Advances in Effect of Germanium or Germanium Compounds on Animals—A Review

Lingjun Li¹, Tao Ruan¹, Yingnan Lyu², Bangyuan Wu¹,³*

¹College of Life Science, China West Normal University, Nanchong, China
²Department of Microbiology and Immunology, National University of Singapore, Singapore
³Key Laboratory of Southwest China Wildlife Resources Conservation (China West Normal University), Ministry of Education, Nanchong, China

Email: *wubangyuan2008@163.com, *wby2008@cwnu.edu.cn

Abstract

An increasing number of researches have been focused on the relationship between trace elements and animal health. Germanium, as a widely used trace element, exists ubiquitously as germanium or germanium compounds in the living environment of human and animals, and plays important roles in animal production or health. With the intensive study of the physiological function of germanium and its compounds, the effects of germanium on animal physiological functions and health have been gradually confirmed. In this review, we discuss the metabolic distribution, physiological characteristics, biological function, germanium deficiency and germanium toxicity. Furthermore, we focus on the effects of germanium or germanium compounds on the immunity of animals. It is concluded that germanium or germanium compounds not only has positive effect but also has negative effect on animals. This review aims to provide a reference for the future research or application of the germanium or germanium compounds on animals or human beings.

Keywords

Germanium, Germanium Compounds, Physiological Function, Toxicity, Immunity

1. Introduction

Germanium (Ge) was first discovered and named by the German chemist Winkler in 1886, and then it has been found and detected as a trace element from the plants and animals. After 1960s, the biological function of germanium and mechanism of interaction with body have become the hot topics in scientific research. In the past twenty years, as a semiconductor material, germanium was
widely used in the electronic fields. Germanium also possesses many significant biological functions, such as antibacterial, antiviral, anti-inflammatory, anti-cancer or antitumor functions, and elimination of the free radicals, prevention of cell aging, regulation of immunity and so on. Nowadays, some food and medical materials containing germanium have been found to have special health effects. Therefore, the germanium or germanium compounds (especially the organic form) is known as “a patron saint of the human health”. Therefore, germanium has been successfully applied in medical and healthcare fields, and now widely used in animal husbandry. This review aims to discuss the application of germanium in animals from the aspects of metabolic distribution, physiological characteristics, biological functions, germanium deficiency or toxicity, and the influence of germanium on animal immunity, as showed in below Chart 1.

2. Distribution, Absorption and Metabolism of Germanium

2.1. Distribution in the Animal Tissues and Organs

Germanium is widely distributed throughout the body and is not selectively retained in any tissue [1]. The concentration of germanium is generally very low in animal tissues or organs, and is different in different tissues and organs: from high to low in kidney, liver, lung, stomach, muscle, heart and brain [2]. Germanium can also be found in many enzymes of the body, such as guaninase, cytochrome oxidase, carbonic anhydrase, and in some other subcellular organelles including the cell wall, mitochondria and chromosomes [3].

2.2. Absorption and Metabolism

The contact of animals to germanium is mainly through drinking water, food intake, respiration, intramuscular or intraperitoneal injection. Animal experimental results showed that germanium compounds, both inorganic and organic, are rapidly and almost completely absorbed into the lungs and gastrointestinal tract mucosa [2] [4]. The germanium and plasma proteins can be transported in an unbound state if they are injected into the blood directly, and are excreted by both the kidney and the gastrointestinal tract, where the kidney is the chief excretory organ (80% versus 13%) [5] [6] [7].

Chart 1. Effect of germanium or germanium compounds on animals.
3. Germanium Compounds with Physiological Activity

There are usually two forms of germanium compounds, which are inorganogerianium and organogerianium. Inorganogerianium is very toxic to organisms, which is banned strictly in use, and the organogerianium is beneficial to human and animal health, but the accuracy of dosage used should be monitored carefully. The organogerianium sesquioxide and its derivatives are the most studied organogerianium compounds. In recent years, drugs containing organogerianium compounds, such as 2-Carboxyethyl germanium sesquioxide (Gee-132), spirogerianium, and germanium-lactate-citrate, have been widely used in the treatment of AIDS and cancer [8].

3.1. 2-Carboxyethyl Germanium Sesquioxide (Ge-132)

Ge-132 (with structural formula GeCH₂CH₂COOH₂O₃), is an organogerianium compound with some important biological functions, such as antioxidant effect and immunoregulatory activities [9] [10]. Ge-132 is also an immune stimulant with broad spectrum of anti-tumor activities [11] [12]. Subsequently, many Ge-132 derivatives and analogues were synthesized, such as organogerianium sesquioxide and sesquisulfide, which all connect with molecules with good efficacy to increase the efficiency of the drugs. Ge-132 is widely used as it belongs to the non-toxic active substances, and the acute toxicity or chronic toxicity is very low [10]. Consequently, it has been used as an ingredient in health foods and supplements in many countries nowadays [13].

3.2. Spirogerianium Compounds

Spirogerianium is a new metallic investigational anticancer drug, which is synthesized by Rice et al. in 1974. Spirogerianium is a metal-containing compound reported to have antitumor, antiarthritic, antimalarial and immunoregulatory activities [5] [14] [15]. Spirogerianium compounds have pivotal biological functions, including lymphocyte atrophy or degeneration, and nucleus fragmentation, and they play a key role in cell lysis by inhibiting protein synthesis [16]. As a novel heterocyclic anticancer drug, spirogerianium compounds exert anti-cancer activity by inhibiting the synthesis of DNA or RNA and enhancing the immune responses [17] [18] [19]. Nevertheless, excess dose of the spirogerianium compounds have toxic effects on lymphoid tissues, bone marrow, liver, central nervous system and red blood cells (RBCs) [20].

3.3. Amino Acid Germanium

Amino acid germanium, is characterized by the low toxicity and a wide range of functions, such as anticancer, anti-hypertension and anti-inflammation activities [21]. Germanium histidine complex exhibits very strong cytotoxic effects on the ehrlich ascites carcinoma (EAC) cells [22] [23]. Methionine germanium has positive effects on immune promotion and antitumor [24] [25]. Alanine germanium also has the function of anti-tumor activity and immuno-enhancement, which
can prolong the survival time of mice transplanted with H22 hepatoma and inhibit the growth of S180 sarcoma obviously [26]. Gao et al. (1990) and Zhao et al. (1990) [27] [28] reported that amino acid germanium oxide (AGO) also played important role in anti-tumor activity, while germanium arginine complex exhibited a poor effect on tumor cells [22].

3.4. Lactic Acid-Citrate Germanium

Lactic acid-citrate germanium has an inhibiting effect on lipid peroxidation [29], which can enhance the immune function as an "immunostimulant" [30] [31]. Besides, it has an obvious anti-tumor effect [32]. However, long term and overdose intake of germanium lactate-citrate (a cumulative dose of 32.1 g germanium) could lead to damages to organs or tissues [33].

3.5. Other Germanium Compounds

In additional to the above-mentioned germanium compounds, some other new germanium compounds with biological functions have been synthesized and applied in a wide spectrum of fields. For instance, p-dimethylaminophenylgermanium sesquioxide (Ge-162) has the effect of inhibiting the growth of the tumor [34]. Germanium yeast (Ge-168) has important nutritional values and plays an important part in inhibiting the hepatic tumor induced by aflatoxin B1 [35] [36]. In addition, novel organogermainium sulfide compound, organogermainium sesquioxide and sulfide, Ge-132 amide derivatives, germanium amino acid derivatives, α-phenyl-β-(N-Amido) ethyl germanium semi oxide and alkyl thio germanium compound [37], are being synthesized and applied in an increasingly large scale in animal production. Studying all of the germanium compounds pave the way for the search of more effective anticancer drugs containing germanium, and lay a foundation for the studying the biological functions of the germanium or germanium compounds.

4. Biological Function of Germanium

4.1. Antitumor Function of the Germanium Compounds

Organogermainium compounds have some advantages, such as low toxicity and antitumor activity, which suggest a great potential in the prevention and treatment of cancer and adjuvant radiotherapy. Their low bone marrow toxicity also make them great choices for chemotherapy. The in vitro and in vivo experiments showed that most of the organogermainium or polycacid derivatives could inhibit tumor cells growth and has a dose dependency [38] [39] [40] [41] [42]. Ge-132 has a significant inhibitory effect on the occurrence and development of the tumor induced by broiler Marek’s disease virus (MDV) [43]. Germanium dioxide (GeO2) can inhibit the formation of tumor by enhancing the communication of the intercellular connection [44]. Caffie acid germanium can inhibit the growth of the U14 tumor in mice and induce the apoptosis of U14 tumor cells [45].
4.2. Participation in the Metabolism of Oxygen in Vivo

There are many Ge-O (germanium and oxygen) bonds in organogermanium, which have strong ability of oxidative dehydrogenation. Germanium enters the organism and binds to hemoglobin, thereby ensuring normal cellular aerobic metabolism [46]. In addition, the germanium compounds can capture the hydrogen ions and other harmful ions in the metabolites, and play a role in purifying blood at different degrees [47].

4.3. Antioxidant and Scavenging the Free Radicals

Germanium can scavenge the free radicals and enhance the body’s antioxidant capacity. As a result, organogermanium can reduce the lipid peroxidation, protect the cell membrane from injury, and reduce the lipid peroxide level in plasma, liver or brain tissues [48] [49] [50] [51]. Ge-132 can significantly increase the glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) activity in broilers [52] [53], and reduce the amount of free radicals in liver and kidney of rats [54]. In addition, the in vitro studies have also found that G-132 is able to scavenge reactive oxygen species and prevent reactive oxygen species from inducing injury to cells [55] [56]. Appropriate concentration of lactic acid citrate germanium can increase the levels of reduced glutathione (GSH) in rat hepatocytes [57]. On one hand, the mechanisms of the organogermanium antioxidation and free radical scavenging consist the increase of SOD and GSH-Px activity in blood as well as the reduction of serum lipid peroxide (LPO). On the other hand, due to the unique electronic layer structure of organogermanium, the outer electrons can become the free electronic, which could also scavenge the free radicals eventually [58].

4.4. Regulation of the Lipid Metabolism

Germanium or germanium compounds can regulate and affect the lipid metabolism. For instance, organic and inorganic germanium may affect the lipid metabolism in chicken and reduce the content of cholesterol in egg yolk [59]. Moreover, with the increase of germanium content in blood and egg, the total blood lipid and triglyceride content are decreased, and the cholesterol content in blood and yolk decrease [60] [61]. It was found that the contents of total fat, glycerin, triglycerides and cholesterol decrease to different degrees with the addition of Ge-132 to the diet [50] [62].

4.5. Stimulating the Hematopoietic Function

Germanium can increase the number of red blood cells (RBCs) and hemoglobin (Hb) in the blood system and stimulate the formation of platelet generating cells (PGCs), thus stimulating the hematopoiesis [63]. For example, germaniumoxide (GeO₂) can promote the generation of RBCs and has a certain therapeutic effect on anemia [64] [65]. In addition, Ge-132 can increase the expression of cell stimulating factor IL-3 in the multifunctional hematopoietic stem cells (HSCs) and involve in the regulation of the differentiation and proliferation of multifunc-
tional hematopoietic stem cells (MHSCs) and the progenitor cells, thus regulating the hematopoietic function in the body [66] [67]. Spirogermanium may promote the maintenance of normal marrow cells in bearing [68]. The main reason for germanium-stimulated hematopoiesis is that germanium could increase blood absorption of oxygen, which can be combined with blood cells and absorbed directly by blood vessels, and then promote the generation of RBCs [69].

4.6. Inhibit Bacterial Growth

Germanium has a strong antibacterial effect. Aso et al. (1982) [70] and Arimori et al. (1981) [71] found that germanium inhibited the growth and propagation of *Fusarium, Escherichia coli, Staphylococcus aureus* and *Bacillus subtilis*. The growth of lactic acid bacteria was inhibited by organic germanium compound-Ge-132 [72]. Mrema et al. (1983) [73] found that spirogermanium was an antimalarial drug with an entirely novel structure that was active in resistant strains. Tributylgermanium acetate has antimicrobial activities, but the main active substances that inhibit fungi are the ethyl and propyl germanium compounds, and the longer chains lead to the more antibacterial activities [74] [75] [76] [77].

4.7. Improve the Growth and Production Performance

Germanium can promote the growth of animals by increasing the content of iodine, including triiodothyronine (T3) and tetraiodothyroxine (T4) content, and enhancing the metabolic function of organisms. Inorganogermanium (such as GeO₂) can obviously promote the growth of chicken, and increase the feed reward and slaughter rate [78] [79] [80]. Ge-132 is also useful for increasing the body weight of young chicken [81] [82]. Moreover, Ge-132 could significantly improve the laying rate, the rate of fertilized eggs and the hatching rate of laying hens [60] [61] and improve egg quality [83]. In addition, organogermanium has certain effects on the reproductive endocrine of animals, and is involved in the regulation of the endocrine system. Other germanium compounds, such as germanium colloid or germanium biotite, also have the positive effects on the animal growth [84] [85].

4.8. Other Physiological Functions of Germanium

Except for what was mentioned above, germanium possesses many other biological functions. It has been proven that germanium can prevent pigmentation and inhibit the production of melanocytes. Ge-132, for example, can reduce the synthesis of melanocytes by reducing the number of organelles, increasing the apoptosis, and decreasing the tyrosinase activity [86]. In addition, Ge-132 can prevent cataract by dissolving glycated proteins and increasing the activity of Na⁺-K⁺-ATP enzymes [87] [88] [89] [90] [91]. Amino acid germanium oxide or organogermanium-Ge-401 can extend the average lifespan and the maximum lifespan of the fruit fly [92]. Ge-132 can inhibit the development of liver necrosis and the increase of serum glutamic pyruvic transaminase (SGPT) which induced by carbon tetrachloride in mice, and then play a key role in protecting the liver.
Organogermanium can improve the ability of animals to survive hypoxia and extend the life of animals in hypoxia [54]. In human, Ge-132 can significantly reduce the level of parathyroid hormone in serum, prevent and treat age-related osteoporosis [94] [95], and could be the prevention of old age amyloidosis [96] [97]. The oxide of germanium could inhibit the genotoxicity of cadmium chloride as well [98].

5. Germanium Deficiency

There is no known biologic requirements for germanium, germanates, or any organogermanium compound. Germanium deficiency has not been demonstrated in any animals, but some evidences suggest that certain concentration of germanium compounds can promote animal growth, digestion and absorption of the food [99] [100]. Further studies are required to clarify whether germanium deficiency can affect the biological functions, such as growth and development, or digestion and absorption function. In addition, it has been reported that taste loss is associated with the germanium deficiency [101].

6. Germanium Toxicity

It has been reported that excessive or long-term exposure to germanium has toxicological effects and damages on the kidneys [102] [103], nervous system [104], and lungs [105] [106]. The toxicity of inorganogermanium is greater than that of organogermanium.

Acute poisoning of germanium can lead to changes in depression, hypothermia, diarrhea, skin cyanosis, pulmonary edema, ascites, edema and swelling of parenchymal cells of the liver, kidney or other organs [107]. Arts et al. (1994) [108] found that the toxicity of high-concentration germanium oxide on mice was greater than that of low concentration, indicating that the impact of germanium oxide on animals was dose-dependent.

Though organogermanium has important physiological functions, improper dosage or long-term exposure may also be toxic to animals. Spirogermanium can have obvious toxic effects on the liver, kidney and hematopoietic system [105]. Other organogermanium compounds such as Ge-132 and Ge-201 can cause nausea, vomiting, diarrhea, and even liver and kidney damage and tremors, and can interfere with phosphorus and calcium metabolism [10] [47].

The above content has been summarized in Table 1.

7. Germanium and Immunity

A large number of reports have pointed out that germanium or germanium compounds have different effects on immune organs, immune cells or other immune factors.

7.1. Effects of Germanium on the Growth and Development of Immune Organs

The effects of organogermanium and inorganogermanium on the development
Table 1. Positive and negative effects of germanium or germanium compounds on animals.

| Metabolic distribution | Germanium compounds with physiological characteristics | Biological functions                        | Germanium deficiency                      | Germanium toxicity                     |
|------------------------|--------------------------------------------------------|--------------------------------------------|-------------------------------------------|----------------------------------------|
| Kidney                 | Antitumor function                                     |                                            |                                           | Kidneys                                |
| Liver                  | Participation in metabolism of oxygen                  |                                            |                                           | Liver                                  |
| Lung                   | Ge-132                                                 | Antioxidant and scavenging the free radicals | No biologic requirements for germanium    | Lungs                                  |
| Stomach                | Spirogermanium compounds                               | Regulation of the lipid metabolism        |                                           | Hematopoietic system                   |
| Muscle                 | Amino acid germanium Lactic                            | Stimulating the hematopoietic function     |                                           | Nervous system                         |
| Heart                  | Acid-citrate germanium                                 | Inhibit bacterial growth                   |                                           | Phosphorus and calcium metabolism      |
| Brain                  |                                                        | Improve the growth and production performance|                                           |                                        |

of immune organs in animals remain controversial, some reports have pointed out that germanium or germanium compounds could influence the development of immune organs, while others not. Barley containing rich germanium can increase the weight of immune organs (spleen) [109]. The immune organs (thymus, bursa and spleen index) gain weight more quickly after hatching with the breeding egg containing more germanium [110]. Germanium citrate significantly increased the weight of immune organs (thymus and spleen) of Kunming mice [31]. However, Niu et al. (2001) [111] reported that the additional organogeranium had no significant effects on the growth of immune organs in broilers at different stages, and the organogeranium Ge-201 had no significant effect on thymus and spleen index in mice [112] [113]. It can be seen that the effects of germanium or germanium compounds on the growth of immune organs are still inconsistent and further study is required.

7.2. Effects of Germanium on Nonspecific Immunity

Nonspecific immunity, also known as innate immunity, mainly involves phagocytes, killer cells, and dendritic cells. The phagocytosis rate, phagocytosis index and phagocytosis of macrophage in mice can be significantly enhanced by the administration of appropriate doses of organogeranium or inorganogeranium [114] [115] [116] [117]. In addition, barley with rich amount of germanium could significantly improve the phagocytosis of peritoneal macrophages in healthy Kunming mice (male) [109]. Studies have revealed that Ge-132 activated immune cells, inducing the activation of NK cells and macrophages [70]. Organogeranium Ge-201 by intravenous injection also significantly increased carbon clearance rate, phagocytosis percentage and phagocytic index of mice [113]. Moreover, germanium biotite can increase the lysozyme activity [118].

7.3. Effects of Germanium on Humoral Immunity

Humoral immunity is achieved by production of antibodies by B cells, which then perform the protective function to the organism. Germanium affects the
humoral immunity mainly through the actions on antibodies or antibodies producing cells. An appropriate amount of germanium could significantly increase the amount of antibodies against chicken red cells and the number of antibody producing cells in mice [109]. Citrate germanium can significantly boost antibodies level against serum hemolysin of Kunming mice [31]. Organogermanium Ge-132 can significantly enhance humoral immune response in mice [119]. Organogermanium Ge-401 can increase the ability of murine B lymphocytes in antibody production [120]. Tang et al. (1996) reported that the serum antibody and the levels of IgG and IgM increased significantly in offspring of chickens when the breeding chicken of parent generation consume the germanium diet. Ge yeast can also increase the production of antibodies by B cells [121]. High level of IgG and IgA titers in serum and saliva were observed in the germanium biotite treated group [118].

7.4. Effects of Germanium on Cellular Immunity

T cells are the major cells involved in cellular immunity and the effect of germanium on cellular immunity is mainly through T cells. Some studies indicated that Ge-132 could significantly contribute to the higher T lymphocyte transformation rate in chickens inoculated with Marek’s virus [43] or experimental murine ascites tumors [122]. Besides, Ge-132 can not only significantly enhance the cytotoxicity of NK cells to target cells [115], but also increase the ratio of total T lymphocyte subsets (CD3⁺, CD4⁺, CD8⁺) and ratio of CD4⁺/CD8⁺ [123] [124]. All discussion above suggests that Ge-132 are essential for enhancing cellular immune function of animals. The germanium biotite can increase percentage of CD4⁺ lymphocytes and major histocompatibility complex (MHC) I'II' cells in peripheral blood mononuclear cells (PBMCs), responding to stimulation by ConA [118].

7.5. Effects of Germanium on Cytokines

Cytokines are synthesized and secreted by immune cells (such as monocytes, macrophages, T cells, B cells, and NK cells etc.) and some non-immune cells (endothelial cells, epidermal cells, and fibroblasts etc.). They are small molecular proteins with a wide range of biological significances. Organogermanium has been reported to induce cellular production of interleukin (IL) and interferon (IFN) [125]. For instance, Ge-132, has a strong activity on inducing the generation of exogenous IFN in chickens [116] [126] [127]. The propagermanium can improve hepatitis through reducing the generation of TNF-α [128]. The levels of IFN-γ, IL-1α, IL-1β, and IL-4 gene expression were also significantly increased after treated with germanium biotite [118].

Therefore, the effect of the germanium on the immunity mainly involved in the growth and development of immune organs, immune cells (such as killer cells, dendritic cells, NK cells and macrophages, T cell and B cell and so on), production of antibodies or immunoglobulins, and cytokines. The mechanisms may be refer to the oxidative function, because the germanium participate in the
regulation of the lipid metabolism or oxygen metabolism in vivo. In addition, we speculate that the germanium could affect some enzymes activities or subcellular organelles of immune organs or immune cells, and then pose direct or indirect effect on immune system. But the exact mechanisms of the effect of germanium or germanium compounds on immunity should be clarified in the future study.

8. Research Perspectives

Organogermanium compounds have many biological activities and pharmacological effects, and the investigation of this kind of compounds requires more attention. However, germanium has not been yet proven to be a necessary trace element in the animal body and germanium deficiency has not been reported in any animal at present. Therefore, it might be feasible to develop and apply organogermanium as a new type of feed additive, but definitely with further studies. In the future, we should focus on the investigation of the effect of germanium on the development of immune organs in broilers and the mechanism of action from the aspects of histology and histochemistry. In addition, the study of germanium and germanium compounds toxicity needs to be further studied. It remains to be resolved and researched on how to reduce the toxicity of germanium and germanium compounds and exert their anti-tumor effects as the new anticancer drugs.

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