

## Stroke, angiogenesis and phytochemicals

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## 1. ABSTRACT

Stroke, or brain attack, is the third leading cause of death and the leading cause of adult disability worldwide. There is a great demand for intervention therapy. Unfortunately, although more than 700 drugs that target neuroprotection showed beneficial effects in preclinical animal studies, none of them proved efficacious in treating stroke patients. There is recent interest in understanding mechanism for post-ischemic angiogenesis in the penumbra area, and correlation of the extent of angiogenesis with survival in stroke patients. It is postulated that besides replenishing oxygen and nutrients to ischemic tissue, angiogenesis may play a crucial role in neural protection and tissue recovery. Consequently, therapeutic agents to promote angiogenesis and formation of new vessels after stroke can offer promising approach. Several large population epidemiological and clinical studies have revealed a reciprocal relationship between intake of phytochemicals and incidence of stroke. However, the detailed cellular and molecular mechanisms leading to these beneficial effects remain to be elucidated. In this article, we review the current knowledge on phytochemicals and post-ischemic angiogenesis, and discuss the possibility of a combinatorial treatment, including neuroprotection, angiogenesis, neurogenesis, and phytochemicals regimen for stroke.

## 2. INTRODUCTION

Stroke (occlusion of cerebrovessels) is a clinical syndrome including focal infarction or hemorrhage in the brain. According to the National Institutes of Health, stroke is the third leading cause of death and the leading cause of adult disability in the United States. It is estimated that around 6.4 million people in the USA suffer strokes daily; of those, 2.5 million are males and 3.9 million are females. In the USA, approximately 795,000 patients suffer strokes every year (including 610,000 new and 185,000 recurrent cases), and about 20% of them die. Around 15 million people worldwide survive minor strokes each year (1). Unfortunately, besides the tissue-type plasminogen activator (tPA), no other treatment is available to limit brain damage. Because of the seriousness of the disorder and its prevalence, there is great need for intervention.

Recently, large population epidemiological and clinical studies have shown an inverse correlation between incidences for cardiovascular diseases (CVD) and the intake of vegetables, fruits, and tea as well as herbs (2 ~ 6). This beneficial effect on human health has been attributed largely to the bioactive ingredients in these botanicals (also known as phytochemicals). However, the exact mechanisms underlying the beneficial effects are largely unknown. Phytochemicals are nonnutritive bioactive plant

**Table 1.** Key steps in the evolution of angiogenesis

A.	Initiation phase: (1) Angiogenic factors release from inflammatory cells, and endothelial cells activation. (2) Activated endothelial cell releases proteases to degrade ECM.
B.	Propagation phase: (3) Branch points formation in the vessel wall. (4) Endothelial cells recruiting and migrating into the extracellular space. (5) Endothelial cells proliferation, differentiation and tubule-lumen structure formation.
C.	Maturation phase: (6) Re-synthesis of basement membrane and incorporation of pericytes. (7) Fusion with parental vessel and blood flow initiation.

substances including phenolic compounds, terpenes, betalains, and organosulfides (7). Since CVD are diseases of the heart and blood vessels, which also include stroke, it is important to understand the extent of dietary phytochemicals that may prevent and influence the outcome of these abnormalities.

### 3. STROKE

Stroke, or brain attack, is defined when the blood supply to some part of the brain is suddenly halted. This condition was attributed to the limitation of blood flow to the brain, as first described by Giovanni Battista Morgagni, the Father of Modern Anatomic Pathology, in 1761. Stroke can be due to ischemia (lack of blood flow) caused by blockage (thrombosis, arterial embolism or systemic hypoperfusion), or a hemorrhage (leakage of blood), which leads to rapid neural cell death and loss of brain functions. Symptoms in stroke include: (1) sudden numbness or weakness in the face, arm, or leg; (2) trouble with seeing, speaking, or walking; and (3) dizziness or severe headache with no known cause (NINDS). Epidemiological and clinical studies revealed several risk factors for stroke (8). Some are non-modifiable factors, such as age, sex, race, and family history, while others are modifiable factors, such as hypertension, diabetes, smoking, obesity, and atrial fibrillation. Although stroke ranked as the number three killer disease around the world, luckily, up to 80% of all strokes are preventable, and better control of the modifiable risk factors is likely responsible for the decline of the stroke death rate. Nearly one quarter of strokes occur in people under the age of 65, and in some cases even involving the teenage population. Intriguingly, the age threshold for stroke incidence is decreasing. There is evidence that risk factor profiles for stroke and mechanisms of ischemic injury differ between young and elderly patients (9). Therefore, there is a growing interest in studying the mechanisms that underlie stroke in young population.

The hypothetical cellular and molecular mechanism underlying stroke-induced cerebral infarct and neural cell death include: (1) energy failure; (2) acidosis; (3) glutamate excitotoxicity; (4) calcium overload; (5) ROS oxidative stress; and (6) others, such as inflammation, apoptosis, etc (9, 10 ~ 13). Currently, three major approaches have been used in treating acute stroke: neuroprotection; thrombolysis; and surgical clot removal. For the past few decades, despite promising results of neuroprotectants in preclinical stroke animal research, translation of experimental data into clinical therapy has been disappointing (14). One possible reason is the

heterogeneity of the disease in human population, which differs from studies using young animal models. It is conceivable that genetic variance between experimental animals and human plays an important role. For example, differences in scale, gray/white matter and neuron/glia ratios, circle of Willis/arterial/venous anatomy, heart beat and metabolic rates. Furthermore, one can limit all variables to the issue being tested in rodents; however, one cannot control or even recognize all possible variables in human conditions. Finally, certain quality-related sources of bias, such as: defects in statistical analysis, lack of blinding and randomization, lack of quality-control, and negative publication bias all limited a smooth translation of preclinical data into clinical settings (14, 15). Presently, the tissue-type plasminogen activator (tPA; alteplase; clot-dissolving drug) is the only FDA-approved thrombolysis treatment for acute ischemic stroke. However, due to the risk of intracranial hemorrhage and a narrow 3 h therapeutic window, only 3 to 5% of those who suffer a stroke could reach the hospital in time to be considered for this treatment.

### 4. ANGIOGENESIS

The development of vascular supply is a fundamental requirement for organ development and differentiation during embryogenesis as well as for healing wounds and reproductive functions in adults (16). Neovascularization is accomplished via the concerted efforts of two major cellular processes. The first is vasculogenesis, a *de novo* synthesis of endothelial cells from either angioblasts or hemangioblasts. The second is angiogenesis, which is the growth or derivation of vascular structures from preexisting vessels (17). Three forms of angiogenesis have been characterized: (1) remodeling of vessels into smaller ones (intussusceptive vascular growth); (2) endothelialization of a vessel growing both in length and width (arteriogenesis); and (3) sprouting angiogenesis which is the most common process in vascular remodeling. Angiogenesis involves multiple interactions among inflammatory cells, endothelial cells, surrounding pericytes, extracellular matrix (ECM), proteases and angiogenic cytokines/growth factors (18, 19). The key phases of angiogenesis are listed in Table 1.

Angiogenesis is a complex *in vivo* system involving developmental organ formation and adult physiological response, such as, menstruation, pregnancy, hair cycling, wound healing, bone fracture repair, and ischemia induced collateral formation. On the other hand, excessive angiogenesis is associated with several

pathological conditions, such as hemangioma, tumor growth, loss of central vision by choroidal neovascularization (diabetic vasculopathy), rheumatoid arthritis, and atherosclerosis (plaque neovascularization). Thus, angiogenesis needs to be tightly regulated and the detailed cellular and molecular mechanisms of angiogenesis need to be elucidated. In general, angiogenic activity is controlled by a delicate balance between angiogenic (positive) and angiostatic (negative) factors of blood vessel growth and is suppressed under normal physiological conditions.

### 4.1. Angiogenic factors

In 1948, Isaac Michaelson postulated that neovascularization was due to the release of a diffusible factor from the ischemic retina (20). Since this time, attempts to isolate this Michaelson x-factor have led to the discovery of a myriad of “angiogenic factors”. Folkman *et al.* (1971) reported the isolation of the first angiogenic diffusible factor, which was subsequently called the “tumor angiogenesis factor” (TAF) (21). Nevertheless, this was a mixture of carbohydrate, RNA, and protein. It was not until 1984 that the first purified angiogenic factor, also known as the fibroblast growth factor (FGF), was identified (22). Since then, a huge number of angiogenic inducers such as: vascular endothelial growth factor (VEGF), angiopoietins, platelet-derived growth factor (PDGF), angiogenin, angiotropin, transforming growth factors (TGF), tumor necrosis factor (TNF), placental growth factor (PIGF), integrins, ephrins, endoglin, cadherins, matrix metalloproteinase (MMP), plasminogen activator (PA), hepatocyte growth factor (HGF), epidermal growth factor (EGF), granulocyte-colony stimulating factor (G-CSF), interleukins, connective tissue growth factor (CTGF), stromal cell-derived factor-1 (SDF-1), hypoxia-inducible factor (HIF), cyclooxygenases-2 (COX-2), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), nitric oxide (NO), and chemokines were subsequently identified (16, 23 ~ 30).

Along with angiogenic factors, many angiostatic (anti-angiogenic) factors were also identified, e.g., angiostatin, endostatin, thrombospondin-1 (TSP-1), angiopoietin 2, pigment epithelium-derived factor (PEDF), interferon, krigle 5, tissue inhibitors of metalloproteinase inhibitors (TIMPs), plasminogen activator inhibitor (PAI), platelet factor-4 (PF4), prolactin 16kD fragment, thrombocyte factor 4 (TF4), interleukin-12, transforming growth factor-beta (TGF- $\beta$ ), retinoic acid (RA), somatostatin, 2-methoxyestradiol, interferon-alpha (IFN-alpha), IFN-gamma, IL-4, IL-12, IL-13 and leukemia inhibitory factor (LIF), tumstatin, brain-specific angiogenesis inhibitor 1 (BAI1), neuropilin 1, soluble VEGFR-1, and osteopontin (OPN). Although a large number of angiogenic and angiostatic factors have been recognized to play a role in development, cancer and cardiovascular diseases, only a few of them have been studied in the ischemic brain. Thus, the specific roles of these endogenous mediators in post-ischemic angiogenesis remain to be established (31, 32).

### 4.2. Angiogenesis after ischemic stroke

Among the different types of strokes, 87% are ischemic, 10% are intracerebral hemorrhage, and 3% are subarachnoid hemorrhage (1). Hemorrhagic stroke usually

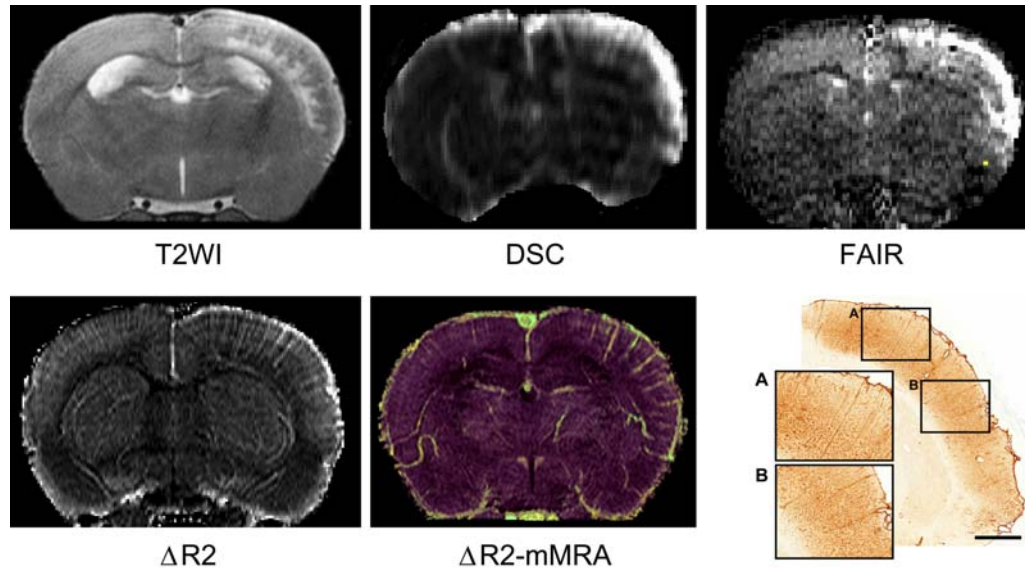
affects a larger area of the brain, is more severe, and carries a higher risk for death. This type of stroke is much less studied. In this review, we will focus primarily on the relationship between angiogenesis and ischemic stroke.

Acute ischemic stroke is the consequence of severe reduction of blood supply to the affected brain region. The resulting low tissue oxygen tension after ischemia often leads to compensatory neovascularization in order to meet the metabolic demand (33, 34). The extent of angiogenesis has been correlated to survival in stroke patients (35). Several putative angiogenic factors, including VEGF, bFGF, and angiopoietin, are up-regulated after cerebral ischemia (36 ~ 45). Interestingly, VEGF, bFGF and angiopoietin each showed a characteristic temporospatial profiles, suggesting different roles for these angiogenic factors during vessel remodeling (41, 42). The expression of these angiogenic genes is associated with an increase in vascular density (39, 41, 42) and CBF (42, 46). Despite the induction of angiogenic factors, several angiostatic factors are also up-regulated upon ischemic insult (42, 47). The mechanism underlying this post-ischemic induction of vascular remodeling genes is very complicated and poorly understood (43, 48, 49).

After ischemia, all three forms of angiogenesis are noted in the ischemic cerebral cortex at various times (40). Although hyper-perfusion has been documented in early post-ischemic time in animal stroke model, there is no consensus as to the beneficial or detrimental effects on the size of the eventual infarct (50). Various reperfusion-induced processes such as free radical formation (51), vasogenic edema and breakdown of the blood brain barrier (BBB) (52), enhancement of inflammatory processes (53), and secondary hemodynamic disturbances (54) may contribute to the reperfusion injury (55). However, a study by Manoonkitiwongsa *et al* (2001) suggests that ischemia-induced microvessels are formed to facilitate macrophage infiltration and removal of necrotic brain tissues (56). This is in-lined with the observation that regression of angiogenesis after ischemia is accompanied by tissue liquefaction (41). Whether enhancing and/or prolonging angiogenic sprouting can affect the ischemic outcome remains to be studied.

### 4.3. Therapeutic angiogenesis in ischemic stroke

Therapeutic angiogenesis is a clinical term referring to the enhancement of vessels growing within the ischemic tissue. Currently, there are three major ways to promote angiogenesis, namely, protein, gene, and cell therapies (57). The promising results of direct injection or gene transfer of angiogenic factors to reduce myocardial infarction and limb ischemic injury have attracted considerable attention of clinicians and scientists to test the phenomenon in stroke research. However, although similar approaches have been applied to treat ischemic stroke, the outcome has not been as great as in CVD. This is probably due to: (1) the unique structure of the blood-brain barrier (BBB) in the CNS-brain; (2) brain edema due to an increase in vascular permeability and intracranial pressure; (3) the time window mismatch between angiogenesis and neural cell death; (4) the decrease in ability for



**Figure 1.** Increasing the resolution of cerebral vascular image with the rapid advancement in MRI technology. T2W: T2-weighted image was used to evaluate cerebral infarct; DSC: dynamic susceptibility contrast was used to study relative cerebral blood volume (CBV); FAIR: flow-sensitive alternating inversion recovery was used to evaluate relative cerebral blood flow (CBF);  $\Delta R2$ : Transverse relaxation rate change in spin-echo was used to study blood volume in small vessels;  $\Delta R2$ -mMRA:  $\Delta R2$ -based, flow-independent microscopic magnetic resonance angiography was used to monitor cerebral vessels. Last, the laminin immunostaining for cerebral vessels. Bar = 1mm.

regeneration/angiogenesis with increasing age as well as other complications in elderly patients; and (5) concerns about the adverse effects of angiogenic factors such as hypotension and off-target tumorigenesis (58 ~ 62). Therefore, a better understanding of the cellular and molecular signaling of these angiogenic factors is needed before a successful therapeutic application and implementation into clinical settings. Also, there is a great demand for the development of non-invasive tools that could longitudinally monitor and quantify angiogenesis *in vivo*. The ability to accurately monitor and quantify angiogenesis would also allow drug efficacy to be evaluated at the early stage of treatment, as well as identifying patients that do not response to treatment.

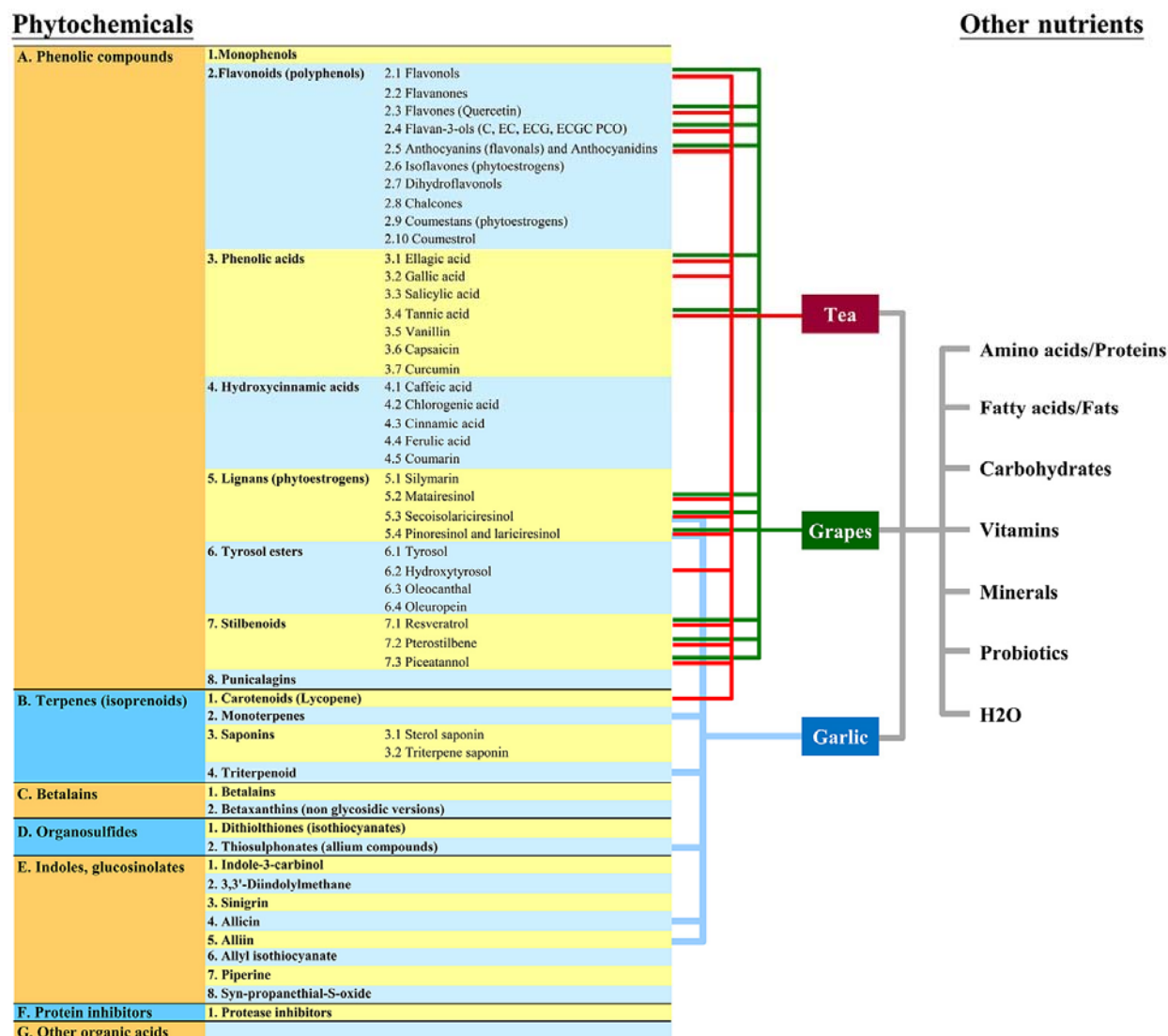
#### 4.4. Imaging post-ischemic angiogenesis by MRI

Several non-invasive imaging modalities have been employed to monitor *in vivo* vascular remodeling in diseased conditions. These include using magnetic resonance imaging (MRI), x-ray computed tomography (CT), single-photon emission computed tomography (SPECT), positron emission tomography (PET), ultrasound, and optical imaging (63, 64). Among them, MRI is the most prevailing one for monitoring vascular remodeling. The advantages of using MRI include non-invasive ionizing radiation, excellent delineation of anatomic structures that produce sectional images of equivalent resolution in any projections and multiple planes, providing full 3D data with similar spatio-temporal resolution, acquisition of various physiological parameters such as blood flow, blood volume, and diffusion of water, and advancing in contrast agents, all of which are well-tolerated by patients.

We have previously reported post-ischemic angiogenesis in a rat MCA occlusion model (41, 65). Surprisingly, this post-ischemic angiogenesis was rather short-lived and was completely terminated within a few weeks. Using diffusion- (DWI), perfusion- and T2-weighted MRI (T2WI), a delayed induction peak of both cerebral blood flow (CBF) and volume (CBV) could be observed in the ipsilateral cortex after transient focal brain ischemia *in vivo*. This increase is in accord with the induction of angiogenic factors and the progression of post-ischemic vascular remodeling (42, 46). Nevertheless, the spatiotemporal changes in vascular permeability, vascular density, and vessel size remain to be studied. Recently, with an advancement in contrast-enhanced MRI, we were able to discriminate signals from large vessels against small vessels-capillaries (66, 67; Figure 1). We further show that the increase in post-ischemic CBV can be divided into the early and late phases. The early phase of increased CBV is likely due to the improvement of collateral circulation (large vessels), and the late phase is attributed to the surge of angiogenesis (capillaries) (66). Furthermore, there was a prolonged increase in vascular permeability (probably due to BBB leakage) in the outer cortical layers where increased CBF and CBV were noted (66). However, whether this increase in vascular permeability is due to leakage of the newly formed capillaries or the existing vessels deserves further investigation.

#### 4.5. Angiogenesis, Neuroprotection and Neurogenesis

Despite that the extent of angiogenesis has been correlated with survival in stroke patients, this post-ischemic angiogenesis is short-lived and may completely terminate within a few weeks after ischemia. This



**Figure 2.** Representative phytochemicals and nutrients found in teas, grapes, and garlic. Tens to hundreds of different phytochemicals can be found in one plant. The classification of phytochemicals was adopted from Wikipedia (7).

observation is in-line with functional improvement in most stroke survivors occur during the initial months after the ischemic incidence (68). The molecular mechanism underlying this transient functional improvement is poorly understood. The BBB is a unique feature in the brain in which cerebral microvascular endothelial cells, astrocytes, pericytes, neurons, and the extracellular matrix constitute a “neurovascular unit” that is essential for the health and function of the CNS (69). Recent studies showed that many angiogenic factors also have neurotrophic effects. For example, bFGF not only is an angiogenic factor, but it may also be a neurotrophic factor for neuronal populations in CNS. The major source for bFGF is astrocytes, neurons, and endothelial cells (39). Intracisternal bFGF enhances functional recovery after ischemia by promoting the expression of the neuronal sprouting marker-GAP-43 (70).

VEGF also has been noted in cortical neurons, pial cells, and glial cells (42), and it has been shown that VEGF can protect neuronal cells against ischemic insults (71). Astrocytes have been shown to regulate cerebral blood flow through dynamic signaling within the neurovascular unit (72).

Neural stem cells (NSCs) are multipotent cells and arise from specific germinative zones in the central nervous system (CNS). These cells proliferate in response to growth factors like basic fibroblast growth factor (bFGF). It has been well-documented that stroke is associated with neurogenesis in the subependymal lining of the ventricles of lateral ventricle (SVZ). As the newborn neural progenitor cells migrate to areas of ischemic boundary, they mature and release angiogenic and neurotrophic factors and contribute

**Table 2.** Representative hormetic diets that modulate angiogenesis and their effectors

Foods and drinks	Phytochemicals	Pro-angiogenic	Anti-angiogenic
Grapes, red wine	Resveratrol	VEGF <sup>(1)</sup> , MMP2, MMP9, NO, PGC1, eNOS	VEGF <sup>(2)</sup> , MMP2, MMP9, NO
	Quercetin	VEGF <sup>(3)</sup> , HIF1	VEGF <sup>(4)</sup> , eNOS, MMP2, MMP9
Teas	Quercetin	VEGF <sup>(3)</sup> , HIF1	VEGF <sup>(4)</sup> , eNOS, MMP2, MMP9
	Catechin		VEGF <sup>(5)</sup> , MMP2
	Epicatechin(EC)	eNOS	MMP2
	EGCG	PI3K/AKT pathway, eNOS, NO, MMP9	VEGF <sup>(6)</sup> , MMP2, MMP9, bFGF, PDGFR, HIF1, VE-cadherin
Chocolate	Cocoa	NO, inducing cerebral vascular blood flow	ErB2(EGFR), MMP2
Ginkgo biloba	extract	VEGF <sup>(7)</sup>	VEGF <sup>(8)</sup> , PDGF, TGFb2
Ginseng	Ginsenoside-Rg1	HIF1, VEGF <sup>(9)</sup> , eNOS, NO, E-cadherin, FGFR-1	
	Ginsenoside-Rb1		PEDF
	Ginsenoside-Rb2		VEGF <sup>(10)</sup>
	Ginsenoside-Re	endothelial cell proliferation, migration	
	Ginsenoside-Rg3		VFGF <sup>(11)</sup> , MMP2, MMP9, bFGF, heparin
Danshen	Salviamic acid B	MMP2	VFGF <sup>(12)</sup> , HIF1
Danggui	extract	VEGF <sup>(13)</sup>	VEGF <sup>(14)</sup>
Rhodiola rosea	extract	VEGF <sup>(15)</sup> , HIF1, Flt-1, KDR, Tie-2	ID1, ID3
Astragali radix	Astragaloside	ZO-1, MMP2	MMP2, MMP9
	Calycosin	VEGF <sup>(16)</sup> , VEGFR1, VEGFR2	

Numbers in parentheses are representative reference specific for VEGF, and their PMID are listed below: <sup>(1)</sup>16198371, <sup>(2)</sup>15629234, <sup>(3)</sup>16611395, <sup>(4)</sup>19704917, 20804812, 14519939, <sup>(5)</sup>18562575, 17574044, <sup>(6)</sup>20346928, 17569617, 17451194, <sup>(7)</sup>19466634, <sup>(8)</sup>10744206, <sup>(9)</sup>17008323, <sup>(10)</sup>17502003, <sup>(11)</sup>18772102, <sup>(12)</sup>18622062, 12567275, <sup>(13)</sup>15015388, 17497682, <sup>(14)</sup>19228635, 19307054, <sup>(15)</sup>19326475, 19435557, <sup>(16)</sup>15998873

to the functional recovery after stroke (73, 74). Intriguingly, the migration neuroblasts are closely associated with cerebral vessels, as activated cerebral endothelial cells secrete the stromal-derived factor 1alpha (SDF-1alpha) to attract neuroblasts and guide them to the lesion site (74).

Based on these studies, there is strong evidence that angiogenesis, neuroprotection, and neurogenesis are tightly coupled. It is likely that ischemia induced angiogenic factors, such as bFGF and VEGF, are crucial for neuroprotection and neurogenesis. Further studies are worthwhile to delineate the relationship between angiogenesis and functional recovery.

## 5. PHYTOCHEMICALS (OR PHYTONUTRIENTS)

Natural products are chemical compounds or substances found in living organisms such as terrestrial plants, marine organisms, or microorganisms, and many have distinctive pharmacological effects. Based on their biological and geographical diversity, many natural products isolated from different sources contain novel and structurally unique chemical components. Natural health products are manufactured and sold for medical or health-related uses, such as for maintaining or promoting health, preventing or treating diseases. These products include vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines, probiotics, as well as amino acids and essential fatty acids (from Wikipedia).

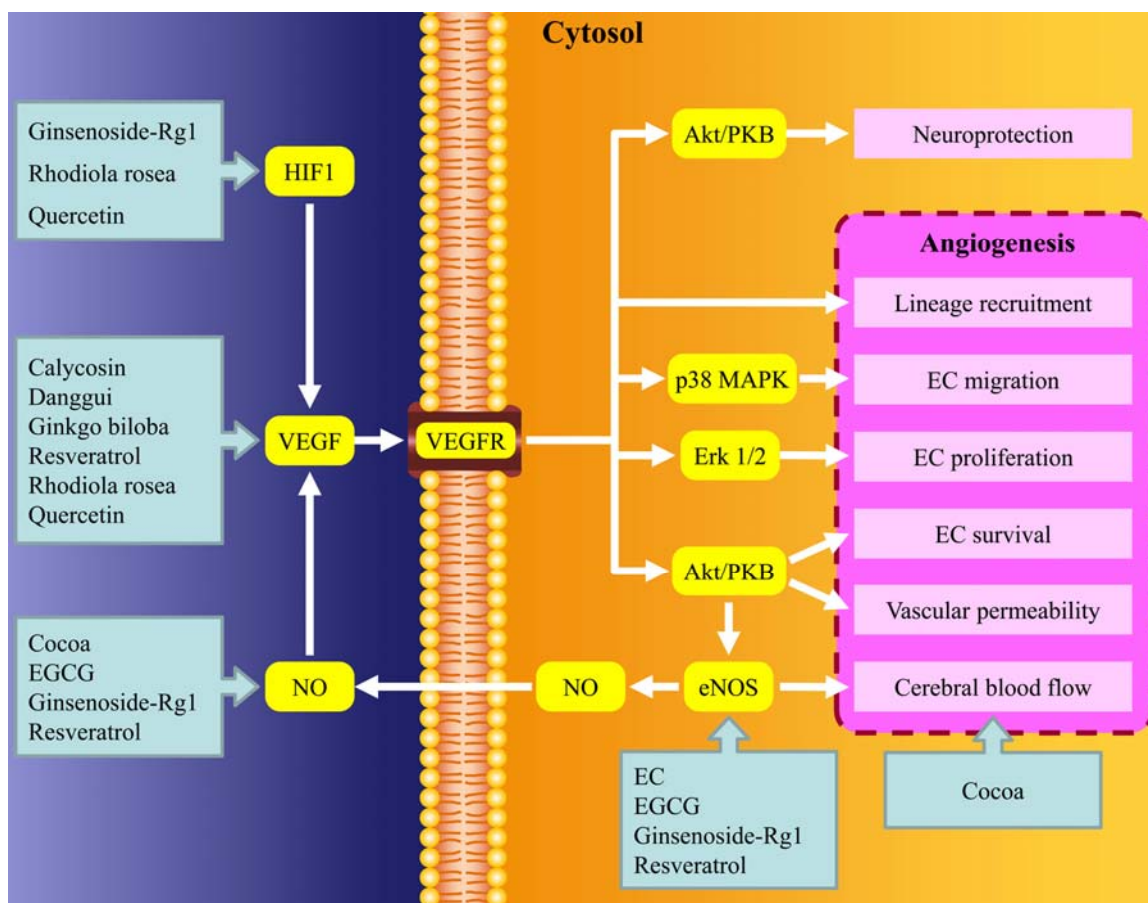
Phytochemicals are nonnutritive bioactive plant substances (apart from vitamins, minerals and macronutrients) that have beneficial effects on human health, but are not yet established as essential nutrients. Phytochemicals contribute to the flavor, color, texture, and smell of plants; they are not only highly enriched in

colorful vegetables and fruits, but also in tea, chocolate, and nuts. There are thousands of phytochemicals which can be classified into subgroups according to their structures (7; Wikipedia; Figure 2). Most of them are not well-described and their modes of action are not well-established. In general, phytochemicals's beneficial effects are attributed to their antioxidant, antiviral, and antibacterial properties, and their ability to boost the immune system, improve hormonal action, and protect cell viability (5, 75, 76; Wikipedia).

### 5.1. Phytochemicals, neuroprotection and stroke

Large population epidemiological and clinical studies have shown an inverse correlation between incidence of cardiovascular disease and the intake of vegetables and fruits; in particular, plants that contain high levels of flavonoids and sulfur compounds (2 ~ 6). Recently, a meta-analysis of studies on tea consumption and stroke in humans also concluded that daily consumption of either green or black tea could prevent the onset of ischemic stroke (77). These studies further show that green tea extract can protect neurons against ischemic brain insult *in vitro* and *in vivo* (78 ~ 84). In a number of studies with animal models, treatment with grape extract have also shown neuroprotective effects and reduction of ischemic infarct (85 ~ 92). The underlying mechanisms of these beneficial effects has been attributed to the antioxidative, antithrombotic, anti-inflammatory, lipid-lowering, and vasculoprotective properties of the most vital ingredient - polyphenols (5, 76). However, it is worth noting that a number of well-controlled studies did not show a strong relationship between single flavonoid component consumption and cardiovascular outcomes or stroke (4, 93, 94). It has been shown that apocynin (i.p. injection) is rapid transported to plasma, liver and brain (95), PPAR-gamma siRNA or recombinant protein (i.c.v. infusion) is able to reduce or increase, respectively, its





**Figure 3.** The potential signal transduction processes associated with phytochemicals-mediated beneficial effects on angiogenesis.

protein level in cerebral cortex (96), and blood-borne 14C-bFGF is accumulated in CA1 pyramidal neurons (97). Furthermore, there are areas in the brain without a blood brain barrier (BBB), such as: pituitary gland, median eminence, area postrema, preoptic recess, paraphysis, pineal gland, and endothelium of the choroid plexus. Last but not the least, since BBB breakdown is one of the key early signs for stroke, so the bioavailability of phytochemicals in the brain tissue should not be a major concern. It is possible that besides phytochemicals, other components in plants (vitamins, minerals, and macronutrients) act in parallel or sequentially for the apparent reduction in CVD and stroke (Figure 2).

## 5.2. Phytochemicals and post-ischemic angiogenesis

It is well documented from clinical and epidemiological studies that natural products can serve not only as chemopreventive, but also as chemotherapeutic agents (98, 99, 100). This beneficial effect has been attributed largely to their anti-angiogenic properties. Many natural health products, phytochemicals in particular, have been shown to possess anti-angiogenic activity (101, 102). However, how these anti-angiogenic phytochemicals prevent CVD and stroke remains paradoxical, since the extent of angiogenesis has been correlated to the outcome and survival in stroke patients (35). Intriguingly, some

noxious phytochemicals which are present to prevent insects and pests from invading the plants, can induce a preconditioning-like neuroprotective effect at relatively low doses (99). In fact, recent studies have revealed a biphasic effect of phytochemicals on neuroprotection (99). For example, low doses of red wine polyphenolic compounds are pro-angiogenic while high doses are anti-angiogenic in the rat peripheral ischemic model (103). Similar pro-angiogenic and anti-angiogenic at low and high doses of resveratrol, respectively, have also been reported in swine myocardial ischemia (104) and in human vascular endothelial cells (105). Tea polyphenols also share similar biphasic anti- and pro-angiogenic effects (106, 107). This U-shape-like dose response, which is named hormesis, has been noted with numerous pharmacologically active compounds, including corticosteroids and receptor agonists, although the mechanisms underlying this biphasic actions remain largely unknown (108, 109, 110). Several examples of the hormetic role of dietary phytochemicals and antioxidants in neurodegenerative diseases have been reported (111, 112). Some of the hormetic dietary phytochemicals that are linked to the progression of angiogenesis as well as their potential downstream effectors are highlighted in Table 2. It is conceivable that information of different dosage thresholds of phytochemicals is needed for treating different diseases like

cancer and CVD. The potential signal transduction processes associated with phytochemicals-mediated beneficial effects on angiogenesis are summarized in

## 6. PERSPECTIVE

It is hypothesized that one out of six people worldwide will have a stroke during their lifetime, and brain damage and dysfunction after stroke is very complex. The need for prophylaxis and treatment is great. Unfortunately, more than 700 neuroprotective drugs, which are found to be effective in animal models, have not been proven efficacious in treating stroke patients. It is conceivable that it is not sufficient to target only neuroprotection, but a combinatorial intervention is needed for battling this disease. Considerations of therapeutic angiogenesis and neurogenesis seem to be a good strategy for combination therapy; although we still have a long way to go before reaching this goal. As quoted from Louis Pasteur (1822 - 1895): "When meditating over a disease, I never think of finding a remedy for it, but instead a means of preventing it." Large population epidemiological and clinical studies have revealed an inverse correlation between CVD/stroke incidence and vegetables/fruits consumption. The American Heart Association also recommends eating a balanced diet containing a wide variety of fruits, vegetables, and whole-grain products in stead of nutritional supplements to prevent having CVD/stroke. Therefore, young people should consider diets rich in phytochemicals as well as exercise for a healthy life. Finally, I would like to end with a famous remark by Hippocrates (460 - 359 BC): "Let your food be your medicine and your medicine be your food."

## 7. ACKNOWLEDGEMENT

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