# CRUDE DRUG EXTRACTS, AND METHODS FOR MAKING AND STANDARDIZING SAME

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## FIELD OF THE INVENTION

The present invention relates to crude drug extracts containing soluble silicon compounds as an effective component, methods for making the crude drug extracts, and also to standardization methods for crude drugs and their extracts.

## BACKGROUND OF THE INVENTION

Living organisms conducting living phenomenon are composed of cells where functional abnormality in the cells introduces the living organisms to a diseased state. Living organisms survive as an individual by adjusting and maintaining their physical and chemical states to and within certain stable physiological conditions corresponding to changes in internal and external circumstances. It is well known that the maintenance and the normalization of the biofunction are especially carried out by various receptors on cell surfaces and the ion channels such as sodium, potassium, calcium, etc. However, if the above-mentioned biofunctions are unbalanced for some reason and it becomes chronic, so-called morbidity results causing various diseases.

The cell membrane consists of lipid bilayers and has an important and complicated function for maintenance of life such as selective permeability, active transport, generation of bioelectricity, expression of immunoactivity, etc. Although normal cells have fluidity and exhibit self-repairing ability to injury, the fluidity of the cell membrane decreases due to internal and external invasions. Exemplary of such invasions are aging, various diseases, and excessive stress stimulation including viral and bacterial infection. The invasions and consequent decrease in fluidity deteriorates maintenance of the homeostasis of a living body. For example, it is well known that vascular endothelial cells and nerve cells are injured by hyperlipemia, hypertension, diabetes mellitus, aging, smoking, etc. resulting in arteriosclerosis, renal diseases, peripheral nervous disorder, etc.

A known mechanism for adjusting the complicated functions in vivo, is an enzymatic system called the kallikrein-kinin system. With respect to this plasma kallikrein-kinin system, it is believed that a blood coagulation factor XII (a Hageman factor, abbreviated as FXII) is activated due to stimulation by a lesion or an invasion to the tissues in vivo whereby a series of enzymatic reactions is induced. Thus, the activated blood coagulation factor XII (abbreviated as FXIIa) acts on plasma prekallikrein which exists in the same plasma to convert it to plasma kallikrein which is an enzyme in activated form. Then, the plasma kallikrein acts on high-molecular-weight kininogen (abbreviated as HK) in the plasma to liberate bradykinin.

The bradykinin which is a product of the plasma kallikrein-kinin system exhibits various physiological activities such as dilation of peripheral blood vessels, acceleration of permeation of blood vessels, induction of pain, generation of inflammation, migration of leucocytes, etc. Bradykinin has also been known as a mediator for induction of pain, inflammation and allergic reactions. Accordingly, when an excessive liberation and production of bradykinin is inhibited, it is possible to relieve pain, inflammation, allergic syndromes, etc. and to make such unhealthy states normal.



The plasma kallikrein-kinin system acts in vivo having a close relationship with various other enzymatic reaction systems such as the renin-angiotensin system, the blood clotting system, the fibrinolysis system, the complement system as well as the catecholamine and arachidoic acid cascade mainly related to prostaglandins, leukotrienes and thromboxanes. Accordingly, the kallikrein-kinin system is closely related to blood pressure regulating action, action through the blood clotting-fibrinolysis-complement system or bioregulation and improving action for peripheral circulation by various physiologically active substances produced by the arachidoic acid cascade and plays an important role in the regulation of functions in vivo. Thus, the plasma kinin-kallikrein system basically relates to biofunctions and participates in various bioregulation systems. Therefore, it has been suggested that a substance having an effect on the plasma kinin-kallikrein system shows various pharmacological activities.

The present inventor has conducted a study, where a plasma kallikrein-kinin system is utilized, paying attention to silicon compounds which regulate immune action and autonomic action of nerve cells in living organisms. Silicon is widely distributed in the animal and vegetable kingdoms. Especially in animal tissues, it is abundantly present as silicic acid in skin, hair, bone and various organs such as the lung, adrenal gland, thymus, pancreas and spleen. Silicon is known to be an essential component for the formation of bones. Further, in animal tissues, silicic acid forms a collagen cross-linking chain and is contained as a constituting component of acidic mucopolysaccharides and it has been suggested that elasticity of skin is related to the amount of silicic acid.

Crude drugs have been used in medical treatment since ancient time but their quality has been mostly confirmed only by means of empirical extracting methods for many years. For example, in the methods of evaluating the quality of crude drugs in the Japanese Pharmacopoeia (13th Edition), many of the methods are merely a confirmation test by means of color reaction or spots in thin layer chromatography. Under such circumstances, there has been a strong demand for establishing a standardization for the substances so that a predetermined effect for the crude drug can be guaranteed. Standardization for quality of various crude drugs by means of a substantial index related to pharmaceutical effect would contribute to providing crude drug extracts having a stable quality and would greatly contribute to an appropriate standardization of pharmaceuticals.

The present inventor has studied silicon compounds in living organisms and regulated the quality of crude drugs using silicon compounds to express their pharmaceutical effect in vivo whereupon the present invention has been accomplished. The present invention provides crude drug extracts containing soluble silicon compounds as an effective component which exhibit inhibitory action against the production of plasma kallikrein. The present invention also provides methods for manufacturing crude drug extracts, and standardizing methods for crude drugs and extracts thereof.

## SUMMARY OF THE INVENTION

A crude drug extract which inhibits production of plasma kallikrein may be produced by subjecting a plant or animal crude drug to extraction with water or an aqueous-based extracting solvent to obtain an extract having at least about 0.05 mg of at least one soluble silicon compound calculated as silicon per gram of dry extract, as an effective component.