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Review

Manipulation of oxalate metabolism in plants for improving food quality and productivity

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ABSTRACT

Oxalic acid is a naturally occurring metabolite in plants and a common constituent of all plant-derived human diets. Oxalic acid has diverse unrelated roles in plant metabolism, including pH regulation in association with nitrogen metabolism, metal ion homeostasis and calcium storage. In plants, oxalic acid is also a pathogenesis factor and is secreted by various fungi during host infection. Unlike those of plants, fungi and bacteria, the human genome does not contain any oxalate-degrading genes, and therefore, the consumption of large amounts of plant-derived oxalate is considered detrimental to human health. In this review, we discuss recent biotechnological approaches that have been used to reduce the oxalate content of plant tissues.

1. Introduction

Oxalic acid is a small dicarboxylic acid that is in many plant-derived human diets. Oxalic acid is also a common metabolite in plants and may constitute 3–80% of plant dry mass (Libert and Franceschi, 1987; Tooulakou et al., 2016). Oxalic acid is secreted by filamentous fungi during host interaction and is also synthesized by certain bacteria (Hamel et al., 1999; Nakata and He, 2010). Oxalic acid has two pKa values of 1.23 and 4.26 and is a strong dicarboxylic acid. Because of the powerful metal chelating potential, oxalic acid generally exists as oxalate salts in plants and humans (Peck et al., 2016). The bulk of the content of both the soluble and insoluble oxalate in plant tissues is located in the vacuole (Walker and Famiani, 2018), and at the pH of the vacuole, sodium and potassium oxalates are soluble salts, but calcium oxalates are insoluble crystals.

In plants, oxalate has diverse unrelated functions and these depend on both plant species and tissue. Such functions include both pH and metal ion homeostasis and plant defence (Walker and Famiani, 2018). The oxalate content of plant tissues varies massively among both different species of plants and different tissues of a given plant (Nguyên and Savage, 2013; Walker and Famiani, 2018). In angiosperms, calcium oxalate crystals can be found in any tissue or organ as an intracellular or extracellular deposit. Intracellular calcium oxalate crystals occur particularly in the vacuoles of specialized cells called crystal idioblasts (Franceschi and Nakata, 2005). However, in gymnosperms, most of the crystals form in the cell wall (Oladele, 1982; Kinzel, 1989; Fink, 1991a, 1991b). The crystals may have a role in regulating free calcium levels in plants (Franceschi and Nakata, 2005). Oxalic acid is also considered a pathogenesis factor in plants because it is synthesized and secreted by several phytopathogenic fungi during host colonization, resulting in significant loss of crop produce (Dutton and Evans, 1996). Oxalic acid creates a low pH environment for the action of cell wall-degrading enzymes secreted by these phytopathogens. Oxalic acid also weakens the cell wall by chelating Ca^{2+} in plant cell walls to create the opportunity for fungal infection (Dutton and Evans, 1996). High accumulation of oxalic acid during fungal infection increases the level of reactive oxygen species in tobacco plants, resulting in wilting of plant tissue and cell death (Kim et al., 2008). Oxalic acid activates an early anionic efflux, which is an upstream event for the ethylene synthesis required for programmed cell death in *Arabidopsis thaliana* cells (Errakhi et al., 2008). Moreover, oxalic acid induces stomatal opening (Guimarães and Stotz, 2004) and is toxic when applied to plant leaves (Dong et al., 2008).

For human health, oxalate is a serious concern because of health-related hazards due to high oxalate levels in certain plant-derived foods (Nguyên and Savage, 2013). Hyperoxaluria, excessive urinary excretion of oxalate, can develop from overabsorption of oxalate in the gastrointestinal tract or endogenous overproduction of oxalate in the liver (Williams and Wandzilak, 1989). Further, accumulation of oxalate can cause several other pathological disorders associated with hyperoxaluria, such as cardiomyopathy, cardiac conductance disorders, hypocalcemia, calcium oxalate stone disease, renal failure and even toxic

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death Camici et al. (1982); Lindsjo et al. (1989); Williams and Wandzilak (1989); Rodby et al. (1991); Curhan et al. (1993). In humans, calcium oxalate accounts for nearly 80% of all kidney stones, and in severe cases, end-stage renal disease can develop (Moe, 2006; Taylor and Curhan, 2008; Alexander et al., 2012). Data from National Health and Nutrition Examination Surveys (NHANES) show that in the USA, kidney stone prevalence increased from 3.2% in 1980 to 8.4% in 2010 for both males and females and also in children (Scales et al., 2012). Kidney stones affect up to 5% of the population, with a lifetime risk of passing a kidney stone of approximately 8–10% (Parmar, 2004). Moreover, oxalic acid is also a precursor for the biosynthesis of a neurotoxin, β-N-oxalyl-L-α,β-diaminopropionic acid (β-ODAP) (Xiong et al., 2015). The grass pea (*Lathyrus sativus)* contains a high amount of β-ODAP, and therefore, prolonged consumption of *L. sativus* causes neurolathyrism in humans, a disease characterized by spasticity of leg muscles and paralysis of lower limbs (Yan et al., 2006).

2. Oxalate metabolism: pathways and enzymes

In plants, metabolism of oxalate is a somewhat complex process, and various pathways can be used depending on the tissue and cell type (Walker and Famiani, 2018). Oxalate is proposed to have three primary precursors, namely, glyoxylate/glycolate, oxaloacetate, and ascorbate (Fig. 1A). The oxidation of glyoxylate/glycolate results in the accumulation of oxalate during photorespiration and the glyoxylate cycle in plants (Libert and Franceschi, 1987; Franceschi and Nakata, 2005). The oxidation of oxaloacetate can also form oxalate and acetate. Another significant precursor of oxalate in many plant species is L-ascorbic acid. The breakdown of oxalate is conducted by the activities of the following enzymes: (1) Oxalate oxidase, (2) Oxalate decarboxylase, (3) Oxalyl-CoA synthetase or Oxalate-CoA ligase and (4) Oxalyl-CoA decarboxylase/formyl-CoA transferase. In plants, the precursor/pathway used for oxalate biosynthesis is debatable. However, based on the available literature, the breakdown of oxalate in plants is mediated by primarily oxalate oxidase and oxalyl-CoA synthetase. Moreover, scientists have also decreased the oxalate content in plants by expressing oxalate decarboxylase from fungi. Oxalate oxidase (EC 1.2.3.4), a member of the family of oxidoreductases, catalyses the oxygen-dependent oxidation of oxalate and produces carbon dioxide and hydrogen peroxide (Fig. 1B). Oxalate decarboxylase (EC 4.1.1.2) converts oxalic acid into carbon dioxide and formate (Fig. 1B). Oxalyl-CoA synthetase (EC 6.2.1.8) is an ATP-dependent enzyme that catalyses the CoA-dependent pathway of oxalate catabolism and forms oxalyl-CoA (Fig. 1B). Oxalyl-CoA decarboxylase (EC 4.1.1.8) is a thiamin-dependent enzyme that converts oxalyl-CoA to formyl-CoA and CO_2 (Fig. 1B). In contrast to Oxalyl-CoA decarboxylase, formyl-CoA transferase (EC 2.8.3.16) uses the substrates oxalate and formyl-CoA for the synthesis of formate and oxalyl-CoA (Fig. 1B).

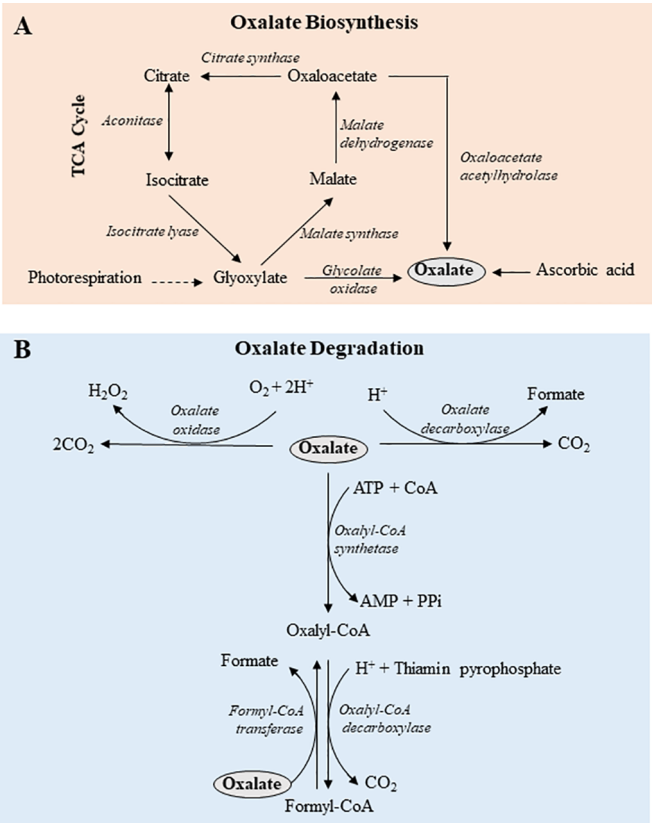

Fig. 1. Schematic representation of oxalic acid biosynthesis and degradation. (A) Oxalic can be formed via three main precursors namely, glyoxylate/glycolate, oxaloacetate and ascorbate (B) Degradation of oxalic acid takes place by Oxalate Decarboxylase, Oxalate Oxidase, Oxalyl-CoA Decarboxylase/Formyl-CoA Transferase.

3. Biotechnological approaches for low oxalate crops

As discussed earlier, oxalate plays various beneficial roles in plants, and high oxalate accumulation is toxic to cell growth and decreases the nutritional quality of plant foods. Therefore, the content of oxalate in plant-derived food must be strictly regulated, and a better understanding of oxalate metabolism is of theoretical and practical importance for crop nutritional quality and productivity. To regulate the content of oxalate in plant-derived food, various oxalate-metabolizing enzymes and particularly oxalate-degrading enzymes have been targeted. The oxalate-metabolizing enzymes (either from plants or microbes) and their genes have been widely used in numerous biotechnological applications, such as crop improvement, development of genetically engineered food with low oxalate content for human consumption, and human diagnostic and therapeutic applications. These applications are summarized in Table 1.

3.1. Expression of oxalate oxidase in plants

Oxalate oxidase activity is observed in many plants, such as amaranthus, beet, maize, oats, rice, and rye, among others, and is specifically associated with germin proteins of wheat and barley (Dumas et al., 1993; Lane et al., 1993). The wheat germin gf-2.8 is a well characterized oxalate oxidase, and heavy metals, polyamines, wounding and viral infection significantly increase the expression (Berna and Bernier, 1999). Donaldson et al. (2001) first reported plant resistance against the fungus *S. sclerotiorum* in a transgenic plant expressing wheat germin gf-2.8. These soya bean transgenic plants showed reduced disease progression and lesion length after inoculation with *S. sclerotiorum.* Further, these transgenic lines were tested for alteration of genome-wide gene expression in response to *S. sclerotiorum* using microarray analysis (Calla et al., 2014). The study identified several specific genes and gene families related to defence response, pathogenesis-related (PR) proteins, cell wall metabolism, ethylene, jasmonate pathways and phenylpropanoid pathways that were modulated as a direct consequence of oxalic acid secreted by the pathogen during infection, suggesting that transgenic soybean expressing wheat germin gf-2.8 was more resistant by initiating a stronger and more rapid defence response than that of the wild type. Furthermore, in several other crops, such as sunflower, peanut and *Brassica napus,* expressing barley or wheat germin protein also increases resistance to *Sclerotinia* (Thompson et al., 1995; Livingstone et al., 2005; Dong et al., 2008; Partridge-Telenko et al., 2011). In tobacco, germin gf-2.8 was expressed to increase OxO activity and H_2O_2 concentration to increase the tolerance to oxidative stress (Wan et al., 2009). Notably, these transgenic tobacco plants showed increased tolerance to methyl viologen (MV) or high light-induced oxidative stress in both short-term and long-term tests. Further,

Table 1
Biotechnological applications of oxalate degrading enzymes/genes.

Source of Gene/Enzyme	Application	Reference
Oxalate Oxidase		
Triticum aestivum	Regulation by biotic and abiotic stress in transgenic tobacco	Berna and Bernier (1999)
Triticum aestivum	Enhanced resistance to *Sclerotinia sclerotiorum* in soya bean	Donaldson et al. (2001)
Triticum aestivum	Increased *Septoria musiva* resistance in poplar	Liang et al. (2001)
Triticum aestivum	Enhanced resistance to *Sclerotinia sclerotiorum* in sun flower	Hu et al., 2003
Hordeum vulgare	Enhanced resistance to *Sclerotinia minor* in peanut	Livingstone et al. (2005)
Triticum aestivum	Improved resistance to European corn borer (*Ostrinia nubilalis*) in *Zea mays*	Mao et al. (2007)
Triticum aestivum	Enhanced resistance to *Sclerotinia sclerotiorum* in *Brassica napus*	Dong et al. (2008)
Triticum aestivum	Increased tolerance to oxidative stress in tobacco	Wan et al. (2009)
Hordeum vulgare	Resistance to Sclerotinia blight in virginia-type peanut	Partridge-Telenko et al. (2011)
Triticum aestivum	Reduced *Cryphonectria parasitica* induced necrosis in *Castanea dentata*	Zhang et al., 2013a,b
Oryza sativa	Enhanced resistance against sheath blight in rice	Molla et al. (2013)
Hordeum vulgare/Sorghum bicolor	Quantification of urinary oxalate	Petrarulo et al. (1994); Pundir et al. (2008)
Bougainvillea glabra	Reduction in urinary oxalate in hyperoxaluric rat model by liposome encapsulated oxalate oxidase	Dahiya and Pundir, 2013
Oxalate Decarboxylase		
Flammulina velutipes	Enhanced tolerance to *Sclerotinia sclerotiorum* in transgenic soya bean	Cunha et al. (2010)
Flammulina velutipes	Reduced necrosis induced by Nep1-like protein of *Moniliophthora perniciosa* in transgenic tobacco	da Silva et al. (2011)
Flammulina velutipes	Enhanced resistance against *Sclerotinia sclerotiorum* in transgenic tobacco	Kesarwani et al. (2000)
Flammulina velutipes	Enhanced resistance against *Sclerotinia sclerotiorum* in transgenic tomato	Kesarwani et al. (2000)
Flammulina sp.	Enhanced tolerance to *Sclerotinia sclerotiorum* in transgenic lettuce (*Lactuca sativa*)	Dias et al. (2006)
Flammulina velutipes	Improved nutritional quality in tomato	Chakraborty et al. (2013)
Burkholderia phytofirmans	Role of oxalotrophy in root colonization	Kost et al. (2014)
Coniothyrium minitans	Regulation of mycoparasitism and antibiosis of *Coniothyrium minitans* against *Sclerotinia sclerotiorum*	Zeng et al. (2014)
Sclerotinia sclerotiorum	Role in host infection related to compound appressorium formation and function	Liang et al. (2015)
Flammulina velutipes	Improved nutritional quality and resistance against *Sclerotinia sclerotiorum* in soya bean	Kumar et al. (2016)
Flammulina velutipes	Improved nutritional quality and resistance against *Sclerotinia sclerotiorum* in grass pea	Kumar et al. (2016)
Dichomitus squalens	Oxalate degradation in wood decaying white-rot fungus *Dichomitus squalens*	Mäkelä et al., 2009, 2014
Bacillus subtilis	Oxalate degradation by recombinant *Lactobacillus plantarum* for probiotic dairy and pharmaceutical preparations	Anbazhagan et al., 2013
Bacillus subtilis	Reduced urinary oxalate in hyperoxaluric rat model	Lee et al. (2014); Sasikumar et al. (2014)
Bacillus subtilis	Protection against oxidative stress in human embryonic kidney (HEK293) cells	Albert et al. (2017)
Oxalyl-CoA decarboxylase/Formyl-CoA transferase		
Bifidobacterium animalis	Oxalate-Degradation in *Bifidobacterium animalis*	Turroni et al. (2010)
Lactobacillus acidophilus	Oxalate degradation in *Lactobacillus* for probiotic dairy and pharmaceutical preparations	Turroni et al. (2007)
Oxalobacter formigenes	Oxalate degradation in human embryo kidney (HEK) 293 cells	Ye et al. (2007)
Bifidobacterium lactis	Oxalate degradation in *Bifidobacterium lactis* for probiotic dairy and pharmaceutical preparations	Federici et al., 2004
Lactobacillus reuteri	Role of *frc* in oxalate metabolism, host colonization and acid stress response	Kullin et al. (2014)
Oxalyl-CoA synthetase		
Arabidopsis thaliana	Oxalate degradation, seed development and increased resistance to *Sclerotinia sclerotiorum* in *Arabidopsis thaliana*	Foster et al. (2012)
Saccharomyces cerevisiae	Oxalate degradation and protection against oxidative stress in *Saccharomyces cerevisiae*	Foster and Nakata (2014)
Medicago truncatula	Role in pathogenesis of *Sclerotinia sclerotiorum* in *Medicago truncatula*	Foster et al. (2016)
Vigna umbellata	Oxalate degradation and Al tolerance in tobacco	Lou et al. (2016)
Oryza sativa	Role in pathogenesis of bacterial blight and Al toxicity in rice	Peng et al. (2017)

the activities and gene expression of key antioxidant enzymes, such as superoxide dismutase, catalase, ascorbate peroxidase and glutathione reductase, were increased in these transgenic tobacco plants. This study suggested that H_2O_2 produced by OxO also provided resistance to oxidative stresses via induction of the antioxidative defence system (Wan et al., 2009).

A major insect defence mechanism in corn plants is mediated by hydroxamic acid (DIMBOA) and related compounds of the shikimate pathway and the synthesis of phenolic acids (Frey et al., 1997). Transgenic *Zea mays* expressing a wheat oxalate oxidase, *oxo*, showed altered levels of hydroxamic acids and phenolic acids resulting in improved resistance against European corn borer (*Ostrinia nubilalis*) in the field (Mao et al., 2007). To degrade the oxalic acid secreted by the fungus *Cryphonectria parasitica* to infect host American chestnut (*Castanea dentata*), the *oxo* from wheat was transferred to American chestnut plants (Zhang et al., 2013a). These plants were more tolerant against the fungus *C. parasitica*. To evaluate the role of oxalate oxidase in woody plants, the wheat *oxo* gene was introduced into a hybrid poplar clone, *Populus* × *euramericana* ('Ogy'). The *oxo*-transformed plants exhibited improved resistance towards the poplar pathogenic fungus *Septoria musiva* (Liang et al., 2001). Oxalate oxidase also degrades oxalates during the growth of the white rot fungi *Ceriporiopsis subvermispora and Dichomitus squalens* on natural spruce wood substrate and produces hydrogen peroxide that is required for lignin degradation (Escutia et al., 2005; Mäkelä et al., 2014). In the high calcium oxalate-accumulating species *Theobroma cacao*, the calcium oxalate crystals during infection of *Moniliophthora perniciosa*, (the causal pathogen of witches' broom disease of *T. cacao*) are degraded by oxalate oxidase (Ceita et al., 2007). Furthermore, rice oxalate oxidase 4 (*Osoxo4*) has been overexpressed in a green tissue-specific manner (Molla et al., 2013), and the transgenic rice leaves are more tolerant to exogenous oxalic acid than those of the control and exhibited significantly increased durable resistance to sheath blight pathogen *Rhizoctonia solani* via modulating the expression of defence-related genes in response to pathogen infection. However, Zhang et al. (2013b) suggest that the role of OxO as a disease resistance factor in rice is doubtful. They reported change in expression of all four *OsOxO* gene family members and OxO activity under biotic stress. The overexpression of *OsOxO1* increased the expression of *OsOxO3* but reduced that of *OsOxO4*. When they overexpressed *OsOxO4,* the up-regulation of *OsOxO3* was observed

without altering the other two genes. However, they did not determine the mechanism underlying this observed gene expression profile. Additionally, the transgenic rice plants with higher OxO activity were not more resistant to *Magnaporthe oryzae* and *Xanthomonas oryzae* than the wild type (Zhang et al., 2013b). Recently, Qi et al. (2017) showed increased resistance to *Magnaporthe oryzae* and *Rhizoctonia solani* in rice (*Oryza sativa* L.) by expressing another oxalate-degrading enzyme, the oxalate decarboxylase protein Bacisubin from *Bacillus subtilis*.

Apart from applications in crop improvement, oxalate oxidases have been successfully utilized in diagnostics and therapeutics of human diseases. The oxalate oxidases of plant origin are used to quantitate oxalate in various biological samples, such as serum, urine, and plasma, among others (Petrarulo et al., 1994; Pundir et al., 2008). Moreover, an oxalate oxidase purified from *Bougainvillea* leaves was immobilized onto ethylene maleic anhydride (EMA) to reduce the urinary oxalate excretion by hyperoxaluric rats (Dahiya and Pundir, 2013). The EMA-oxalate oxidase encapsulated liposome caused oxalate degradation in experimental hyperoxaluria suggesting that oxalate oxidase could be used as a therapeutic agent in hyperoxaluria leading to urinary stones.

3.2. Expression of oxalate decarboxylase in plants

Oxalate decarboxylase (OXDC) was first identified in the basidiomycete fungi *Flammulina (Collybia) velutipes* (Shimazono, 1955) and is active in other fungi, such as *Aspergillus* sp., *Agaricus bisporus, Coriolus versicolor*, *Myrothecium verrucaria*, *Postia placenta,* and *Sclerotinia* sp. The oxalate decarboxylases purified from different organisms have some differences in their biochemical properties but share several intriguing features. First is the requirement of molecular oxygen for catalytic turnover of OXDC (Tanner et al., 2001; Reinhardt et al., 2003). Second, they are highly specific for oxalate as substrate and require an acidic pH for their optimum activity (Tanner et al., 2001; Reinhardt et al., 2003). Third, all these enzymes contain manganese as cofactor (Tanner et al., 2001).

Mehta and Datta (1991) first cloned the gene of OXDC from the edible fungus *Flammulina (Collybia) velutipes*. They also purified and characterized the oxalic acid inducible OXDC enzyme (FvOXDC) from *Flammulina velutipes*. This enzyme not only has an acidic pI but also is very stable over a wide pH range (Azam et al., 2001). Further, to elucidate the molecular regulatory mechanism of *FvOXDC* expression, Azam et al. (2002) identified a low pH responsive element (LPRE) in the *FvOXDC* promoter. They proposed that low pH-induced activation of *FvOXDC* is mediated by the binding of a novel transcription factor through the LPRE site in the *FvOXDC* promoter (Azam et al., 2002). Recently, *FvOXDC* was also found to be transcriptionally regulated by a calmodulin (CaM)-like EF hand protein, FvCaMLP. The FvCaMLP binds to E-box elements of the *FvOXDC* promoter in the presence of Ca^{2+} to regulate *FvOXDC* expression upon oxalic acid induction (Kamthan et al., 2015).

Kesarwani et al. (2000) transferred the *FvOXDC* in tobacco and tomato and generated stable transgenic lines. These *FvOXDC*-expressing transgenic lines not only contained a low oxalate level but also showed resistance to *S. sclerotiorium*. The improved resistance was possibly due to induced expression of pathogenesis-related proteins in the *FvOXDC*-expressing transgenic lines (Kesarwani et al., 2000; Chakraborty et al., 2013). Further, transgenic *Lactuca sativa* expressing *FvOXDC* also has improved resistance against *S. sclerotiorum* (Dias et al., 2006). Moreover, transgenic tobacco plants expressing *FvOXDC* were also resistant to another oxalic acid-producing pathogen *Moniliophthora perniciosa*, the causal agent of witches' broom disease of *T. cacao* (da Silva et al., 2011). Recently, Kumar et al. (2016) reported the expression of *FvOXDC* reduced oxalic acid level in soya bean and grass pea seeds without ill effects on seed protein quality. They also suggested that the decrease in the oxalate level in grass pea further corresponded to a reduction in neurotoxin β-ODAP level. Moreover, they also reported that constitutive and seed-specific expression of *FvOXDC* in soya bean and grass pea resulted in increased tolerance to *S. sclerotiorium* (Cunha et al., 2010; Kumar et al., 2016).

To understand the oxalic acid accumulation and virulence of *S. sclerotiorum*, two oxalate decarboxylase-encoding genes (*Ss-odc1* and *Ss-odc2*) were characterized (Liang et al., 2015). The expression of *Ss-odc1* increased in vegetative hyphae, apothecia, early stages of compound appressorium development and during plant colonization, whereas *Ss-odc2* accumulated during mid to late stages of compound appressorium development and down-regulated the oxalic acid accumulation. Moreover, deletion mutants in appressorium development and infection at the pre-invasive stage were defective. Thus, a fine-tuned regulation of oxalic acid accumulation occurs during *S. sclerotiorum* pathogenesis. To evaluate the role of oxalic acid in mycoparasitism and antifungal activity of *Coniothyrium minitans* against *S. sclerotiorum*, the *Cmoxdc1*-encoding oxalate decarboxylase was characterized. Disruption of *Cmoxdc1* in *C. minitans* significantly decreased the mycoparasitism and antibiosis of *C. minitans* on *S. sclerotiorum* in which OA accumulated (Zeng et al., 2014). Kost et al. (2014) showed that oxalotrophy, the ability to use oxalate as a carbon source, is required for successful plant colonization by the broad-host endophyte *Burkholderia phytofirmans*. They reported that the oxalate decarboxylase mutant of *B. phytofirmans* lost the ability to grow on oxalate and was significantly impaired in early colonization of both lupine and maize compared with the wild type. Oxalate degradation by *Burkholderia* is considered a plant-protecting feature because lowering the oxalate levels on plant surfaces might alleviate the infection potential of oxalate-producing phytopathogenic fungi or bacteria.

Oxalate decarboxylase has also been widely used in therapeutics and probiotic dairy and pharmaceutical preparations. Scientists expressed *Bacillus subtilis OXDC* in *Escherichia coli* and *Lactobacillus plantarum* and observed oxalate-degrading activity *in vitro* and in an *in vivo* rat model (Jeong et al., 2009; Lee et al., 2014; Sasikumar et al., 2014). Moreover, Albert et al. (2017) expressed the *Bacillus subtilis YvrK* gene encoding *OXDC* into Human Embryonic Kidney 293 (HEK293) cells and observed an increase in the survival rate of HEK293 cells pre-incubated with oxalate.

3.3. Expression of oxalyl-CoA decarboxylase and formyl-CoA transferase

Oxalyl-CoA decarboxylase and formyl-CoA transferase are necessary for the utilization of oxalate by intestinal bacteria and are generally present in *Bacillus oxalophilus, Oxalobacter formigenes*, and *Pseudomonas oxalaticus*, among others. Oxalyl-CoA decarboxylase activity has also been identified in *Saccharomyces cerevisiae*, *Neurospora crassa, Torula utilis*, *Triticum vulgare*, *Cucurbita pepo*, *Pisum sativum* and bean. The Oxalyl-CoA decarboxylase and formyl-CoA transferase enzymes were first purified from *Oxalobacter formigenes* (Baetz and Allison, 1989, 1990). The genes for Oxalyl-CoA decarboxylase (*oxc*) and formyl-CoA transferase (*frc*) were cloned from *Oxalobacter formigenes* and *Bifidobacterium lactis* and expressed into *E. coli* cells (Lung et al., 1991). These recombinant *E. coli* cells decreased oxalate significantly after the addition of oxalic acid. Further, oxalate-degrading activity in several *Lactobacillus* species was also identified (Turroni et al., 2007). In *Lactobacillus acidophilus, frc* and *oxc* form an operon because two predicted terminators flank the two genes (Azcarate-Peril et al., 2006). The HEK293 cells transfected for expression of *oxc* and *frc* genes from *Oxalobacter formigenes* degrade the oxalates significantly (Ye et al., 2007). Turroni et al. (2010) studied the oxalate degradation potential of fourteen *Bifidobacterium* strains and isolated the *oxc* by screening a genomic library of *Bifidobacterium nimalis*. Recently, a significant role during host colonization and survival of acid stress by *Lactobacillus reuteri* was determined for formyl-CoA transferase (Kullin et al., 2014). The intestinal bacteria expressing *oxc* and *frc* could be used as bacterial probiotics and pharmaceutical preparations in lowering hyperoxaluria and other oxalate-related disorders (Abratt and Reid, 2010; Peck et al., 2016). Recently, Yang et al. (2018) identified and cloned an oxalate-

inducing oxalyl-CoA decarboxylase1 (OCD1) from *Zea mays*. The breakdown of oxalyl-CoA into formyl-CoA and CO_2 is catalysed by ZmOCD1 downstream of oxalyl-CoA synthetase. They reported increased oxalate accumulation in the *Zmocd1* mutant seeds of *Zea mays* compared with that of the control and suggested that ZmOCD1 affects endosperm development, seed metabolome and nutritional quality in *Zea mays*.

3.4. Expression of oxalyl-CoA synthetase

Giovanelli in 1966 first purified oxalyl-CoA synthetase from pea seeds. The oxalate inducible Acyl Activating Enzyme 3 (AAE3) gene encoding an oxalyl-CoA synthetase has been reported in Arabidopsis, *Medicago truncatula*, rice bean (*Vigna umbellate*), rice, and *Saccharomyces cerevisiae* (Foster et al., 2012, 2016; Foster and Nakata, 2014; Lou et al., 2016; Peng et al., 2017). In contrast to oxalate oxidase, which is localized to the cell wall, oxalyl-CoA synthetase is localized in the cytoplasm (Foster et al., 2012). In Arabidopsis, *AAE3* is required for oxalate degradation, playing a role in defending plants against oxalate-secreting fungal phytopathogens, normal seed development and regulation of calcium oxalate crystal accumulation (Foster et al., 2012, 2016). The transcriptome data from three crop plants rice bean, buckwheat and amaranth show that *AAE3* genes are up regulated by aluminium stress (Chen et al., 2017). Moreover, Lou et al. (2016) demonstrate that oxalate accumulation is associated with aluminium-induced root growth inhibition, and overexpression of *VuAAE3* in tobacco improves aluminium tolerance because of the decrease in oxalate accumulation. Recently, an *AAE3* gene from rice was suppressed with RNAi, which led to increased oxalate content in transgenic rice plants resulting in increased susceptibility towards *Xanthomonas oryzae* and increased resistance to aluminium toxicity (Peng et al., 2017).

In addition to application of oxalate-degrading enzymes/genes in crop improvement and human diagnostic and therapeutic uses, they have potential applications in other areas. In the pulp and paper industry and in forest biorefineries, oxalate-degrading enzymes are used in the prevention of scaling (Cassland et al., 2010). Similarly, in the brewery industry, the use of these enzymes reduces calcium oxalate deposits in beer production (Hiatt and Owades, 1987). Oxalate-utilizing microbes are also capable of enzymatic degradation of oxalic acid and oxalates in the soil. Several oxalate-degrading bacteria, such as *Pandoraea* sp. and *Streptomyces* sp., from the plant rhizosphere and forest soils have been reported and characterized (Sahin, 2004; Jin et al., 2007). These microbes not only contribute to soil formation and fertility but also to retaining/cycling of the essential elements for plant growth and development.

4. Conclusions and future prospects

In the recent years, various biotechnological tools have revolutionized our studies on oxalic acid/oxalate degradation pathways for disease diagnosis and therapeutics, improved food quality and productivity and industrial applications. Oxalate-degrading enzymes and their genes and oxalate-degrading bacteria have been successfully applied in the development of improved food quality (Murphy et al., 2009; Mogna et al., 2014; Murru et al., 2017). Several genetically modified plants and bacteria expressing/suppressing oxalate-degrading enzymes, which may not have use for human consumption, have nevertheless been developed for specific industrial applications. Various transgenic crops containing a low oxalate level have been generated that may be commercialized in the future (Chakraborty et al., 2013; Kumar et al., 2016). Further research focusing on oxalates and oxalate metabolic pathways can provide valuable insights into mechanisms of plant metabolism and other associated pathways controlling plant growth and development under environmental stress responses. Most of the available studies are based on genetic manipulation of oxalate-degrading enzymes; therefore, further attention is required to understand the transcriptional regulatory mechanism of oxalate metabolism in plants. Moreover, studies based on omics approaches, protein crystal structure-enzyme function and mutations in the active site of oxalate-degrading enzymes will be particularly interesting to better understand oxalate metabolism in plants. The recent biotechnological tools of genome engineering, such as CRISPR-Cas9, can significantly accelerate the removal of oxalic acid/oxalates by modifying existing oxalate-degrading genes and targeting oxalate-degrading genes to specific sites in the genome for various crop improvement programs, human health applications and traits for industrial use.

Author contribution

AD proposed the concept of article. VK and MI wrote the article. AD corrected the article. VK, MI and AD read and approved the final version of article.

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