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Review

Bioactivity of phenolic acids: Metabolites *versus* parent compounds: A review

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ABSTRACT

Phenolic acids are present in our diet in different foods, for example mushrooms. Due to their bioactive properties, phenolic acids are extensively studied and there is evidence of their role in disease prevention. Nevertheless, *in vivo*, these compounds are metabolized and circulate in the organism as glucuronated, sulphated and methylated metabolites, displaying higher or lower bioactivities. To clarify the importance of the metabolism of phenolic acids, knowledge about the bioactivity of metabolites is extremely important.

In this review, chemical features, biosynthesis and bioavailability of phenolic acids are discussed, as well as the chemical and enzymatic synthesis of their metabolites. Finally, metabolite bioactive properties are compared with that of the corresponding parental compounds.

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1. Introduction

Mushrooms are rich sources of bioactive compounds with an enormous variety of chemical structures (Ferreira, Barros, & Abreu, 2009). In particular, different bioactive properties have been attributed to phenolic acids from mushrooms, namely antitumor (Heleno, Ferreira, Calhelha, Esteves, & Queiroz, 2014a; Vaz, Almeida, Ferreira, Martins, & Vasconcelos, 2012), antimicrobial (Alves et al., 2013), and antioxidant (Piazzon et al., 2012).

However, very little is known about the phenolic acid bioactive forms *in vivo* and the mechanisms by which they may contribute towards disease prevention. Moreover, several studies dealing with the biological effects of phenolic acids have ignored the question of their achievable concentrations in the circulation after ingestion as well as the possibility of metabolism (Rechner et al., 2002). There is accumulating evidence suggesting that phenolic acids are rapidly metabolized in the human body (Nardini et al., 2009; Rechner et al., 2002; Scalbert & Williamson, 2000).

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After absorption from the gastrointestinal tract, these molecules suffer conjugation reactions causing several changes in their initial structure, and circulate in human plasma in their conjugated forms, such as glucuronide, methylated and sulphated derivatives. These changes in their structures may increase or decrease the bioactivity of the initial phenolic acids (Piazzon et al., 2012; Rechner et al., 2002).

Therefore, detailed knowledge concerning the conjugative and metabolic events and resulting plasma levels following the ingestion of a polyphenol-rich diet is crucial for understanding their bioactivity (Rechner et al., 2002). Despite the large amount of data concerning the bioactivity of phenolic acids, only a few studies deal with the bioactive properties of their metabolites, especially as most of those molecules are not commercially available (Piazzon et al., 2012).

In this review, several features of the phenolic acids found in mushrooms will be discussed, namely their chemical characterisation, biosynthetic pathways, bioavailability and metabolism, as well as the chemical and enzymatic synthesis of glucuronated, sulphated and methylated metabolites of different phenolic acids. The antioxidant, antimicrobial and antitumor properties of the metabolites will be discussed and compared with the bioactivities of the corresponding parental phenolic acid.

2. Chemical features and biosynthesis of phenolic acids usually found in mushrooms

Mushrooms have been extensively studied during the last few decades due to their bioactive potential (Ferreira et al., 2009), attributed to different molecules including phenolic acids. These compounds (Fig. 1) have been identified in different mushroom species around the world (Kim et al., 2008; Puttaraju, Venkateshaiah, Dharmesh, Urs, & Somasundaram, 2006; Ribeiro, Valentão, Baptista, Seabra, & Andrade, 2007; Valentão et al., 2005).

Phenolic acids can be divided into two major groups, hydroxybenzoic acids and hydroxycinnamic acids, which are derived from non-phenolic molecules of benzoic and cinnamic acid, respectively. Chemically, these compounds have at least one aromatic ring in which at least one hydrogen is substituted by a hydroxyl group (Fig. 1).

Phenolic compounds, including phenolic acids, are secondary metabolites from plants and fungi. These compounds are produced for protection against UV light, insects, viruses and bacteria. There are even certain plant species that develop phenolic compounds to inhibit the growth of other plant competitors (allelopathy). Examples of phenolic acids with this allelopathic action are caffeic and ferulic acids. It is believed that phenolic compounds were fundamental for plants to conquer their terrestrial environment, such as lignin which stimulates the development of the vascular system, giving stiffness to the vessels (Gross, 1985).

Phenolic acids are synthesized from the shikimate pathway from L-phenylalanine or L-tyrosine (Rice-Evans, Miller, & Paganga, 1996) (Fig. 2 and Table 1). Phenylalanine and tyrosine are very important amino acids in this pathway since these amino acids are the common precursors for the majority of the natural phenolic products (Fig. 2 and Table 1).

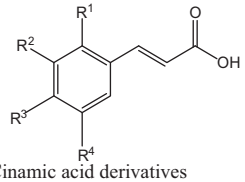
Firstly, a deamination of the phenylalanine and/or the tyrosine occurs giving cinnamic and/or *p*-coumaric acids, respectively. Cinnamic and *p*-coumaric acid aromatic rings are then hydroxylated and methylated to form its derivatives *e.g.*, ferulic and caffeic acids. Deamination, hydroxylation and methylation are the main three reactions involved in the formation of phenolic acids (Fig. 2 and Table 1) (Gross, 1985). Benzoic acid formation can result from degradation of the side chain of cinnamic acid. As mentioned for cinnamic and *p*-coumaric acids, the same hydroxylation and methylation reactions can occur in the aromatic ring of benzoic acid giving the correspondent derivatives *e.g.*, protocatechuic and *p*-hydroxybenzoic acids (Gross, 1985).

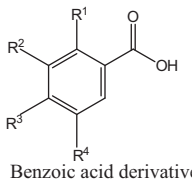
3. *In vivo* human metabolism of phenolic acids

3.1. Bioavailability of phenolic acids

Despite the extensive literature describing the biological effects of phenolic acids, little is known about how they are absorbed from diet.

Phenolic acids are present in almost all plant-derived foods, representing a significant portion of the human diet. The average phenolic acid intake in humans has been reported to be in the order of 200 mg/day depending on diet habits and preferences (Clifford & Scalbert, 2000). The most frequently encountered and studied phenolic acids are caffeic and ferulic acids. Caffeic acid is also found in the form of esters, chlorogenic acid being the most frequently encountered (Clifford & Scalbert, 2000). Coffee is normally studied for the absorption of these molecules since it is a good source of bound phenolic acids, such as caffeic, ferulic and *p*-coumaric acids (Nardini, Cirillo, Natella, & Scaccini, 2002). In patients that ingested a specific quantity of coffee, (Marmet, Actis-Goretta, Renouf, & Giuffrida, 2014) several methylated, glucuronated and sulphated metabolites of phenolic acids circulating in plasma, were identified. In another study, Fumeaux et al. (2010) described that after a specific dose of coffee, several





Substitution	Cinamic acid derivatives	Benzoic acid derivatives
R^1=OH	*o*-Coumaric acid	-
R^3=OH	*p*- Coumaric acid	*p*- Hydroxybenzoic acid
R^3=R^4=OH	Caffeic acid	Protocatechuic acid
R^2=OCH_3,R^3=OH	Ferulic acid	Vanillic acid
R^2=R^3=OCH_3	-	Veratric acid
R^2=R^3=R^4=OH	-	Gallic acid
R^1=R^4=OH	-	Gentisic acid
R^2=R^4=OCH_3, R^3=OH	Sinapic acid	Syringic acid
R^1=OH, R^4=HSO_3	-	5- Sulphosalicylic acid
R^2=R^3=OH	3,4 or 5-*O*-caffeoylquinic acid *	-

* The carboxylic group is esterified with quinic acid.

Fig. 1. Chemical structures of benzoic and cinnamic acid derivatives usually found in mushrooms.