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

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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 quinquifolium (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, Rc, Re, Rf, Rg1, Rg2, and Ro.14) However, the major components of red ginseng are ginsenosides Rg3, Rg5, Rk1,
Rh2, Rh3, Rk2, Rb1, Rb2, Re, Rf, Rg1, Rg2, and Ro.\(^{15-17}\)

In Korean ginseng, many acidic and neutral polysaccharides have been isolated: panaxans A-U, GRI-4 and GL1-5, ginsenos 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 Rh 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 Rb1 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

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![Diagram](image-url)

**Fig. 1.** Proposed fate of orally administered drugs in human. Ab, absorption; D, drug; Di, distribution; Ex, excretion; IM, intestinal microflora; M, metabolites; mM, modified metabolites; PE, pharmacological effect.
showed the most potent inhibitory activity. However, most ginsenosides tested had anti-allergic effects in vivo.

To solve this mystery, many researchers have studied the metabolism of ginseng saponins by intestinal bacteria. When protopanaxadiol ginsenosides were incubated with human intestinal microflora, the main metabolite was compound K. This metabolic pathway was catalyzed by *Bifidobacterium* K-110, *Bifidobacterium* H-1, *Prevotella oris*, *Fusobacterium K*-60, *Bacteroides JY*-6, *Eubacterium A*-44, and *Bifidobacterium* K-506 (Fig. 2).

The protopanaxadiol ginsenosides were easily transformed to ginsenoside Rg3 by mild acids. Ginsenoside Rg3 was transformed to ginsenoside Rh2 by human intestinal bacteria. These metabolic pathways proceeded through β-glucosidase, α-arabinofuranosidase and/or α-arabinopyranosidase from *Fusobacterium K*-60 and *Bifidobacterium K*-110. *Bifidobacterium K*-110 also produced β-xylosidase, which transformed ginsenoside Ra1 and Ra2 to ginsenoside Rb2 and Rc. These results suggest that protopanaxadiol ginsenosides can be metabolized to

![Proposed metabolic pathway of ginsenosides Rb1, Rb2, and Re by intestinal microflora in human intestine.](A)

![Proposed metabolic pathway of protopanaxtriol glycosides.](B)

**Fig. 2.** Proposed metabolic pathway of ginsenosides Rb₁, Rb₂, and Re by intestinal microflora in human intestine. (A), Proposed metabolic pathway of protopanaxtriol glycosides. (B), Proposed metabolic pathway of protopanaxtriol glycosides.
compound K in the intestine by intestinal microflora, and to ginsenoside Rh2 by acid and intestinal bacteria. Protopanaxatriol ginsenosides Re and Rg1 were easily transformed to ginsenoside Rh1 or propanaxatriol by human intestinal bacteria. This metabolic pathway was catalyzed by *Fusobacterium* K-60, *Bacteroides* YJ-6, *Eubacterium* A-44, and *Bacteroides* HJ-15.57,58 The most potent ginsenoside metabolizing *Bacteroides* YJ-6, an anaerobic, gram-negative, non-spore forming, rod-shaped, α-rhamnosidase-positive, β-glucosidase-positive and non-gas-producing bacterium, mainly transformed ginsenoside Re to ginsenosides Rh1 and F1, with propanaxatriol as a minor component. These results suggest that propanaxatriol saponins can be metabolized to ginsenoside Rh1 or protopanaxatriol by intestinal bacteria. Ginsenoside Re was a good substrate for *Bacteroides* JY-6, an anaerobic, gram-negative, non-spore forming, rod-shaped, β-glucosidase-positive and non-gas-producing bacterium, which mainly transformed ginsenoside Re to ginsenosides Rh1 and F1, with propanaxatriol as a minor component. These results suggest that propanaxatriol saponins can be metabolized to ginsenoside Rh1 or protopanaxatriol by human intestinal bacteria. This metabolic pathway was catalyzed by *Fusobacterium* K-60, *Bacteroides* YJ-6, *Eubacterium* A-44, and *Bacteroides* HJ-15.57,58 The most potent ginsenoside metabolizing *Bacteroides* YJ-6, an anaerobic, gram-negative, non-spore forming, rod-shaped, α-rhamnosidase-positive, β-glucosidase-positive and non-gas-producing bacterium, mainly transformed ginsenoside Re to ginsenosides Rh1 and F1, with propanaxatriol as a minor component. These results suggest that propanaxatriol saponins can be metabolized to ginsenoside Rh1 or protopanaxatriol by intestinal bacteria. Ginsenoside Re was a good substrate for *Bacteroides* JY-6. However, this enzyme did not transform ginsenoside Rg1. Ginsenoside Rg1 was a good substrate for β-glucosidase. Nevertheless, β-glucosidase only weakly hydrolyzed ginsenosides Rh1 and F1 compared to ginsenoside Rg1.

Many kinds of polysaccharides, including acidic and neutral polysaccharides, have been isolated from ginseng: panaxans A-U, GR1-4 and GL1-5, ginsenans PA, PB, SIA, and SIIA, and ginsans.63-65 These polysaccharides are degraded into low molecular weight molecules by heat processes. In particular, the content of acidic polysaccharides, such as panaxans M (800 kDa) and T (11 KDa), was increased by steaming, but their molecular weights were gradually reduced. When ginseng was orally administered to humans, neutral and acidic polysaccharides were metabolized by intestinal bacteria, such as *Eubacterium* A-44. These results suggest that many polysaccharides contained in orally administered ginseng may be transformed by intestinal microflora.

**BIOLOGICAL ACTIVITY OF GINSENG METABOLITES**

**Compound K**

Compound K dramatically suppressed the growth of HL-60 cell by inducing programmed cell death through activation of caspase-3 protease as well as in cisplatin-resistant human pulmonary adenocarcinoma cells.60 The compound K-treated U937 cells up-regulated the expression of p21, an inhibitory protein of cyclin-CDK complex, and then arrested in the G1 phase.57 Compound K suppressed TNF-α promoted metastasis by suppressing NF-κB signaling in murine colon cancer cells.51 Compound K also reduced doxorubicin toxicity in mice.68 Thus, the body weight, spermatogenic activities (Sertoli cell repopulation and epididymal indices), and serum levels of creatine phosphokinase were significantly decreased by doxorubicin treatment, while the combined treatment of compound K with doxorubicin resulted in parameters similar to the control. In the tissues of doxorubicin-treated animals, almost all of the germ cells disappeared and were replaced by fibrinoid debris in the seminiferous tubules. Germ cell injury was significantly attenuated by compound K co-administration. These results suggest that the main constituents of ginseng protopanaxadiol ginsenosides may be metabolized to compound K following oral administration of ginseng and then express anticancer effects. Compound K also inhibited inflammation reactions in LPS-stimulated microglial cells and TNF-α-induced astrocytes, which activated the NF-κB and JNK pathway.69 Compound K also inhibited MMP-9 expression via the AP-1 and MAPK signal pathway in TPA-treated astroglia cells.70

While compound K inhibited NO and PGE2 biosynthesis in LPS-stimulated RAW264.7 cells,71 it also potently ameliorated allergic reactions, such as chronic dermatitis and scratching behavior. For example, it inhibited histamine- and compound 48/80-induced scratching behaviors as well as oxazolone-induced chronic dermatitis in mice.55,56,72,73 Also, compound K activated the DNA repair reaction against UV-induced damage and apoptosis in keratinocytes.74 Not only did compound K induce hyaluronan synthetase 2 gene expression in transformed human keratinocytes, but it also increased hyaluronan in hairless mouse skin.75 Compound K reduced endotoxin-induced lethal shock as well as tert-butyl hydroperoxide-induced hepatic injury in mice.76,77 Furthermore, compound K not only inhibited glucose uptake in Caco-2 cells,78 but also improved diabetic markers in db/db mice.79 Together with metformin, compound K synergistically ameliorated diabetic mellitus.80 Compound K reduced stress in mice and reduced cortisone levels in intracerebroventricular injection-induced stress.81 These results suggest that compound K may improve inflammatory diseases, hepatic injuries, diabetes, and stress.

**Ginsenoside Rh2**

Ginsenoside Rh2 showed hypoglycemic and hypolipidemic effects in mice.82 In streptozotocin-induced diabetic rats, Rh2 increased insulin secretion to lower plasma glucose.83 Niu et al. reported that ginsenoside Rh2 increased adipogenesis in 2T3-L1 cells via activation of glucocorticoid receptor, which regulates lipid metabolism
by promoting lipogenesis in adipose tissue.\textsuperscript{84} Ginsenoside Rh\textsubscript{2} can promote adipocyte differentiation by activating glucocorticoid receptor. Hwang \textit{et al.} also reported that ginsenoside Rh\textsubscript{2} effectively inhibited adipocyte differentiation via PPAR-\textgamma inhibition.\textsuperscript{85} Ginsenoside Rh\textsubscript{2} significantly activated AMPK in 3T3-L1 adipocytes. Lee \textit{et al.} reported that ginsenoside Rh\textsubscript{2} improved insulin sensitivity and, based on studies in rats, it seems suitable to use ginsenoside Rh\textsubscript{2} as an adjuvant for diabetic patients and/or subjects wishing to increase insulin sensitivity.\textsuperscript{86} Ginsenoside Rh\textsubscript{2} did not exhibit cytotoxicity through p53 and the caspase signaling pathway in HepG2 and neuroblastoma cells,\textsuperscript{87} but induced apoptosis independently of Bcl-2, Bcl-xL, and Bax in C6Bu-1 cells.\textsuperscript{88} Ginsenoside Rh\textsubscript{2} also induced apoptosis of SK-HEP-1 cells via caspase-3-dependent protein kinase C delta, as well as mitochondrial depolarization and apoptosis via reactive oxygen species- and Ca\textsuperscript{2+}-mediated c-Jun NH2-terminal kinase-1 activation in HeLa cells.\textsuperscript{88-90} Rh\textsubscript{1} inhibited the \textit{in vitro} invasiveness of glioma cells by inhibiting MMP-1, -3 and -9.\textsuperscript{91} Ginsenoside Rh\textsubscript{2} also inhibited the proliferation of prostate cancer cells, colon cancer cells, and human malignant melanoma A375-S2 cells.\textsuperscript{92,93} Ginsenoside Rh\textsubscript{2} inhibited the anti-metastatic effect of 3T3 cells in BALB/c mice,\textsuperscript{48} as well as tumor growth in nude mice bearing human ovarian cancer cells.\textsuperscript{52} Ginsenoside Rh\textsubscript{2} not only synergistically enhanced the effects of paclitaxel or mitoxantrone in prostate cancer models, but also hypersensitized multi-drug resistant tumor cells to chemotherapy.\textsuperscript{94,95}

Ginsenoside Rh\textsubscript{2} and fermented red ginseng, of which main constituent is ginsenoside Rh\textsubscript{2}, ameliorated transient focal ischemia in rats,\textsuperscript{32,90} and provided potent protection against ischemic injury to the brain. Ginsenoside Rh\textsubscript{2} also inhibited NMDA receptors in cultured rat hippocampal neurons.\textsuperscript{97} Furthermore, ginsenoside Rh\textsubscript{2} can increase pituitary adenylate cyclase-activating polypeptide (PACAP) to activate PAC1,\textsuperscript{33} but not estrogen receptor, thereby attenuating A\textbeta-induced toxicity. Thus, ginseng seems useful in the prevention of dementia.

Ginsenoside Rh\textsubscript{1} inhibited allergic reactions such as degranulation, passive cutaneous anaphylaxis and contact dermatitis \textit{in vivo} and \textit{in vitro}.\textsuperscript{98,99} Not only did ginsenoside Rh\textsubscript{2} inhibit iNOS synthesis in LPS-stimulated murine peritoneal macrophages,\textsuperscript{100} but it also inhibited the activation of AP-1 and protein kinase A pathway in lipopolysaccharide/interferon-\gamma-induced BV-2 microglial cells.\textsuperscript{101} In addition, ginsenoside Rh2 improved tert-butyl hydroperoxide-induced liver injury in mice\textsuperscript{102} and cyclophosphamide-induced genotoxic effects.\textsuperscript{103} Ginsenoside Rh\textsubscript{1}

\textbf{Ginsenoside Rh\textsubscript{1}}

Ginsenoside Rh\textsubscript{1}, a metabolite of ginsenosides Re and Rg\textsubscript{1} produced by intestinal microflora, exhibits various biological effects. Rh\textsubscript{1} inhibits iNOS and COX-2 induced by lipopolysaccharide in RAW264.7 cells and rat peritoneal macrophages.\textsuperscript{100} It also inhibits oxazolone-induced chronic dermatitis in mice.\textsuperscript{104} Ginsenoside Rh\textsubscript{1} more potently inhibits inflammatory reactions than ginsenoside Re and potently inhibits allergic reactions, such as passive cutaneous anaphylaxis and scratching behaviors, by inhibiting the degranulation of mast cells/basophils and vascular permeability, respectively.\textsuperscript{105}

Ginsenoside Rh\textsubscript{1} showed anticarcinogenicity by the regulation of protein kinase C in NIH 3T3 cells and cytotoxicity against some tumor cells.\textsuperscript{47,106-108} Rh\textsubscript{1} had an estrogenic effect in MCF9 cells\textsuperscript{109,110} and stimulated the secretion of lipoprotein lipase in 3T3-L1 adipocytes.\textsuperscript{111} These results suggest that ginsenoside Rh\textsubscript{1} may improve osteoporosis and increase adipogenesis.

Ginsenoside Rh\textsubscript{1} increases memory \textit{via} hippocampal excitability in rats.\textsuperscript{112} However, ginsenoside Rh weakly stimulated, rather than inhibited the activity of CYP2E1.\textsuperscript{113} This result suggests that ginsenoside Rh\textsubscript{1} may play an important role in ginseng-associated drug-drug interactions.

\textbf{Protopanaxatriol}

Protopanaxatriol increases memory \textit{via} hippocampal excitability in rats.\textsuperscript{114} Protopanaxatriol binds glucocorticoid and estrogen receptors in endothelial cells and stimulates these receptors.\textsuperscript{115} PPT also has an estrogenic effect in MCF9 cells.\textsuperscript{109} These results suggest that PPT may improve osteoporosis.\textsuperscript{116} In addition, PPT has an adjuvant effect and activates PPAR\gamma in 3T3-L1 adipocytes.\textsuperscript{117} PPT also inhibits COX-2 and iNOS by inhibiting NF-kB activation in RAW264.7 cells stimulated by LPS.\textsuperscript{118} Protopanaxatriol dose-dependently inhibits the proliferative activity in an angiogenesis model of human umbilical vein endothelial cells.\textsuperscript{119}

\textbf{Acidic polysaccharide}

Water-soluble polysaccharides and oligosaccharides from \textit{Panax ginseng} C. A. Meyer, such as lentinan and krestin, have a number of effects on immune and host defense functions.\textsuperscript{120} This fraction activates macrophages against \textit{Candida albicans},\textsuperscript{121} potentiates anti-complement activity,\textsuperscript{122} induces IFN-\gamma and TNF-\alpha production in lymphocytes and peritoneal macrophages,\textsuperscript{123,124} stimulates phagocytosis in polymorphonuclear leukocytes,\textsuperscript{125} stimulates natural killer-cell activity\textsuperscript{126} and activates compo-
nents of cell-mediated immunity\textsuperscript{127} including interleukin-2 (IL-2) expression.\textsuperscript{128} Of polysaccharides from Panax ginseng, acidic polysaccharides (Ginsan) induce expression of mRNA for IL-2, IFN-γ, IL-1, and GM-CSF, as well as lymphokine-activated killer (LAK) cells and CD8+T cells.\textsuperscript{129} The anti-septicemic effect of a polysaccharide isolated from Panax ginseng in C57BL/6j mice was observed by increased nitric oxide production from the stimulated macrophages.\textsuperscript{130} The phagocytic activity of macrophages treated with ginsan was significantly enhanced against \textit{Staphylococcus aureus}. However, the production of the pro-inflammatory cytokines, TNF-α, IL-1β, IL-6, IFN-γ, IL-12, and IL-18, was markedly down-regulated in ginsan-treated mice compared with those in control-infected mice. The expression of Toll-like receptor 2 and the adaptor molecule MyD88, which was greatly increased in septic macrophages, was significantly reduced by ginsan treatment \textit{in vitro}. Similarly, the expression of phospho-JNK1/2, phospho-p38 MAPK, and NF-kB was decreased in the same culture system.\textsuperscript{131}

Red ginseng acidic polysaccharide (RGAP), which has B cell-specific mitogenic activity, induced the secretion of interleukin-6 (IL-6) in spleen cells in a concentration-dependent manner. RGAP also restored the proliferation of splenocytes and NK cell activity suppressed by paclitaxel. Additionally, a synergistic effect of RGAP and paclitaxel increased the tumoricidal activity of macrophages.\textsuperscript{132}

The anti-bacterial and anti-viral activities of \textit{Panax ginseng} may be dependent on the immunomodulatory activity of its acidic polysaccharides.

**INDUSTRIAL APPLICATION**

Recently, many fermented ginseng products have been released onto the market. Why is the ginseng fermented? When the ginseng is orally administered to human, its hydrophilic components are inevitably brought into contact with intestinal microflora in the alimentary tract and transformed prior to absorption from the gastrointestinal tract; their pharmacological activities are then expressed.

All individuals possess characteristic indigenous strains of intestinal bacteria. The activities that metabolize these constituents to bioactive compounds differ significantly between individuals. For example, when the metabolism of ginsenosides Rb\textsubscript{1} and Rb\textsubscript{2} to active compound K was measured, these activities varied significantly between individuals. Therefore, ginsengs containing bioactive and absorbable metabolites, ginsenosides, are valuable for improving various diseases. Thus, to develop ginsengs containing these metabolites, the ginsengs have been fermented using enzymes or microbes.\textsuperscript{133-137} However, before using these enzymes and probiotics, their safety and biotransforming activity should first be assessed. If these sources are satisfactory, fermentation biotechnology may be invaluable for developing new ginseng products (Fig. 3).

Finally, intestinal microflora play an important role in

![Fig. 3. Proposed fate of the constituents of orally administered ginsengs by intestinal microflora in human and its industrial application using probiotics. Ab, absorption; IM, intestinal microflora; PB, probiotics; PS, polysaccharides.](image-url)
the pharmacological action of ginseng. Therefore, to evaluate the pharmacological activities of ginsengs, we must also consider the metabolism of their constituents by intestinal microflora.

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