Therapeutic Applications of Microbial Enzymes in the Management of Kidney Stone Diseases

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Abstract

Nephrolithiasis is a terrible pathological condition marked by the presence and formation of kidney stones. It affects around 3–20% of the community in the world. Several environmental, physiological, and nutritional conditions influence this disease. Not only the food sources but also the body's own metabolism add up oxalate content in the human body. The increased intake of oxalate leads to hyperoxaluria, which often results in the formation of calcium oxalate stones, commonly known as kidney stones. The incidences of kidney stone are very common, and the current therapeutic measure of its cure is not much effective. Therefore, new therapeutic approaches are needed. In the last few years, the use of gut microbiome with oxalate-degrading activity has emerged as an excellent therapeutic approach to treat kidney stones. As the genes responsible for oxalate-degrading enzymes are not found in humans use of bacterial enzymes with the ability to degrade oxalate in intestinal digestion has a significant therapeutic impact. This chapter summarizes the roles of microbial enzymes produced by gut microflora involved in the solubilization of the dietary oxalates, and their potential applications in kidney stone diseases.

13.1 Introduction

Kidney stone or urolithiasis is a condition primarily attributed to the deposition of an enhanced level of calcium oxalate in the form of crystals due to supersaturation (of calcium oxalate) during removal of water from urine (Peck et al. 2016). Although oxalic acid is a general component present in human diets, it is also endogenously

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produced during amino acid metabolism. Moreover, oxalic acid is absorbed in the stomach, small bowel, and colon from the dietary sources (Nazzal et al. 2016). Binding with different cations such as sodium, potassium, magnesium, and calcium results in the formation of different oxalate salts but mostly calcium oxalate (Mogna et al. 2014). Ingestion and exposure of a high amount of oxalate lead to building up of oxalate crystals in the kidneys, which might be lethal and cause hypocalcemia, azotemia, and hemorrhage in the visceral organs (Aslani et al. 2011). Oxalates of calcium and phosphate are the main constituents of kidney stones (Bungash et al. 2011). Apart from the formation of stones in the kidney, oxalate crystals can destruct epithelium in the oral cavity and gastrointestinal tract, causing inflammation, diarrhea, and gastric hemorrhage which indirectly becomes a cause of death (Ellis et al. 2015).

As humans lack the enzyme for directly metabolizing oxalate, alternate pathways are used to regulate this potentially toxic compound (Mogna et al. 2014). Current remedial strategies which are used for kidney stones are inefficient and have been proven to be unsuccessful in preventing the recurrence of the disease (Sutherland et al. 1985). However, therapeutic measures such as allopurinol, thiazide, potassium alkali, and tiopronin along with dietary modifications and intake of adequate fluids have been used for a long time to limit urolithiasis (Trinchieri 2013). Hence the evolution of new therapeutic strategies aiming to prevent recurrent stone formation has become the need of the hour. Since a decade, attempts have been made to use plants and oxalate-degrading microbial enzymes to solubilize oxalate kidney stones, and some success has been achieved (Peck et al. 2016). The roles of gut enzymes produced through microflora in the solubilization of the dietary oxalates are a new frontier area for treating kidney stone disease. This chapter provides a brief insight into current research and the roles of gut microbial enzymes for the treatment of kidney diseases (Fig. 13.1).

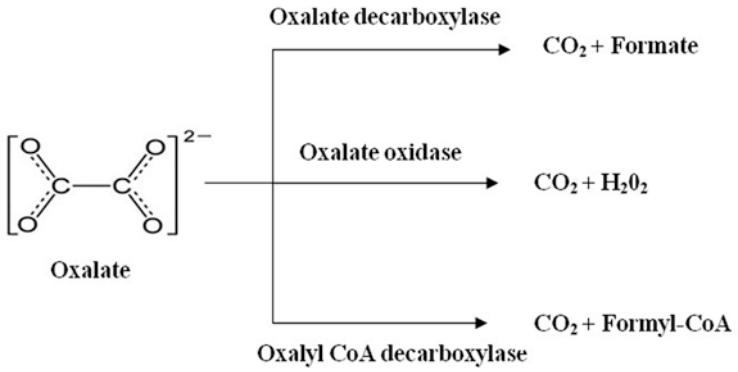

Fig. 13.1 Enzymatic degradation of oxalate

13.2 Role of the Gut Microbiome in Oxalate Degradation

Formation of oxalate stones in humans may be prevented by two symbiotically existing bacterial genera, *Oxalobacter* and *Lactobacillus,* in the gut. Both bacterial genera have been found to act on some biochemical pathways by the intervention of their oxalate-degrading enzymes (Sadaf et al. 2017). It has also been hypothesized that the *Oxalobacter formigenes*, a Gram-negative, obligate anaerobe found in the gastrointestinal tract and in humans, performs a significant role in mediating mammalian oxalate homeostasis (Svedruzic et al. 2005). The bacterium *O. formigenes* colonizes the gut in nearly 70–80% of the healthy population and utilizes oxalate as the sole material for energy and carbon source. Formyl-CoA transferase and oxalyl-CoA decarboxylase are the two enzymes from *O. formigenes,* which catalyze oxalate for biosynthesis (Hoppe et al. 2005). By transferring the coenzyme-A moiety to lactic acid and oxalic acid that is connected with calcium oxalate and calcium phosphate, degradation reaction occurs which results in elevation of oxalate and lactate level (Salminen et al. 2010).

Further, oxalate is broken down into CO_2 and formate, which is further metabolized and excreted via the feces (Hoppe et al. 2005). It has been found that in standard colonization conditions *O. formigenes* can degrade more than 1 g of oxalate per day. However, attempts to culture this bacterium out of fecal specimens have given low colony counts, i.e.. up to 10^6 CFU per gram of wet sample (Allison and Cook 1981). As investigated by Peck et al. (2016) in most of the cases gut of children between the age of 1 and 6 years is more naturally colonized by *O. formigenes,* while 20–25% of the colonization is lost during early adulthood and adolescence in healthy populations (Peck et al. 2016). In addition to *O. formigenes*, other oxalate-degrading bacterial genera are *Lactobacillus*, *Enterococcus*, *Eubacteria*, and *Bifidobacterium*. Amongst them, *Enterococcus faecalis* uses oxalate as a sole carbon and energy source in a nutrient-deficit environment; otherwise it can also consume other substrates for growth (Miller and Dearing 2013). In some circumstances, along with other microflora, natural colonization of *O. formigenes* in the gut is affected. However, continuous use of antibiotics, e.g., in patients with cystic fibrosis, or therapeutic use in diseases such as Crohn's disease also exacerbates kidney stone formation (Kumar et al. 2004; Hatch 2014).

13.3 Probiotic Therapies for the Treatment of Kidney Stones

Use of probiotics as a therapeutic and preventive measure in kidney stone and hyperoxaluria has gained much attention. It has been found that in the form of probiotics, aerotolerant *Lactobacillus* and obligatory anaerobe *Bifidobacterium* present in the intestine show oxalate-degrading activity, which is considered useful for the prevention of stone formation (Abratt and Reid 2010). Studies confirmed that through treatment with *Bifidobacterium lactis* DSM 10140, *Bifidobacterium longum* MB 282, and *Bifidobacterium adolescentis* MB 238 strains, the degradation of oxalate could be achieved up to 61%, 35.2%, and 57%, respectively (Turroni et al. 2007; Abratt and

Reid 2010). Both *Lactobacillus* and *Bifidobacterium* break down oxalate only in the presence of glucose and lactose; however, they do not use oxalate as a sole source of carbon and hence they are also known as "generalist oxalobacters" (Sadaf et al. 2017). Studies reveal that *Lactobacillus acidophilus* NCFM contains genes that code for the oxalate CoA decarboxylase (Oxc) and oxalate CoA transferase (frc) enzymes and constitute the functional oxalate-degrading formyl-CoA. A number of natural sources such as milk, yogurt, pickles, tomato, cucumber, spinach, and dieffenbachia plant are found to contain natural population of *Lactobacillus* and *Oxalobacter* probiotics used in the prevention of kidney stones (Gomathi et al. 2014). In a study, Lieske et al. (2010) reported that application of mixed cultures of *Bifidobacterium infantis, L. acidophilus, Streptococcus thermophilus*, and *Lactobacillus brevis* sold under the brand name of "Oxadrop" with a low-oxalate diet did not produce any effect on the inhibition of kidney stone formation but when given with a normal diet it reduced oxalate excretion. The probiotic capability of *O. formigenes* in the prevention of kidney stone formation has also been reported. However, studies have demonstrated that only an unabated inoculation of *O. formigenes* with an oxalate-rich diet reduced the concentration of urinary oxalate and restoring back to low-oxalate diet resulted in low oxalate degradation with apparent loss of *O. formigenes* colonization (Miller and Dearing 2013).

13.4 Oxalate Degradation by Microbial Enzymes

Absence, deficiency, or complete lack of oxalate degradation enzymes evokes the formation of calcium oxalate. Hence, utilization of oxalate-degrading enzymes in the prevention and treatment of calcium oxalate stones has suddenly increased (Cai et al. 2018). Three major types of microbial enzymes (Table 13.1) reported for oxalate degradation are (1) oxalate decarboxylase (ODC, oxalate carboxylyase, EC 4.1.1.2), (2) oxalate oxidase (OXO, oxalate: oxygen oxidoreductase, EC 1.2.3.4), and (3) oxalyl-CoA decarboxylase (oxalyl-CoA carboxylyase, EC 4.1.1.8) (Mäkelä et al. 2010).

13.4.1 Oxalate Decarboxylase

Oxalate decarboxylase (EC 4.1.1.2) was first discovered in basidiomycetes fungi, *Collybia (Flammulina) velutipes* and *Coriolus hirsutus* (Twahir et al. 2015). Apart from fungal sources, in some cases animal tissue (liver of guinea pigs) has also been described to exhibit oxalate decarboxylase activity (Murthy et al. 1981). Later, bacteria, plants, and fungi were characterized as established sources of oxalate decarboxylase (Svedruzic et al. 2005). Basically, in the presence of dioxygen, which acts as a co-catalyst, the enzyme produces formate and carbon dioxide by the heterolytic cleavage of unreactive carbon–carbon bond in oxalic acid. A little bit of oxalate oxidase activity leading to the formation of carbon dioxide and hydrogen peroxide in the place of formate has also been reported (Twahir et al. 2015).

Table 13.1 Sources and mechanism of action of enzymes of oxalate degradation

Enzyme	Source	Mechanism of action	References
Oxalate decarboxylase	**Bacteria**	Cleaves the oxalate carbon–carbon bond heterolytically to formate and CO_2 through a radical based catalytic cycle that involves electron transfer from the coordinated Mn^{2+} ion to the bound dioxygen	Yu-Hu et al. (2008); Mäkelä et al. (2010); Alberta et al. (2017)
	Agrobacterium tumefaciens *Bacillus subtilis* *Thermotoga maritima* and *Pandorea* sp.		
	Fungi		
	Trametes hirsuta (Coriolus hirsutus) *Flammulina (Collybia) velutipes* *Agaricus bisporus* *Postia placenta* *Pleurotus ostreatus* and *Aspergillus* sp.		
Oxalate oxidase	**Plant materials**	Oxalic oxidase at first gets oxidized by O_2 which upon catalysis cleaves oxalic acid into two CO_2 molecules along with generation of H_2O_2	Svedruzic et al. (2005); Hu et al. (2015)
	Barley seedlings, stems, and roots *Amaranthus* leaves Beet stems and leaves Sorghum leaves Maize, oats, rice, and rye Banana, azalea		
	Fungi		
	White-rot fungi basidiomycetes		
Oxalyl-CoA decarboxylase	**Bacteria**	Converts activated oxalyl-CoA to formyl-CoA and CO_2 employing thiamin pyrophosphate as a cofactor	Svedruzic et al. (2005); Mäkelä et al. (2010)
	Pseudomonas oxalaticus *Bacillus oxalophilus* *O. formigenes* *Bifidobacterium lactis* *Lactobacillus acidophilus* and *Thiobacillus novellus*		

Fungal and bacterial oxalate decarboxylases belong to a functionally varied superfamily of proteins known as the cupins and contain a range of conserved residues forming β-barrels which support the binding of different metal cofactors (Yu-Hu et al. 2008). Cupin proteins share primary and tertiary structure with two conserved histidine-containing Mn^{2+}-binding motifs separated by an inter-motif region, which varies in length (Mäkelä et al. 2010). Functional oxalate decarboxylase consists of two

trimers of the bicupin subunits, therefore, probably making it a hexameric enzyme (Anand et al. 2002). The fungal oxalate decarboxylases are secretory enzymes while bacterial ones are involved in the energy metabolism and are probably confined to cytosol (Yu-Hu et al. 2008). The most thoroughly studied oxalate decarboxylase belongs to *Bacillus subtilis* (Anand et al. 2002). The expression of oxalate decarboxylase gene *oxdC* in *B. subtilis* in response to low pH is regulated by sigma factor, YvrI, and its co-regulators, YvrHa and YvrL, which function as an anti-sigma factor (Just et al. 2007; MacLellan et al. 2008; MacLellan et al. 2009). It is unexpectedly present in vesicles on the cell wall (Antelmann et al. 2007). *B. subtilis* oxalate decarboxylase consists of a pentapeptide loop (amino acid residues 161–165) that makes up the lid structure which is involved in determining the reaction specificity and enzyme's catalytic efficiency (Burrell et al. 2007; Svedruzic et al. 2007).

Moreover, oxalate decarboxylase activity may convert into oxalate oxidase activity by forming H_2O_2 due to a mutation in the amino acids of the lid region (Burrell et al. 2007). Earlier it was proposed that the activity of *B. subtilis* oxalate decarboxylase to convert oxalate into formate and CO_2 is conserved in its N-terminal domain (Just et al. 2004; Burrell et al. 2007; Svedruzic et al. 2007) but later evidence showed that both N- and C-terminal domains may catalyze the decarboxylation reaction (Tabares et al. 2009). The structural and spectroscopic studies revealed that site 1 acts as the catalytic site, in the presence of two manganese-binding sites in *B. subtilis*. The data also suggests that site 1 contains formate bound to it in one crystal structure, that the lid carries a suitable proton donor Glu162 that can cause isolation of site 1 in solution, and that site 2 shows marked inaccessibility to solvents in both known structures (Just et al. 2007). A mutation leading to the replacement of the Glu162 results in no oxalate decarboxylase activity and significant oxalate oxidase activity (Just et al. 2004).

Although the activity of oxalate decarboxylase has been observed in the cell wall or released in the culture media or bound to the extracellular polysaccharide matrices, fungal oxalate decarboxylase is known to show intracellular enzyme activity which is predominantly confined close to the plasma membrane or in vesicles (Sato et al. 2007). In several ascomycetous and basidiomycetous species, the enzyme's translated genes contain N-terminal secretion leader peptides that aid in the release of oxalate decarboxylase of fungal origin (Sato et al. 2007; Mäkelä 2009; Mäkelä et al. 2009).

The relevance of oxalate decarboxylase in biotechnology has been discovered way back in the 1960s when the enzyme was analyzed in a brewing process for the removal of oxalic acid (Haas and Fleischman 1961). Later, the enzyme was applied in clinical samples as a diagnostic tool for knowing the oxalate levels in clinical samples. Plants expressing oxalate decarboxylase were also used in the control of plant pathogens (Kesarwani et al. 2000; Dias et al. 2006; Jin et al. 2007; Walz et al. 2008). However, the therapeutic use of this enzyme in kidney stone removal and prevention of hyperoxaluria is more widely accepted (Grujic et al. 2009; Jeong et al. 2009; Kolandaswamy et al. 2009; Cowley et al. 2010; Mäkelä et al. 2010).

In the last few years, use of food-grade probiotics products with oxalate decarboxylase activity has emerged as an effective therapeutic option for lowering the concentration of dietary oxalates (Fig. 13.2). The impact of probiotics with oxalate

decarboxylase enzymes has been evaluated on human gut and result showed that probiotic properties make them a potentially safe option for prophylaxis of calcium oxalate stone disease. Transgenic plants expressing fungal oxalate decarboxylase may lower the nutritional stress of oxalate content in herbivores (Dias et al. 2006). Breakdown of intestinal oxalate and oxalic acid using oxalate decarboxylase is a prominent solution to oxalate degradation in humans (Cowley et al. 2010). Studies also confirmed that recombinant *B. subtilis* oxalate decarboxylase expressed in *Escherichia coli* given orally to rat was able to decrease oxalate concentration in urine (Jeong et al. 2009), while in other experiments on mice, the treatment with OxDc-CLEC®, a crystalline, cross-linked formulation containing recombinant *B. subtilis* oxalate decarboxylase, showed substantial decrease in symptoms of hyperoxaluria, urolithiasis, and nephrocalcinosis (i.e., increased level of calcium in the kidneys) as well (Grujic et al. 2009).

13.4.2 Oxalate Oxidase

Oxalate oxidase (EC 1.2.3.4) was initially discovered in a mold, and after that it has been reported from various plant sources such as barley seedlings and roots, beet stems, and sorghum leaves (Koyama 1988). Along with the formation of hydrogen

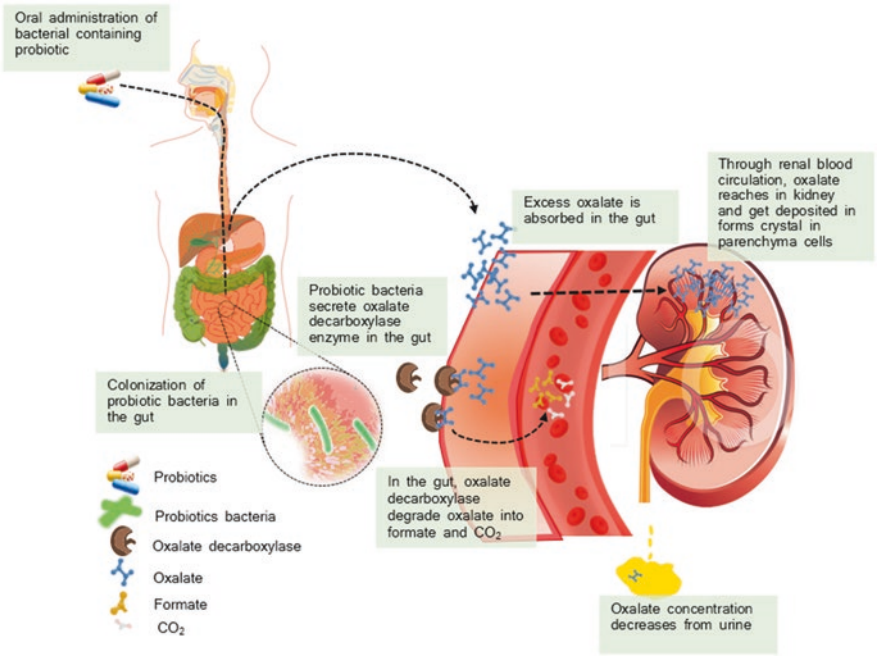

Fig. 13.2 Use of food-grade probiotics with oxalate decarboxylase enzyme activity in kidney stone removal

peroxide in an oxygen-dependent manner, oxalate oxidase catalyzes the oxidation of oxalic acid into carbon dioxide (Whittaker and Whittaker 2002). It has been assumed that H_2O_2 production by oxalate oxidase is applied as a defense mechanism against pathogenic infections (Svedruzic et al. 2005). Intracellular oxalate oxidase activity has been studied in white-rot basidiomycetous fungi *Ceriporiopsis subvermispora* and *Abortiporus biennis* even though the enzyme is principally native to plants (Aguilar et al. 1999; Grąz et al. 2009). Indeed, the activity of both these oxalate-degrading enzymes, i.e., oxalate oxidase and oxalate decarboxylase, was first reported in the fungal species *Ceriporiopsis subvermispora* (Aguilar et al. 1999; Watanabe et al. 2005). Oxalate oxidase present in the cell wall of plants has a role in cell morphogenesis, and it also promotes plant's defense mechanisms against diseases and other environmental stresses. Oxalate oxidase found in higher plants, fungi, and bacteria is now part of preventive therapy of hyperoxaluria, urolithiasis, and medical diagnosis of oxalate content in urine, whereas the food and papermaking industries also use this enzyme for various applications (Hu et al. 2015).

13.4.3 Oxalyl-CoA Decarboxylase

Oxalyl-CoA decarboxylase (EC 4.1.1.8), a thiamin-dependent oxalate-degrading enzyme, performs the catalysis of oxalyl-CoA to formyl-CoA and CO_2 (Svedruzic et al. 2005). The enzyme was discovered around 50 years ago and is mainly found in bacterial species including *B. lactis, Oxalobacter formigenes*, *L. acidophilus,* and *Thiobacillus novellus* (Federici et al. 2004; Turroni et al. 2007; Mäkelä et al. 2010). In *O. formigenes*, oxalyl-CoA decarboxylase is involved in oxalate-dependent ATP synthesis. Along with the degradation of oxalate by oxalyl-CoA decarboxylase, a proton-motive force that drives ATP synthesis is generated in *O. formigenes* due to antiporting of oxalate and formate (Mäkelä et al. 2010).

13.5 Conclusion

Oxalic acid is found in a vast range of foods and often consumed by the humans. It is a well-established fact that whether dietary intake or production during metabolism, oxalic acid can be detrimental to human health. Assimilation of oxalate is highly toxic to humans and ultimately causes hyperoxaluria and other related ailments. Owing to the limitations and inadequate success of current therapeutic drugs used in the treatment of kidney stone, the need for novel and better prophylactic measures have become an important issue. Although the use of probiotic bacteria has attracted significant attention, the use of crude enzyme with oxalate-degrading potential showed astonishing results. Oxalate decarboxylase and oxalate oxidase have already demonstrated great capabilities to dissolve calcium oxalate crystals in in vitro investigations. However, putting these enzymes to work in clinical practice still requires great investigation and research.

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