 months. C: control group; LDP: low dose peppers group; HDP: high dose peppers group; data are expressed as means  $\pm$  SE.  $n = 6$  in each group. #  $P < 0.05$  and ##  $P < 0.01$  vs control group.



**Figure 3:** Effects of pepper on the serum level of the Th2-associated cytokines in rabbits. (A) Represents the change in serum level of IL-5 in before and after administrated peppers for 3 months. C: control group; LDP: low dose peppers group; data are expressed as means  $\pm$  SE.  $n = 6$  in each group. \* $P < 0.05$  vs control group; (B) the change in serum level of IL-10 in before and after administrated peppers for 3 months. C: control group; HDP: high dose peppers group; Each value represents the mean  $\pm$  SE.  $n = 6$  in each group. #  $P < 0.05$  vs control group.

### Discussion

Causes of allergic constitution are complex and diverse, both genetic factors and acquired factors affect the formation of allergic constitution. Whether in innate and acquired factors, the individual immune dysfunction plays a key role in the formation of allergic constitution [13]. The main characteristics of the immune function disorder of allergic constitution are high level serum immunoglobulin, abnormal in the proportion of Helper T cells 1(Th1) and Helper T cells 2(Th2) class two cells and often Th2 cell dominant, high level serum histamines, leukotriene (LT) and interleukin 16 (IL-16), an allergic asthma related chemokine, etc.. Latest research shows that excessive accumulation of free radicals in the body is closely related to formation of allergic constitution and allergic attack [14,15]. Our data indicate that often taking peppers could change body constitution to allergi constitution through induce individual immune dysfunction such as enhancement of IgM, IL-2, IL-5, IL-16, LTD4 and IFN- $\gamma$ , abnormal in the proportion of Th1 and Th2 class two cells, and increased free radicals, increase of BA and immune cells, especially EO and LY in the serum. These effects of peppers are more predominant in low dose of peppers which the dose often consumed by most people.



**Figure 5:** Effects of pepper on the contents of IL-16 and BA in the serum of rabbits. (A) Change in the contents of IL-16 in before and after administrated peppers for 3 months. C: control group; LDP: low dose peppers group; HDP: high dose peppers group; data are expressed as means  $\pm$  SE.  $n = 6$  in each group. \* $P < 0.05$  and \*\* $P < 0.01$  vs control group; (B) Change in the contents of BA in before and after administrated peppers for 3 months. C: control group; LDP: low dose peppers group; HDP: high dose peppers group; data are expressed as means  $\pm$  SE.  $n = 6$  in each group. #  $P < 0.05$  and ##  $P < 0.01$  vs control group.

### Enhancement of IgM, IL-2, IL-5, IL-16 and LTE4 in the serum by taking peppers

Our results shows that the contents of IgM, IL-2, IL-5, IL-16, LTD<sub>4</sub> and IFN- $\gamma$  in the serum were enhanced by administration of peppers and most of these effects is more predominant in low dose of peppers. Elevated IgM is common in chronic liver disease, type II and III allergic reaction, and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus [16], etc.. Therefore, the IgM class antibody can cause immune damage to the body. IL-2 is an important immunoregulatory factor produced by activated lymphocytes; the abnormal activity of IL-2 leads to a series of cellular and humoral immune disorders such as allergic purpura, allergic asthma and allergic shock [17]. Enhancement of IL-5 plays an important role in the pathogenesis of infectious diseases and allergic diseases, especially allergic asthma [18]. Elevated LTD<sub>4</sub> is common in allergic diseases such as allergic asthma, allergic rhinitis and allergic dermatitis [19]. IL-16 is a chemotactic factor for a variety of immune cells, involved in the body's inflammatory response, also related to allergic reactions, autoimmune diseases, etc. other diseases, especially related allergic asthma, act as a primary chemotactic factors in allergic asthma, and positively correlated with IL-4, a major cytokine in allergic diseases[20]. Therefore, peppers, especially in low dose peppers may lead to immune dysfunction via these effects.

### Excessive free radical generation by often taking peppers

Our data shows that the activities of SOD were decreased, whereas the concentrations of MDA were increased by administration of peppers. This effect was more obvious in low doses of pepper and also more obvious for long term taking peppers, it may be because of the free radicals are gradually accumulated by peppers. Free radicals that damage to human immune system are the basis for the formation of allergic constitution, and it also directly oxidized human mast cells and basophils, lead to cell membrane

### Enhancement of BA in the serum by taking peppers

In the present study, the concentrations of BA were significantly increased by administrated with both low dose and high dose of peppers. This effect was more obvious in low doses of peppers. Elevated BA is common in chronic liver disease, a manifestation of liver cell injury. Excessive BA has multiple toxic effects including cytotoxicity, acute and chronic toxicity, liver injury and systemic multiple organ damage, eventually lead to cirrhosis, liver failure and death [22]. In clinical, excessive BA in the serum appear itching and allergic asthma like symptoms, especially in pregnant women. In addition, in the Traditional Indian Medicine (Ayurvedic medicine), Traditional Mongolian Medicine and Traditional Tibetan medicine, Individuals with "Biliary" type constitution more prone to suffering from allergic diseases and autoimmune diseases. Bile is the physical basis for "Biliary" type constitution, main component of bile is BA, so BA may be considered as the molecular basis for "Biliary" type constitution. Moreover, peppers as drug is used to treat "cold" syndrome due to the increased bile [23]. Therefore, in the present study, the results that taking peppers increased BA in the serum are consistent with the traditional medical theory and theory of physical fitness. More interesting is that BA could be the molecular basis for "Biliary" type constitution as well as mechanism underlying the actions of often taking peppers lead to change body constitution to allergic constitution. This needs further research. In the present study, our results indicate that often taking low dose peppers to make the body function in an over sensitive state such as allergic state whereas often taking large dose peppers to make the body function in a loss sensitive state such as morphine-like anesthesia and production of excessive BA to damage systemic multiple organ, because of large dose pepper produced more endorphins, an endogenous morphine-like substance, through capsaicin receptor (vanilloid receptor subtype 1, VRI) elicit morphine-like actions including Pleasure and anesthesia. The production of morphine like substance is the main reason for the addiction of peppers, so more and more people are eating pepper.

### Enhancement of immune cells in the serum by taking peppers

Our data shows that WBC and EO were very significantly increased with beyond normal range at all of the testing points (end of the first month, second month and third month administrated peppers) in the both of low dose peppers group and high dose peppers group, indicating that taking peppers

**Table 1:** Effects of LDP on immune cells in serum of rabbits

Cell types	Pre-treatment				Post-treatment			
	O-Month		First month		Second month		Third month	
	C	LDP	C	LDP	C	LDP	C	LDP
WBC(10 <sup>9</sup> /L)	5.32±0.99	5.58±0.69	5.46±0.74	17.08±1.89**	5.43±0.86	16.48±1.86**	5.40±0.70	15.18±1.64**
NE(10 <sup>9</sup> /L)	2.58±0.93	2.63±0.72	2.61±0.68	7.51±1.08**	2.49±0.63	6.53±1.02**	2.55±0.82	5.93±1.04*
LY(10 <sup>9</sup> /L)	1.73±0.65	1.92±0.62	1.86±0.70	3.03±0.82*	1.69±0.52	6.18±1.03**	1.81±0.57	7.28±108**
MO(10 <sup>9</sup> /L)	0.28±0.04	0.30±0.07	0.26±0.06	0.88±0.13*	0.31±0.08	0.95±0.16**	0.32±0.05	1.10±18**
EO(10 <sup>9</sup> /L)	0.85±0.08	0.89±0.11	0.87±0.07	3.20±0.16**	0.91±0.12	4.08±0.21**	0.88±0.12	4.53±0.19**
WA(10 <sup>9</sup> /L)	0	0	0.01	0.01	0.02	0.01	0.01	0.01

Effects of low dose peppers on immune cells in the serum of rabbits. Represents change in the counts of immune cells in before and after administrated low dose peppers for 3 months. C: control group; LDP: low dose peppers group; WBC: white blood cell; NE: neutrophile granulocytes; LY: lymphocytes; MO: monocytes; EO: eosinophile granulocyte; BA: basophile granulocyte; data are expressed as means ± SE. n = 6 in each group. \*P <0.05 and \*\* P <0.01 vs control group.

**Table 2:** Effects of HDP on immune cells in serum of rabbits

Cell types	Pre-treatment				Post-treatment			
	O-Month		First month		Second month		Third month	
	C	HDP	C	HDP	C	HDP	C	HDP
WBC(10 <sup>9</sup> /L)	5.32±0.99	5.47±0.69	5.46±0.74	14.18±1.19##	5.43±0.36	13.15±1.46##	5.40±0.70	11.60±1.29##
NE(10 <sup>9</sup> /L)	2.58±0.93	2.51±0.58	2.61±0.68	5.98±1.13##	2.49±0.63	4.95±0.55#	2.55±0.82	4.23±0.43#
LY(10 <sup>9</sup> /L)	1.73±0.65	1.83±0.55	1.86±0.70	3.11±0.96#	1.69±0.52	5.18±1.23#	1.81±0.57	5.25±0.80##
MO(10 <sup>9</sup> /L)	0.28±0.04	0.32±0.05	0.26±0.06	0.53±0.08	0.31±0.08	0.68±0.10#	0.32±0.05	0.80±0.12#
EO(10 <sup>9</sup> /L)	0.85±0.08	0.84±0.09	0.87±0.07	2.53±0.17#	0.91±0.12	2.98±0.12#	0.88±0.12	3.33±0.21##
WA(10 <sup>9</sup> /L)	0	0	0.01	0.01	0.02	0.01	0.01	0.02

Effects of high dose peppers on immune cells in the serum of rabbits. Represents change in the counts of immune cells in before and after administrated high dose peppers for 3 months. C: control group; HDP: high dose peppers group; WBC: white blood cell; NE: neutrophile granulocytes; LY: lymphocytes; MO: monocytes; EO: eosinophile granulocyte; BA: basophile granulocyte; data are expressed as means ± SE. n = 6 in each group. # P <0.05 and ## P <0.01 vs control group.

could induce inflammatory reaction and allergic reaction, because of elevated EO is common in allergic diseases such as allergic asthma, urticarial, and allergic dermatitis, etc.[25,26]. Enhancement of NE is dominant at the end of first month administrated peppers; whereas enhancement of LY is dominant at end of third month administrated peppers; suggesting that eat peppers could cause acute inflammation at initial stage and turn into chronic inflammation for long term. In summary, our study suggest that regular consumption of peppers can become an independent cause of allergic constitution and has harmful actions to health

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