African Journal of Biotechnology Vol. 10(22), pp. 4518-4523, 30 May, 2011
Available online at http://www.academicjournals.org/AJB
DOI: 10.5897/AJB10.2201
ISSN 1684–5315 © 2011 Academic Journals

Review

Ellagic acid: Biological properties and biotechnological development for production processes

Leonardo Sepúlveda[1], Alberto Ascacio[1], Raúl Rodríguez-Herrera[1], Antonio Aguilera-Carbó[2] and Cristóbal N. Aguilar[1]*

[1]Department of Food Science and Technology, Universidad Autónoma de Coahuila, Saltillo, Coahuila, México.
[2]Department of Food Science and Nutrition, Universidad Autónoma Agraria Antonio Narro, Buenavista, Saltillo, Coahuila, México.

Accepted 15 April, 2011

Ellagic acid, 2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde]chromene-5,10-dione, is a powerful bioactive compound with many potential pharmacological and industrial applications. In this review, the chemical aspects, biological properties and diverse potential applications of ellagic acid for different industries were described. This review also discussed the advance in ellagitannin biodegradation, focusing on the process of isolation of microorganisms and strain selection, medium and culture optimization, as well as fermentation systems for commercially viable industrial scale production. The performances of various fermentation techniques that have been applied for the production of ellagic acid from residual by-products were compared, while the advantages and disadvantages of each plant source were also discussed.

Key words: Ellagic acid, ellagitannin, biodegradation, fungal physiology, solid-state fermentation, submerged fermentation.

INTRODUCTION

Tannins are polyphenolic compounds present in different plant species, they are water soluble with molecular masses ranging form 500 to 20000 Da (Khanbabaee and Ree, 2001). They are distributed in fruits, stalks, peels, roots and leaves (Haslam and Cai, 1994). Concentration and kinds of these compounds are determined by plant specie. Tannins are considered as secondary metabolites in plant physiology and are generally classified into four groups: gallotannins, ellagitannins, condensed tannins and complex tannins (Khanbabae and Ree, 2001).

These phytochemicals are located in the vacuoles of intact plant cells, and are released upon attack by diverse microorganisms, including viruses, bacteria and fungi, thereby avoiding potential infection of plant tissues. In addition, the astringent properties of tannins are well known to stop the infestation of insects (Koide et al., 1998).

*Corresponding author. E-mail: cristobal.aguilar@uadec.edu.mx. Tel: 52 (844) 4161338. Fax: 52 (844) 415 9534.

Also, these bio-active molecules offer protection against ruminants due to the formation of complexes between plant tannins and animal proteins such as hydroxyproline-rich proteins. Formation of such complexes results in a bitter and disagreeable sensation which deters potential predators. Molecules present in the plants that are susceptible to microbial degradation, such as proteins and polysaccharides, have evolved to become highly resistant to such degradation when linked to tannins (Aguilera-Carbo et al., 2009).

One of the most important roles of tannins is the growth inhibition towards many microorganisms including bacteria, yeasts and fungi. They are therefore recalcitrant to enzyme degradation by most microorganisms. Condensed tannins are more resistant to microbial attack than hydrolysable tannins and are more toxic for foodborne pathogens (Aguilera-Carbo et al., 2005). Tannins retard the decomposition of solid organic material through inhibition of degrading enzymes of attacking microorganisms. When tannins are complexed with microbial proteins or polysaccharides, the interactions formed are often irreversible and this characteristics confer on them the bactericide and bacteriostatic proper-

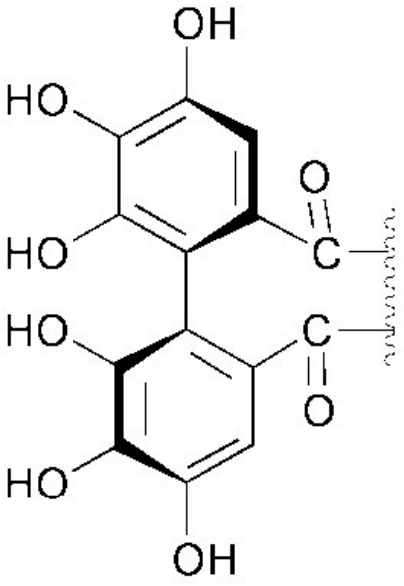

Figure 1. Hexaydroxidiphenic group of ellagitannins.

ties. However, some microorganisms tolerate the presence of tannins and/or use these com-pounds as carbon source. That ability is generated by the production of a tannin-degrading enzyme or tannase, produced mainly by microorganisms of the genus *Aspergillus* and *Penicillium* (Aguilar et al., 2008).

Ellagitannins (ETs) correspond to esters of ellagic acid with glucose or quinic acid. ETs are generated by oxidative interaction of gallotannins with at least 2 galoyl units, originating from a group called hexahydroxy-dyphenic acid (HHDP) (Figure 1). This group is released after hydrolysis of ETs, and spontaneously lactonized or rearranged to generate the ellagic acid. There are more than 500 ellagitannin structures reported (Feldman et al., 1999). The ellagitannins are mainly derived from the bark of oak (*Quercus* spp.). Bianco et al. (1998) indicated ET's can be can be classified according to the number of HHDP groups in the molecule, as monomeric, oligomeric and polymeric structures (grade of polymerization). The principal molecule for the formation or biosynthesis of ETs is pentagaloyl glucose (PGG). The oxidation of this molecule is carried out enzymatically by plant polyphenol oxidase, which performs the coupling of galoyl groups to generate the group HHDP (Figure 2).

ELLAGIC ACID

Ellagic acid (Figure 3) is a molecule with a molecular weight of 302 $gmol^{-1}$. It is a molecule that is highly thermostable (melting point of 350°C) (Ascacio et al., 2010), and has four rings representing the lipophilic domain, four phenolic groups and two lactones, which can act as hydrogen-forming sides and electron acceptors, respectively, and represent the hydrophilic domain (Aguilera-Carbó et al., 2005). Ellagic acid is a compound that has generated commercial interest in recent years due to its properties, applications and benefits to human health.

BIOLOGICAL PROPERTIES OF ELLAGIC ACID

Antioxidants are compound that can delay, inhibit or prevent the oxidation of compounds, trapping free radi-cals and reducing oxidative stress. The presence of ellagic acid in various commercial products giving anti-oxidant activity has also been reported. These molecules have a variety of benefits for their anti-mutagenic, antimicrobial and antioxidant properties, and inhibitors of human immunodeficiency virus (HIV) (Tatsuo et al., 1998; Feldman et al., 1999; Akiyama et al., 2001; Vattem and Shetty, 2003; Ruibal et al., 2003). Ellagic acid prevents the formation of various tumors, this mechanism of action can be possible because compounds such as ellagi-tannins and ellagic acid, explicitly interact with the cells walls or sites with facility to complex proteins, preventing the proliferation of metastatic cells (Tatsuo et al., 1998). Losso et al. (2004) evaluated the potential cytotoxic and anti-proliferative activities of ellagic acid in human cells, lung, colon, breast and prostate cancer, and showed that doses of 1 to 100 µmol/L inhibited the proliferation of the cancers mentioned. It has been demonstrated that ellagic acid acts, possibly causing apoptosis in cancer cells by inhibiting factors that promote metastasis. Huertz et al. (2005) studied a coordinated response between a typical carcinogen such as benzo [α] piren-7, 8-diol-epoxide (BPDE) and ellagic acid, which they see as chemopre-ventive agent in some cancers caused by polycyclic aromatic hydrocarbons (PAHs). The authors proposed a mechanism by which ellagic acid, in the formation of DNA, is adducted by the direct compaction of the carcinogen.

Studies of ellagic acid in cancer cells have demon-strated the induction of apoptosis or cell death, preventing a continuous tumor growth (Ito et al., 1999). This mechanism was proposed by Heather et al. (2007) when polyphenol-rich raspberry extracts were made and fractioned by chromatography on C18 solid phase, reporting that one of the separated compounds identified as ellagic showed the ability to inhibit *in vitro*, the proliferation of human cervical cancer (HeLa) cells, and the possible mechanism explained was that ellagic acid from ETs induces apoptosis through intrinsic mito-chondrial pathway. Other studies have identified impor-tant ETs-type phytochemicals in diverse berry fruit extracts, which are characterized by biological properties such as anticancer (colon, prostate and leukemia), anti-neuodegenarative, anti-viral, etc. (Mertens-Talcott et al.,

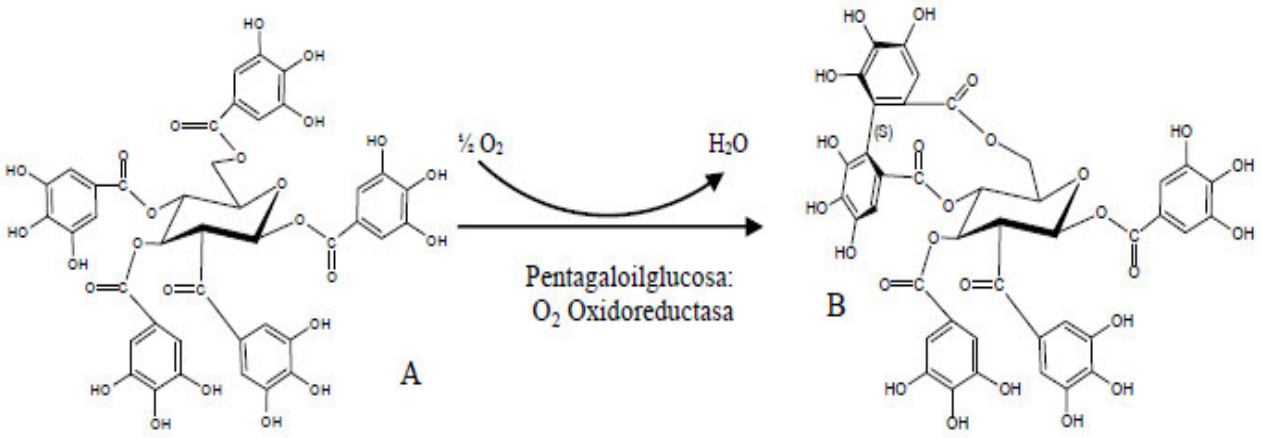

Figure 2. Scheme of PGG oxidation (A) and the ellagitannin telimagrandin II (B) by a phenol oxidase type enzyme (Niemetz et al., 2003).

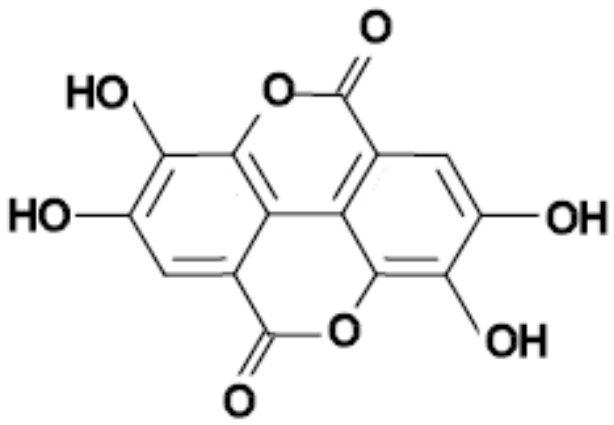

Figure 3. Structure of ellagic acid.

2003; Seeram et al., 2006). Atta-Ur-Rahman et al. (2000) reported that *Pteleopsis hylodendron* extracts, presented substances such as ellagic acid derivates with antioxidant properties, since these substances were significantly able to eliminate free radicals such as DPPH. Ellagic acid was tested in the reduction of incidence of molecules such as N-nitrosometylbenzylamine (NMBA), which explains one of its characteristics as chemoprotective (Ahn et al., 1996).

It is important to emphasize the ability of ellagitannins and ellagic acid as antiviral and antimicrobial agents. It has also been suggested that ellagic acid has the ability to inhibit the growth of pathogens in humans, probably coupled with protein in bacteria walls, such as that of *Bacillus*, *Staphylococcus*, and *Salmonella* (Akiyama et al., 2001). Fruit extracts from pomegranate (*Punica granatum*), which are rich in ellagitannins and ellagic acid were the derived substances from these compounds that caused the inhibition of methicillin-resistant *Staphylococcus aureus* strains (Machado et al., 2002). These biological properties have been attributed to the ETs ability to inhibit gyrase activity which is associated with the cleavage of the DNA strand during replication process (Weidner-Wells et al., 1998). It is pointed out that this bacterium does not have the ability to resist this type of antibacterial action. Also, different concentrations of ellagic acid against the human immunodeficiency virus have been tested, and it demonstrated the ability to inhibit the virus growth and spread due to the ability of ellagic acid to attach to HIV proteins (Notka et al., 2004). Also, viruses do not have the ability to replicate themselves in the presence of ETs; because they inhibit the integrase enzyme involved in the insertion of viral genomic material to host cells (Jegede et al., 2008). This is particular in the case of retroviruses, including HIV, were these very specific phytochemicals also inhibit reverse transcriptase activity (Aguilera-Carbó et al., 2009). Therefore, there is great interest in the developing processes of production and extraction of such compounds, which are found in trace amounts (in milligrams per hundred grams of vegetal source) in wild plants from which they are extracted using chemical processes involving organic solvents.

Others important biological properties of ellagic acid have been reported, for example, in one study, ellagic acid showed ability to inhibit radiation-induced activity protein kinase C (PKC) in cytosolic and particulate fractions of mouse liver cells. It was shown that ellagic acid at a dose of 10 mM inhibits 60% activity of PKC in non-irradiated and radiated cells (Varadkar et al., 2001). Bioassays were also carried out using ellagic acid derivates compounds isolated from the bark of *Elaeocarpus parvifolius* which showed potent antiparasitic properties. These compounds were evaluated for the ability to inhibit *Babesia gibsoni* (Elkhateeb et al., 2005).

Among the newly discovered biological activities of ellagic acid, are those associated with prevention of eye,

kidney, heart and joints of upper and lower extremities damage, which are caused by high blood glucose levels (Ventura-Sobrevilla et al., 2009). This protective action is due to the ability of ellagic acid to inhibit the enzyme aldolase reductase, which is responsible for the production of proteoglycan type compounds in small blood vessels, causing blindness, kidney damage, paralysis, heart attacks and loss of limbs associated with the two types of diabetes. In addition, ellagic acid increases the insulin activity and has several inflammatory effects and oxidative stress reduction (Seeram et al., 2005).

Our research group has generated valuable information that leads to the development of biotechnology processes that allow the production of ellagic acid from ellagitannins using fungal biodegradation of various biological sources, particularly agro-industrial waste generated through the fruit juice processing and production of natural waxes (Robledo et al., 2008; Aguilera-Carbó et al., 2009; Ventura-Sobrevilla et al., 2009).

ELLAGIC ACID PRODUCTION

Commercial ellagic acid is obtained by chemical extraction with acid-methanol mixtures as solvents; generally, concentrated HCl or H_2SO_4 are used to hydrolyze the rich-ellagitannin plant materials, (Lei et al., 2001; Wilson and Hagerman, 1990), resulting in processes that are highly contaminant, expensive, aggressive and have low yields (Aguilera-Carbo et al., 2009). For this reason, in the last six years, several attempts have been made to develop a bioprocess to produce ellagic acid through fermentation technology.

All production processes via fermentation of compounds of commercial interest have to be evaluated once factors that significantly influence the accumulation of metabolites have been identified. However, several negative situations can affect yields, for this reason, is imperative to optimize fermentation systems (Ertola et al., 1994). Among these are, lack of information about performance ratios of macro and micro elements for a given organism, existence of hidden nutritional limitations, especially those of trace elements and growth factors, use of culture media containing elements in excess of nutritional requirements of given organism, which can cause growth alterations, activating and inhibition of growth and product formation, and use of unconventional sources of nutrients (Aguilar et al., 2008).

To our knowledge, Vattem and Shetty (2002) reported for the first time, the biotechnological production of ellagic acid using solid-state fermentation of cranberry pomace using *Rhizopus oligosporus,* which degraded the polyphenolic compounds after 10 days of fermentation and increased the antioxidant power of the obtained extracts, demonstrating an important increment of ellagic acid (up to 26%). Also, in a similar study, these authors using a food grade fungus, *Lentinus edodes*, found that during the course of fermentation of the same by-product, an increment in phenolic content (including ellagic acid) and antioxidant activity were correlated with the β-glucosidase activity, proposing a possible action of this enzyme on the release of phenols from cranberry pomace (Vattem and Shetty, 2003).

Seeram et al. (2005) established a methodology for recovery of polyphenolic compounds present in peels and seeds of pomegranate fruits. They used different chromatographic techniques such as HPLC coupled with mass chromatography (HPLC-ES-MS) and nuclear magnetic resonance (NMR), to describe the presence of important levels of ETs and ellagic acid. Shi et al. (2005) carried out a fermentation study of valonia tannins on oak tree (*Quercus* with strains of *Aspergillus niger* and *Candida utilis*), demonstrating a biodegradation process of these compounds through solid state fermentation with a correspondent accumulation of ellagic acid.

Huang et al. (2005) reported that tannin acyl hydrolase enzyme produced by *Aspergillus* SHL6 by submerged fermentation can be associated with ellagic acid production, identifying several factors that might influence the release of secondary metabolite, including ellagic acid. These factors are: substrate concentration and sources of nitrogen and carbon, as well as incubation period, temperature, pH among others. Later, Huang et al. (2008) used oak acorns to prepare extracts as a source of ellagitannins, and used *Aspergillus oryzae*, *Endomyces fibulige* and *Trichoderma reesei*, which are able to degrade these compounds and obtain, through solid state fermentation and liquid, the antioxidant enzymes involved. These authors suggested that the possible enzymes involved in the liberation of ellagic acid are ellagitannin acyl hydrolase, β-glucosidase, cellulase and xylanase. In addition, they concluded that a complete optimization of the production process for better yield of ellagic acid will be necessary and this process can be scaled to industrial level.

That same year, Huang et al. (2007) described the partial identification of physicochemical parameters that could influence the release of enzyme ellagitannin acyl hydrolase and ellagic acid. In this case, they used an extract rich in ellagitannins from oak acorns and *A. oryzae*. It was determined that the best enzyme activity value was lower than 7 gL^{-1}. Also, they reported that ellagitannins concentration and incubation time affected enzyme release and ellagic acid accumulation. The maximum accumulation of ellagic acid was reached at 84 h of fermentation with an initial concentration of 4 gL^{-1}, also a correlation between enzyme release and ellagic acid production was demonstrated.

In the Food Science and Technology, School of Chemistry, Universidad Autónoma de Coahuila at Saltillo, Coahuila, México, some studies on ellagic acid production were carried out. Hernández-Rivera et al. (2008)

kinetically evaluated ellagic acid production using pomegranate peel as carbon and energy source and *A. niger* GH1. A maximum accumulation of ellagic acid was reached after 96 h with a concentration of 12.3 mg g^{-1}. These results suggested that an enzyme capable of releasing these compounds is possibly involved. Following this line of research, Ventura et al. (2007) selected different rich-tannins plants from the Mexican semi desert. The plants were collected, washed, dried and pulverized. From this powder, extracts were obtained using organic solvents. Fermentation was done at 30°C, using 3 g of polyurethane foam (PUF), and 7 ml of extract, reactors were inoculated with 2 x 10^7 spores of *A. niger* PSH. A decrease in the concentration of plants extract at 48 h was observed, demonstrating that the *A. niger* PSH strain was able to degrade the extracts, and an accumulation of 7.56 mg g^{-1} of ellagic acid after 48 h of fermentation from tar bush (*Fluorensia cernua*) was observed.

On the other hand, Robledo-Olivo et al. (2008) used peel and pomegranate seeds as source of carbon and energy, and determined the physicochemical characteristics of the plant tissue. For solid-state fermentation reactors, they used a column with PUF as support which was impregnated with the culture medium inoculated with *A. niger* spores, and reactors were incubated at 30°C for 144 h. High polyphenols content in pomegranate fruit peel was observed, showing after fermentation, a maximum value of 6.11 g of ellagic acid, and concluding that this plant material is a good residue for fermentation systems in order to obtain high-value commercial compounds. Some Mexican semi desert plants are characterized because of their high tannins content. For this reason, Aguilera-Carbó et al. (2009) decided to use creosote bush (*Larrea tridentata*) leaves and *A. niger* GH1 for solid state fermentation in order to obtain ellagic acid. Plant tissue was lyophilized to obtain a fine green powder, from this powder were obtained plant extracts which were used to impregnate 3 g of PUF as support in column reactors with a humidity of 70%. The reactors were incubated at 30°C for 96 h. The results showed a maximum concentration of ellagic acid at 36 h with 23.1% total ellagitannins. Later, Aguilar et al. (2008) used extracts from pomegranate fruit and creosote bush leaves for ellagitannins accumulation. Fermentation was performed using flasks containing extracts and culture medium which was inoculated with 2 x 10^7 spores of *A. niger* GH1. Subsequently, these reactors were incubated at 30°C for 48 h. A maximum accumulation of ellagic acid of 0.9 and 0.5% from creosote bush leaves and peel of pomegranate extracts was reached, respectively.

CONCLUSION

Biotechnological production of potent antioxidant has emerged as an attractive alternative to the recovery of bioactive compounds. Fermentation technology is considered as an excellent strategy in the new extractive methodologies. Ellagic acid represents a bioactive molecule with beneficial characteristics in the human and animal physiology and health; however, it is a very expensive compound under the current commercial conditions. It is necessary to find new forms for its recovery. For the particular case of biotechnological production of ellagic acid, important efforts have been developed and new challenges will be attended to, to elucidate all possible effects and interactions among the factors that may influence the accumulation of this bioactive compound. Studies of optimization of its production under different culture systems and the development of recovery protocols will be also be needed in the near future.

ACKNOWLEDGEMENTS

The authors would like to thank funding program SEP-CONACYT for the financial support through the project: 24348 CB-2005-2010. Author L. Sepulveda Torre appreciates the economic grant from the National Council of Science and Technology of Mexico for his post-graduate program in Food Science and Technology.

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