Title

Pharmaceutical Compositions Containing Polydatin or Its Salts and Their Application

Background of the Present Invention

Field of Invention

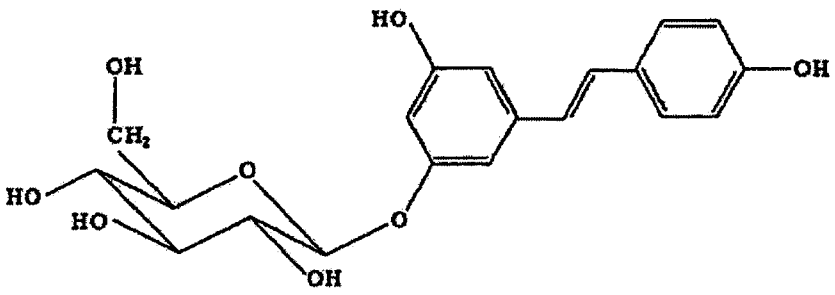
The present invention relates to a pharmaceutical composition containing polydatin or its salts and/or pharmacologically acceptable vehicle for improving microcirculation, and further relates to the preparation and making of the pharmaceutical composition of the present invention and the function of the treatment or prevention of related diseases of occlusion of microcirculation through the application of the composition of the present invention. The composition of the present invention is useful in treating or preventing the obstructive microcirculation related diseases such as shock, myocardial ischemia, brain hypoxia, diabetes complication, glaucoma, obstructive microcirculation induced impaired hearing, hemorrhoid, thighbone ischemia, obstructive vasculitis, cirrhosis, chronic ulcer, and skin burn.

Description of Related Arts

Physiology researches show that the physiological function of the microcirculation mainly includes transporting oxygen, nutrients, physiological regulating active substances to cells, and removing metabolic wastes so as to maintain the normal activities of life. Many kinds of diseases are related to or arisen from the abnormal microcirculation, such as acute inflammatory diseases, traumatism, shock, chronic ulcer, cirrhosis, cardiovascular diseases, and diabetes mellitus. Therefore, improving the microcirculation is a very important and meaningful subject in the treatment and prevention of many diseases, and it is a highly recognizable subject in the medical and pharmaceutical industry for finding an effective medication for improving microcirculation.

Anisodamine hydrobromide, Atropine and Anisodine are the exemplary conventional medications for improving the microcirculation system, which share the common characteristics of having the effect of dilation of capillary, increasing the blood flow of tissues and organs. They are widely used in the treatment of different diseases.

Polydatin was first found in the plant Polygonum cuspidatum Sieb. Et Zucc. in the 60's in the 20 century (Nomura, 1963), and was then found in other plants such as peicin, grape and peanut. The chemical formula of polydatin is 3, 4', 5-trihydroxy-trans-stilbene-3-_-D-glucose, where the 3, 4', 5-trihydroxy-trans-stibene is also called resveratrol. The chemical structure of polydatin is shown as follows:



Since the 70's of the 20 century, a variety of researches of the pharmaceutical effect and activities of polydatin have been conducted in China. It is found that polydatin has the effect of lowering the cholesterol level of blood, e.g. polydatin 2.2mg/kg/d P.O. could lowering the total cholesterol, LDL/HDL cholesterol ratio, and blood platelet aggregation rate of a hyperlipoidemia patient (ZHANG, Pei Wen, 1995), the effect of inhibiting the aggregation of blood platelet and the formation of thrombus, e.g. 6~100 mol/L polydatin could inhibit the platelet aggregation and the production of thromboaxane B_2 (B_2 thrombus) which are induced by AA and ADP (SHAN, Chun Wen, 1993), the effect of inhibiting blood platelet aggregation induced by adrenaline (YANG, Su Qin, 1992), the effect of inhibiting the blood platelet aggregation and carotid thrombosis from endothelial damage in rabbit (by WANG, Yue Zhong, 1995), the effect of preventing platelet from deformation and inhibiting release reaction of platelet (by LIU, Lian Pu, 1998), the effect of reducing adhesion rate between neutrophils and endothelial cell (by JIN, Chun Hua, 1998), the positive inotropic effect (JIN, Xing Zhong, LUO, Su Fang, 1992), the effect of increasing the frequency and extent of contractility on cultured myocardial cells (JIN, Chun Hua, 2000), the effect of vascular dilation such as dilated pulmonary arteries in vitro (LUO, Su Fang, 1992), the effect of non-competitive

inhibition on the contraction of aorta strip induced by histamine (WANG, Yue Zhong, 1994), the effect of anti-oxidation such as the inhibiting or scavenging effect on free radicals induced by respiratory burst of PMNs from human blood, Xanthin-Xanthin oxidase system, and VitC-Cu^{2+} system (JIN, Wei Jun, 1993), the protective effect on intestinal and multi-organs injuries induced by intestinal ischemia reperfusion in rabbit (XIE, Zhong Lin, 1997), the protective effect on lungs injury induced by endotoxin in rats (MO, Guo Yu, 1993), the effect of inhibiting increase in endothelin concentration of external blood flow induced by damages and decreasing the level of carbon monoxide (ZHAO, Wu Min, 1998), the effect of regulating complementary activities for patients with burnt (XU, Chuan Lin, 1994). Furthermore, polydatin has liver protective function (HUANG, Zhao Sheng, 1998), and regulatory effect on immune system (LUO, Rong Jiang, 1992).

Recently, many researches on the aglycon of polydatin, namely resveratrol, have been carried out and attracted international attention. 'France paradox' has been proposed in 1992 and the cardiovascular protective function of resvertrol has been reported. Then, more documentations reported the pharmaceutical activity of resvertrol, such as, report of the anti-oxidative function and inhibiting effect on LDL peroxidation for preventing arteoclerosis (Pace-Asciak, 1996), and report on inhibiting the formation and developing of tumor (Jang M, Udeani GO et, Science 1997; 275: 218).

Recently, many patents related to resveratrol have found. For example, the PCT application WO 01/30336 A2 has disclosed the use of resvertrol for treating epidermal diseases, the PCT application WO 01/91714 A1 has disclosed the use of resvertrol in cosmetic products for treating dandruff or scurf, the PCT application WO 00/38620 has disclosed the use of resvertrol on treating periodontal diseases, the PCT application WO 00/12534 has disclosed the use of stilbene composition in treating hepatitis, the European patent EP 1138323 A2 has disclosed the use of resvertrol on treating eczema and psoriasis, the US patent US 6008260 A has disclosed the use of resvertrol on preventing tumor, the PCT application WO 00/44370 has disclosed the use of resvertrol derivative on treating osteoporosis and high blood pressure, the China patent 00121100.5 has disclosed the extraction of resvertrol and polydatin, the China patent 99115156.9 has disclosed the extraction of resvertrol from polydatin, the China patent 00113914.2 has disclosed the production method of cell having the composition resvertrol.

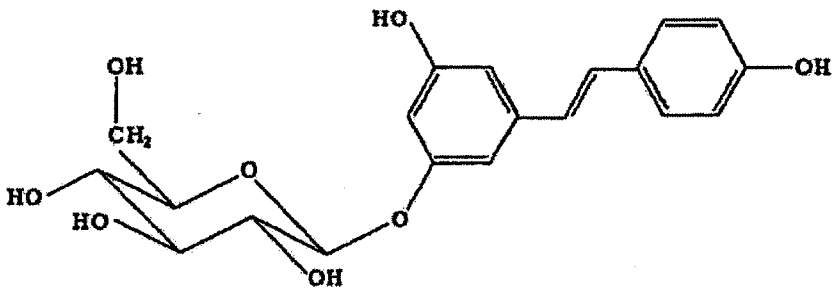
However, reports of composition containing polydatin or its derivatives for improving microcirculation and treatment or preventing shock symptoms is not found. Moreover, the water solubility of polydatin is relatively poor which indicated there is some technical difficulties composition containing polydatin for venous injection. The polydatin used for venous injection is not found in different documentation in patent or patent.

Summary of the Present Invention

A main object of the present invention is to provide a pharmaceutical composition comprising a quantity of polydatin or a quantity of pharmacologically acceptable salt of polydatin for improving the microcirculation. The pharmaceutical composition is useful in treating or preventing the diseases related of obstructive microcirculation which comprise the step of administration a composition comprising an effective quantity of polydatin or salt of polydatin to patients in needed.

Another object of the present invention is to provide a method of preparing a composition comprising polydatin or a pharmacologically acceptable salt thereof for improving microcirculation.

Accordingly, in order to accomplish the above objects, the present invention provides a pharmaceutical composition which is useful in treating or preventing obstructive microcirculation related diseases such as myocardial ischemia, wherein the composition comprises an active ingredient of polydatin or a pharmacologically acceptable salt thereof, and one or more one vehicle such as carriers and/or excipients. The chemical formula of polydatin is 3, 4', 5-trihydroxy-trans-stilbene-3-_-D-glucose.



The salt of polydatin is defined as a salt or an ester formed by polydatin and an appropriate acid including an organic acid or an inorganic acid, or and an appropriate alkaline including an organic or an inorganic alkaline.

One of the embodiments of the present invention is to provide a composition comprising polydatin or pharmacologically acceptable salts thereof which is applied parenterally.

wherein the composition which is applied parenterally may be in the forms of solution, or an appropriate carrier such as injection solution, injection powder adapted for making an aqueous solution, or a frozen dry injection powder.

A preferred solvent of the aqueous solution of the present invention is physiological buffer or physiological saline which is physiologically applicable to a body. When making the aqueous solution for injection, the pH of the aqueous solution may be suitably adjusted such that the aqueous solution is neutral or alkaline under acceptable pharmacological conditions. For example, a range between pH 7.0 and pH 10.0 is used to increase the solubility of the active composition. The pH is preferably adjusted to pH 8.0 to 9.5 by sodium carbonate (Na_2CO_3), sodium bicarbonate ($NaHCO_3$), or sodium hydroxide (NaOH), or a PBS buffer having a pH range between 8.0 and 9.5.In one of the embodiment of the present invention, the aqueous solution comprises 10 to 30% propandiol and 30 to 50% ethanol, and that the aqueous solution is diluted 25 to 50 times which is applicable to venous, muscular, or intravenous injection.

The aqueous solution of the present invention may comprise an appropriate solubilizing agent, a lacquer solvent or a cosolvent for increasing the stability and solubility of the active composition of the present invention. For example, the aqueous solution comprises a predetermined quantity of low alcohol such as 5 to 20% 1, 2-propandiol which is capable of increasing the solubility of the active composition of the present invention, and a predetermined quantity of superficial active agent such as 0.1 to 1% Tween 80 (Polyoxyethylene sorbitan monooleat) which is capable of increasing the stability of the aqueous solution. The solvent may also be a cosolvent system comprising propandiol, manitol, non-polar superficial active agent, hydrated organic polymer and water. The cosolvent system is in aqueous state.

A process of making the lyophilization powder of the present invention comprises the step of providing an aqueous solution of the active ingredient of the present invention and lyophilizatiing under an appropriate condition for lyophilization.

A composition of the present invention may be prepared into a suspension solution by dispersing the active composition of the present invention into lipophilic solvent or carrier. Examples of the lipophilic solvent or carrier include fatty oil or fatty acid ester such as triacylglycerol or liposome. The suspension may further comprise components which increases the viscosity such as sodium carboxyl methyl cellulose, sorbitol, or glucosans. An appropriate stabilizing agent or solubility improving agent may be added for making concentrated aqueous solution.

The composition for external application preferably comprises the active ingredient having a unit dose comprising polydatin or its salt between the range of 1.0-1000mg and the preferred unit dose is between 50 mg and 250 mg.

A second embodiment of the present invention is providing preparation for oral administration which comprises polydatin or its pharmacologically acceptable salts.

The composition of the present invention for oral application may be in the form of tablet, pill, granule, capsule, solution, gel, syrup, and suspended solution.

A method of making the composition of the present invention for oral application may comprise a step of adding an appropriate excipient such as microcrystallized cellulose, sucrose, lactose, glucose, starch, and manitol, binding agent such as syrup, Arabic gum, glutin, sorbitol, tragacanth gum, methyl cellulose and polyvinyl pyrrolodione; adding an appropriate disintegrating agent such as starch, carboxymethyl cellulose and its calcium salt, microcrystalline cellulose, polyethylene glycol, cross-linked polyvinyl pyrrolidone, agar, alginic acid or its salt such as sodium alginate; adding an appropriate glidant such as talc powder, magnesium stearate, calcium stearate, and silica, lubricating agent such as magnesium stearate, sodium luarate, and glycerol, or the like. The method may also comprise the steps of mixing the active ingredient and a solid vehicle and optionally grounding to a mixture, if necessary, the mixture may be granulated. The granule may be further made into a tablet or a tablet core for coating, and the tablet core is then properly coated by a coating materials such as concentrated sugar solution which optionally contain materials selected from the group

comprising Arabia gum, talc, polyvinyl pyrrolidone, resin of carboxyl polymer preferrably carbopol, polyethylene glycol, and/or titanium dioxide, lacquer solution, and a suitable organic solvent or solvent mixture. The mixture in the forms of tablet or pill may combine with a dying agent or pigment for distinguishing or representing a different dosage group.

The forms of oral administering composition further include capsule made with gelatin, and soft capsule made from gelatin and plasticizing agent. The capsule may comprise active ingredient and a second ingredient preferably a filling agent such as lactose, binding agent such as starch and/or lubricating agent such as talc or magnesium stearate, and stabilizing agent. A soft capsule with active ingredient may be dissolved or suspended in suitable solution such as fatty oil or aqueous polyethylene glycol. Furthermore, it may contain stabilizing agent or lacquer solvent.

The oral administrative composition of the present invention is preferred to have an active ingredient in the quantity of unit dose, the unit dose can be polydatin or its salt in the range of 1.0 to 1000 mg, and preferably of 50 to 250 mg.

The composition of the present may also be in the form of a rectal suppository for rectal administration comprising polydatin or its salt in the range of 1.0 to 1000 mg and a suppository agent such as coconut oil or other glyceride.

The composition of the present invention may also be localized administrative agent such as paste, cream, sticker, film former (as a coating agent) comprising polydatin or its salt in the range of 1.0 to 1000 mg, and common supplementary substances such as Vaseline, glycerol, sodium lauryl sulfate, mono stearo glyceride, acetyl cellulose, bubblering oil, paraffin oil, and lanonine.

The method of administration of the composition of the present invention includes oral administration, eye drops administration, rectal suppository, membrane transdermally administration, local administration, or intestinal administration; parenteral administration such as intramuscular, intravenous, and intramarrow injection, and intrathecal or direct intraventricalur, intravenous, intraperitoneal or intraocular injection.

The composition of the present invention has significant dilation effect on capillaries, lowering the blood viscosity level of capillaries, inhibiting the blood cell aggregation and adhesion, increasing the microcapillaries dilation rate, and hence have significant effect on improving the microcirculation and is useful in treatment or preventive measure of microcirculation obstructive disease.

The composition of the present invention can also be used for preventing or treating shock.

One of the symptoms of shock is microcirculation obstruction which induces insufficient irrigation or circulation of blood to important organs and may result in deterioration of function of organs. The active composition of the composition of the present invention is capable of exerting dilating the microvascular vessels of animals, increasing the opening rate of capillaries of organs, increasing difference pressure of arterial blood, thus is capable of effectively improving the blood circulation for different organs under shocking conditions and increasing the animal survival rate in the shock model experiment.

In the treatment for shock, intravenous administration is preferred such as intravenous injection or instillation. The dosage of active ingredient depends on the body weight, age, body conditions and is decided by a physician. For an adult, a preferred suitable dose is about 20 to 600mg per dose, preferably 80 to 300mg per dose.

The present invention is useful to treating or preventing cardiovascular and cerebral vascular diseases.

Cardiovascular and cerebral vascular diseases are usually related to microcirculation obstruction. For example, cerebral hypoxia, and insufficient blood flow resulted from insufficient supply of blood such as myocardial ischemia are diseases related to microcirculation obstruction. The active ingredient of the composition of the present invention can improve the microcirculation and thus improve the blood flow to heart and brain such that the aim for treating or preventing cardiovascular and cerebral vascular diseases is achieved.

When the composition of the present invention is used for treating and/or preventing vascular diseases, the composition can be in the form of oral administrable

medication or medication for parenteral use. The appropriate dosage is decided by practitioner according to the weight, age, body conditions of the patient. The appropriate dosage for an adult is 20-600mg per day which can be applied in a single dose or divided into several doses. The preferable dose is 20-80mg per application, at a frequency of 2-3 doses for day.

The present invention is useful as a medication for treatment and preventive measure for some of the obstructive diseases of sense organs.

Some of the disorders of sense organs such as decrease in visual acuity resulted from microcirculation obstruction, or deaf caused by microcirculation obstruction. The active ingredient of the pharmaceutical composition of the present invention can improve the circulation of these sense organs and thus treating and preventing the visual and hearing obstructive diseases.

When the composition is used for treating or preventing visual and hearing diseases in eye and ear, the applications of the composition of the present invention can be applied as system administration such as oral administration or venous administration, and as localized administration such as eye dropping and intraocular injection. The appropriate dosage is decided by practitioner according to the weight, age, body condition of the patient. In the application as system administration, the appropriate daily dosage is between 20 and 600 mg which can be applied as a single dose or divided into separated dose.

The composition of the present invention can be used as a medication for treatment and preventive measure for complications of diabetes mellitus.

The obstructive metabolizability of diabetes mellitus patients may result in pathological changes of nerve or blood vessel in some tissues or organs, and furthermore result in some complications, such as the obstruction of retina, cerebrovascular disease and cardiopathy etc. Just as said above, the composition of the present invention is valid in treatment or preventive to all these diseases.

As the medicine for treatment or preventive to the complications of diabetes mellitus, the composition of the present invention can be applied as system administration, such as oral administration or venous administration. The appropriate

dosage is decided by practitioner according to the weight, age, body condition of the patient. To an adult, the appropriate daily dosage is between 20 and 600 mg.

The composition of the present invention can also be used for treating or preventing other related diseases of microcirculation obstruction. For example, the composition of the present invention can be used for venous thrombosis, external hemorrhoid caused by blood clot, skin damage or burn. The application of treating and preventing these diseases by the composition of the present invention can be system administration or localized administration.

The present invention is first using polydatin composition for improving the microcirculation in the pharmaceutical mediation, such that can be used for treating and preventing a variety of microcirculation obstructive diseases. In those intravenous medication, since the solubility of polydatin is relatively poor, under normal solubility condition and medication volume, it is difficult to provide an effective quantity of active composition in its aqueous solution. The present invention comprises alkaline solvent and solubilizing agent for effectively increasing the solubility of polydatin.

Detailed Description of the Preferred Embodiment

These and other objectives, features, and advantages of the present invention will become apparent from the following detailed description, the accompanying drawings, and the appended claims. However, the description of the embodiments are not the restrict of claims of the present patent.

Embodiment 1: Preparation of polydatin aqueous solution for injection.

Embodiment 1-1: According to a first exemplary illustration of the first embodiment, a process of making an aqueous solution for injection is described wherein the aqueous solution has

PRESCRIPTION		
Polydatin	40	g
NaOH aqueous solution at pH 8.5	8	L
3.6% NaCl aqueous solution to	10	L

Divided into	1000	Units

The process of making an aqueous solution for injection comprises the steps of dissolving 40g polydatin in 8 L NaOH aqueous solution at pH 8.5; adding a quantity of 3.6% NaCl aqueous solution until the total volume is 9.8L; adjusting the pH to 8.5 and adding 3.6% NaCl aqueous solution until the total volume is 10L; filtering using 0.22_m microfilter membrane; and dividing the solution into 1000 units and keeping in ampoules or bottles.

Embodiment 1-2: According to a second exemplary illustration of the first embodiment, a process of making an aqueous solution for injection is described wherein the aqueous solution has

PRESCRIPTION		
Polydatin	80	g
NaOH aqueous solution at pH 8.5	6	L
Propandiol	2	L
Tween 80	50	ml
3.6% NaCl aqueous solution to	10	L
Divided into	1000	Units

The process of making an aqueous solution for injection in the embodiment 1-2 comprises the steps of dissolving 40g polydatin in 2L propandiol solution; adding 50ml Tween 80 and NaOH aqueous solution sequentially and mixing; adding a quantity of 3.6% NaCl until the total volume is 9.8L; adjusting the pH to 8.5 and adding NaCl aqueous solution until the total volume is 10L; filtering using 0.22_m microfilter membrane; and dividing the solution into 1000 units and keeping in ampoules or bottles.

Embodiment 1-3: According to a third exemplary illustration of the first embodiment, a process of making an aqueous solution for injection is described, wherein the aqueous solution has

PRESCRIPTION		
Polydatin	100	g
Anhydrous alcohol	2250	ml
Propandiol	1000	ml
buffer solution of sodium carbonate to	5000	ml
Divided into	1000	Units

When being used for administration the aqueous solution in each unit is diluted 25 to 50 times by 0.9% sodium fluoride or 5% glucose injection solution.

The process of making an aqueous solution for injection in the embodiment 1-3 comprises the steps of dissolving 20g polydatin in 450ml anhydrous alcohol; adding 100ml buffer solution and mixing by ultrasound or stirring for 2 to 5 minutes such that the polydatin is dissolved; adding 200ml propandiol and the remaining buffer solution until the total volume is 1L; filtering using 0.22_m microfilter membrane; and refilling nitrogen and dividing the solution into 1000 units which are kept in brown ampoules or bottles.

The buffer solution is prepared by mixing one unit of 0.1 mol/L sodium carbonate and nine units of 0.1mol/L sodium hydrocarbonate.

Embodiment 2: A process of making a lyophilized powder of polydatin for injection.

Embodiment 2-1:

A process of making a polydatin solution is illustrated in embodiment 2-1. The process of making a polydatin solution in the embodiment 2-1 comprises the steps of dissolving 40g polydatin in 8L pH 8.5 NaOH aqueous solution; adding a quantity of 5% aqueous manitol solution until the total volume is 9.8L; adjusting the pH to 8.5 and adding 3.6% NaCl aqueous solution until the total volume is 10L; filtering using 0.22um microfilter membrane; and dividing the solution into 1000 units and keeping in vial for dry powder.

A process of freeze dry for lyophilization is also illustrated in the embodiment 2-1, comprising the step of obtaining the solution obtained from the process of making a polydatin solution, and placing the solution in a freeze dry condition with a temperature at –35_ such that the solution is kept in –30_ for 3 hours; and the condensation temperature is at –40_, then vacuum pumping and increasing the temperature to 40_ gradually such that the frozen solution is increased gradually; drying the frozen solution and that the lyophilized product is obtained. The product can then be packed and pressed with piston, enclosed and labeled as a polydatin injection powder.

The powder is adapted for dissolving in normal saline for injection use.

Embodiment 2-2:

A process of making a polydatin solution is illustrated in embodiment 2-2. The process of making a polydatin solution in the embodiment 2-2 comprises the steps of dissolving 80g polydatin in 8L pH 9.5 NaOH aqueous solution; adding a quantity of 5% aqueous manitol solution until the total volume is 9.8L; adjusting the pH to 8.5 and adding 3.6% NaCl aqueous solution until the total volume is 10L; filtering using 0.22_m microfilter membrane; and dividing the solution into 1000 units and keeping in vial for freeze dry powder.

A process of freeze dry is also illustrated in the embodiment 2-2, comprising the step of obtaining the solution obtained from the process of making a polydatin solution, and placing the solution in a freeze dry condition with a temperature at –30_ such that the solution is kept in –30_ for 3 hours; and the condensation temperature at –40_, vacuum pumping and increasing the temperature to 40_ gradually such that the frozen solution is increased gradually; drying the frozen solution and that the freeze dry product is obtained. The product can then be packed and pressed with piston, enclosed and labeled as a polydatin injection powder. The powder is adapted for dissolving in physiological saline for injection use.

A process of making an injection solution of the present invention is illustrated in the embodiment 2-2, comprising the steps of mixing 2L propandiol and 500ml 0.5% hydrochloric acid; adding a predetermined quantity of physiology saline such that the total volume is 10L, filtering using 0.22_m microfilter membrane; and dividing the solution into 1000 units and keeping in vial. Each of the vials comprises 10ml of injection solution.

A package comprising a 10ml injection solution and a unit of freeze dry powder is preferred such that the freeze dry powder is capable of dissolving in the injection solution for injection.

Embodiment 3: A process of making a composition of polydatin tablet.

1000 tablet each having a composition of 50 mg polydatin are prepared according to the routine making process, and that the composition of polydatin comprises

Polydatin	50 g
Lactose	107 g
Starch	25 g
Polyvinyl pyrrolidone K30	16 g
Magnesium stearate	2 g
Total weight	200 g

The polydatin is mixed with lactose and starch to form a mixture. The mixture is transformed into a granule form by using polyvinyl pyrrolidone K30 and passing through sieve No. 16. After drying, the granule is mixed with magnesium stearate and pressed into a predetermined shape. Other polydatin in tablet form having different active composition of polydatin can be made by varying the ratio of the quantity of polydatin and vehicle, or the force of pressing device.

Embodiment 4: A process of making a composition of polydatin in capsule form.

The process is comprising the steps of: mixing a quantity of polydatin, a quantity of lactose, a quantity of microcrystalized cellulose, and a quantity of magnesium stearate. In the embodiment 4, 200 capsules having 50mg active composition of polydatin are prepared from

Polydatin	10 g
Lactose	19.5 g
Microcrystalized cellulose	10 g
Magnesium stearate	0.5 g
Total weight	40 g

Embodiment 5: A process of making a composition of polydatin in ointment form.

In embodiment 5, a 1% polydatin ointment is prepared from

Polydatin	1 g
Olive oil	10 g
White Vaseline	89 g

Total weight	100	g

The process is comprising the steps of: mixing and stirring a quantity of polydatin and a quantity of olive oil; and adding a quantity of dissolved white Vaseline while stirring; and mixing thoroughly. The ointment is then canned.

Embodiment 6: A process of making a composition of polydatin in suppository form.

In embodiment 5, a 1% polydatin suppository is prepared from

Polydatin	1	g
Glycerol	5	g
Glycerol gelatin	89	g
Total weight	100	g

The process is comprising the steps of: mixing and stirring a quantity of polydatin and a quantity of glycerol; and adding a quantity of dissolved glycerol gelatin while stirring; and mixing thoroughly. The suppository is then canned.

Embodiment 7: Therapeutic effect of composition of polydatin on hemorrhagic shock.

The observation is based on the experiment carried out comprising the steps of

(1) anaesthetizing two groups, namely a treatment group and a control group, of SD rats with Urethane Ketamine, inducing bleeding by intubulation at femoral artery and recording blood pressure; wherein femoral vein is used for medication and blood transfusion and cremasteric specimen is prepared by Baez method;

(2) inducing bleeding from femoral artery such that an average arterial blood pressure is maintained between 5.1 to 5.6kPa;

(3) administering a composition of polydatin injection through femoral vein after one hour wherein the dosage of the composition is 0.6ml/kg, that the concentration of polydatin is 4mg/ml and the dosage is 2.4mg/kg in the treatment group and the composition of polydatin is replaced by physiological saline in the control group;

(4) conducting blood transfusion after 20 minutes such that the 1/2 volume of blood loss due to bleeding is equal to the volume of blood loss due to blood transfusion; and

(5) observing for two hours and detaching the intubulation.

The records are made by using Olympus microscope, Hitachi monitoring system and physiological recording meter to observe and record microcirculation and blood dynamics. The survival period of each subject of the two groups are recorded.

Result:

(1) Survival period: a ratio of the survival time of the treatment group and the control group is larger than 5.5, wherein 9/10 of the treatment group has a survival period of 24 hours, 8/10 of the treatment group has a survival period of 48 hours, and 6/10 of the treatment group has a survival period of 72 hours. All the subjects in the control group die within 24 hours.

(2) Blood pressure: After experienced shock for 1 hour, the average arterial blood pressure is 5.3+0.2kPa. After 30 minutes of medication of polydatin, the arterial pressure is increased to 8.6+0.8kPa in the treatment group, while there is no significant difference in blood pressure in the control group receiving physiological saline.

(3) Diameter of micro blood vessel: After experienced shock for 1 hour, the diameter of micro-aneurysm is reduced to 63.3% of the diameter in average before shock. The diameter is then increased by 20.3% after medication of polydatin and there is no significant difference of diameter in the control group.

(4) Number of opening capillaries: Before shock, the number of open capillary is 5.1±0.4 per _m^2. After induced bleeding, the number of open capillary is decreased to 2.2±0.6 per _m^2. The number increased to 4.2±0.5 per _m^2 in 10 minutes after polydatin medication. There is no significant difference of number of opening capillaries in the control group before and after the administration of physiological saline.

Embodiment 8: Therapeutic effect of composition of polydatin on burn shock .

The observation is based on the experiment carried out comprising the steps of: anaesthetizing two groups, namely a treatment group and a control group, of SD rats with Urethane Ketamine, burning about 35% of body surface below waist for 30 seconds with 80_ water; administering 0.6ml/kg polydatin injection (comprising 4mg/ml polydatin and the dosage is 2.4mg/kg) by venous injection after half hour of burning in the treatment group and replacing the polydatin injection by physiological saline in control group.

Result: The average survival period of the treatment group is longer than 13.3 hours while the average survival period of the control group is 7.0±2.6 hours.

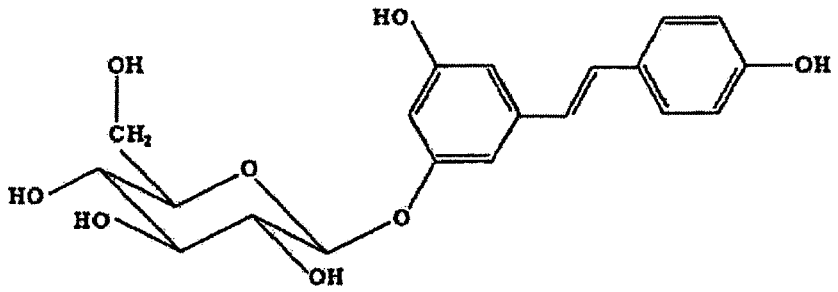
What is Claimed is:

Claim 1: A composition having the effect of improving the microcirculation, comprising:

an effective amount of active ingredient of polydatin or its pharmacologically acceptable salt ; and

pharmaceutically acceptable carrier and vehicle such that said carrier carries said active ingredient and said vehicle provides a medium for said active ingredient;

wherein said polydatin has a chemical formula of 3,4',5-trihydroxy- trans-stilbene-3-_-mono-D-glucoside and a chemical structure:



Claim 2: The composition, as recited in claim 1, having an injection form applicable for administration by injection.

Claim 3: The composition, as recited in claim 2, wherein said injection form is an aqueous solution.

Claim 4: The composition, as recited in claim 3, wherein said aqueous solution has a pH in the range between 7.0 and 10.0.

Claim 5: The composition, as recited in claim 3, wherein said aqueous solution has a pH in the range between 8.0 and 9.5.

Claim 6: The composition, as in claim 3, 4 or5, further comprising a quantity of propandiol having a concentration in the range between 5% and 50%.

Claim 7: The composition, as in claim 3, 4 or5,, further comprising a quantity of propandiol having a concentration in the range between 10% and 30% and a quantity of ethanol having a concentration in the range between 30% and 50%, wherein said

injection is adapted to be diluted 25 to 50 times for injection selected from the group of administration consisting of intravenous injection, intramuscular injection, and hypodermis injection.

Claim 8: The composition, as recited in claim 2, wherein said composition has a lyophilized powder form.

Claim 9: The composition, as recited in claim 1, wherein said composition has an oral administrative form.

Claim 10: The composition, as recited in claim 8, wherein said composition has a tablet form.

Claim 11: The composition, as recited in claim 8, wherein said composition has a capsule form.

Claim 12: The composition, as recited in claim 1, wherein said composition has a suppository form.

Claim 13: The composition, as recited in claim 1, wherein said composition has a a localized applicable form selected from the group comprising an ointment form, a cream form, a sticker form, and a paste form.

Claim 14: The composition, as recited in any one claim of 1~12, wherein said composition is manufactured for treating and preventing microcirculation obstruction related diseases including the group selected from shock, cardiac and cerebral vascular disease, sensory organ related disease, diabetes complications, vasculitis related to blockage of blood vessel, hemorrhoid related to microcirculation obstruction, skin injury and burn.

Claim 15: The composition, as recited in any one claim of 1~12, wherein said composition is in an unit dose and said unit dose comprises a quantity of active composition selected from the group of polydatin and a salt of polydatin having the same activity as said polydatin and said quantity of active composition is in the range between 1mg and 1000mg.

Claim 16: The composition, as recited in any one claim of 1~12, wherein having the effect of improving microcirculation wherein said composition is an active substance

used in a process of making a predetermined pharmaceutical composition for improving microcirculation.