Red vine leaf

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The knowledge of the medicinal potential of grape vine (*Vitis vinifera*) can be traced back far in history. In Europe the red vine leaf is used in traditional medicine in case of venous diseases. In an actual clinical trial it was possible to proof the efficacy of preparations from red vine leaf in the treatment of venous insufficiency. Recent studies have focused on wine produced from *Vitis vinifera*. It has been suggested that red wine is effective in decreasing the risk of coronary heart disease mortality. Many investigations have demonstrated that red wine components like polyphenols from the flavonoid group but also the stilben trans-resveratrol have antioxidant potential and thus may have an influence on cardiovascular diseases like atherosclerosis. These proposals open the discussion about an expanded range of indication for the red vine leaf.

Botany of *Vitis vinifera*

In the French pharmacopeia the red vine leaf is monographed as the part used for medicinal preparations from the plant *Vitis vinifera L.,* that is to say those varieties with dark grapes and red pulp [1].

Vitis vinifera L., Grape vine, is a perennial, defoliating climber with a wooden often twisted stem which can reach a length of 30 meters, whereas in culture it is usually cut back to one to three meters. The shrub develops climbing branches forking to twigs from where the long-stemmed, alternating arranged leaves protrude. The vine leaf is heart-shaped, thin, showes five to seven dendate lobes, divided by more or less deep and open sinuses and can reach a diameter of over 20 cm. At the lower tendrils the flower panicles with numerous yellow-greenish flowers are formed. The fruits, arranged in large and long clusters are soft and pulpy berries with yellow-green, reddish or purplish dark-blue skin [1, 2, 3].

Fig. 1:
18th Century wood-engraving of a fruit bearing grape vine twig (*2Rätsch C., page 536*)

Vitis vinifera belongs to the *Vitaceae* family. Several subspecies and varieties are distinguished among which is the subspecies *sylvestris* (*Gmelin*) *Berger*, recognised as the spontaneous form of *Vitis vinifera L. ,* the subspecies *caucasica Vavilov*, occurring in both sponatneous and cultivated form. It is supposed that from these two, the cultivated form *Vitis vinifera* ssp. *sativa DC* has been grown [2, 4].

Origin and History of *Vitis vinifera*

Vitis vinifera presumably originates from Western Asia, from the area between the Caspian Sea region and Asia Minor, where also its cultivation seems to have begun [4, 5]. In Godin Tepe (Iran) finds of terracotta drinking-cups were proven by chemical analysis to have been used for wine consumption. These archeological finds, up to this day the oldest documentation for the use of grape vine products in human culture, were dated to 3500 - 2900 B.C. [6]. In progress of spreading west, towards Europe, grape vine reached, coming from the East Mediterranean area, first Greece and later on Italy, France and Central Europe. Almost simultaneously with the westward extension, the cultivation of vine spread towards East over Iran, Pakistan and India so that it reached China at the end of the second century B.C. [5]. Today, *Vitis vinifera* has reached all continents but is successfully cultivated only in temperate climate regions with warm and dry summers and relatively mild winters with sufficient rain [4].

Grape vine is cultivated predominantly because of its fruits, which are used fresh, dried or processed into wine. Already in antiquity pharmacological properties were attributed to the fermented juice of grape berries, where it was used especially against diseases of the gastrointestinal tract or as a general tonicum and prophylacticum [2, 5]. Grape berries are listed in many pharmacopeias, for example in the British and the American, where the ripe fruits are prescribed as laxans, diureticum and in case of gastrointestinal- and circulatory disturbances, adipositas, gout and against liver or kidney diseases. In the traditional medicine of different cultures also preparations of other parts of the plant *Vitis vinifera* are known. In Europe the juice of young shoots was applied to treat skin diseases or inflammatory of the eye, in the traditional Chinese medicine antiemetic and diuretic effects are attributed to the roots of grape vine [7].

Nevertheless, also of the leaves of *Vitis vinifera* are documentated in the literature of traditional medicine, where their adstringent and homeostatic properties are utilized in the treatment of diarrhea, bleedings, haemorrhoids or varicose veins [8].(Table 1)

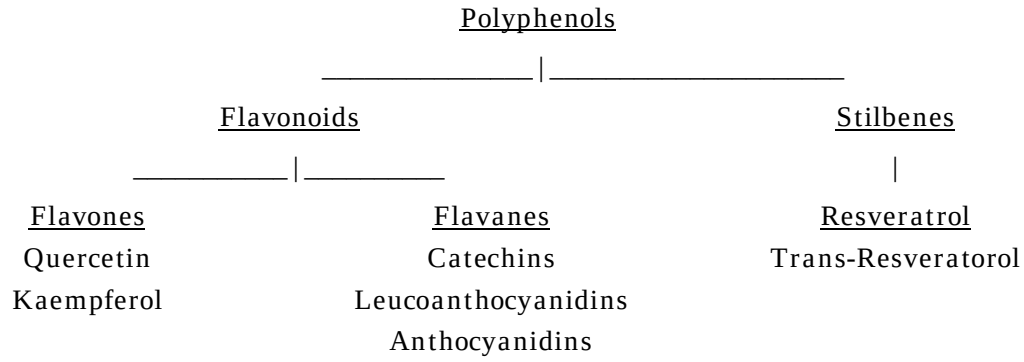
(Table 1) Medical Use of Grape Vine in Tradition

	Medical Use	Country
Grape berries	laxative diureticum adipositas gout liver or Kidney disease	England America
Juice of young shoots	skin disease inflammatory of the eye	Europe
Roots of grape vine	diureticum antiemetica	China
Oil of grape seeds	laxative neutralize hydrochloric acid promote bile secretion	Europe
Grape leaves	diarrhea bleedings haemorrhoids varicose veins	Europe

Components of grape vine

Since the beginning of the last century in many studies the chemical constituents of the different parts of grape vine have been investigated. Fruit acids, tannins and pigments are the substances mainly responsible for taste, odour and color of the wine. From a pharmacological point of view the polyphenols, for example flavonoids, are the most important substance group [4].

(Table 2-1) Phenolic compounds in Grape Vine



(Table 2-2) Polyphenolic compounds in Grape Vine

Anthocyans	present in every higher plant responsible for the blue and red coloring of leaves, flowers and fruits The concentration of anthocyans in the red colored leaf is high.
Catechins	• Red vine leaf is rich in cathechins • Concentration of cathechins is dependent on: ->the leaf's position on the plant the phase of development of the leaf • In autumn cathechin, gallocathechin, epicathechingallat are present in the leaf.
Resveratrol	• belong to the stilbenes (phenolic sub group) is a phytoalexin= stress-induced plant metabolite resveratrol can be found only in stressed leavesstress factors : i.e. fungal infection, UV-irritation,injury ->resveratrol is present in different forms depending on the stage of the plant's stress answer: o piceid= transport form? o trans-resveratrol= depositonform

Characteristic for all flavonoids is a carbon frame, which is biogenetically synthesized from three acetate units (C6) and one phenylpropane unit (C6-C3). Quercetin and kaempferol belong to the flavons, Catechins, Leucoanthocyanidins and Anthocyanidins to the flavans, both sub-groups of flavonoids [4, 9]. The leaves of the red varieties are very rich in tannins from the catechin group. The composition in tannins of leaves depends on the phase of development and on their position on the plant. In autumn catechin, gallocatechin and epicatechingallat can be found in the leaves. From catechins and / or leukoanthocyanidines so called oligomeric proanthocyanidins, colorless substances, are formed. Anthocyans, Anthocyanidins tied up with a sugar molecule, are present in

every higher plant and are responsible for the red and blue coloring of flowers, leaves and fruits. In grape vine the greatest part of anthocyans consists of malvidin glucosides but also delphinidin, cyanidin and pertunidin glucosides occur. The highest content of anthocyans can be detected in the red leaf especially in autumn, in the time between the vintage and the shedding of leaves. [4, 7, 10]. According to the French pharmacopeia the dried leaves of red vine should contain at least 4% of total polyphenols and 0.2% of anthocyans [1].

The phytoalexin trans-resveratrol (Fig. 2), another polyphenolic substance belonging to the stilbene group, can also be found in grape vine. Phytoalexins are metabolites that are produced by plants in response to fungal infection or abiotics such as heavy metal ions, UV light or physical injury. Hence it follows that trans-resveratrol is not present in healthy leaves but accumulates in UV-irritated, infected or injured leaves [11, 12]. Dependent on the stage and the degree of the stimulus by the stress factors involved different forms of resveratrol, like the piceid isomers being the glucosidic transport forms or the deposition form trans-resveratrol can occur in the affected tissue. Measuring the trans-resveratrol concentration of certain parts of the plant, like leaves for example, these factors should be taken into consideration [13].

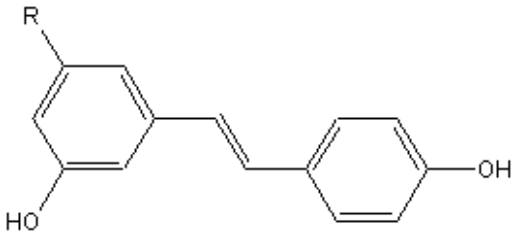


Fig. 2 : Chemical structure of the stilbene sceletal type; R = 3-O-beta-D-glucoside: Piceid; R = OH: Trans-resveratrol, 3,4‘,5-trihydroxy-stilbene.
The phytoaxlexin trans-resveratrol, a non-flavonoid phenolic compound that can be found in the skin of grape vine berries, in grape vine leaves and also in wine.

In grape vine leaves, also organic acids, mainly malic and oxalic acid but also tartaric acid appear. Citric, fumaric and succinic acid can be detected in the leaves only in traces. Com-pared to the grape berries, grape leaves are richer in the content of carotinoids and vitamin C [7].

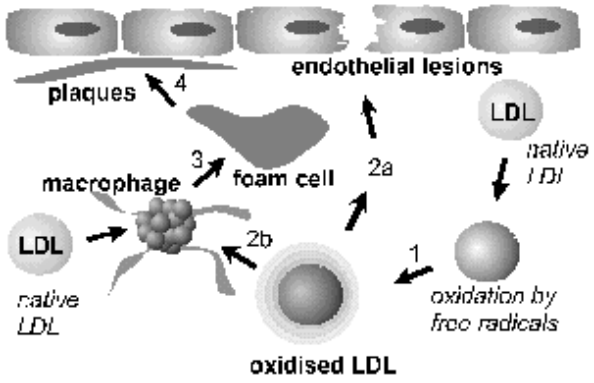
Pharmacology

Numerous investigations of recent date have focused on the French Paradox, a phenomenon referring to the fact that the incidence of death due to coronary heart disease in France is relatively low, even though that risk factors such as a diet with high proportions of saturated fatty acids, high cholesterol levels, high blood pressure and smoking are just as frequent as in other highly industrialised countries. Statistical analysis of the various factors have shown that the consumption of red wine is one of the contributory causes of this phenomenon. In the context of this cardioprotective effect three polyphenolic substance groups, present in red wine, are of main importance: procyanidins, anthocyans and trans-resveratrol [14, 15].

The hydroxy-stilbene trans-resveratrol has to date been reported in very few components of the human diet, red wine being the only significant source [16]. The antioxidant potential of resveratrol has been the basis of intensive investigation. Antioxidants are substances, which can neutralize radicals, reactive oxygen species regarded as triggers for many degenerative diseases or mutagenic processes. Resveratrol, found to be such an antioxidant, is supposed to act as a radical scavenger

and thus, indicates its possible chemopreventive value in regard to heart disease for example [17]. Although the role of radicals in the pathogenesis of heart disease is not completely understood yet, it is generally accepted that radical induced oxidative stress in the cardiac muscle can promote subcellular disfunctions that may induce pathogenic changes [18]. The increased presence of radicals in the blood stream leads to modulations in the oxidative status of low-density lipoproteins (LDL), one of the transport forms of cholesterol. In this way modified, the oxidized LDL is taken up by macrophages as an answer of congenital immune defence. Since the „scavenger" receptor system of these defensive cells is not regulated, they become loaded with lipids and convert into so-called foam cells, which accumulate in fatty streaks, believed to be an early sign of atherosclerosis (Fig. 3). It has been demonstated that resveratrol was very efficient in protecting LDL from oxidation [17].

Fig. 3: Development of atherosclerotic plaque by oxidised LDL: 1) Oxidised LDL is formed by radical chain-reaction; 2a) Oxidized LDL can have a direct toxic influence on the endothelial cells of the artery; 2b) Uncontrolled uptake of oxidised LDL by macrophages; 3) Macrophages turn into foam cells; 4) Through adhesion at the cell wall and bursting of the foam cells atherosclerotic plaque is formed.
[after: Stumpe KO (1996) Vitamin E und Arteriosklerose, DAZ Extra-Beilage 42: 1-4]



Another event in the development of atherosclerosis, a multifactorial disease associated with a hardening and narrowing of the arteries, is the aggregation of blood-platelets. The role of blood platelets in the progression of atherosclerotic plaque through adherence to vascular walls as well as their potential to lead to acute coronary heart disease by forming blood coagulation or thrombus is well understood and realized. The aggregation of blood-platelets is influenced by the eicosanoid metabolism. Eicosanoids play an important role in the local signal transmission. There are two ways of eicosanoid synthesis in human platelets. One of them, the cyclo-oxygenase pathway leads to the formation of thromboxanes, known to be involved in propagating platelet aggregation [18]. Resveratrol has been shown to strongly inhibit the cyclo-oxygenase pathway and thus to influence platelet aggregation [16, 19].
The efficacy of resveratrol was tested not only in the context with the cardiovascular disease but also with cancer. Proceeding from its antioxidant activity it is conceivable that resveratrol may suppress tumor development by removal of reactive oxygen species, which are regarded as having carcinogenic potential. In this way it was possible to demonstrate an inhibition of tumor development by resveratrol [20].
Since trans-resveratrol has structural similarity to estrogenic agents a study was initiated to investigate the estrogenic potential of the substance. The results of the study suggested that trans-resveratrol is a very potent antagonist to the binding of the sexual hormone estradiol to its receptors. An effect, which may provide some beneficial effects in areas such as breast cancer [21].

A great number of studies have dealt with the different other polyphenols contained in grape vine or grape vine products. In a laboratory test examining the antioxidant activity of different polyphenol fractions from red wine it was concluded that red wine polyphenols can associate with LDL particles and, in doing so, inhibit the uptake of the lipoproteins by macrophages. The fraction containing monomeric anthocyanidins and catechines turn out to be most effective [22]. Quercetin, like resveratrol, showed an inhibition of platelet aggregation in a dose-dependent manner [16]. Implications for protection against coronary heart disease can be attributed to all polyphenols from grape vine investigated to date.

The vascular-protective properties of grape vine leaves stand in the center of its traditional indication like venous insufficiency, functional disturbances of the cutaneous capillaries or haemorrhoids [23]. By the continous distension of the venes, in case of disturbances of the back-flow of the blood towards the heart, the wall of the veins becomes injured. The support elements of the wall of the vein, like collagen, elastin and hyaluronic acid, experience a loss of function. A progressive catabolism of hyaluronic acid leads to increasing permeability of the vascular wall, so that water can flow out from the blood stream and accumulate in the surrounding tissue [7]. It has been demonstrated that flavonoids of the procyanidine-type can inhibit hyaluronidase, the enzyme degrading hyaluronic acid, as well as other enzymes of the vascular wall, like collagenase and elastase. This capillary protective action is based on a pluricentric mechanism including also radical scavenging and antioxidant activity [24].

The red vine leaf in therapy and possible future applications

The efficacy and relevance of preparations from red vine leaves in the treatment of venous insufficiency has been clinically proven in a randomized, double-blind, placebo-controlled study [25]. With these results the positive expericences from the traditional use of red vine leaves in the therapy of venous disease could scientifically be confirmed.

Although corresponding clinical studies regarding the effectivity of grape vine preparations in the field of coronary heart disease still lack, there were successful efforts to assess the antioxidant potential of red wine and red wine polyphenols also in human studies [26]. Despite the fact that most data originate from studies with red wine the cardioprotective effects cannot be explained only by the alcohol component, though there are indications for a beneficial effect of low doses of alcohol on arterial disease [18, 27]. In laboratroy studies ethanol was found to be less active in inhibiting platelet aggregation compared to dealcoholized red wine polyphenol fractions [19], and preparations from alcohol free wine polyphenols showed a strong antioxidant activity [17]. Epidemological data demonstrate a much lower indidence of coronary heart disease among wine drinkers than among those who usually consume spirits or beer [28]. Implying these findings the pharmacologic potential of red wine and red wine polyphenols demonstrated in laboratory in vitro and in vivo experiments, may be of relevance also in man. It is known from biochemical analysis that the red wine polyphenols investigated, are also present in the red vine leaf, some of them, like flavonoids, even in their highest concentrations [7]. For this reason, red vine leaves or preparations from red vine leaves, could be of interest for the development of new prophylactic or therapeutic agents in the field of coronary heart disease.

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