Soy-derived phytoalexins: mechanism of in vivo biological effectiveness in spite of their low bioavailability

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Abstract The well-demonstrated bioefficacy of phytochemicals in spite of their paradoxically low bioavailability has long puzzled scientists. Glyceollins, a family of soy-derived phytoalexins, have been reported to exert a variety of biological effects in vitro and in vivo systems in spite of poor systemic bioavailability after oral administration, suggesting that secondary messengers generated in gastrointestinal tract would transfer signals to target organs and tissues to manifest any effect. This review focuses on the potential mechanisms of how the poorly bioavailable glyceollins could still exert in vivo biological effects.

Keywords Phytochemicals · Nrf2 · Heme oxygenases · Carbon monoxide · Glyceollins

Introduction

Glyceollins, a family of phytoalexins produced from soybeans exposed to exogenous stressors, have been reported to exhibit numerous biological activities, including antioxidative, estrogenic/antiestrogenic, anti-inflammatory, and anticarcinogenic effects (Burow et al., 2001; Kim et al., 2010a; Kim et al., 2011b; Kim et al., 2012a; 2012b; Kim et al., 2014a; Kim et al., 2015). Although the glyceollin content in unstressed soybean is negligible, it is

dramatically increased under stressful environments, such as fungal infection, irradiation, physical damage, and exposure to some chemicals (Boue et al., 2000; Darvill and Albersheim, 1984).

The precursor of glyceollins is daidzein, which is one of the typical isoflavones in soybeans and synthesized from phenylalanine through multiple enzymatic steps. Daidzein is then converted to glycinol (the non-prenylated precursor of glyceollins) (Bamji and Corbitt, 2017; Weinstein and Albersheim, 1983), which is then biotransformed into glyceollin isomers I, II, and III through prenylation and cyclization steps (Bamji and Corbitt, 2017). Intriguingly, glyceollins seem to have systemic effects in most tissues in spite of their poor bioavailability (Boue et al., 2012). This review focuses on the potential mechanism through which the phytoalexins with low bioavailability exert biological effects in the whole body system.

Bioavailability, metabolism, and transport of glyceollins

Bioavailability

Natural polyphenols are usually absorbed to a limited extent and have a relatively short half-life under in vivo conditions (Estrela et al., 2017). The prenylation of flavonoids has been reported to lower their intestinal absorption (Mukai, 2018). Therefore, glyceollins, which belong to a family of prenylated pterocarpanes, are expected to have a poor absorption rate. In a study on postmenopausal female monkeys fed glyceollin-enriched soy protein, the plasma level of glyceollins was extremely low at less than 1 nM, whereas the plasma levels of equol and daidzein were 171.9 and 15.3 nM, respectively (Salvo et al., 2006).

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Despite their poor bioavailability, glyceollins have been demonstrated to manifest biologically beneficial effects *in vivo* (Bamji et al., 2015; Kim et al., 2015; Lee et al., 2014; Seo et al., 2010; Seo et al., 2017; Wood et al., 2006). Thus, it remains highly controversial how the underlying mechanisms of action of phytoalexins are compatible with their bioavailable concentrations and biological half-life (Estrela et al., 2017).

Metabolism

Although the health benefits and working mechanisms of glyceollins have been well documented, studies of their metabolism are limited. Absorbed phytochemicals are typically metabolized by phase I and II enzymes in the liver and are eventually eliminated by excretion via the urine and bile. Phase I metabolism includes nonsynthetic, functionalization reactions (e.g., oxidation, reduction, and hydrolysis), whereas phase II metabolism is associated with synthetic, conjugation reactions (e.g., acetylation, methylation, sulfation, glucuronidation, and glutathione conjugation) (Heinonen et al., 2003; Hu et al., 2003). The direct conjugation of phytochemicals with glucuronic acid, sulfate, and glutathione in the gastrointestinal (GI) tract is a significant cause of their poor bioavailability (Quadri et al., 2014). Glyceollins were previously reported to be sulfated, glucuronidated, and conjugated with glutathione, according to analyses of glyceollin metabolites in rat plasma using liquid chromatography-electrospray ionization tandem mass spectrometry (Quadri et al., 2013; Quadri et al., 2014). Once metabolized, phytochemicals become hydrophilic and difficult to be transported into cells, and are instead eliminated from the body.

Transport

The permeability of glyceollins, examined using Caco-2 cell culture (a well-established model of the human small intestine), is very high and comparable to other compounds with 100% absorption (Chimezie et al., 2014; Gres et al., 1998). At 10 and 25 μM , the glyceollin permeability was $2.4 \pm 0.16 \times 10^{-4}$ and $2.1 \pm 0.15 \times 10^{-4}$ cm/s, respectively, in the absorptive direction (Chimezie et al., 2014). In addition, the basolateral to apical permeability at 25 μM was $1.6 \pm 0.10 \times 10^{-4}$ cm/s, suggesting the high absorption potential of glyceollins by a passive diffusion-dominated mechanism in the GI tract (Chimezie et al., 2014).

Generation of signaling molecules by glyceollins in the GI tract

The GI tract is a well-known endocrine organ that secretes a variety of hormones, such as ghrelin, gastrin, secretin, cholecystokinin, glucagon-like peptide, leptin, bombesin, growth factors, peptide YY, and neurotensin. Although the enteroendocrine cells in the GI tract represent only a small fraction ($< 1\%$) of the total epithelial cells, they constitute the largest endocrine organ in the body, producing more than 20 hormones that act locally, peripherally, and centrally (Breer et al., 2012; Rehfeld, 2004). It is highly plausible that phytochemicals affect or interact with enteroendocrine cells while passing through the GI tract, altering the secretion of hormones and thereby exerting their positive or negative biological effects. Our previous study demonstrated that glyceollins could exert insulinotropic action by boosting glucagon-like peptide-1 secretion and thereby increasing insulin sensitivity, leading to the improvement of diabetic conditions (Seo et al., 2010). Phytochemicals were identified to be sensed by specific receptors in the gut, such as transient receptor potential receptors (Premkumar, 2014). The receptors are ligand-gated ion channels that provide an inward cation current when stimulated. Allyl isothiocyanate present in cruciferous vegetables, which is a typical antioxidant enzyme/phase 2 enzyme inducer like glyceollins, is known to promote the release of cholecystokinin from STC-1 cells (Purhonen et al., 2008) and of serotonin (5-hydroxytryptamine) from isolated enteroendocrine cells (Furness et al., 2013; Nozawa et al., 2009).

Most phytochemicals, including glyceollins, have low bioavailability while showing *in vivo* biological effectiveness. Furthermore, even if very limited, the dietary phytochemicals that are absorbed through absorptive cells lining the GI tract are rapidly metabolized into biologically inactive metabolites by conjugation with glucuronic acid, sulfate, and glutathione, resulting in a small percentage of bioactive free forms in the bloodstream. The metabolites can be recycled by the intestinal tract, converted into active free forms in the liver, and taken up by the cells; however, plasma levels of the free form of phytochemicals are usually too low to exert any significant biological effect (Gao and Hu, 2010; Garcea et al., 2005; Wang et al., 2014).

This apparently contradictory phenomena between low bioavailability and observed *in vivo* efficacy may be explained if there is signaling molecule(s) traveling through blood and/or lymph. For instance, the phytochemical epigallocatechin 3-gallate (EGCG), which is known to have a variety of health benefits, interacts with proteins and phospholipids in the plasma membrane of the mammalian cell and regulates signal transduction

pathways, transcription factors, DNA methylation, mitochondrial function, and autophagy (Estrela et al., 2017; Kim et al., 2014b). It suggests that EGCG itself could serve as a signaling molecule. Another example of a signaling molecule generated by phytochemicals is nitric oxide (NO), which is involved in endothelium-dependent vasorelaxation and modulation of the tissue stress response. NO is intracellularly and transiently generated by nitric oxide synthase upon cell exposure to some antioxidative flavonoids (Upadhyay and Dixit, 2015). The NO signal generated in a cell can be easily transmitted to neighboring cells or tissues since the gaseous molecule can penetrate freely through lipid membranes (Farrugia and Szurszewski, 2014). In addition, carbon monoxide (CO) and hydrogen sulfide (H₂S) have also been reported to exert similar biological effects albeit through different mechanisms (Bianco and Fukuto, 2015). All of these gaseous signaling molecules exhibit complex effects in inflammation, with both pro- and anti-inflammatory effects. It is most likely that cell function is controlled not by the activity of any single gas in isolation but by the combined activity of all three of these gases (Li et al., 2009).

Carbon monoxide as a potential mediator of in vivo biological effects

Among the gaseous molecules, CO is the most stable and is therefore supposed to have long-lasting biological effects compared with NO and H₂S. Furthermore, it has high binding affinity to the heme prosthetic group-carrying molecules, such as hemoglobin, myoglobin, and cytochromes. As CO can bind to hemoglobin in the blood, it can travel throughout the body and exert systemic effects. Intracellular CO is produced by heme oxygenases (HO), which catalyze the breakdown of heme into CO, biliverdin IX α , and ferrous iron (Fe²⁺). Of the two genetically distinct heme oxygenase isozymes, HO-1 is sensitively and transcriptionally regulated by cellular stimuli, whereas HO-2 is constitutively expressed (Keyse and Tyrrell, 1989; Maines et al., 1986; Ryter et al., 2018).

A number of studies have demonstrated that some phytochemicals, such as curcumin, resveratrol, EGCG, and sulforaphane, activate nuclear factor (erythroid-derived 2)-like-2 factor (NFE2L2 or Nrf2)-mediated signal transduction, inducing its downstream antioxidative and phase II detoxifying enzymes (Chen and Kong, 2004; Jadeja et al., 2016; Na and Surh, 2008). Under normal conditions, Nrf2 exists as a heterodimer with its cytoplasmic repressor Keap1, and is constantly degraded via the ubiquitin-proteasome pathway. However, endogenous and/or exogenous

Fig. 1 Hypothetical action mechanism for health benefits of glyceollins. *Nrf2* nuclear factor (erythroid-derived 2)-like 2, *HO-1* heme oxygenase 1, *Hb-CO* carboxyhemoglobin

stress factors facilitate the release of Nrf2 from the Nrf2–Keap1 heterodimer and its translocation into the nucleus. There, nuclear Nrf2 promotes the expression of numerous genes, including those encoding HO-1, NAD(P)H:quinone oxidoreductase, glutathione reductase, glutathione *S*-transferase, and other phase II detoxifying and antioxidative enzymes (Itoh et al., 1997; Jaiswal, 2004; Jeong et al., 2006; Kang and Pezzuto, 2004; Kensler et al., 2007; Kim et al., 2003).

HO-1 is one of the seminal enzymes under the control of the Nrf2 transcription factor and is upregulated by a variety of phytochemicals. Although HO-1 is known to play a major role in health beneficial effects through its cytoprotective, mitochondrial biogenesis, antioxidative, and anti-inflammatory activities, the enzyme has not received proper attention as a mediator for the in vivo effectiveness of dietary phytochemicals.

We found that glyceollins could significantly induce HO-1 in an Nrf2-mediated manner and thereby reduce intracellular levels of reactive oxygen species (Kim et al., 2011a). In addition, the anti-inflammatory, insulinotrophic, and neuroprotective effects of glyceollins appear to be mediated by CO, the concentration of which is increased by the action of glyceollin-induced HO-1. In fact, CO-releasing molecules including RuCl(gly)(CO)₃, Fe(CO)₅, Mn₂(CO)₁₀ are in development as anti-inflammatory drugs, protective agents against organ transplant- and cisplatin-induced nephrotoxicity, and wound healing drugs (Mottetlini and Otterbein, 2010; Nikam et al., 2016). Considering the traits of CO, such as its chemical stability, ability to travel through the bloodstream, and a variety of biological activities, we speculate that the majority of phytochemicals activating the Nrf2 signaling pathway may exert their biologically beneficial effects not by acting directly on target molecules in cells but rather by triggering the generation of CO, which is an enzymatic product of the HO-1 reaction and also further upregulates HO-1 via Nrf2-mediated modulation.

A number of phytochemicals, including soy-derived glyceollins, have been reported to induce antioxidative and phase II detoxifying enzymes and thereby exert a variety of biological effects (Chen and Kong, 2004; Kim et al., 2010b; Kobayashi et al., 2009; Na and Surh, 2008). However, because most phytochemicals have low bioavailability, the mechanisms underlying their in vivo effects have remained unclear until now. We found that glyceollins induced HO-1 consistently in several cell lines and in vivo systems in an Nrf2-mediated manner (Kim et al., 2011a; Kim et al., 2015; Seo et al., 2018). As CO, a product of the HO-1 reaction, has been known to play a major role in health benefits, we speculate that glyceollins and natural Nrf2 activators may stimulate the Nrf2/HO-1 signaling system in hepatic cells as well as gut epithelial

cells and thereby promote the production of CO, which could then be channeled through the bloodstream and exposed to the target cells (Fig. 1). Although this hypothesis enables us to explain the in vivo effects of the poorly bioavailable phytochemicals, direct evidence for the CO production in hepatic and enteroepithelial cells at an appropriate level for the biological effectiveness, the CO transfer from the cells to the blood, and the transport of blood CO to the target tissues or cells is still needed.

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