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(54) **Title:** METHOD FOR STABILIZATION OF REDUCED COENZYME Q_{10}

(54) 発明の名称: 還元型補酵素Ｑ$_{10}$の安定化方法

(57) **Abstract:** Disclosed are a method and a composition for stabilizing a reduced coenzyme Q_{10} which is useful as a food, a food with a nutrient function, a food for specified health uses, a nutritional supplement, a nutritional product, a veterinary drug, a beverage, a feeding stuff, a cosmetic, a pharmaceutical product, a therapeutic agent, a prophylactic agent and the like. The method is characterized by allowing a reduced coenzyme Q_{10} to coexist with a reduced coenzyme Q_9 and/or a reduced coenzyme Q_{11}. The composition comprises a reduced coenzyme Q_{10} and a reduced coenzyme Q_9 and/or a reduced coenzyme Q_{11}.

(57) 要約: 食品、栄養機能食品、特定保健用食品、栄養補助剤、栄養剤、動物薬、飲料、飼料、化粧品、医薬品、治療薬、予防薬等として有用な還元型補酵素Ｑ$_{10}$を安定化するための方法並びに組成物の提供を目的とする。
還元型補酵素Ｑ$_{10}$に還元型補酵素Ｑ$_9$および／または還元型補酵素Ｑ$_{11}$を共存させることを特徴とする還元型補酵素Ｑ$_{10}$の安定化方法、および、還元型補酵素Ｑ$_{10}$と還元型補酵素Ｑ$_9$および／または還元型補酵素Ｑ$_{11}$を含有する組成物を提供する。

WO 2007/126083 A1

DESCRIPTION

METHOD FOR STABILIZATION OF REDUCED COENZYME Q_{10}

Technical Field

The present invention relates to a method of stabilizing reduced coenzyme Q_{10}, and a reduced coenzyme Q_{10}-containing composition stable against oxidation. As compared to oxidized coenzyme Q_{10}, reduced coenzyme Q_{10} shows high oral absorbability, and is a compound useful as a superior food, food with nutrient function claims, food for specified health use, nutritional product, nutritional supplement, animal drug, drink, feed, pet food, cosmetic, pharmaceutical product, therapeutic drug, prophylactic drug and the like.

Background Art

It is known that reduced coenzyme Q_{10} can be obtained, for example, by a method comprising producing coenzyme Q_{10} by a conventionally known method such as synthesis, fermentation, extraction from a naturally occurring substance and the like, and concentrating a reduced coenzyme Q_{10} fraction in an eluate from chromatography and the like (patent reference 1). The patent reference 1 describes that, in this case, oxidized coenzyme Q_{10} contained in the above-mentioned reduced coenzyme Q_{10} may be reduced with a general reducing agent such as sodium borohydride, sodium dithionite (sodium hydrosulfite) and the like, and concentrated by chromatography, and that the reduced coenzyme Q_{10} can also be obtained by a method comprising reacting existing highly pure coenzyme Q_{10} with the above-mentioned reducing agent.

In addition, production methods for conveniently obtaining reduced coenzyme Q_{10} are also disclosed (e.g., patent references 2 - 4).

However, reduced coenzyme Q_{10} is easily oxidized by molecular oxygen into oxidized coenzyme Q_{10}, and therefore, stabilization of reduced coenzyme Q_{10} is an important issue when it is processed into a food, food with nutrient function claims, food for specified health use, nutritional product, nutritional

supplement, animal drug, drink, feed, pet food, cosmetic, pharmaceutical product, therapeutic drug, prophylactic drug and the like, or a material or composition therefor, or preserved after processing and the like. Complete removal or blocking of oxygen during the above-mentioned processing and preservation is extremely difficult, and remaining or admixed oxygen particularly during heating for processing and long-term preservation exerts a markedly adverse effect. The above-mentioned oxidation is directly related to quality problems such as the by-product oxidized coenzyme Q_{10}.

As mentioned above, stabilization of reduced coenzyme Q_{10} (protection of oxidation) is a highly important object. However, since reduced coenzyme Q_{10} is not commercially available to date, the study of methods and compositions for stable retention of reduced coenzyme Q_{10} has not been undertaken very much.

As a conventionally-known method for stably retaining reduced coenzyme Q_{10}, a method including addition of a reducing agent is known. However, some of the reducing agents used therefor are not suitable for food and pharmaceutical agents. For example, patent reference 5 disclosing a composition concurrently containing a reducing agent and a production method thereof also discloses, (1) a composition comprising reduced coenzyme Q_{10}; a reducing agent in an amount effective for eliminating oxidation of reduced coenzyme Q_{10} into oxidized coenzyme Q_{10}; a surfactant, vegetable oil or a mixture thereof in an amount effective for dissolving the above-mentioned reduced coenzyme Q_{10} and the above-mentioned reducing agent; and a solvent as necessary, (2) a composition for oral administration wherein the above-mentioned composition is prepared into a gelatin capsule or a tablet, and (3) a method of preparing the above-mentioned composition containing reduced coenzyme Q_{10} in situ using oxidized coenzyme Q_{10} and a reducing agent. However, no detailed description relating to the quality, stabilizing effect and the like of the reduced coenzyme Q_{10} contained in the

composition is provided, and the expected level of stabilization is not clear.

In addition, the above-mentioned composition and preparation method thereof are highly complicated and complex since plural roles are conferred to the composition (i.e., firstly, a role as a reaction site for reducing oxidized coenzyme Q_{10} to reduced coenzyme Q_{10}, and secondly, a role of stably retaining reduced coenzyme Q_{10}). Moreover, the above-mentioned composition and a preparation method thereof are not entirely safe because the reaction mixture is used as it is. In other words, ascorbic acids to be used as reducing agents are oxidized to produce a considerable amount of dehydroascorbic acids, and the dehydroascorbic acids get mixed in with the above-mentioned composition, posing a problem. Dehydroascorbic acids and oxalic acid produced by decomposition from dehydroascorbic acids are highly noxious, unlike ascorbic acids. For example, an increased amount of lipid peroxide, a decreased amount of antioxidants in the liver and kidney and an increased amount of oxalic acid in the kidney have been reported, and side effects such as decreased resistance to oxidation stress, easy onset of ureteral lithiasis (non-patent reference 1) and the like are feared.

patent reference 1: JP-A-10-109933

patent reference 2: WO03/06408

patent reference 3: WO03/06409

patent reference 4: WO03/32967

patent reference 5: WO01/52822

non-patent reference 1: Nutrition Research Vol. 13, page 667-676, 1993

Disclosure of the Invention

Problems to be Solved by the Invention

In view of the above, it would be advantageous if at least preferred embodiments of the present invention were to provide a convenient and preferable method and a composition for stably retaining reduced coenzyme Q_{10} by protection against oxidation while maintaining high safety, during processing into

a food, food with nutrient function claims, food for specified health use, nutritional product, nutritional supplement, animal drug, drink, feed, pet food, cosmetic, pharmaceutical product, therapeutic drug, prophylactic drug containing reduced coenzyme Q_{10} and the like, or a material or composition therefore, and/or preservation after processing and the like.

Means of Solving the Problems

The present inventors have conducted intensive studies in an attempt to solve the above-mentioned problems and found that reduced coenzyme Q_{10} can be stabilized by the co-presence of reduced coenzyme Q_9 and/or reduced coenzyme Q_{11}, which are analogs of reduced coenzyme Q_{10} and reduced coenzyme Q_{10}.

That is, they have found that reduced coenzyme Q_{10} can be stably retained by protecting the reduced coenzyme Q_{10} from oxidation by the co-presence of reduced coenzyme Q_9 (not less than 0.6 wt% relative to reduced coenzyme Q_{10}) and/or reduced coenzyme Q_{11}, even when a reducing agent is not used as a necessary component to be added, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

[1] A method for stabilizing reduced coenzyme Q_{10}, comprising achieving the co-presence of the following (a) and/or (b):

(a) not less than 0.6 wt% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and

(b) reduced coenzyme Q_{11}.

[2] The method of [1], wherein the amount of the aforementioned (a) reduced coenzyme Q_9 is not less than 1 wt%.

[3] The method of [1] or [2], wherein the aforementioned (a) reduced coenzyme Q_9 and (b) reduced coenzyme Q_{11} are separately prepared and added.

[4] The method of [1] or [2], wherein the co-presence is achieved by reducing the oxidized coenzyme Q_{10} comprising oxidized coenzyme Q_9 and/or oxidized coenzyme Q_{11}.

[5] The method of any one of [1] to [4], wherein the co-presence is achieved under a deoxygenation atmosphere.

[6] A reduced coenzyme Q_{10}-containing composition comprising the following (a) and/or (b) in combination:

(a) not less than 1.5 wt% to not more than 99% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and

(b) reduced coenzyme Q_{11},

wherein not less than 0.01 wt% of reduced coenzyme Q_{10} is contained in the composition.

[7] The composition of [6], wherein the reduced coenzyme Q_{10} is a crystal.

[8] The composition of [6], wherein the reduced coenzyme Q_{10} is dissolved or suspended in a solvent.

[9] The composition of [6], wherein the reduced coenzyme Q_{10} is a melt.

[10] The composition of [6], which is in a form administrable to a mammal and comprises reduced coenzyme Q_{10} as an active ingredient.

[11] The composition of [6], comprising at least one kind selected from the group consisting of an excipient, a disintegrant, a lubricant, a binder, an antioxidant, a coloring agent, an anticoagulant, an absorption promoter, a solubilizing agent for the active ingredient, a stabilizer and an active ingredient other than reduced coenzyme Q_{10}.

[12] The composition of [11], which is a capsule.

[13] The composition of [12], wherein the capsule is a microcapsule, a soft capsule or a hard capsule.

[14] A method for producing a reduced coenzyme Q_{10}-containing composition comprising the following (a) and/or (b) in combination:

(a) not less than 0.6 wt% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and

(b) reduced coenzyme Q_{11},

which comprises separately preparing and adding (a) and/or (b).

[15] A method for producing a reduced coenzyme Q_{10}-containing composition comprising the following (a) and/or (b) in combination:

(a) not less than 0.6 wt% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and

(b) reduced coenzyme Q_{11},

which comprises reducing oxidized coenzyme Q_{10} containing oxidized coenzyme Q_9 (not less than 0.6 wt% relative to oxidized coenzyme Q_{10}) and/or oxidized coenzyme Q_{11}.

Effect of the Invention

According to the present invention, a stabilization method of reduced coenzyme Q_{10} can be provided by a mere co-presence of an analog of reduced coenzyme Q_{10} even when multiple components, particularly a reducing agent, are not used as necessary components to protect the reduced coenzyme Q_{10} from oxidation. Therefore, highly safe reduced coenzyme Q_{10} can be provided, which is free of a noxious substance such as dehydroascorbic acid, oxalic acid and the like produced when ascorbic acid and the like is used as a reducing agent.

Moreover, reduced coenzyme Q_9 and reduced coenzyme Q_{11} show the same effect in the body as reduced coenzyme Q_{10}. Therefore, when reduced coenzyme Q_9 and reduced coenzyme Q_{11} contained in reduced coenzyme Q_{10} are ingested, the effect of the reduced coenzyme Q_{10} is not prevented and a greater effect of coenzyme Q can be exhibited as compared to a composition containing reduced coenzyme Q_{10} alone, and the like. Furthermore, since the absorbability of reduced coenzyme Q_9 in the body is greater than that of reduced coenzyme Q_{10}, a composition containing reduced coenzyme Q_9 and reduced coenzyme Q_{10} in combination shows higher absorbability in terms of the total amount of coenzyme Q.

Brief Description of the Drawings

(Fig. 1) Fig. 1 shows the measurement results of the concentration of the total coenzyme Q in each plasma in the reduced coenzyme Q_9 administration rat and the reduced coenzyme Q_{10} administration rat.

(Fig. 2) Fig. 2 shows the measurement results of the concentration of the total coenzyme Q in each plasma in the

reduced coenzyme Q_{10} administration rat, and the reduced coenzyme Q_{10} and reduced coenzyme Q_{11} mixture administration rat.

Best Mode for Embodying the Invention

The present invention is explained in detail in the following. In the present specification, when simply expressed as coenzyme Q_{10}, it includes an oxidized form, a reduced form and a mixture thereof when they are both present.

In the present invention, reduced coenzyme Q_{10} may contain oxidized coenzyme Q_{10}. When oxidized coenzyme Q_{10} is also present, the proportion of reduced coenzyme Q_{10} in the total amount of coenzyme Q_{10} (the total amount of reduced coenzyme Q_{10}) and oxidized coenzyme Q_{10} is not particularly limited. It is, for example, not less than 20 wt%, normally not less than 40 wt%, preferably not less than 60 wt%, more preferably not less than 80 wt%, particularly not less than 90 wt%, especially not less than 96 wt%. While the upper limit is not particularly limited, it is 100 wt%, normally not more than 99.9 wt%.

Reduced coenzyme Q_{10} can be obtained by various methods mentioned above and, for example, reduced coenzyme Q_{10} having a high proportion of reduced coenzyme Q_{10} relative to the total amount of coenzyme Q_{10} can be efficiently obtained by the method described in WO03/06408.

The stabilization method of the reduced coenzyme Q_{10} of the present invention (hereinafter to be also referred to as the stabilization method of the present invention) is a method characterized by the co-presence of (a) not less than 0.6 wt% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and/or (b) reduced coenzyme Q_{11}, which suppresses oxidation of reduced coenzyme Q_{10} into oxidized coenzyme Q_{10} by molecular oxygen, and stably retains the reduced coenzyme Q_{10}.

While the amount of reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} contained in reduced coenzyme Q_{10} is not particularly limited, the amount of the reduced coenzyme Q_9 is generally not less than about 0.6 wt%, preferably not less than about 1 wt%, more preferably not less than about 1.5 wt%, more

preferably not less than about 2 wt%, particularly preferably not less than about 3 wt%, relative to reduced coenzyme Q_{10}.

The amount of reduced coenzyme Q_{11} is generally not less than about 0.1 wt%, preferably not less than about 0.5 wt%, more preferably not less than about 1 wt%, relative to reduced coenzyme Q_{10}.

While the upper limit of reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} contained in reduced coenzyme Q_{10} is not particularly limited, it is generally not more than about 99 wt%, preferably not more than about 90 wt%, more preferably not more than about 80 wt%, particularly preferably not more than about 70 wt%, more preferably not more than about 60 wt%, most preferably not more than about 50 wt%, especially not more than about 40 wt%. It is needless to say that both reduced coenzyme Q_9 and reduced coenzyme Q_{11} may be contained in reduced coenzyme Q_{10}.

In the stabilization method of the present invention, the aforementioned (a) and/or (b) may be separately prepared. For example, the separate preparation can be preparation by extraction and purification from a naturally occurring substance, reduction of oxidized coenzyme Q_9 and oxidized coenzyme Q_{11} according to the aforementioned method described in WO 03/06408, or coupling reaction of isoprenyl side chain with 2-methyl-5,6-dimethoxy-1,4-benzohydroquinone and the like. The reduced coenzyme Q_{10} can also be stabilized by adding reduced Q_9 and/or reduced coenzyme Q_{11} obtained by such preparation to reduced coenzyme Q_{10}.

The stabilization method of the present invention also includes the co-presence of reduced coenzyme Q_{10} and (a) and/or (b) by the reduction of oxidized coenzyme Q_{10} containing oxidized coenzyme Q_9 and/or oxidized coenzyme Q_{11}.

The method of reducing oxidized coenzyme Q_{10} containing oxidized coenzyme Q_9 and/or oxidized coenzyme Q_{11} may be performed according to the method described in WO03/06408 and the like.

The reduced coenzyme Q_{10}-containing composition of the present invention (hereinafter to be also referred to the composition of the present invention) is a composition characterized by the co-presence of (a) not less than 0.6 wt% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and/or (b) reduced coenzyme Q_{11}.

Preferable amounts of reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} to be contained in reduced coenzyme Q_{10} are as mentioned above.

The composition of the present invention may be obtained by adding separately prepared reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} to reduced coenzyme Q_{10}, or reducing oxidized coenzyme Q_{10} containing oxidized coenzyme Q_9 and/or oxidized coenzyme Q_{11}.

The production method of the reduced coenzyme Q_{10}-containing composition of the present invention (hereinafter to be also referred to as the production method of the present invention) is a production method of a reduced coenzyme Q_{10}-containing composition comprising the aforementioned (a) and/or (b) in combination, which includes separately preparing and adding (a) and/or (b).

The production method of reduced coenzyme Q_{10} containing reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} is not particularly limited. The step of separately preparing and adding (a) and/or (b) is a step for adding (a) and/or (b) separately prepared as mentioned above, and the preparation and addition are performed by a method known per se.

The production method of the present invention includes a step of reducing oxidized coenzyme Q_{10} containing of oxidized coenzyme Q_9 (not less than 0.6 wt% relative to oxidized coenzyme Q_{10}) and/or oxidized coenzyme Q_{11}. By this step, reduced coenzyme Q_{10}-containing composition containing (a) and/or (b) in combination can be finally obtained.

It is needless to say that the method (step) of reducing oxidized coenzyme Q_{10} containing oxidized coenzyme Q_9 and/or

oxidized coenzyme Q_{11}, and the method (step) of adding reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} prepared separately may be employed in combination.

The form of the reduced coenzyme Q_{10}-containing composition containing reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} in combination of the present invention is not particularly limited, and may be a crystal; dissolved or suspended in a solvent; a melt maintained at not less than the melting point; or in a form for administration to mammals such as agent for oral administration, external preparation and the like.

In the present invention, the form of contact between reduced coenzyme Q_{10} and reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} is not particularly limited and, for example, reduced coenzyme Q_{10} and reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} may be present as crystals, or dissolved and/or suspended in any solvent. It is needless to say that reduced coenzyme Q_9 and/or reduced coenzyme Q_{11} may be dissolved in a melted solution of reduced coenzyme Q_{10}.

As the solvent usable in the present invention is not particularly limited, and hydrocarbons, fatty acid esters, ethers, alcohols, fatty acids, ketones, nitrogen compounds (including nitriles and amides), sulfur compounds, fats and oils, water and the like can be used. These solvents may be a mixture of any two or more kinds of solvents.

While hydrocarbons are not particularly limited, for example, aliphatic hydrocarbon, aromatic hydrocarbon, halogenated hydrocarbon and the like can be recited. Particularly, aliphatic hydrocarbon and aromatic hydrocarbon are preferable, and aliphatic hydrocarbon is especially preferable.

Aliphatic hydrocarbon may be cyclic or non-cyclic, saturated or unsaturated and is not particularly limited. Generally, saturated one is preferably used.

Normally, aliphatic hydrocarbon having 3 to 20 carbon atoms, particularly 5 to 12 carbon atoms, especially 5 to 8 carbon atoms, is preferably used.

Specific examples include propane, butane, isobutane, pentane, 2-methylbutane, hexane, 2-methylpentane, 2,2-dimethylbutane, 2,3-dimethylbutane, heptane, heptane isomer (e.g., 2-methylhexane, 3-methylhexane, 2,3-dimethylpentane, 2,4-dimethylpentane), octane, 2,2,3-trimethylpentane, isooctane, nonane, 2,2,5-trimethylhexane, decane, dodecane, 2-pentene, 1-hexene, 1-heptene, 1-octene, 1-nonene, 1-decene, cyclopentane, methylcyclopentane, cyclohexane, methylcyclohexane, ethylcyclohexane, p-menthane, cyclohexene and the like.

Of these, pentane, 2-methylbutane, hexane, 2-methylpentane, 2,2-dimethylbutane, 2,3-dimethylbutane, heptane, heptane isomer (e.g., 2-methylhexane, 3-methylhexane, 2,3-dimethylpentane, 2,4-dimethylpentane), octane, 2,2,3-trimethylpentane, isooctane, nonane, 2,2,5-trimethylhexane, decane, dodecane, cyclopentane, methylcyclopentane, cyclohexane, methylcyclohexane, ethylcyclohexane, p-menthane and the like are preferable, and particularly, pentane, 2-methylbutane, hexane, 2-methylpentane, 2,2-dimethylbutane, 2,3-dimethylbutane, heptane, heptane isomer (e.g., 2-methylhexane, 3-methylhexane, 2,3-dimethylpentane, 2,4-dimethylpentane), octane, 2,2,3-trimethylpentane, isooctane, cyclopentane, methylcyclopentane, cyclohexane, methylcyclohexane, ethylcyclohexane and the like are preferable.

In general, heptanes, not to mention heptane, analogous heptane such as methylcyclohexane having 7 carbon atoms and the like and a mixture of two or more of them are preferably used.

Generally, pentanes having 5 carbon atoms (e.g., pentane etc.), hexanes having 6 carbon atoms (e.g., hexane, cyclohexane etc.), heptanes having 7 carbon atoms (e.g., heptane, methylcyclohexane etc.) and the like are preferably used. Heptanes (e.g., heptane, methylcyclohexane etc.) are most preferable and heptane is especially preferable.

While aromatic hydrocarbon is not particularly limited, normally, aromatic hydrocarbon having 6 to 20 carbon atoms, particularly 6 to 12 carbon atoms, especially 7 to 10 carbon atoms, is preferably used.

Specific examples include benzene, toluene, xylene, o-xylene, m-xylene, p-xylene, ethylbenzene, cumene, mesitylene, tetralin, butylbenzene, p-cymene, cyclohexylbenzene, diethylbenzene, pentylbenzene, dipentylbenzene, dodecylbenzene, styrene and the like.

Of these, toluene, xylene, o-xylene, m-xylene, p-xylene, ethylbenzene, cumene, mesitylene, tetralin, butylbenzene, p-cymene, cyclohexylbenzene, diethylbenzene, pentylbenzene and the like are preferable, and particularly, toluene, xylene, o-xylene, m-xylene, p-xylene, cumene, tetralin and the like are preferable. Cumene is most preferable.

Halogenated hydrocarbon may be cyclic or non-cyclic, saturated or unsaturated, and is not particularly limited. In general, non-cyclic one is preferably used.

Generally, chlorinated hydrocarbon and fluorinated hydrocarbon are preferable, and chlorinated hydrocarbon is particularly preferable.

Halogenated hydrocarbon having 1 to 6 carbon atoms, particularly 1 to 4 carbon atoms, especially 1 or 2 carbon atoms, is preferably used.

Specific examples include dichloromethane, chloroform, carbon tetrachloride, 1,1-dichloroethane, 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1,1,2-tetrachloroethane, 1,1,2,2-tetrachloroethane, pentachloroethane, hexachloroethane, 1,1-dichloroethylene, 1,2-dichloroethylene, trichloroethylene, tetrachloroethylene, 1,2-dichloropropane, 1,2,3-trichloropropane, chlorobenzene, 1,1,1,2-tetrafluoroethane and the like.

Of these, dichloromethane, chloroform, carbon tetrachloride, 1,1-dichloroethane, 1,2-dichloroethane, 1,1,1-trichloroethane, 1,1,2-trichloroethane, 1,1-dichloroethylene,

1,2-dichloroethylene, trichloroethylene, chlorobenzene, 1,1,1,2-tetrafluoroethane and the like preferably, particularly, dichloromethane, chloroform, 1,2-dichloroethylene, trichloroethylene, chlorobenzene, 1,1,1,2-tetrafluoroethane and the like are preferable.

While fatty acid esters are not particularly limited, for example, propionic acid ester, acetic acid ester, formic acid ester and the like can be used.

Particularly, acetic acid ester and formic acid ester are preferable, and acetic acid ester is particularly preferable.

While ester group is not particularly limited, in general, alkyl ester or aralkyl ester having 1 to 8 carbon atoms, preferably aralkyl ester having 1 to 6 carbon atoms, more preferably aralkyl ester having 1 to 4 carbon atoms is preferably used.

Specific examples of propionic acid ester include methyl propionate, ethyl propionate, butyl propionate and isopentyl propionate.

Specific examples of acetic acid ester include methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, sec-butyl acetate, pentyl acetate, isopentyl acetate, sec-hexyl acetate, cyclohexyl acetate, benzyl acetate and the like.

Of these, methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate, sec-butyl acetate, pentyl acetate, isopentyl acetate, sec-hexyl acetate, cyclohexyl acetate and the like are preferable. Methyl acetate, ethyl acetate, propyl acetate, isopropyl acetate, butyl acetate, isobutyl acetate and the like are more preferable, and ethyl acetate is particularly preferable.

Examples of formic acid ester include methyl formate, ethyl formate, propyl formate, isopropyl formate, butyl formate, isobutyl formate, sec-butyl formate, pentyl formate and the like.

Of these, methyl formate, ethyl formate, propyl formate, butyl formate, isobutyl formate, pentyl formate and the like are preferable. Ethyl formate is more preferable.

Ethers may be cyclic or non-cyclic, saturated or unsaturated, and is not particularly limited. In general, saturated one is preferably used.

Normally, ether having 3 to 20 carbon atoms, particularly ether having 4 to 12 carbon atoms, especially ether having 4 to 8 carbon atoms, is preferably used.

Specific examples include diethyl ether, methyl tert-butyl ether, dipropyl ether, diisopropyl ether, dibutyl ether, dihexyl ether, ethylvinyl ether, butylvinyl ether, anisole, phenetol, butylphenyl ether, methoxytoluene, dioxane, furan, 2-methylfuran, tetrahydrofuran, tetrahydropyran, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, ethylene glycol dibutyl ether, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol dibutyl ether and the like.

Of these, diethyl ether, methyl tert-butyl ether, dipropyl ether, diisopropyl ether, dibutyl ether, dihexyl ether, anisole, phenetol, butylphenyl ether, methoxytoluene, dioxane, 2-methylfuran, tetrahydrofuran, tetrahydropyran, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, ethylene glycol dibutyl ether, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether and the like are preferable, and particularly, diethyl ether, methyl tert-butyl ether, anisole, dioxane, tetrahydrofuran, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether and the like are preferable.

Diethyl ether, methyl tert-butyl ether, anisole, dioxane, tetrahydrofuran and the like are most preferable, and dioxane and tetrahydrofuran are particularly preferable.

Nitriles may be cyclic or non-cyclic, saturated or unsaturated, and is not particularly limited. In general, saturated one is preferably used.

Normally, nitrile having 2 to 20 carbon atoms, particularly nitrile having 2 to 12 carbon atoms, especially nitrile having 2 to 8 carbon atoms, is preferably used.

Specific examples include acetonitrile, propionitrile, malononitrile, butyronitrile, isobutyronitrile, succinonitrile, valeronitrile, glutaronitrile, hexanenitrile, heptyl cyanide, octyl cyanide, undecanenitrile, dodecanenitrile, tridecanenitrile, pentadecanenitrile, stearonitrile, chloroacetonitrile, bromoacetonitrile, chloropropionitrile, bromopropionitrile, methoxyacetonitrile, methyl cyanoacetate, ethyl cyanoacetate, tolunitrile, benzonitrile, chlorobenzonitrile, bromobenzonitrile, cyanobenzoic acid, nitrobenzonitrile, anisonitrile, phthalonitrile, bromotolunitrile, methylcyanobenzoate, methoxybenzonitrile, acetylbenzonitrile, naphtonitrile, biphenylcarbonitrile, phenylpropionitrile, phenylbutyronitrile, methylphenylacetonitrile, diphenylacetonitrile, naphthylacetonitrile, nitrophenylacetonitrile, chlorobenzyl cyanide, cyclopropanecarbonitrile, cyclohexanecarbonitrile, cycloheptanecarbonitrile, phenylcyclohexanecarbonitrile, tolylcyclohexanecarbonitrile and the like.

Alcohols may be cyclic or non-cyclic, saturated or unsaturated, and is not particularly limited. In general, saturated one is preferably used.

Normally, alcohol having 1 to 20 carbon atoms, particularly alcohol having 1 to 12 carbon atoms, especially alcohol having 1 to 6 carbon atoms, particularly monovalent alcohol having 1 to 5 carbon atoms, divalent alcohol having 2 to 5 carbon atoms or trivalent alcohol having 3 carbon atoms is preferably used.

Specific examples of these alcohols include methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, isobutyl alcohol, tert-butyl alcohol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-1-butanol, isopentyl alcohol, tert-pentyl alcohol, 3-methyl-2-butanol, neopentyl alcohol, 1-hexanol, 2-methyl-1-

pentanol, 4-methyl-2-pentanol, 2-ethyl-1-butanol, 1-heptanol, 2-heptanol, 3-heptanol, 1-octanol, 2-octanol, 2-ethyl-1-hexanol, 1-nonanol, 1-decanol, 1-undecanol, 1-dodecanol, allyl alcohol, propargyl alcohol, benzyl alcohol, cyclohexanol, 1-methylcyclohexanol, 2-methylcyclohexanol, 3-methylcyclohexanol, 4-methylcyclohexanol, 2-methoxyethanol, 2-ethoxyethanol, 2-(methoxymethoxy)ethanol, 2-isoproxy ethanol, 2-butoxy ethanol, 2-(isopentyloxy)ethanol, 2-(hexyloxy)ethanol, furfuryl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, diethylene glycol monobutyl ether, triethylene glycol monomethyl ether, 1-methoxy-2-propanol, 1-ethoxy-2-propanol, dipropylene glycol monomethyl ether, dipropylene glycol monoethyl ether, tripropylene glycol monomethyl ether, 1,2-ethanediol, 1,2-propanediol, 1,3-propanediol, 1,2-butanediol, 1,3-butanediol, 1,4-butanediol, 2,3-butanediol, 1,5-pentanediol, 2-butene-1,4-diol, 2-methyl-2,4-pentanediol, 2-ethyl-1,3-hexanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, polyethylene glycol, dipropylene glycol, polypropylene glycol, glycerol and the like.

Preferable examples of monovalent alcohol include methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, isobutyl alcohol, tert-butyl alcohol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-1-butanol, isopentyl alcohol, tert-pentyl alcohol, 3-methyl-2-butanol, neopentyl alcohol, 1-hexanol, 2-methyl-1-pentanol, 4-methyl-2-pentanol, 2-ethyl-1-butanol, 1-heptanol, 2-heptanol, 3-heptanol, 1-octanol, 2-octanol, 2-ethyl-1-hexanol, 1-nonanol, 1-decanol, 1-undecanol, 1-dodecanol, benzyl alcohol, cyclohexanol, 1-methylcyclohexanol, 2-methylcyclohexanol, 3-methylcyclohexanol, 4-methylcyclohexanol, 2-methoxyethanol, 2-ethoxyethanol, 2-(methoxymethoxy)ethanol and the like, and particularly, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, isobutyl alcohol, tert-butyl alcohol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-1-butanol, isopentyl alcohol, tert-pentyl alcohol, 3-methyl-2-butanol, neopentyl alcohol, 1-hexanol, 2-methyl-1-pentanol, 4-methyl-2-pentanol, 2-

ethyl-1-butanol, cyclohexanol and the like are preferable, and methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, isobutyl alcohol, tert-butyl alcohol, 1-pentanol, 2-pentanol, 3-pentanol, 2-methyl-1-butanol, isopentyl alcohol, tert-pentyl alcohol, 3-methyl-2-butanol, neopentyl alcohol and the like are particularly preferable.

Methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, isobutyl alcohol, 2-methyl-1-butanol, isopentyl alcohol and the like are most preferable, methanol, ethanol, 1-propanol and 2-propanol are particularly preferable and ethanol is especially preferable.

As divalent alcohol, 1,2-ethanediol, 1,2-propanediol, 1,3-propanediol, 2-butene-1,4-diol, 2-methyl-2,4-pentanediol, 2-ethyl-1,3-hexanediol, diethylene glycol, triethylene glycol, tetraethylene glycol, polyethylene glycol, dipropylene glycol, polypropylene glycol and the like are preferable, and 1,2-propanediol and polyethylene glycol are most preferable. As trivalent alcohol, glycerol is preferable.

Ketones are not particularly limited, and ketone having 3 to 6 carbon atoms is generally preferable.

Specific examples include acetone, methylethylketone, methylbutylketone, methylisobutylketone and the like, and particularly, acetone and methylethylketone are preferable, and acetone is particularly preferable.

Examples of nitrogen compounds include nitromethane, acetonitrile, triethylamine, pyridine, formamide, N-methylformamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone and the like, and acetonitrile is particularly preferable.

Examples of sulfur compounds include dimethyl sulfoxide, sulfolane and the like. Dimethyl sulfoxide is preferable.

Examples of fatty acids include formic acid, acetic acid, propionic acid, oleic acid, linoleic acid, linolenic acid and the like. Formic acid and acetic acid are preferable, and acetic acid is more preferable.

Fats and oils are not particularly limited, and may be natural fats and oils from plants and animals, synthetic fats and oils or processed fats and oils.

Examples of vegetable oil include olive oil, coconut oil, palm oil, palm kernel oil, flaxseed oil, camellia oil, brown rice germ oil, canola oil, rice oil, peanuts oil, corn oil, wheat germ oil, soy bean oil, perilla oil, cottonseed oil, sunflower kerel oil, kapok oil, evening primrose oil, shea butter, sal butter, cacao butter, sesame oil, safflower oil and the like, and examples of animal fats and oils include lard, milk fat, fish oil, beef fat and the like. Furthermore, fats and oils obtained by processing them by fractionation, hydrogenation, transesterification(e.g., hydrogenated oil) and the like are also included. It is needless to say that medium-chain triglyceride (MCT), partial glyceride of fatty acid, phospholipid and the like can also be used.

Examples of medium-chain triglyceride include triglyceride wherein fatty acid has 6 to 12 carbon atoms, preferably 8 to 12 carbon atoms, and examples of partial glyceride of fatty acid include monoglyceride and diglycerides wherein fatty acid has 6 to 18 carbon atoms, preferably 6 to 12 carbon atoms.

Of the above-mentioned fats and oils, vegetable fats and oils, synthetic fats and oils and processed fats and oils are preferable from the aspects of handlability, odor and the like.

Fats and oils are preferably selected in consideration of the price of fats and oils, stability of reduced coenzyme Q_{10}, solubility of coenzyme Q_{10} and the like.

For example, olive oil, coconut oil, palm oil, palm kernel oil, canola oil, rice oil, soy bean oil, cottonseed oil, MCT and the like are preferable, olive oil, rice oil, soy bean oil, canola oil, MCT and the like are particularly preferable.

From the aspect of the solubility of coenzyme Q_{10}, MCT can be particularly preferably used.

When the composition of the present invention is used for food or pharmaceutical agent, ethanol, water and fats and oils

usable for food or pharmaceutical agent are preferably used, from among the above-mentioned solvents. The composition of the present invention may contain other appropriate materials, besides the above-mentioned solvent. That is, excipient, disintegrant, lubricant, binder, antioxidant, coloring agent, anticoagulant, absorption promoter, solubilizing agent for the active ingredient, stabilizer, or active ingredient other than reduced coenzyme Q_{10} may be contained.

While the above-mentioned excipient is not particularly limited, for example, sucrose, lactose, glucose, cornstarch, mannitol, crystalline cellulose, calcium phosphate, calcium sulfate and the like can be used.

While the above-mentioned disintegrant is not particularly limited, for example, starch, agar, calcium citrate, calcium carbonate, sodium hydrogencarbonate, dextrin, crystalline cellulose, carboxymethylcellulose, tragacanth and the like can be used.

While the above-mentioned lubricant is not particularly limited, for example, talc, magnesium stearate, polyethylene glycol, silica, hydrogenated vegetable oil and the like can be used.

While the above-mentioned binder is not particularly limited, for example, ethylcellulose, methylcellulose, hydroxypropylmethylcellulose, tragacanth, shellac, gelatin, gum arabic, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, sorbitol and the like can be used.

While the above-mentioned antioxidant is not particularly limited, for example, ascorbic acid, tocopherol, vitamin A, β-carotene, sodium hydrogensulfite, sodium thiosulfate, sodium pyrrosulfite, citric acid and the like can be used.

While the above-mentioned coloring agent is not particularly limited, for example, those allowed to be added to pharmaceutical products and food and the like can be used.

While the above-mentioned anticoagulant is not particularly limited, for example, stearic acid, talc, light

anhydrous silicic acid, water-containing silicon dioxide and the like can be mentioned.

While the above-mentioned absorption promoter is not particularly limited, for example, higher alcohols, higher fatty acids, sucrose fatty acid ester, surfactants such as sorbitan fatty acid ester, sorbitan polyoxyethylene fatty acid ester and the like, and the like can be used.

While the solubilizing agent for the above-mentioned active ingredient is not particularly limited, for example, organic acids such as fumaric acid, succinic acid, malic acid and the like, and the like can be mentioned.

While the above-mentioned stabilizer is not particularly limited, for example, benzoic acid, sodium benzoate, ethyl parahydroxybenzoate and the like can be mentioned.

The active ingredient other than the above-mentioned coenzyme Q_{10} is, for example, amino acid, vitamin, mineral, polyphenol, organic acid, saccharides, peptide, protein and the like.

While the amount of the reduced coenzyme Q_{10} contained in the composition of the present invention is not particularly limited, the weight of the reduced coenzyme Q_{10} contained in the whole composition is generally not less than about 0.01 wt%, preferably not less than about 0.1 wt%, more preferably not less than about 1 wt%, particularly preferably not less than about 2 wt%, more preferably not less than about 3 wt%.

While the upper limit is not particularly limited, it is generally not more than about 70%, preferably not more than about 60 wt%, more preferably not more than about 50 wt% in consideration of the viscosity of the composition and the like.

When practicing the present invention, the temperature is not particularly limited. To exhibit the reduced coenzyme Q_{10}-stabilizing effect to the maximum, it is normally not more than 50°C, preferably not more than 40°C, more preferably not more than 30°C.

When processing into a dosage form for the oral administration mentioned below, moreover, the composition of the present invention is more preferably a liquid (including not only solution but also suspension, slurry or liposome) at ambient temperature or a temperature not less than the ambient temperature.

While the composition of the present invention can be used as it is, it may be processed into a dosage form for oral administration such as capsule (microcapsule, hard capsule, soft capsule), tablet, syrup, drink and the like and used preferably.

In addition, it can be processed into a dosage form for parenteral administration such as cream, suppository, toothpaste and the like and used preferably. Particularly preferred is capsule, especially soft capsule.

The capsule base material is not particularly limited, and gelatin derived from beef bones, cattle skin, pig skin, fish skin and the like, and other base materials (e.g., gum stabilizers that can be used as food additives, such as seaweed-derived products (e.g., carageenan, alginic acid and the like), vegetable seed-derived products (e.g., locust bean gum, guar gum and the like), agents for production (e.g., celluloses) and the like) can also be used.

The stabilization method and production method of the present invention are preferable performed in combination under a deoxygenation atmosphere. That is, to exert the effect of the invention to the maximum extent, for example, the method of the present invention is preferably performed and the composition of the present invention is preferably prepared and/or preserved under a deoxygenation atmosphere such as inert gas atmosphere (e.g., nitrogen atmosphere etc.) and the like.

The above-mentioned processing and preservation after processing are also preferably performed under the above-mentioned deoxygenation atmosphere such as inert gas atmosphere and the like.

As mentioned above, by the co-presence of reduced coenzyme Q_{10} and reduced coenzyme Q_9 and/or reduced coenzyme Q_{11}, the stability of reduced coenzyme Q_{10} can be improved.

Reduced coenzyme Q_9 and reduced coenzyme Q_{11} exhibit the same effect as provided by reduced coenzyme Q_{10} in the body. Therefore, even when reduced coenzyme Q_9 and reduced coenzyme Q_{11} contained in the reduced coenzyme Q_{10} are ingested, they do not prevent the effect of the reduced coenzyme Q_{10} but act in the same manner as the reduced coenzyme Q_{10}.

The present inventors have moreover studied intensively and found that the absorbability of reduced coenzyme Q_9 in the body is greater than that of the reduced coenzyme Q_{10}.

As mentioned above, since reduced coenzyme Q_9 and reduced coenzyme Q_{10} act in the same manner in the body, a composition containing reduced coenzyme Q_9 and reduced coenzyme Q_{10} in combination is expected to show higher absorption of coenzyme Q as a whole.

According to the present invention, reduced coenzyme Q_{10} can be preferably protected from oxidation, and a composition free of an oxidation product of reducing agent such as dehydroascorbic acids and the like can be provided optimally. Moreover, a composition showing high biological absorbability of reduced coenzyme Q_{10} can also be provided.

Examples

The present invention is explained in more detail in the following by referring to Examples, which are not to be construed as limitative.

In Examples, the purity of reduced coenzyme Q_{10}, and the weight ratio of reduced coenzyme Q_{10} and oxidized coenzyme Q_{10} were determined by HPLC analysis mentioned below. However, the purity of the obtained reduced coenzyme Q_{10} does not define the limit value of the purity in the present invention. Likewise, the proportion of reduced coenzyme Q_{10} in the weight ratio of reduced coenzyme Q_{10} and oxidized coenzyme Q_{10} does not define the upper limit value thereof.

(HPLC analysis conditions)

column: SYMMETRY C18 (manufactured by Waters) 250 mm (length) 4.6 mm (inner diameter), mobile phase; C_2H_5OH:CH_3OH=4:3 (v:v), detection wavelength; 210 nm, flow rate; 1 ml/min, retention time of reduced coenzyme Q_{10}; 9.1 min, retention time of oxidized coenzyme Q_{10}; 13.3 min.

(Production Example 1)

Oxidized coenzyme Q_{10} (100 g) and L-ascorbic acid (60 g) were added to 1000 g of ethanol, and the mixture was stirred at 78°C to perform a reduction reaction. After 30 hr, the mixture was cooled to 50°C, and 400 g of ethanol was added while maintaining at the same temperature. The ethanol solution (containing 100 g of reduced coenzyme Q_{10}) was cooled 2°C at a cooling rate of 10°C/hr with stirring to give a white slurry. The obtained slurry was filtered under reduced pressure, the wet crystals were washed with cold ethanol, cold water and cold ethanol in this order (temperature of cold solvent used for washing, 2°C) and dried under reduced pressure (20 - 40°C, 1 - 30 mmHg) to give white dry crystals (95 g). All operations except reduced-pressure drying were performed under a nitrogen atmosphere. The weight ratio of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} of the obtained crystals was 99.4/0.6.

(Production Example 2)

Oxidized coenzyme Q_9 (10 g) and L-ascorbic acid (7 g) were added to 100 g of ethanol, and the mixture was stirred at 78°C to perform a reduction reaction. After 30 hr, the mixture was cooled to 50°C, and ethanol (40 g), hexane (140 g) and water (140 g) were added in this order while maintaining at the same temperature. After removing the aqueous layer, and the organic layer was concentrated under reduced pressure to give reduced coenzyme Q_9 as crystals.

(Production Example 3)

The reduced coenzyme Q_{10} (9.85 g) obtained in Production Example 1 and reduced coenzyme Q_9 (0.15 g) obtained in Production Example 2 were mixed to give reduced coenzyme Q_{10} containing 1.5

wt% of reduced coenzyme Q_9 (reduced coenzyme Q_{10}/oxidized coenzyme Q_{10}=99.4/0.6).

(Production Example 4)

Oxidized coenzyme Q_{10} (10 g) containing 0.1% of oxidized coenzyme Q_{10} and L-ascorbic acid (6 g) were added to 100 g of ethanol, and the mixture was stirred at 78°C to perform a reduction reaction. After 30 hr, the mixture was cooled to 50°C, and 40 g of ethanol and water (10 g) were added while maintaining the same temperature. The ethanol solution (containing 10 g of reduced coenzyme Q_{10}) was cooled to 2°C at a cooling rate of 10°C/hr with stirring to give a white slurry. The obtained slurry was filtered under reduced pressure, the wet crystals were washed with cold ethanol, cold water and cold ethanol in this order (temperature of cold solvent used for washing, 2°C) and dried under reduced pressure (20 - 40°C, 1 - 30 mmHg) to give white dry crystals (9.5 g). All operations except reduced-pressure drying were performed under a nitrogen atmosphere. The obtained crystals contained 0.1% of reduced coenzyme Q_{10} and the weight ratio of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} of the obtained crystals was 99.4/0.6.

(Example 1)

The reduced coenzyme Q_{10} (reduced coenzyme Q_{10}/oxidized coenzyme Q_{10}=99.4/0.6) containing 1.5 wt% of reduced coenzyme Q_9 obtained in Production Example 3 and crystals of reduced coenzyme Q_{10} (reduced coenzyme Q_{10}/oxidized coenzyme Q_{10}=99.4/0.6) free of reduced coenzyme Q_9, which were obtained in Production Example 1, were preserved in a condition exposed to air at 25°C. The results of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} ratio after the lapse of 24 hr are shown in Table 1.

Table 1

	weight ratio of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10}
reduced coenzyme Q_{10} containing 1.5% of reduced coenzyme Q_9	96.7/3.3
reduced coenzyme Q_{10} free of reduced coenzyme Q_9	95.5/4.5

(Example 2)

50 mg of the reduced coenzyme Q_{10} (reduced coenzyme Q_{10}/oxidized coenzyme Q_{10}=99.4/0.6) containing 1.5 wt% of reduced coenzyme Q_9 obtained in Production Example 3 or 50 mg of reduced coenzyme Q_{10} (reduced coenzyme Q_{10}/oxidized coenzyme Q_{10}=99.4/0.6) free of reduced coenzyme Q_9, which were obtained in Production Example 1, was added to 5 g of ethanol and stirred in the air at 25°C. The results of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10} ratio after stirring for 6 hr are shown in Table 2.

Table 2

	weight ratio of reduced coenzyme Q_{10}/oxidized coenzyme Q_{10}
reduced coenzyme Q_{10} containing 1.5% of reduced coenzyme Q_9	90.2/9.8
reduced coenzyme Q_{10} free of reduced coenzyme Q_9	87.2/12.8

(Example 3)

Crj:CD (SD) rats (5-week-old, 15 males, 15 females, body weight 260 g - 300 g) were divided into 3 groups (5 per group) for each of male and female. A first group was used as a control group and corn oil (3 ml/kg) was orally administered once a day for 14 days. A second group was orally administered a corn oil solution of the reduced coenzyme Q_9 obtained in Production Example 2, which was prepared to meet the dose of reduced coenzyme Q_9 of 600 mg/kg, once a day for 14 days at a dose of 3 ml/kg. A third group was orally administered a corn oil solution

of reduced coenzyme Q_{10} obtained in Production Example 1, which was prepared to meet the dose of reduced coenzyme Q_{10} of 600 mg/kg, once a day for 14 days at a dose of 3 ml/kg. At 24 hr after the final administration, blood samples were collected to give plasma samples. Using HPLC, the concentration of coenzyme Q in the obtained plasma was measured. The results are show in Fig. 1.

In Fig. 1, the vertical axis shows the concentration of total coenzyme Q in the plasma, and each bar shows the average ±standard deviation. As is clear from Fig. 1, in both male and female, the concentration of total coenzyme Q in the plasma increased in the reduced coenzyme Q_9 administration group as compared to the reduced coenzyme Q_{10} administration group.

(Preparation Example)

To a mixture of canola oil, diglycerol monooleate (Poem DO-100 V manufactured by Riken Vitamin), hydrogenated oil, bees wax and lecithin were added crystals of reduced coenzyme Q_{10} containing 0.6 wt% of oxidized coenzyme Q10 and 0.1 wt% of reduced coenzyme Q_{11}, and a soft capsule of gelatin containing 30 mg of reduced coenzyme Q_{10} and having the following formulation was prepared by a conventional method.

reduced coenzyme Q_{10}	10.0 wt%
diglycerolmonooleate	32.0 wt%
canola oil	33.0 wt%
hydrogenated oil	17.0 wt%
bees wax	6.0 wt%
lecithin	2.0 wt%

(Example 4) (oral absorbability test)

Crj:CD(SD) rats (about 77-week-old, 10 male rats) were prepared and reduced coenzyme Q_{10} was orally administered to 5 of them, and a mixture of reduced coenzyme Q_{10} and reduced coenzyme Q_{11} (containing 0.1% of reduced coenzyme Q_{11}) was orally administered to the remaining 5 of them, each as a 25 mg/ml soy bean oil solution at a dose of 4.0 ml/kg. At 2 hr from the administration, blood was drawn and centrifuged to give plasma

samples. Using HPLC, the concentration of coenzyme Q_{10} in the obtained plasma was measured. The results are shown in Fig. 2. As is clear from Fig. 2, the concentration of coenzyme Q_{10} in the plasma was about 3.4 μg/ml in the administration of both reduced coenzyme Q_{10} and a mixture of reduced coenzyme Q_{10} and reduced coenzyme Q_{11}.

While some of the embodiments of the present invention have been described in detail in the above, those of ordinary skill in the art can enter various modifications and changes to the particular embodiments shown without substantially departing from the novel teaching and advantages of the present invention. Such modifications and changes are encompassed in the spirit and scope of the present invention as set forth in the appended claims.

This application is based on application No. 2006-126897 filed in Japan, the contents of which are incorporated hereinto by reference.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

The claims defining the invention are as follows:

1. A method for stabilizing reduced coenzyme Q_{10}, comprising achieving the co-presence of the following (a) and/or (b):

(a) not less than 0.6 wt% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and

(b) reduced coenzyme Q_{11}.

2. The method of claim 1, wherein the amount of the aforementioned (a) reduced coenzyme Q_9 is not less than 1 wt%.

3. The method of claim 1 or 2, wherein the aforementioned (a) reduced coenzyme Q_9 and (b) reduced coenzyme Q_{11} are separately prepared and added.

4. The method of claim 1 or 2, wherein the co-presence is achieved by reducing the oxidized coenzyme Q_{10} comprising oxidized coenzyme Q_9 and/or oxidized coenzyme Q_{11}.

5. The method of any one of claims 1 to 4, wherein the co-presence is achieved under a deoxygenation atmosphere.

6. A reduced coenzyme Q_{10}-containing composition comprising the following (a) and/or (b) in combination:

(a) not less than 1.5 wt% to not more than 99% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and

(b) reduced coenzyme Q_{11},

wherein not less than 0.01 wt% of reduced coenzyme Q_{10} is contained in the composition.

7. The composition of claim 6, wherein the reduced coenzyme Q_{10} is a crystal.

8. The composition of claim 6, wherein the reduced coenzyme Q_{10} is dissolved or suspended in a solvent.

9. The composition of claim 6, wherein the reduced coenzyme Q_{10} is a melt.

10. The composition of claim 6, which is in a form administrable to a mammal and comprises reduced coenzyme Q_{10} as an active ingredient.

11. The composition of claim 6, comprising at least one kind selected from the group consisting of an excipient, a disintegrant, a lubricant, a binder, an antioxidant, a coloring agent, an anticoagulant, an absorption promoter, a solubilizing agent for the active ingredient, a stabilizer and an active ingredient other than reduced coenzyme Q_{10}.

12. The composition of claim 11, which is a capsule.

13. The composition of claim 12, wherein the capsule is a microcapsule, a soft capsule or a hard capsule.

14. A method for producing a reduced coenzyme Q_{10}-containing composition comprising the following (a) and/or (b) in combination:

(a) not less than 0.6 wt% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and

(b) reduced coenzyme Q_{11},

which comprises separately preparing and adding (a) and/or (b).

15. A method for producing a reduced coenzyme Q_{10}-containing composition comprising the following (a) and/or (b) in combination:

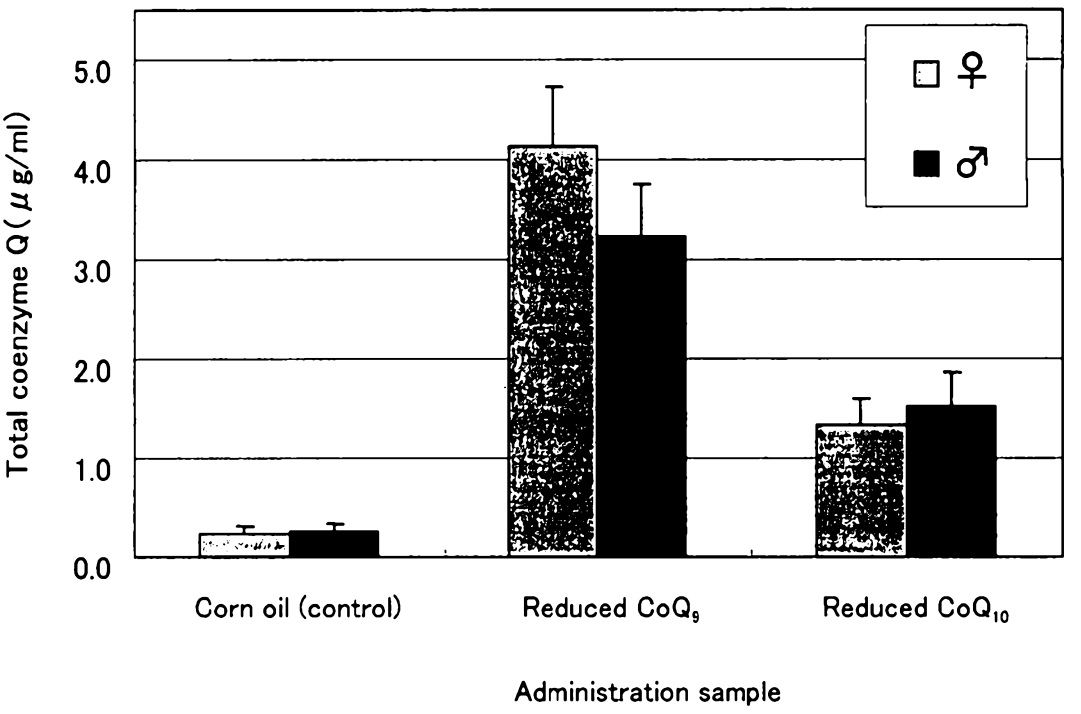
(a) not less than 0.6 wt% of reduced coenzyme Q_9 relative to reduced coenzyme Q_{10}, and

(b) reduced coenzyme Q_{11},

which comprises reducing oxidized coenzyme Q_{10} containing oxidized coenzyme Q_9 (not less than 0.6 wt% relative to oxidized coenzyme Q_{10}) and/or oxidized coenzyme Q_{11}.

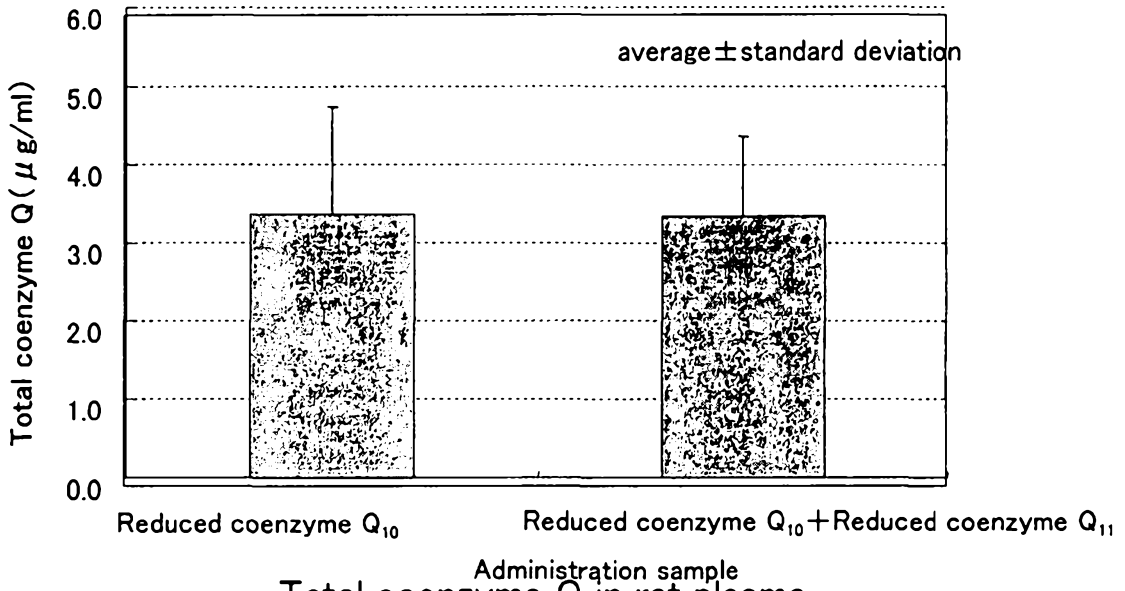
16. The method of claim 1, 14 or 15, or the reduced coenzyme Q_{10}-containing composition of claim 6, substantially as hereinbefore described with reference to any one of the Examples.

FIG. 1



Total coenzyme Q in rat plasma

FIG. 2



Total coenzyme Q in rat plasma