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The exposure of water to a cold atmospheric pressure plasma (CAP) enables the production of plasma activated water (PAW), having high content of reactive species, whose applications were tested on grapevine plants both in greenhouse and in vineyard conditions. Two different CAPs were used for PAW production, evaluating their effectiveness as a possible mean to control plant diseases. Grapevines infected with yellows associated with the presence of phytoplasmas were treated evaluating qualitative and quantitative yield parameters, phytoplasma presence, and gene expression. The results show the capability of PAW to enhance plant defence mechanisms and, as demonstrated in the field trials, confirmed its ability to improve the health status of the treated plants. Quantitative (q)RT-PCR analyses allowed to determine the transcription level of genes involved in the plant defence response (phenylalanine ammonia-lyase, pal) and in the plant phytoalexin metabolism of PAW-treated materials. The number of symptomatic grapevine plants in vineyards was significantly reduced by the treatments. Transcriptional and post-transcriptional molecular analyses highlighted the PAW's ability to enhance the expression of genes encoding the main enzymes involved in the phytoalexin biosynthetic pathway (flavonoids and stilbenes). The PAW ability to enhance some of the plant defence mechanisms also improving the health status of the treated plants was therefore experimentally demonstrated. After three years of trials the overall results demonstrated the possible use of PAW to reduce the disease severity, induce plant resistance both in open field and greenhouse, improving plant healthy status and grapevine yield production.