Metabolism of Ginsenosides to Bioactive Compounds by Intestinal Microflora and Its Industrial Application

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(Received July 15, 2009; Revised September 8, 2009; Accepted September 10, 2009)

Abstract: Korean ginseng, which contains ginsenosides and polysaccharides as its main constituents, is orally administered to humans. Ginsenosides and polysaccharides are not easily absorbed by the body through the intestines due to their hydrophilicity. Therefore, these constituents which include ginsenosides Rb1, Rb2, and Rc, inevitably come into contact with intestinal microflora in the alimentary tract and can be metabolized by intestinal microflora. Since most of the metabolites such as compound K and protopanaxatriol are nonpolar compared to the parental components, these metabolites are easily absorbed from the gastrointestinal tract. The absorbed metabolites may express pharmacological actions, such as antitumor, antidiabetic, anti-inflammatory, anti-allergic, and neuroprotective effects. However, the activities that metabolize these constituents to bioactive compounds differ significantly between individuals because all individuals possess characteristic indigenous strains of intestinal bacteria. Recently, ginseng has been fermented with enzymes or microbes to develop ginsengs that contain these metabolites. However, before using these enzymes and probiotics, their safety and biotransforming activity should be assessed. Intestinal microflora play an important role in the pharmacological action of orally administered ginseng.

Key words: Panax ginseng, ginsenoside, intestinal microflora, metabolism, fermentation

INTRODUCTION

Ginseng usually refers to the dried roots of several species in the plant genus Panax (family Araliaceae). Three major commercial ginseng are Panax ginseng CA Meyer (Korean ginseng), which has been used as an herbal medicine for more than 2000 years,1) Panax quiquifolium (American Ginseng), and Panax notoginseng (Chinese Ginseng).2,3) Among them, Panax ginseng is the most commonly used and extensively researched. Approximately 200 substances, including ginsenosides, polysaccharides, polyacetylenes, peptides and amino acids, have been isolated from Korean ginseng.4) Its major components are ginseng saponin and polysaccharides. The representative pharmacological effect of ginseng is adaptogenic; in other words, it enhances physical performance, promotes vitality, increases resistance to stress and aging, and possesses immunomodulatory activity.5-7) The adaptogenic properties of ginseng are believed to be due to its effects on the hypothalamic-pituitary-adrenal axis.8-10) Its immunomodulatory activity improves defense systems that can overcome tumors and microbial infection.

The fresh harvested ginseng root is called Susam; dried, it is called white ginseng. Red ginseng is the steamed and dried fresh ginseng root. Red ginseng is frequently used as an herbal medicine in Asian countries because its long-term storage and taste are better. Many scientists have isolated bioactive constituents from ginsengs and identified their structures to clarify their pharmacological activities. Nevertheless, these structures were not established until 1960. In 1963, Shibata et al. isolated the major ginseng saponins and named them ginsenosides.11,12) The major saponins were dammarane oligoglycosides, but an oleanane-type was also later identified.13) Based on the structure of the aglycone or sapogenin, dammarane-type (protopanaxadiol, protopanaxatriol, etc.) and oleanane-type have been isolated in ginsengs. The major components of Korean Susam or white ginseng are protopanaxadiols, protopanaxatriols, and oleanane: malonyl-ginsenosides Rb1, Rb2, Rc, and Rd, ginsenosides Rb1, Rb2, Re, Rf, Rg1, Rg2, and Ro.14) However, the major components of red ginseng are ginsenosides Rg3, Rg5, Rk1,
Rh2, Rh3, Rk2, Rb1, Rb2, Rc, Re, Rf, Rg1, Rg2, and Ro.15-17) In Korean ginseng, many acidic and neutral polysaccharides have been isolated: panaxans A-U, GR1-4 and GL1-5, ginsenans PA, PB, SIA, and SIIA, and ginsans. Acidic polysaccharides were increased by steaming.18,19)

**METABOLISM OF BIOACTIVE CONSTITUENTS OF GINSENG**

Ginseng has various pharmacological activities *in vitro* and *in vivo*. Its bioactive constituents are considered ginsenosides (ginseng saponins) and polysaccharides, although the pharmacological activities of all components have not been clarified. The ginsenosides have been reported to show antitumor,20-22) antidiabetic,23,24) anti-inflammatory,25) antiallergic,26,27) endothelium-independent aorta relaxation,28) adjuvant-like,29) immunomodulatory,30,31) and neuroprotective effects.32,33) The polysaccharides reportedly show anti-inflammatory,34) antidiabetic,35,36) antitumor,37) and immunostimulatory effects.38)

When ginseng is orally administered to humans, its main constituents, *i.e.*, ginsenosides and polysaccharides, cannot be easily absorbed from the intestine due to their hydrophilicity. Therefore, these constituents inevitably come into contact with intestinal microflora in the alimentary tract and can be metabolized by intestinal microflora.39,40) The metabolites are then easily absorbed from the gastrointestinal tract since most of the metabolites are nonpolar compared to the parental components. These absorbed metabolites may express pharmacological actions (Fig. 1).

For example, when ginseng was orally administered to humans, compound K and ginsenosides Rh1 and F1 were detected in the blood.41,42) Ginsenosides Rb1 and Rb2 were not detected. When ginsenoside Rb1, a main constituent of ginseng, was orally administered to conventional rats, compound K was detected in the intestinal contents, blood and urine.43,44) Ginsenoside Rb1 was not detected. Furthermore, compound K was detected in the blood and intestinal contents when ginsenoside Rb1 was orally administered to gnotobiotic rats.45) However, when ginsenoside Rb1 was orally administered to germ-free rats, compound K and ginsenoside Rb1 were not detected in the blood and intestinal contents. Therefore, to evaluate the pharmacological effects of ginsengs, we should investigate those of the metabolites.

Many researchers have reported the anti-tumor effect of ginsengs *in vivo* and *in vitro*.46-48) Among the isolated ginsenosides, compound K and 20(S)-ginsenoside Rh2 exhibited the most potent cytotoxicity against tumor cells.49,50) Ginsenosides Rb1 and Rb2 did not exhibit cytotoxicity against the tumor cell lines. In general, the order of cytotoxic potency of tested ginsenosides against tumor cells was compound K > ginsenoside Rh2 >> ginsenoside Rg3 > ginsenoside Rb1 and Rb2. However, most ginsenosides have anti-tumor activities *in vivo*.51,52) Nevertheless, orally administered ginsenosides Rb2 and Rg3 had a potent anti-metastatic effect.53,54) These results suggest that ginseng saponins may be metabolized to active compounds, such as compound K and ginsenoside Rh2, and may be good anti-tumor candidates.

When the anti-allergic activity of ginsenosides was evaluated *in vitro*, ginsenoside Rh1, Rh2, and compound K