BMB
Reports

Invited Mini Review

Biological activities of lignin hydrolysate-related compounds

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Lignin hydrolysates contain many different chemical species, including ferulic acid, coumaric acid, vanillic acid, vanillin, syringaldehyde and furfural. From the perspective of biofuels, these compounds are problematic and can cause downstream loss of product if not removed prior to beginning the fermentative process. In contrast, a search for these compounds within the literature turns up many papers where the same compounds have beneficial properties pertaining to human health, including as antioxidants and in cancer prevention, or are involved in bacterial cell-to-cell signaling. Consequently, this article reviews the dual nature of these and other compounds found in lignin hydrolysates, highlighting both their detrimental and beneficial activities. [BMB Reports 2012; 45(5): 265-274]

INTRODUCTION

Lignocellulosic biomass has a vast potential as a feedstock for the production of biofuels. It is the most abundant material and is available as a variety of types, such as crop residues, grass, hard and soft woods (1). Considering it is not a foodstuff, it is regarded an essential material source for environmental friendly fuels (2). Moreover, the production of bioethanol or biobutanol using different types of lignocellulosic biomass has been tested by several groups, with the research results showing plant biomass-derived cellulose to be potential and feasible source of sugars (3-5).

Lignocellulose, as a chemical, is a complex biopolymer composed of mainly three parts: cellulose, hemicellulose and lignin (6). Cellulose is a long polymer of β-1, 4-linked D-glucose units having a high degree of crystallinity (7). Hemicellulose is a heterogeneous component containing the pentoses (D-xylose and L-arabinose) and hexoses (D-mannose, D-glucose, and D-galactose) within a branched poly structure. Lignin is also a heterogeneous polymer of aromatic compounds, not carbohydrate components like the others (6). Due to this complexity of lignocellulosic biomass, one of the key steps in biofuel production is a pretreatment step to liberate fermentable sugars from the lignin. Currently, a number of suitable technologies to achieve this are known, including biological and/or physical-chemical pretreatment, with each depending on plant material properties (8).

During biomass hydrolysis, undesirable components are generated in addition to monomeric sugars. These components can be generally classified based on their structure and include weak acids, furan derivatives and phenolic compounds (9, 10). These compounds have been found to be toxic to the microbes employed to ferment the sugars and produce the useful solvents (5, 11). For instance, phenolics, such as *p*-coumaric acid and ferulic acid, showed inhibitory effects on the production ABE by clostridial strains, while in tests with *E. coli*, phenolic compounds and furan derivatives, such as furfural and HMF, inhibited the cell growth and fermentation (12, 13). Moreover, the toxicity of these compounds to these microbes has been demonstrated in gene transcription level (unpublished data from our lab). Based upon this data, we recently constructed a biosensor strain, *E. coli* strain SP4, where the expression of the *lux* reporter genes corresponded with the toxicity experienced by the culture (14). Therefore, prior to fermentation of the sugars, one more important step is needed to ensure an effective conversion of lignocellulosic materials to biofuels, namely detoxification where the lignin portion and the components formed during hydrolysis are removed (15).

It should be noted, though, that whereas these inhibitory compounds negatively impact the activity of fermentative bacterial strains, they also affect other species in both positive and negative ways. In this review, therefore, we present recent research looking at the biological activities of these compounds.

BIOLOGICAL ACTIVITIES OF LIGNOCELLULOSIC HYDROLYSATE-RELATED COMPOUNDS

Hydroxycinnamic acids from lignin hydrolysis

When the lignin portion of plant biomass is hydrolyzed, various phenolic acids are released. Despite the different substituent groups that may be present, they are mainly based on the structure of benzoic and cinnamic acids (16). The most common derivatives of hydroxybenzoic acids are p-hydroxybenzoic and vanillic acids, while p-coumaric and ferulic acids are the most commonly found derivatives of hydroxycin-

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http://dx.doi.org/10.5483/BMBRep.2012.45.5.265

Received 31 October 2011

Keywords: Antioxidant, Hydrolysates, Lignocellulosic biomass, Phenolics

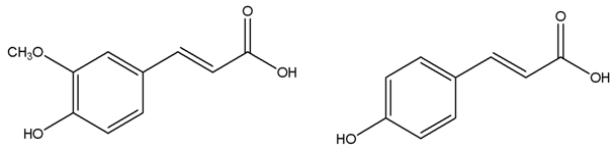

Fig. 1. Derivatives of hydroxycinnamic acid: ferulic acid (left) and p-coumaric acid (right).

namic acids (Fig. 1) (17).

One of the best well-known biological activities of hydroxycinnamic acid is its antioxidant properties due to its free radical scavenging capabilities (18). This antioxidant action is attributed to the distinctive structure of hydroxycinnamic acid with electron donating groups, leading to resonance stabilization of the compound (19). These properties have been shown to prevent DNA and lipids from oxidation by reactive oxygen species (20). Therefore, it should not be surprising that both ferulic acid and p-coumaric acid offer various benefits and have been highlighted as potential therapeutic agents to treat diseases linked to oxidative stress (21).

For example, neurodegenerative diseases, such as Alzheimer's or Parkinsons's disease, are characterized by oxidative stress in brain mediated by free radical leading to neurotoxic damage (18). The reaction of reactive oxygen species (ROS) or reactive nitrogen species (RNS) generated in the brain mediated by free radicals can subsequently cause protein, RNA and DNA oxidation, which is can contribute to neuronal cell death (20). The antioxidant properties of these components have been shown to reduce free radical attack and prevent oxidative modifications. In the reports, ferulic acid and p-coumaric acid protected the neurotoxicity induced by amyloid beta-peptide (1-42) (22) and 5-S-cysteinyl-dopamine (22, 23), respectively. For instance, 25 μM of ferulic acid significantly protected against amyloid beta-peptide (1-42)-induced toxicity, such as ROS accumulation, by direct modulation of the oxidative stress and the induction of protective protein expression, such as HSP 72, in hippocampal cultures (22).

Derivatives of hydroxycinnamic acid have also garnered attention as potential inhibitors of several cancers (23-26). Free radicals play a key role in the etiology of cancer and cause critical oxidation damage to cellular molecules, such as DNA, protein and lipids (24). With their ability to quench ROS, ferulic acid and p-coumaric acid exhibits anticarcinogenic effects against various cancer cells, including both human breast and colon cancer and colon cancer in rats (25-28). One striking example of this was the dose-dependent study of ferulic acid by the Kawabata group, where they showed ferulic acid could block azoxymethane-induced colon carcinogenesis in F344 rats (26). Moreover, these compounds are known to possess hepatoprotective, pulmonary protective and antiapoptotic effects (29-31).

One well known oxidative stress-related disease is diabetes. Although the mechanism has not been elucidated because of its pathophysiological complexity, it is known that diabetes can be caused by the overproduction of free radicals, which leads to an endocrine disorder, *i.e.*, low insulin levels (32). Ferulic acid and p-coumaric acid scavenge the free radicals and thereby decrease the oxidative stress/toxicity on the pancreas. As a result, the activity of these compounds helps increase the insulin level in the blood. Several studies have reported that treatment with ferulic acid or p-coumaric acid showed effective hypoglycemic activity in diabetic mice and that derivative compounds stimulated insulin secretion (33-35).

Furthermore, the hydroxycinnamic acids have been utilized as potent UV-radiation absorbent compounds. Exposure of UV light can generate the reactive oxygen species, while a chronic exposure to UV radiation results in sunburn, skin aging and skin cancer (36). As noted above, the special structures of ferulic acid and p-coumaric acid, with their scavenging capacities, provide stable phenoxyl radicals which allow them to terminate free radical chain reactions. Consequently, several research groups have studied their protective effects and have shown them to be effective against UV radiation-induced skin damage (37-39), making them an important ingredient in topical UV-shielding agents, such as sunscreens.

These compounds have also been shown to provide a protective effect for cardiovascular disease and related diseases, such as hypertension and atherosclerosis. Cardiovascular disease is the leading cause of death globally, with the chances of cardiovascular disease developing increasing when the patient has hypertension. It is known that hypertension is correlated with increased ROS levels and, consequently, can be mitigated with antioxidants (40). Previous studies have reported the effectiveness of hydroxycinnamic acids, particulrly ferulic acid, on attenuating increases in a patient's blood pressure, *i.e.*, they are hypotensive (41, 42). Another cardio benefit offered by these lignin-related compounds is that they are anti-atherogenic. Atherosclerosis, as another type of cardiovascular disease, is derived from the oxidative modification of lipids and proteins in the vascular wall (43), leading to the build up and depositing of plaque within the vessels and the constriction of blood flow. Administration of ferulic acid and p-coumaric acid has demonstrated its influence on atherosclerosis by lowering the cholesterol level in blood (44, 45).

Besides the antioxidant effects mentioned above, one recent report has shown another important biological activity of p-coumaric acid, namely that it acts as a new class of quorum sensing molecules (46). Within many bacteria, fatty acids are usually used to synthesize fatty acyl-homoserine lactone signals that they use for cell-to-cell communication. The process and components involved in bacterial communication with each other, current techniques and applications within labs, as well as a discussion about the purpose of cell-to-cell signaling amongst bacteria was recently reviewed by our group and provides much more information about this remarkable facet of microbiology (47). The photosynthetic bacterium, *Rhodopseudomonas palustris* includes a *luxI-luxR* type homologous pair

in its chromosome, designated *rpaI-rpaR*. Using this pair of genes, Schaefer *et al*. recently found that *rpaI* expression and activity is dependent on p-coumaric acid being present within the culture (46). Their report shows that *R. palustris* produces a novel signaling molecule by covalently linking p-coumaric acid with the acyl-homoserine lactone (HSL) ring, generating p-coumaroyl-HSL, which has a unique structure not seen previously, namely that the fatty acyl chain is replaced with an aromatic ring. This finding of p-coumaroyl-HSL opens up a new domain of inter-species signaling between bacteria and plants, which produces p-coumaric acid as a precursor for lignin generation (48).

Hydroxybenzoic acids from lignin hydrolysis

Another group of phenolic acids is the hydroxybenzoic acids (Fig. 2), which include 4-hydroxybenzoic acid and vanillic acid, both of which are benzoic acid derivatives and generated during the hydrolysis of plant-derived polyphenols. These also can scavenge free radical species and, therefore, exert an antioxidant effects as hydroxycinnamic acids do. Several studies have demonstrated the antioxidant capacities of 4-hydroxybenzoic acid and vanillic acid using 1,1-diphenyl-2-picrylhydrazyl (DPPH) (49, 50). Although these two compounds, which were isolated from walnut kernels in their study, showed only relatively low scavenging activities, they are still potential antioxidant components (49). Moreover, it was shown that vanillic acid scavenges the stable radical species, DPPH, in a dose-dependent manner, with the highest scavenging effects seen with 60 μM of vanillic acid (50).

Due to the antioxidant activity of vanillic acid, like the hydroxycinnamic acids above it has protective capabilities, such as hepatoprotective effects, against several diseases which are associated with oxidative deterioration (50-52). Furthermore, vanillic acid might suppress fibrogenesis and inflammation in chronically injured livers (51, 52). The cardioprotective effect of vanillic acid has also been demonstrated where, due to an increased scavenging of free radicals by vanillic acid during isoproterenol metabolism, there is a decreases in lipid production, lipoproteins are better maintained and apoptosis in the myocardium is prevent (50). Another study determined the beneficial effects of vanillic acid on ulcerative colitis (53). The administration of vanillic acid showed significant change in physiological characteristics of the mice, including weight loss and gene expression patterns. Based upon the anti-inflammatory response induced, vanillic acid was suggested as a treatment for ulcerative colitis.

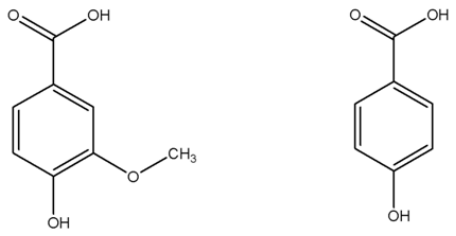

Fig. 2. Derivatives of hydroxybenzoic acid: vanillic acid (left) and 4-hydroxybenzoic acid (right).

In addition, vanillic acid has another unique activity, partially inhibiting the potency of snake venom. It was found that vanillic acid selectively inhibited the 5′-nucleotidase activity of several enzymes identified within snake venom, making this hydrolysate-related compound a potential tool in evaluating the role of 5′-nucleotidase activities during snake envenomation (54).

4-hydroxybenzoic acid shows the least toxicity among the lignin-derived phenolics based upon tests with *E. coli* (14). This can be attributed to the fact that it is a naturally produced metabolite of *E. coli* and that an efflux pump system exists, *i.e.*, AaeA and AaeB, to push out any excess that may build up within the cell. In fact, it has been reported that the addition of 4-hydroxybenzoic acid exogenously results in the up-regulation of the *aaeXAB* expression levels which encodes for the putative efflux proteins (55). The authors theorized that this efflux system serves as a metabolic relief valve to reduce the toxicity of the compound. Nevertheless, 4-hydroxybenzoic acid exhibited antimicrobial activities and fungitoxicity, since strongly inhibited the growth of Ganoderma boninense at a concentration of 2.5 mg/ml, which was the highest concentration tested (56). In another report, the algal toxicity of 4-hydroxybenzoic acid was evaluated (57). The toxicity to algae was not very great and actually had the least effect among the various monohydroxybenzoic acids. Furthermore, although 4-hydroxybenzoic acid inhibited the algae growth at high concentrations, stimulation of growth at lower concentrations (0.3-1.0 mmol/L) was reported, suggesting that this compound may be a metabolite for the algae but becomes toxic when added at too high of concentrations.

Although, as mentioned above, 4-hydroxybenzoic acid shows some free radical scavenging activity, unlike vanillic acid it did not have any clear inhibition of or protection against oxidative DNA damage (58). Although 4-hydroxybenzoic acid cannot act as an antioxidant for DNA damage caused by oxidative stress in human, it potentially plays a role in plants. To induce freezing and drought tolerance within plants, one of the essential factors plants require is a good antioxidant capability (59, 60). Consequently, the Horvath group has reported that the addition of exogeneous 4HBA improved the tolerance of spring wheat plants towards freezing as well as enhanced the drought tolerance of winter wheat plant (61).

Another biological activity of 4-hydroxybenzoic acid is its oestrogenic activity, which was demonstrated within human and animal models (62-64). An assay using human breast cells was used to provide evidence of its oestrogenic effect (64). In that study, p-hydroxybenzoic acid bound to the oestrogen receptor instead of oestradiol, leading to an increased expression of an oestrogen-responsive reporter gene. Moreover, 4-hydrox-

ybenzoic acid induced the growth of breast cancer cells that are dependent on oestrogen, demonstrating the effects of this compound on this signaling pathway.

Phenolic aldehydes resulting from lignin hydrolysis

Various phenolic aldehydes are also generated from the hydrolysis of lignin. Most of them are the aldehyde type of phenolic acids referred in the previous section, such as vanillin (aldehyde type of vanillic acid). Due to the similar structure to acid forms, their biological activities are not significantly different.

Vanillin is one of the components widely used as flavoring agents in food and cosmetics (Fig. 3). In addition to its flavor qualities, it exhibits the antimicrobial activity as other lignin hydrolysate-related compounds do and has been tested for its radical scavenging ability using DPPH (65, 66), Based upon the findings in both reports, vanillin can be classified as a potent antioxidant, a fact which was shown previously in a study where it was used to prevent oxidative damage to membranes in rat liver mitochondria (67).

In addition to being an antioxidant, vanillin can also exert antimutagenic effects. It was shown to reduce mutations in bacterial models (68, 69), as well as prevent chemically or physically induced mutagenesis in human cells (70, 71). Another benefit of this compound is its chemoprotective activities against inflammation and cancer. Recently, it was reported that vanillin exerts an anti-inflammatory activity in ICR mice, and the authors suggested that this is due to the release of inflammatory mediators being blocked during the first stage (72). A subsequent study further demonstrated the anti-inflammatory effect of vanillin during a treatment of inflammatory bowel diseases where vanillin prevented trinitrobenzene sulfonic acid-induced colitis and reduced established colitis in mice (73). Finally, vanillin decreased angiogenesis and showed protected against hepatocarcinogenesis (74), while also displaying anti-cancer properties as evidenced by its inhibition of matrix metalloproteinase-9 and P13K gene expression levels and regulation of the cell cycle and apoptosis in HepG2 cells, through which it suppressed the invasion and migration of cancer cells (66, 75, 76).

Syringaldehyde is a naturally occurring aromatic aldehyde (Fig. 3), and it inhibits cellulose hydrolysis in wet cake by endo- and exo-cellulases, and cellobiose hydrolysis by beta-glucosidase (77). The inhibitory effect of on metabolism of *Candida guilliermondii* yeast during xylose to xylitol bioconversion was evaluated and concluded that syringaldehyde may affect cell growth and metabolism of this organism (78). Furthermore, the inhibitory effects of syringaldehyde on a fermentation by *Saccharomyces cerevisiae* K35 was investigated and it was found that concentrations higher than 5 g/L of syringaldehyde were toxic (79). Cortez and Roberto studied the effects of syringaldehyde, which was selected as a model compound liberated during chemical hydrolysis of lignocellulosic materials, by evaluating the xylose-to-xylitol bioconversion of *C. guilliermondii* FTI 20037 (80). Syringaldehyde concentrations of more than 2 g/L inhibited cell growth to certain degrees but were completely inhibitive when combined with vanillin at 2.0 g/L while xylitol production was strongly repressed.

Syringaldehyde is found to be cytotoxic and identified in medicinal plant extracts. For example, syringaldehyde was found in the cytotoxic fraction isolated from the stem of *Casearia membranacea* (Flacourtiaceae) (81) and, stem wood of *Machilus ovatifolio* (82). Extracts of *Gymnosporia trigyna* showed DNA strand-scission activity (83). Four active compounds were identified, including syringaldehyde, which is now recognized as a new type of DNA strand-scission agent. Another group identified syringaldehyde in fruiting bodies of *Elaphomyces granulates* which show cyclooxygenase-2 (COX-2) inhibitory activity and demonstrated that syringaldehyde moderately inhibits COX-2 activity, with an IC_{50} of 3.5 μg/ml (84). The inhibitory activity of syringaldehyde was also demonstrated with prostaglandin synthetase, which was inhibited in a dose-dependent manner (85). The authors determined that, compared to aspirin, syringaldehyde had about half the potency when applied topically, and showed a dose-dependent inhibition of an ethyl phenylpropionate-induced edema of the rat ear, with an active range of 20-100 μg syringaldehyde/ear. Syringaldehyde and its derivatives are also good antioxidants. Lee *et al*. investigated syringaldehyde-based dendrimers and showed that they have strong antioxidant activities, as much as twice as effective and 10 times stronger than quercetin and Trolox, respectively (86). Syringaldehyde also acts as natural mediators and was shown to greatly enhances Laccase-based oxidation during the degradation of several pharmaceuticals such as anti-inflammatories (87). Unfortunately, in the presence of transition metals, antioxidants, including polyphenols with potent antioxidant activities, may also exhibit pro-oxidant

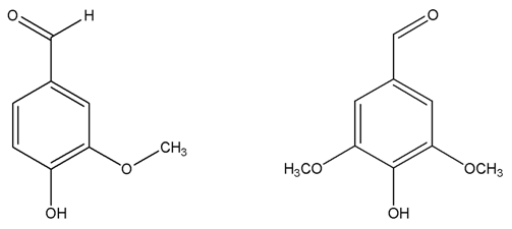

Fig. 3. Phenolic aldehydes from lignin, vanillin (left) and syringaldehyde (right).

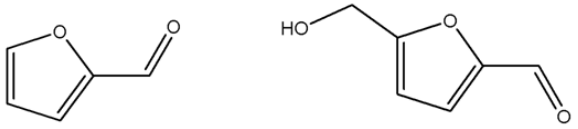

Fig. 4. Sugar-based aldehydes, furfural (left) and HMF (right).

effects, which can irreversibly damage DNA. Therefore, antioxidants with strong free radical-scavenging abilities and devoid of pro-oxidant effects, including lignin- derived phenolic compounds (88), would be of immense biological importance (89),

Furan components from cellulose and hemicellulose

During hydrolysis of lignocellulosic biomass, the sugar components present within the cellulose and hemicellulose can also be degraded to produce furfural or 5-hydroxy-methyl-furfural (HMF) (Fig. 4). The toxicity and effects of these aldehydes have been extensively studied, but particularly within yeast and bacterial systems.

Both of these compounds are known to affect the specific growth rate of fermentative organisms, however the degree of inhibition depends on its concentration in the fermentation medium (90). For instance, furfural concentrations of 1 mg/L or more were found to significantly decreased CO_2 evolution by resuspended yeast cells (91). Furfural also affects the activity of certain enzymes, particularly glycolytic enzymes and dehydrogenases, suggesting that these enzymes are more sensitive and that they are probably responsible for the inhibition of alcohol production (91). Moreover, the inhibitive effects of furfural on microbial growth and metabolism in ethanol fermentation have been studied with various organisms, e.g., *Saccharomyces cerevisiae* (92-96), *Pachysolen tannophilus* (97) and *E. coli* (98), as well as with cellulase production in *Trichoderma reesei* (99). The addition of furfural also inhibited ABE production by *Clostridium acetobutylicum* (100) and xylitol production by *C. guilliermondiA* (101). Within *Saccharomyces cerevisiae*, cell replication was halted when this aldehyde was added and was reportedly due to the formation of acetaldehyde (102, 103).

A study on the toxicity and detoxification of both furfural and HMF was conducted with seventeen different enteric bacterial strains, including the genera *Klebsiella, Enterobacter, Escherichia, Citrobacter, Edwardsiella* and *Proteus* (104), while the effects of HMF on the growth rate and final cell densities of the fermentative strain, *Zymomonas mobilis* 8b, was studied (105). HMF was also found to inhibit the growth, decrease the metabolic activity and reduce the ethanol production of various fermentative microorganisms, including *Saccharomyces cerevisiae* (95, 96) *Zymomonas mobilis, Pichia stipitis*, *Candida shehatae* (95) and *E. coli* (98). In all the experiments, furfural and HMF had inhibitory effects on the strains. It is remarkable, therefore, that these compounds had little or no effect on the activity of *C. beijerinckii*, even at a concentration of 3 g/L (106). The toxicity of furfural on the *Trichosporon fermentans* was studied and, although it depended on the inoculum size, temperature, initial pH and lipid content of the organism, the study suggests that it is less toxicity than aromatic aldehydes (107).

Furfural is also toxic to mammalian cells. Castellino *et al*. evaluated and showed the detrimental effects of HMF in terms of its toxicity and vein damaging properties in rabbits (108). Moreover, Hessov demonstrated that both furfural and HMF are toxic to *Daphnia magna* (109). When furfural was orally administered to rats, almost 90% of the furfural ingested was absorbed through the gastrointestinal tract, of which 83-88% was excreted through the urine and only 2-4% was excreted in the feces, suggesting that furfural will be extensively metabolized within the body prior to excretion (110). The various effects of HMF, including its cytotoxic, growth inhibitive, mutagenic and DNA damaging capacities, were investigated in mammalian cells and *Salmonella typhimurium* (111). It was found that HMF induced a moderate cytotoxicity and that DNA damage was detectable, while a mild reduction in cell viability was seen. Furthermore, HMF was only weakly mutagenic, suggesting that HMF does not pose a serious health risk, even with the high concentrations seen in specific food (111).

Furfural derivatives can also act as antioxidants. HMF can be found in many foods in high concentrations, sometimes ex-

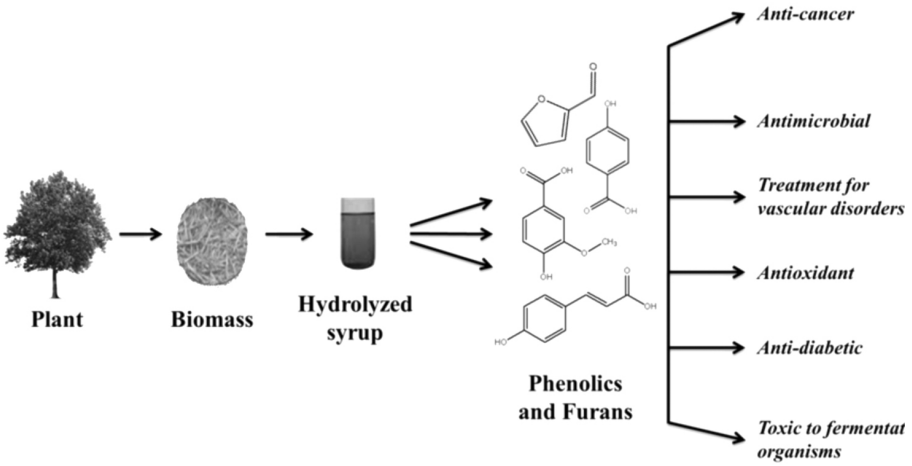

Fig. 5. Overview illustrating the biological activities of plant hydrolysate-related compounds.

ceeding 1 g/kg in certain dried fruits and caramel products. Pearson *et al*. analysed antioxidant compounds in vegetables and food having various concentration of aldehyde (112). These aldehydes will be present in most of the fruits that may have beneficial effects on human health. Also, by investigating the herb-derived antioxidant agents in *Flos lonicerae* (*Lonicera japonica* flowers), one group identified 11 active compounds, including HMF (107).

Furthermore, furfural derivatives have also been used for therapeutic purposes. For instance, HMF is a potential candidate for treating sickle cell anemia (113). An *in vitro* evaluation showed that HMF forms a high-affinity Schiff-based adduct with HbS and inhibits red cell sickling. Furthermore, transgenic sickle mice showed that orally administered HMF was rapidly absorbed into the blood stream from the gastrointestinal tract without being destroyed and that a pre-treatment with HMF inhibited the formation of sickle cells. These results strongly demonstrate the feasibility of using HMF as a candidate for sickle cell therapies. Furthermore, an analysis of chemical constituents present within an anti-arthritic fraction of Capparidaceae fruits was performed, confirming the presence of HMF, suggesting that it may play a major role as an anti-arthritic drug (114).

CONCLUSIONS

This review looked at the literature and recent research regarding the biological activities of compounds found within plant hydrolysates (Fig. 5). Although much of the research related with fermentative processes has found these compounds to be detrimental to the bacterial cultures being cultivated, this is clearly not the complete story or picture, as evidenced by research performed in a wide array of fields, including cancer studies and inflammation-related conditions. Many of the studies highlighted in this article clearly demonstrate the benefits of these compounds, albeit when used in moderation. Furthermore, it seems clear that these compounds cannot be avoided entirely since they have been identified within the foods that we eat. In conclusion, this review suggests that collaboration between biorefineries and biofuel researchers, who work with lignocellulose and lignin hydrolysates, and scientists in other fields, such as cancer biology, medicine, pharmaceuticals and cosmetics, may bring to light new information and applications of hydrolyzed plant lignin.

Acknowledgements

This was supported in part by the National Research Foundation of Korea (NRF) (Grant # NRF-2011-616-D00042) and by the Ministry of Education, Science and Technology (Grant # NRF-2009-C1AAA001-2009-0093479). We are grateful for their support.

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