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Review

Red raspberry and its anthocyanins: Bioactivity beyond antioxidant capacity

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ABSTRACT

Background: Known as the "golden fruit", red raspberry is rich in anthocyanins with documented biological activities, many of which were systematically investigated. Nowadays, raspberry anthocyanins' importance for Food and Pharmaceutical industries is mainly based on the existed scientific works evidencing their potential effects on chemoprevention, inflammation, and immune-regulation. Although, much of the work in these respective areas which has been conducted in cell culture systems, animal and human studies have been steadily rising.
Scope and approach: In this review, We review and summarize the latest and available literature that assesses the health-promoting potential of red raspberries and their anthocyanin components in modulating metabolic disease risk, especially cardiovascular disease, cancer, all of which share critical metabolic, oxidative, and inflammatory links.
Key findings and conclusions: We also suggested a better evaluation of the pharmacological profile of raspberry and its anthocyanins with a clear-cut choice of possible human pathologies. Future studies aimed at enhancing the absorption of anthocyanins or their metabolites are likely to be necessary for their ultimate use for chemoprevention and anti-inflammation.

1. Introduction

Known as the "golden fruit" (Fig. 1), red raspberries are becoming increasingly appreciated for their culinary versatility and other applications. The harmless natural edible pigment of red raspberry was conspicuous to topic in the pharmaceutical and food scientific researches. Red raspberries possess a unique polyphenol profile that is characterized primarily by their anthocyanins. The anthocyanins are important natural organic compound, besides of being taken as the edible pigment, it also has the vital significance to prevent diseases, such as tumor, senile and cardiovascular of humanity, as well as the effects on oxidative stress. Since anthocyanins, which are sub-categorized into the flavonoids, have strong anti-oxidative activities, they can safeguard cells and body away from oxidation by scavenging free radicals (Chen & Kang, 2013, 2014; Chen, Xu, Zhang, Li, & Zheng, 2016). Raspberries are widely distributed and cultivated in China. However, industrial development of raspberry products got restrictions because of differences in the variety and cultivation environment, as well as the limitation in preservation and processing techniques, and etc. In recent years, other berry fruits, such as the strawberry, blueberry, cranberry and black raspberry, have been studied for their beneficial effects on health. These health benefits include prevention of certain types of cancer, cardiovascular diseases, neurodegenerative diseases associated with oxidant damage. Comparatively, little work has been done on red raspberries. Therefore, in order to provide a theoretical basis for using and developing raspberry resource, the major objective of this review is to summarize the latest developments on the antioxidant activities of anthocyanin-rich raspberry in cell culture models to discuss their underlying molecular mechanisms which drives chemo-preventative and anti-inflammatory effects.

2. Methods

This review is a descriptive review of literature. Keywords such as "raspberry", "anthocyanin", "extract", were searched separately or combined in national databases such as CNKI, and international

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Abbreviations

AP-1	Activation protein-1
Bcl-2	B cell lymphoma-2
Cdk	Cyclin dependent kinase
COX	Cyclooxygenase
COX- 2	Cycloxygenase-2
ERK	Extracellular signal-related kinase
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
HIF-1α	Hypoxia-inducible factor-1α
HO-1	Heme oxygenase-1
IL	Interleukin
IL-1β	Interleukin-1 β
IL-6	Interleukin-6
IκB-α	Inhibitor of κB-α
IKK	inhibitor of κB-α kinase
iNOS	inducible nitric oxide synthase
JAK	Janus kinase
JNKc	Jun NH_2-terminal kinase
LPS	Lipopolysaccharide
LXRα	liver X receptor α
MAPKs	Mitogen-activated protein kinases
MAP2K	MAPK kinase 1
MMP	Matrix metalloproteinase
NF-κB	Nuclear factor-kappa B
NO	Nitric oxide
Nrf2	Nuclear transcription factor-E2-related factor 2
ORAC	Oxygen radical absorbance capacities
PDGF	Platelet-derived growth factor
PGE_2	Prostaglandin E_2
PI3K	Pphosphatidylinositol 3-kinase
PKC	Protein kinase C
PIP2	Phosphatidylinostol (3, 4)-bisphosphate
PIP3	Phosphatidylinostol (3, 4, 5)-triphosphate
PPARγ	Peroxisome proliferator-activated receptor γ
ROS	Reactive oxygen species
SOD	Superoxide dismutase
TNF-α	Tumor necrosis factor-alpha
VEGF	Endothelial growth factor
VEGFR-2	VEGF receptor-2

databases including Science direct, Pubmed, Springer and Scopus. The searched languages were limited to Chinese and English articles. The search period was limited from 2006 to June 2016. Overall, 382 articles were collected in the first step. Then unrelated articles were excluded according to title and abstract evaluations. Articles with incomplete data along with congress and conference's proceedings were excluded. All of reviewed studies were clinical trial or experimental researches. Finally, 89 studies got inclusion criteria and were included in the study.

3. Extraction

Soaking has been extensively used for anthocyanins extraction. In the wine industry, it is the most recurrent method that consists in grinding the fresh fruit and putting the grape juice in contact with skins to extract the pigments (Ella, Guyot, & Renard, 2003). According to the extraction methods reported in literature, the most frequently used solvents for anthocyanins extraction from raspberry are methanol, ethanol, and acetone (Kahkonen, 2003). Meanwhile, using weak acid media (0.1% formic or acetic acid) into organic solvent to extract anthocyanins could avoid their hydrolysis (Dai & Mumper, 2010). Acidified methanol is widely considered to be the most efficient (Kapasakalidis, And, & Gordon, 2006). For example, anthocyanin extractions with acidified methanol is 73% more effective than pure water, and 20% and 200% more efficient than those extracted with acidified ethanol (Metivier, Francis, & Clydesdale, 1980) and acetone (Lee & Johnson, 2004), respectively. However, ethanol is preferred due to its non-toxicity in food industry. Nevertheless, under these conditions, it is impossible to know whether the hydrolysis of aglycons occurred or not during the extraction of raspberry anthocyanins. Despite the extensive use of acidified methanol as the extractant has been claimed, special care should be taken to avoid degradation of anthocyanins (hydrolysis reaction) under strong acid media, meanwhile, in the case of 3-monoside anthocyanins, the glycoside bonds could also be destroyed (Kapasakalidis et al., 2006). Besides of the acidified extractant, sulfured water by using aqueous SO_2 solution (HSO_3) has also been reported for anthocyanin extraction (Cacace & Mazza, 2002). Bisulfite solution can react with anthocyanins causing a nucleophilic attack in the molecule (Mazza & Brouillard, 1990) and causing a decolorization of monomeric anthocyanins (Berké, Chèze, Vercauteren, & Deffieux, 1998). In the anthocyanin extractions from black currants, an aqueous solution of 80% EtOH saturated with SO_2 was used as extractant, and it was observed that the type of solvent, SO_2 concentration, and the temperature affected the extraction process, and the mass transfer rate was higher in sulphurated water than that in ethanol solution (Cacace & Mazza, 2002). Thus, it can be concluded that weak acidic media might good for improving anthocyanin extraction yield, but hydrolysis of anthocyanins during the process was unclear.

4. Isolation and identification of active anthocyanins

The isolation and identification of active compounds have a critical role in the quality evaluation of raspberry fruit and its processed food. Because of anthocyanins spectral characteristics provide very useful qualitative and quantitative information; actually mass spectrometry (MS) and nuclear magnetic resonance (NMR) of ^{1}H and ^{13}C have become the preferred techniques for anthocyanins identification (Castaneda-Ovando, de Lourdes Pacheco-Hernández, Páez-Hernández, Rodríguez, & Galán-Vidal, 2009). As reviewed by Giusti and Wrolstad (2003), the main methods used in the characterization and quantification of anthocyanins is UV–Vis. HPLC with PDA detector has been also used in the anthocyanins identification and quantification (Kong, Chia, Goh, Chia, & Brouillard, 2003; Teng, Lee, & Choi, 2013; Teng, Lee, & Choi, 2014), but the difficulty to obtain reference compounds and the spectral similarities of the anthocyanins represent an important drawback.

5. Chemistry

Anthocyanins, belong to polyphenol compound, are water-soluble pigments in plants which contribute to the brilliant colors of blue, red, and mauve in flowers, fruits and leaves. The ionic nature of anthocyanins enables changes of the molecular structure according to the prevailing pH, resulting in different colors and hues at different pH values. It occurs principally when glycosides of their respective aglycone anthocyanidin chromophores generally attached at the 3-position on the C-ring (3-monoglycosides) or the 5-position on the A-ring (3, 5-diglycosides) (Prior & Wu, 2007). Anthocyanins are classified according to the number and position