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Vitamin K in Plants

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ABSTRACT

Vitamin K-like compounds are widely diffused in plants, but their role and function are still partially unknown. Vitamin K_1, phylloquinone, is largely present in thylacoid membranes as an electron carrier inside the PSI redox chain. More recently, it has been found that Vitamins K_1 and K_3 may also affect the plasmalemma-bound H^+-ATPase and some redox proteins including b-type cytochromes. The antioxidant role of Vitamin K is also discussed.

Keywords: phylloquinone, photosynthesis, redox activities
Abbreviations: LHC, Light Harvesting Complex; **PSI**, Photosystem I; **ROS**, Reactive Oxygen Species

CONTENTS

INTRODUCTION

When the term "Vitamin K" is used, we generally refer to quite a wide group of naphthoquinonic compounds having antihaemorrhagic properties. Also for this reason, in fact, the letter "K" was chosen by Henrick Dam, winner of the Nobel prize for his discovery of this Vitamin together with Edward Doisy, discoverer of the chemical nature, as the abbreviation of the Danish/German word "Koagulation". Of course, in plants Vitamin K does not govern any coagulation process, and the generic term "Vitamin K" is generally referred to as Vitamin K_1 (2-methyl-3-phytyl-1,4-naphthoquinone) or phylloquinone (**Fig. 1**). Vitamin K_1 was isolated for the first time in 1936 by Almquist from *Medicago sativa* (Almquist *et al.* 1936). Nevertheless other forms of Vitamin K, such as menaquinones (K_2–K_n) and even menadione or Vitamin K_3 (erroneously thought to be only of synthetic origin), have been isolated in tissues of fungi, cryptogamae and phanerogamae (Binder *et al.* 1989). However, their functions are frequently unclear as well as those of hundreds of other naphthoquinonic compounds isolated from tissues of plants, fungi and bacteria (Thomson 1971), of which juglone and plumbagin, are probably the most well known.

BIOSYNTHESIS

Phylloquinone is a metabolite of the shikimate pathway. The last represents an alternative route towards aromatic compounds, in particular the aromatic amino acids L-phenylalanine, L-tyrosine and L-tryptophan, but also benzoic acid, cinnamic acids, flavonoids, benzoquinones, tocopherols and, precisely, naphthoquinones (Bentley 1975). This pathway is widely used by plants and bacteria but not by animals, that, just for this reason, must get through the diet some of these essential compounds, Vitamin K included. Corismic acid is the "first" derivative of shikimic acid and intermediate in the synthesis of phylloquinone; from it, through a series of reactions, 1,4-dihydroxynaphthoic acid is obtained. This last compound is at first alkylated with a molecule of isophytol, and successively methylated in position 2 (**Fig. 2**). Isophytol is a diterpene of primary importance coming from the mevalonate pathway. It can be found as a constituent of the chlorophyll molecule where it functions to anchor the hydrophilic porphyrinic structure to the lipidic bilayer membranes of thylacoids and of other membranes. Prenylation of 1,4-dihydroxynaphthoic acid with an isoprenic chain, other than isophytol, generates the group of menaquinones, widely spread in fungi and bacteria. Actually, the majority of Gram-positive and anaerobic Gram-negative bacteria possess naphthoquinones of the K series rather then benzoquinones, like ubiquinones, and the features of the side chain constitutes a taxonomic criterion (Collins *et al.* 1981). Among menaquinones, the most outstanding is menaquinone 7 or Vitamin K_2, widely investigated for its nutritional and pharmacological properties in humans. The synthesis of bacterial Vitamin K coincides only in part with the synthesis of phylloquinone in plants

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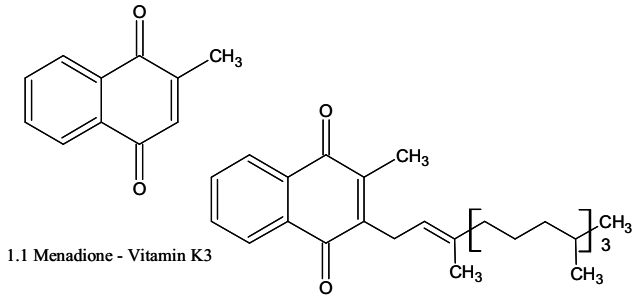
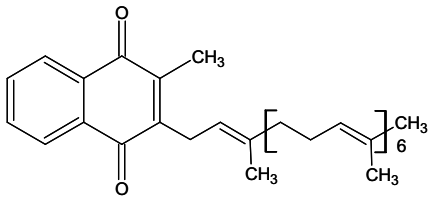
Invited Mini-Review



1.1 Menadione - Vitamin K3

1.2 Phylloquinone - Vitamin K1



1.3 Menaquinone 7 - Vitamin K2

Fig. 1 Vitamin K forms. The basic structure of the K serie is Menadione - Vitamin K_3.

because bacteria may follow several variations of the phylloquinone pathway, starting from corismic acid and also using other precursors (Bentley *et al.* 1982). Recent studies on *Arabidopsis thaliana* mutants, impaired in the biosynthesis of phylloquinone, show that Vitamin K_1 is coded by a single gene that, most likely, evolved from the fusion of four previously individual genes required for the phylloquinone biosynthesis of cyanobacteria and respiratory menaquinones in eubacteria (Gross *et al.* 2006). Interestingly, one of these four individual units codes for the isochorismate synthases; these enzymes are involved in the biosynthesis of both phylloquinone and salicylic acid. This might implicate a sort of connection between phylloquinone synthesis and the resistance system of plants (Gross *et al.* 2006).

DISTRIBUTION

The distribution of Vitamin K among plant tissues forecasts, at least in part, its importance in physiological functioning. Phylloquinone is mostly present in green tissues of plants, in particular in the leaves where its level may range between 75 and 300 µg/100 g fresh weight; in fruit, the content progressively decreases to about 5-20 µg/100 g, while in hypogeous organs the level of Vitamin K is about 1-3 µg/100 g fresh weight (Koivu *et al.* 1997; Damon *et al.* 2005). Generally speaking, it has always been believed that chloroplasts, where Vitamin K is located inside Photosystem I – analogously to antenna pigments – are the main storage organs of phylloquinone; however, the involvement of Vitamin K_1 in other membrane enzymatic systems, that we will discuss later, might lead us to reconsider this assumption. The presence of Vitamin K inside the plasmalemma of maize roots was first demonstrated by Lüthje (Lüthje *et al*. 1995) and successively confirmed (Lüthje *et al*. 1998).

The few studies carried out on Vitamin K distribution show that its content is higher in fully grown leaves that have been exposed to sunlight. On the contrary, it is lower in young tissues and/or partially etiolated leaves (Lichtenthaler 1962; Ferland *et al.* 1992).

PHYSIOLOGICAL FUNCTION IN PLANTS

Redox properties of Vitamin K

The physiological function of Vitamin K in plants is directly linked to its redox properties deriving from the presence on the naphthalenic ring of a double quinonic function. In fact, as many other quinones and naphthoquinones, Vitamin K can be reduced and reoxidised in a cyclical way by several substances and enzymatic pools.

Depending on the type of enzymes and, of course, on the environmental conditions, Vitamin K may react either as a single electron donor or as a two-electron donor. In the first case Vitamin K is reduced to the semi-quinonic form, in the second one it is reduced in the hydro-quinonic form as schematically shown in **Fig. 3**. The one electron reduction of phylloquinone is supposed to be the "preferential" process that Vitamin K_1 undergoes in normal physiological plant conditions because its semi-quinonic form is easily subject to spontaneous re-oxidation and it is suitable to exert cyclic redox reactions inside electron transfer chains. This cycle allows the molecule to be used several times.

On the other hand, the one electron reduction of benzo- and naphthoquinones and the successive spontaneous auto-oxidation of the semi-quinonic forms, may induce an endogenous over production of reactive oxygen species (ROS) which, in the absence of an adequate enzymatic pool and of antioxidant compounds responsible for their scavenging, will cause damage to the cell membranes. This mechanism along with the direct alkylation of SH groups of important proteins are at the origin of the toxicological and pharmacological effects that many quinones exert and for which they have been investigated thoroughly (O'Brien 1991). Phylloquinone does not seem to represent an inducer of oxidative stress like other vitamin K moieties, in particular Vitamin K_3, although some recent works on spinach (*Spinacia oleracea*) indicate that under light saturation conditions Vitamin K_1 may induce oxidative stress (Kruk *et al.* 2003).

In animal cells the two electron reduction of Vitamin K and of Menadione is performed by the enzyme DT-diaphorase which is a flavoenzyme with primary function on the detoxification processes. Plants do not posses this enzyme but it has been shown that a similar two-electron reduction is operated by a NADH-quinone reductase having a different structure (Trost *et al*. 1995; Sparla *et al*. 1998). More likely plants possess more than one NADH-quinone reductase enzyme having different locations, but their precise function is still uncertain (Bérczi *et al.* 2000).

The two main electron transport chains where Vitamin K is involved are the photosynthetic electron transfer from Photosystem I to $NADP^+$ and the membrane-bound electron transfer chain involved in the oxidative phosphorylation of bacteria. This last one involves Vitamin K_n, not phylloquinone and since it is not typical of plants we will not consider it, addressing the reader to the review of Søballe (Søballe *et al.* 1999).

The existence of a third, shorter electron transport chain where Vitamin K is supposed to be involved has been investigated more recently; this is the plasmalemma redox chain (Lüthje *et al.* 1997).

Interestingly, in the animal cell Vitamin K does not seem to be involved in any electron transport chain as in plants, although its physiological function is still related to a redox reaction where the oxidation of reduced Vitamin K to the epoxide form is coupled with the γ-carboxylation of glutamic acid residues of some specific proteins. Due to this site-specific carboxylation, these proteins achieve a strong calcium-chelating activity which is at the base of their physiological functions (Suttie 1985; Vermeer 1990). Vitamin K_1 epoxide is then reduced to the quinonic form by a dithiol-dependent Vitamin K epoxide reductase; subsequently the re-cycle of the quinone moiety is completed through a further reduction. This last step can be catalyzed by either a dithiol-dependent, and warfarin-sensitive, reductase, or by a NADH-dependent reductase (**Fig. 4**). This small

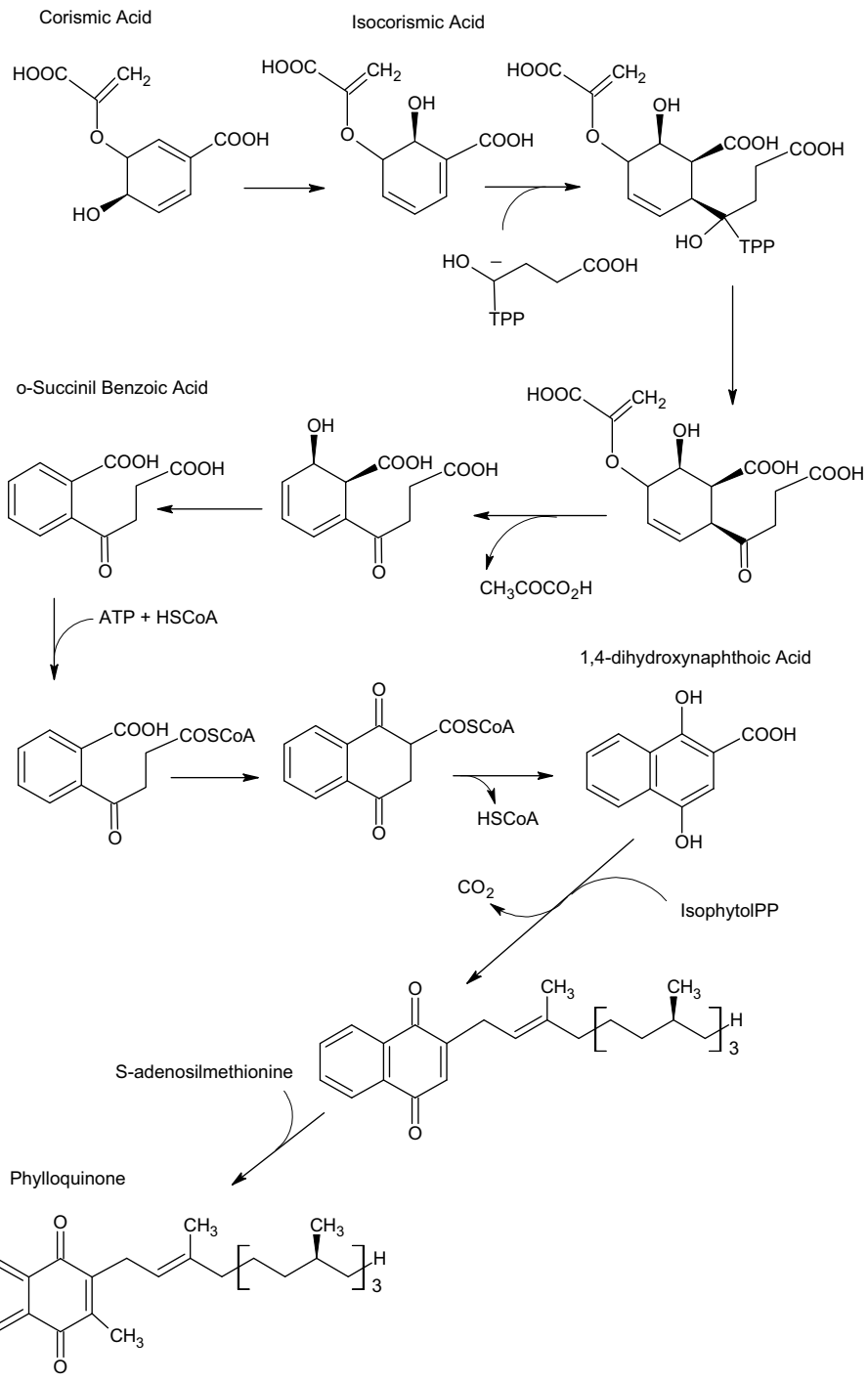


Fig. 2 Phylloquinone biosynthesis. The pattern has been modified from Dewick (1997).

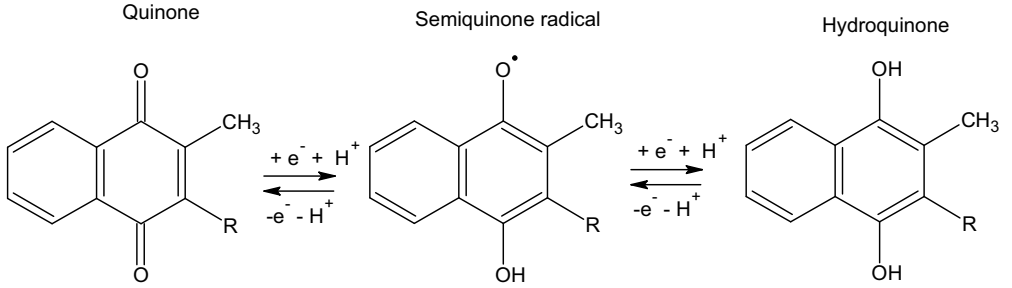


Fig. 3 Naphtoquinone reduction steps. Naphthoquinone reduction may proceed either till the hydroquinonic form through the addiction of two electrons, or simply stop to the semiquinonic form. The reactions may proceed in different directions depending on the redox condition of the environment and on the enzymatic pools involved.

Vitamin K cycle has been studied in depth because it is the target of many common anticoagulants of medical relevance; they interfere with the activity of Vitamin K_1 epoxide reductase uncoupling the redox cycle of Vitamin K and causing a quick depletion of reduced Vitamin K (Suttie 1991).

To the best of our knowledge there are no investigations and consequently no information, on the existence of similar γ-carboxylation reactions and Vitamin K-dependent proteins in plant cells.

The electron transport chain of PSI

We shall now focus briefly on the electron transport chain

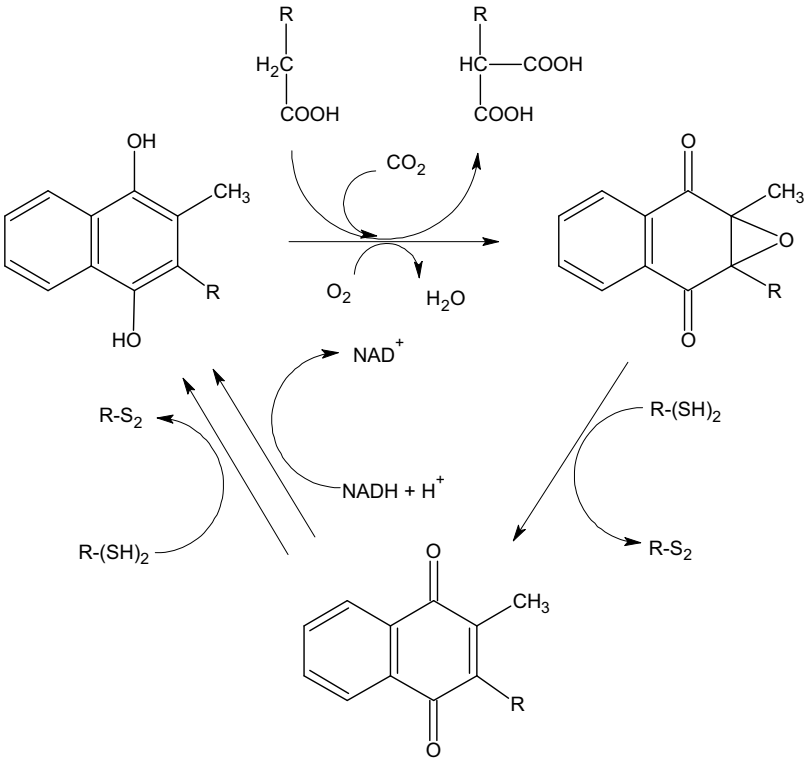


Fig. 4 Vitamin K cycle in animal cell (modified from Suttie 1991). Reduced Vitamin K is oxidised to the epoxide following to the carboxylation of specific glutammic acid residues belonging to K-dependent proteins. The epoxide is reduced first by K_1 epoxide reductase to the quinonic form and then, to the starting hydroquinone. The reduction of the quinone to the hydroquinone may be catalyzed by two different enzymes having different sensibility to warfarin inhibition.

of Photosystem I (PSI) and on the plasmalemma redox chain. Photosystem I consists of a complex of pigments and proteins embedded in the chloroplast thylacoids. This complex allows the one electron flow from the primary donor to the $NADP^+$ molecules in the stroma, thus generating the reducing power necessary for the assimilatory CO_2 reduction in the Calvin cycle. The electron flow is induced by the energy of light captured by the Light Harvesting Complex (LHC) and transferred to the reaction centre of P700, which is composed of a dimer of a special type of chlorophyll *a*. It is already acknowledged that there are six electron conveyors involved in PSI; the primary donor P700 and five acceptors. These are the primary chlorophyll acceptor A_0, the secondary acceptor phylloquinone (the A_1 acceptor), and the three Fe-S proteins F_X, F_A, F_B (Snyder *et al.* 1991; Brettel 1997). Some studies report that several substances can restore the electrons' flow in membranes where phylloquinone has been extracted (Itoh *et al.* 1991; Iwaki *et al*. 1991). Most likely this fact may be correlated with the extraction method or to a sort of low specificity of the quinone binding site (Golbeck *et al.* 1991; Brettel 1997) rather than to the real involvement of other substances different from phylloquinone. Vitamin K_1 turns out to be present with two molecules associated with the PSI reaction centre and bound to protein PsaA and possibly also to PsaB (Golbeck 1992); one of the two molecules of phylloquinone is more easily extractable while the other one is more tightly bound to its hydrophobic matrix. Since the removal of the more easily extractable molecule does not involve the block of the electron flow (Malkin 1986; Biggins *et al.* 1988), these authors believe that the two molecules represent two different ways through which electrons can flow (Golbeck 1992). This peculiarity has been the theme of more recent studies confirming the existence of two active branches for the electron transfer (Guergova-Kuras *et al.* 2001).

As mentioned before, Vitamin K can act as a massive inducer of superoxide anions inside the thylacoids when light saturation conditions occur. This is the consequence of the persisting process of spontaneous autoxidation that does not allow to stop the excessive electron flow, ultimately reducing molecular oxygen. It is interesting to note that a mechanism of photoinhibition of PSI based on the two-electron reduction of phylloquinone is supposed to be present under conditions of light saturation (Inoue *et al.* 1989).

The plasmalemma redox chain

The supposed relevance of the plasmalemma redox chain for the maintenance of a proper electrochemical gradient, in combination with the proton pump, as well as for the absorption of iron (Rabotti *et al.* 1994), for the elongation and growth of the cell (Morré *et al.* 1988) or for the activation of the cell's defence mechanism, is well known and has been discussed in depth by Lüthje *et al.* (1997). Nevertheless, to date there is not an univocal acceptance about which are the constituents of this chain, their number and in which sequence they transfer electrons in the plasmalemma In particular the main area of the uncertainty is related to the compounds which are more deeply embedded inside the plasma membrane (Döring *et al.* 1996).

Barr *et al.* (1992) working on carrot cell plasma membrane showed that the destruction of phylloquinone negatively affected the plasma membrane electron transport and subsequently the same group of researchers showed that the plasma membrane NADH oxidase of soybean possesses Vitamin K_1 hydroquinone oxidase activity suggesting that the electron transfer from cytosolic NAD(P)H to acceptors at the cell surface might proceed via reduced Vitamin K_1 located inside the plant cell membrane (Bridge *et al.* 2000; see also **Fig. 5**).

Studies by several Authors (Döring *et al.* 1992a; Lüthje *et al.* 1992; Lüthje *et al.* 1994; Baroja-Manzo *et al.* 2004) showed that the treatment of root plasmalemma fractions with Vitamin K_3 was able to increase the reduction rate of external electron acceptor, while well known anti-coagulants like warfarin or dicumarol, had an inhibitory effect on the reduction of external electron acceptors. Presumably, most of the experiments done with Vitamin K_3 on plants were performed with menadione sodium bisulphite, its water soluble derivative, and the conclusion that phylloquinone would have given the same results is argued. Furthermore the antagonistic mechanism of coumarins on the Vitamin K function in animal cells could be different in plants, since its activity in the former is strictly linked to K_1 epoxide reductase, as mentioned before.

In any case a sonication pre-treatment of root plasmalemma fractions for five seconds at 50 kHz and in the presence of Vitamin K_3, resulted in a sharp increase of the redox activities in both mono- and dicotyledonous root plasmalemma fractions (De Nisi *et al.* 2006). This would induce

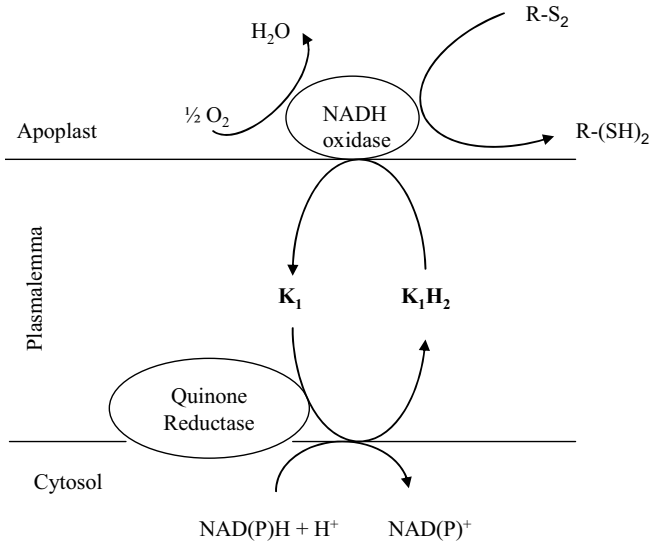


Fig. 5 Vitamin K related activities inside plasmalemma (modified from Bridge *et al.* 2000). Vitamin K is supposed to transfer electrons from the membrane bound quinone reductase to external electron acceptors.

the belief that the probable involvement of the naphthoquinonic component in the redox chain is actually occurring inside the cell membrane. Furthermore, measurements on the redox activities of plasma membranes of plants grown in hydroponic solutions containing Vitamin K_3, showed greater H^+-ATPase and plasmalemma redox activities compared to untreated plants (De Nisi *et al.* 2006). Although the plant metabolization of Vitamin K_3 into K_1 has not been proved, these effects were further confirmed on both root and leaves after the application of Vitamin K_3 through foliar spray on growing plants (De Nisi *et al*., unpublished data). Also these data increase the indirect evidence of the involvement of Vitamin K in the plasmalemma electron transport chain in both mono- and dicotyledonous plants.

As already mentioned, the plasmalemma redox activities may generate ROS which are at the origin of plant defence mechanisms. These compounds trigger the cascade of antipathogenic substances, leading also to the oxidative burst (Lamb *et al*. 1997). Interestingly Borges and co-workers found that MSB, a water soluble derivative of Vitamin K_3, is able to induce a systemic resistance to some common diseases (Borges *et al.* 2003, 2004). In those circumstances the authors hypothesized that the effect might depend on mechanisms related to increased generation of ROS, although the results should induce more in-depth investigation about the possible role of Vitamin K in plant defence systems.

Antioxidant properties

The antioxidant properties of quinones have been thoroughly discussed and accepted (Sies *et al*. 2004). Also Vitamin K moieties have been the object of several investigations in the past, sometimes with contradictory results; in fact, it should never be forgotten that the same quinonic substance might exert an anti-oxidant but also a pro-oxidant effect, depending on the environmental conditions and on the chemical features of the other molecules they react with. As a general consideration, many compounds of the K series have a strong affinity with sulphidrilic groups, and the Vitamin K_1 cycle itself in animal cells is driven by redox reactions with dithiols (Suttie 1985; Soute *et al.* 1992). In an animal cell model Vitamin K_1 exert antioxidant properties against microsomal lipid peroxidation (Vervoot *et al.* 1997); studies with artificial models support the hypothesis of a protective role of phylloquinone as a possible radical scavenger (Mukai *et al.* 1993; Ortiz *et al.* 1999), although in animal cells the membrane protective role is played primarily by tocoferols (Vitamin E) and ubiquinones (coenzyme Q). Since the presence of ubiquinones in the plant plasmalemma is highly uncertain, some authors hypothesized that phylloquinone may exert the function of coenzyme Q in plants (Döring *et al.* 1996; Bridge *et al.* 2000; Lochner *et al.* 2003), and this seems to be feasible, since naphoquinones and benzoquinones frequently and alternatively exert the same roles in different bacterial strains.

On the contrary and as already mentioned, in conditions of light saturation, phylloquinone may play a pro-oxidative effect inside thylacoid membranes in connection to an elevated rate of electron transfer from A_0, but this cannot be considered as a normal physiological situation, and furthermore not related to the plasmalemma.

Many authors reported that a frequent effect of the treatment of plasmalemma fractions with Vitamin K_3 and K_1 is an increase of the acidification rate of the external apoplast (Barr *et al.* 1990; Döring *et al.* 1992b; Lüthje *et al.* 1992; Taylor *et al.* 2001; Baroja-Manzo *et al.* 2004; De Nisi *et al.* 2006). Many of them explained these findings as a straight consequence of the simultaneous shuttle of electrons and H^+ across the plasmalemma by phylloquinone. However, investigations on the electron- and proton-transferring properties of Vitamin K_1 in artificial model membranes lead to the belief that phylloquinone is a poor proton carrier across biomembranes (Herrero *et al.* 1998). Therefore, a different or at least concomitant reason, explaining the apoplast acidification, might be a direct antioxidant action of Vitamin K on the redox state of the sulphidrilic groups of the H^+-ATPase (proton pump). Interestingly, in fact, the efficiency of the H^+-ATPase in plants was shown to be dependent on the oxidation state of its thiol groups and on the NADH/NAD^+ ratio (Katz *et al.* 1987; Elzenga *et al.* 1989). Some authors even suggested that the so-called "standard" redox activity of the root plasmalemma might be explained with the need to maintain a proper oxidation state and a high efficiency of the H^+-ATPase (Bienfait *et al.* 1988). Recently we found that, as a result of Vitamin K_3 addition to the hydroponic solution of growing plants, the activity of H^+-ATPase of root plasmalemma fractions was greatly stimulated. This effect was particularly impressive compared to the results we could achieve with simple preincubation of plasmalemma fractions with Vitamin K (De Nisi *et al.* 2006). We could not ascertain whether the higher H^+-ATPase activity was directly related to an increased availability of naphthoquinonic compounds in the cytosol, or indirectly related to the plasmalemma reductase activity which also increased, but the effect on the H^+-ATPase was definitely consistent and in line with previous findings of other authors (Barr *et al.* 1990; Döring *et al.* 1992b; Lüthje *et al.* 1992; Taylor *et al.* 2001; Baroja-Manzo *et al.* 2004).

CONCLUSIONS

In the last decades interest in the physiological function of Vitamin K in plant metabolism has grown considerably. Furthermore, in addition to its well known relevance in the photosynthetic process, it seems more and more likely that phylloquinone may play an important role also in other compartments of the plant. Several studies, for instance, suggest the involvement of Vitamin K in the transport chain transferring electrons across the plasma membranes, but also the possibility that this molecule contributes to the maintenance of a proper oxidation state of some important proteins embedded in the cell membrane. The presence of different kinds of quinone reductases in the cytosol might also lead to argue the possibility that Vitamin K may be connected with other enzymatic pools out of the plasmalemma. Studies on bacterial nitrate reductase seem to support this hypothesis (Brito *et al.* 1995; Giordani *et al.* 1997). New and deeper investigations are still needed to understand and clarify the whole mechanisms in which phylloquinone looks to be involved.

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