Polyphenols

Subjects: Plant Sciences

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Polyphenols are the most abundant and ubiquitous secondary metabolites present in the plant kingdom with more than 8000 phenolic structures currently known. These compounds play an important role in plant growth and reproduction, providing protection against biotic and abiotic stress such as pathogen and insect attack, ultra violet (UV) radiation and wounding.

grape pomace polyphenols hypertension metabolites characterization

1. Introduction

Dietary intake of (poly)phenols has been estimated to be about 1 g/day [1]. Their intake is 10 times greater than that of vitamin C and 100 times that of vitamin E or the carotenoids [2]. As a result, phenolic compounds are currently receiving much attention because of their favourable health effect related to their antioxidant properties. Indeed, several studies have focused their attention on the components of red wine (mainly polyphenols and especially resveratrol) since the so-called “French paradox” was first described [3] in order to explain the relationship observed between wine consumption and the incidence of cardiovascular disease (CVD). There is extensive evidence to support the influence of wine intake on cardiovascular health [4][5][6][7], controversy remains whether red wine in particular exerts beneficial effects compared with other alcoholic beverages [8][9] or simply alleviates the detrimental influence of alcohol on blood pressure (BP) [10][11]. No changes in BP were observed in acute studies with healthy volunteers but an increase in the heart rate was reported after red wine consumption [12][13], whereas in coronary artery disease (CAD) patients, a decrease in systolic and diastolic BP was noted together with an increase in heart rate, 1 h post wine (red and white) intake [14]. Other studies have reported no changes in hemodynamics or BP after medium-term daily intake of either red wine or its dealcoholized equivalent [15][16].

Overall results of polyphenols consumption may be promising but they remain inconclusive and further prospective studies assessing dietary polyphenol exposure and studies using other methods to evaluate exposure (i.e., markers of consumption, metabolism, excretion) have been recommended, as concluded in a recent meta-analysis summarizing [17]. A recent systematic review using intervention studies confirmed that urinary polyphenol metabolites could serve as dietary biomarkers with high recovery yields and high correlations with intakes of polyphenol-rich food [18].

Different grape pomace extracts were studied for their possible influence against hypertension disease, as they present an important under used residue of the wine making process. A large number of publications evidenced the abundance quantity of polyphenols in grape seeds and skins, showing significant antioxidant capacity. It is

therefore obvious that it is a natural source of polyphenols that accounts for about 20% of grapes weight used to make wine [19][20]. Finally, some metabolites in urine, plasma and tissues were measured for accurate and precise estimation of dietary exposures and possible differences between the grape pomace extracts.

2. Potential Effect Against Hypertension

In order to evaluate the in vivo effect of grape pomace extracts and their potential effect on hypertension, rats were fed with different grape pomace EA70 extracts at a dose of 21 mg/kg/day, equivalent to a daily dose of 70 kg human consumption of 0.5 L of wine. The study was conducted over six weeks including three weeks of treatments, one week of treatment resumption followed again by two weeks of treatment.

Higher levels of *O*-methyl-(epi)catechin-*O*-glucuronide relative to (epi)catechin-*O*-glucuronide were found in every urine sample. Sulphate derivatives of 5-(hydroxyphenyl)-γ-valerolactone were excreted in greater amounts than glucuronides. A decrease of 5-(hydroxyphenyl)-4-hydroxyvaleric acid-*O*-sulfate from 0–8 h to 8–24 h at day 1 was observed while an increase of 5-(phenyl)-4hydroxyvaleric acid-*O*-sulphate occurred at 8–24 h compared to 0–8 h in all rat urines at day 1 and day 7. A previous report on a human almond skin polyphenol bioavailability [21] suggested that partial dihydroxylation reactions occur gradually as colonic metabolism progresses. These authors observed a change in the hydroxylation pattern of the phenyl ring from di- to mono- and unhydroxylated forms. Dihydroxylated derivatives were found 6–10 h after the intake, monohydroxylated forms were observed at 6–24 h and unhydroxylated derivatives were found 10–24 h after the intake.

At day 1, excretion as a percentage of intake varied from 1.02% to 1.57%. Highest recoveries were observed in the SHR5 group (1.57%, over 0–24 h). At day 7, an increase of intake was observed for the two collection periods and, as a consequence, over 0–24 h. The recoveries ranged from 1.43% in SHR6 to 4.41% in SHR5. A large increase in metabolite excretion was observed in SHR5 group with 4.41% of intake at day 7 compared to 1.57% at day 1. These observations suggested that over time, SHR rats may be able to ingest higher doses of polyphenols especially those contained in MOU (EA70) skin pomace extract.

Heart tissues contained more glucuronidated metabolites than sulphated. 5-(hydroxyphenyl)-γ-valerolactone-*O*-sulphate, was detected only in E1 and E5 experimental groups at a level of 0.11 ± 0.00 nmol.

Kidneys contained more 5-(hydroxyphenyl)-γ-valerolactone-*O*-sulphate than the liver.

Liver contained the highest level of metabolites with most present as glucuronides. A 5-(hydroxyphenyl)-γ-valerolactone-*O*-sulphate was only detected in SHR rats fed with ALI (EA70) skin pomace extract + verapamil at 7.24 ± 0.6 nmol. Only SHR from E5, VE5 and VE6 experimental groups contained significantly higher amounts (210 ± 12 nmol, 198 ± 3 nmol and 194 ± 7 nmol, respectively) of 5-(hydroxyphenyl)-γ-valerolactone-*O*glucuronide compared to control groups.

The absorption and arguably metabolism, of flavan-3-ols and procyanidins initially takes place during transfer through the wall of the small intestine after which further phase II metabolism occurs in the liver. As liver appear to be the most important organs involved in flavonoid metabolism, it was not surprising to find such a high level of metabolites. Some of the conjugated metabolites can be actively effluxed back into the lumen of the small intestinal and/or may be transported to other organs through the bloodstream as shown by their presence in the heart. In addition, metabolites were also detected in kidneys no doubt as a consequence of renal excretion. It should be noted that the time of tissue sampling may be of importance and metabolites detection depends on the kinetics of their accumulation and elimination in the tissues. In this study, tissues which were shown to contain metabolites were collected 4 h after the ingestion of grape pomace extracts. A study carried out in 2005 found flavan-3-ol metabolites in the liver of rats 1 h and 4 h after ingestion of a grape seed extract but none were detected 6, 12 and 24 h after intake [22]. This indicates a rapid elimination of flavan-3-ol metabolites in keeping with them being treated as xenobiotics by the body.

3. Conclusions

Substantial levels of polyphenols after the winemaking process, remain in pomace in quantities sufficient to exert anti-hypertensive effects. In addition, according to the extract used and its composition, it is feasible to modulate anti-hypertensive effects by amplifying or decreasing polyphenols absorption. Therefore, it will be interesting to elucidate the exact mechanisms and compounds involved in this phenomenon in order to have a better control on blood pressure regulation and facilitate the choice of effective grape pomace extracts for further experiments. Moreover, it will be useful to investigate the effect of different flavan-3-ol fractions (i.e., oligomeric, monomeric) and anthocyanin fractions (i.e., glucosides, acetylated glucosides and coumarylic glucosides) in order to identify whether anti-hypertensive effects are linked to a particular compound or to the extracts as a whole.

As SHR represents a good model to investigate hypertension, studies could be extended to human clinical trials. For clinical tests, different parameters have to be taken into account such as the subjects (i.e., pre-hypertensive or hypertensive subjects), the dose used, the diet, biological fluid collections and biological markers to be quantified. In addition, different processes will have to be considered such as the election of grape pomace varieties and their parts (seeds/skins), the extraction processes which will be used, the dosage and the galenic formulation used in order to provide great stabilisation of the active substances.

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