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# **Protective Effects of *Panax ginsengon* the Neurotoxicity Induced by Abuse Drugs**

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## Abstract

Ginseng has been useful for the treatment of diverse disease in oriental countries for thousands of years. In addition, a folk medicine prescribed by seven herbal drugs including *Panax ginseng* has been antinarcotics in the treatment of morphine-dependent patients. Many articles have been reported on these works. Therefore, we review the protective effects of *Panax ginseng* on the neurotoxicity induced by abuse drugs.

Ginseng total saponins (GTS) extracted and isolated by *Panax ginseng* antagonized morphine-induced analgesia, and inhibited the development of analgesic tolerance to and physical dependence on morphine. GTS inhibited morphine-6 dehydrogenase, which catalyzes production of morphine from morphine, and increased hepatic glutathione level responsible to toxicity. Therefore, we hypothesized that these dual actions of ginseng can be associated with the detoxication of morphine. In addition, the inhibitory or facilitated effects of GTS on electrically evoked contraction in guinea pig ileum ( $\mu$ -receptors) and mouse vas deferens ( $\delta$ -receptors) were not mediated through opioid receptors, suggesting non-opioid mechanisms. On the hand, antagonism of U-50,488H ( $\kappa$ -agonist)-induced antinociception is mediated by serotonergic mechanisms.

GTS also inhibited hyperactivity, reverse tolerance (sensitization) and conditioned place preference-induced by psychostimulants such as methamphetamine, cocaine and morphine. On the other hand, GTS reduced the dopamine levels induced by methamphetamine. Moreover, GTS blocked the development of dopamine receptor activation, showing antidopaminergic effect. We suggest that GTS prevent the methamphetamine-induced striatal dopaminergic neurotoxicity. In addition, Ginsenoside also attenuates morphine-induced cAMP signaling pathway. These results suggested that GTS might be useful for the therapy of the adverse actions of drugs with abuse liability.

**Key words:** *Panax ginseng*, Ginseng Total Saponin, Neurotoxicity, Abuse Drugs, Morphine, Cocaine, Methamphetamine, Analgesic Tolerance, Hyperactivity, Reverse Tolerance, Conditioned Place Preference, Physical and Psychological Dependence.

## INTRODUCTION

Humans have sought pleasure, abatement of anxiety, and other alternations in state of consciousness through the ingestion of various natural substances such as opium, marijuana, coca leaves, tobacco, and alcohol. Today, both the active ingredients and numerous synthetic preparations of these same classes of compounds have been widely used for their central nervous system (CNS) effects (Colasanti, 1990). However, substance abuse, our number-one preventable health problem, places an enormous burden on our society, harming health, family life, the economy, and public society, and threatening many other aspects of life (Haaga and Reuter, 1995).

Repeated use of addictive drugs produces multiple unwanted changes in brain that may lead to tolerance, sensitization and dependence. Dependence is a biologic phenomenon often associated with "drug abuse". Psychological dependence is manifested by compulsive drug-seeking behavior in which the individual uses the drugs repeatedly for personal satisfaction, often in the face of known risks to health. Cigarette smoking is an example. Deprivation of the agent for a short period of time typically results in a strong desire or craving for it. Physiological dependence is present when withdrawal of the drug produces symptoms and signs that are frequently the opposite of those sought by the user. It has been suggested that the body adjusts to a new level of homeostasis during the period of drug use and reacts in opposite fashion when the new equilibrium is disturbed. Alcohol withdrawal syndrome is perhaps the best-known example, but milder degree of withdrawal may be observed in people who drink a lot of coffee every day. Psychological dependence almost always precedes physiological dependence but does not inevitably lead to it. Addiction is usually taken to mean a state of physiological and psychological dependence (Kosten, and Hollister, 2001).

Enhanced responding to the repeated exposure of a drug is referred to as "sensitization" or "reverse tolerance", occurs when repeated administration of the same drug dose elicits escalating effects. The reinforcing effects of addictive drugs are subject to sensitization. Well-characterized behavioral sensitization, involving an increase in locomotor activity, and the development of stereotyped movements has been observed after repeated intermittent administration of psychostimulants. Similar locomotor sensitization also has been observed in rodents, cats, dogs, nonhuman primates, and human after repeated administration of opiates, nicotine, ethanol, and phencyclidine. Cocaine, methamphetamine and morphine increased the ambulatory activity of mice and the effects are progressively enhanced by repeated administration of these drugs. This phenomenon is a model studying the psychotoxicity of dependent-liable drugs (Segal et al., 1981; Segal et al., 1985; Post and Weiss, 1988). Moreover, cross-sensitization to many of these agents occurs and is consistent with the involvement of common neurobiologic mechanisms (Stripling and Ellinwood, 1977, Post and Contel, 1983). Neurobiologic findings in animal models have also been increasingly confirmed in human studies. Available radioligands have permitted examination in humans of dopamine receptors and transporters, opioid receptors, and functional brain activity based on blood flow or glucose utilization (Di Chiara and Imperato, 1988a). These receptor-neuroimaging studies have demonstrated that chronic abuse of drugs, which can produce tolerance, dependence and sensitization may have associated effects on receptor numbers [eg, Dopamine (D) D2 receptors decrease cocaine abusers] and on transporter numbers (e.g., dopamine transporters increase in cocaine abusers) (Pontieri et al., 1995; Schultz, 1997; Nicola, 2000).

Cocaine as well as morphine and other psychomotor-stimulants such as methamphetamine and opioids that are abused, share a common underlying site of neuronal action that is, at least in part, responsible for their hedonic effects. Although cocaine and morphine have many opposing effects on a variety of physiological functions, both are abused and induce feelings of euphoria in humans, are self-administered by animals, increase the sensitivity of animals to rewarding electrical intracranial stimulation, a model of drug-induced euphoria, and increase dopamine turnover (Pickens and Thompson, 1968; Wood and Altar, 1988). These opposing and similar effects are illustrated in **Figure 1**. The effects shared by these three classes of drugs, represented by cocaine, methamphetamine and morphine, provide a window into the neuronal bases for their hedonic actions, the necessary ingredient for their positive reinforcing effects. A common theme often found in theories of drug abuse is that abused substances restore normal psychological or neurophysiological function (Huston-Lyons and Kornetsky, 1992).

During the last 30 years, substantial progress has been made in elucidating the neurobiology of abused drugs and their effects not only on neurotransmitter receptors and reuptake carriers but also on the cascade of second, third, and fourth intracellular messenger systems (Self et al., 1995). Psychostimulants produce their psychoactive effects by potentiating monoaminergic transmission through actions on dopamine, serotonin and norepinephrine transporters. Cocaine potentiates the actions of monoamines at the presynapse by inhibiting monoamine transporter proteins, which normally carry previously released transmitter back into the nerve terminal (Langer and Enero 1971; Friedman et al., 1975; Scheel-Kruger and Braestrup 1977; Hadfield et al., 1980; Akimoto et al., 1989). Methamphetamine serves as a substrate for monoamine transporter proteins and is transported into the nerve terminals. In the nerve terminal, methamphetamine disrupts the vesicular storage of monoamine transmitters, which leads to an increase in their extracellular levels (Pickens et al., 1968; Ellinwood 1979; Robinson and Becker 1986; Fischerman, 1987; Kuribara and Tadokoro 1989). Repeated administration of psychostimulants produces long-lasting postsynaptic dopamine receptor changes in the nucleus accumbens. An increase in functional D1 receptor sensitivity has been observed electrophysiologically in the nucleus accumbens after long-term treatment of those drugs. Morphine increases extracellular levels of dopamine in striatum and nucleus accumbens and indirectly increases the activity of dopamine neurons in the substantia nigra and ventral tegmental area (Iwatsubo and Clouet, 1977; Mattew and Cerman, 1984; Di Chiara and Imperato, 1988a; Di Chiara and Imperato, 1988b; Spanagel et al., 1990). Dopamine turnover is also increased after morphine administration (Porrino et al., 1988; Suzuki et al., 1995). In association with these facts, the acute morphine administration results in hyperactivity and daily repeated administration results in a progressive increase in locomotor activity, known as reverse tolerance (Babbini and Davis, 1972; Kilbey and Ellinwood, 1977; Kalivas et al., 1990). There are a number of reports, which support a role for the dopaminergic systems in the rewarding effects, and sensitization of drug abuse (Yokel and Wise 1975; Taylor et al., 1979; Ettenberg et al., 1982; Robinson and Becker, 1986; Kalivas et al., 1998). Acute reinforcing effects of abused drugs are clearly a function of specific receptor binding, but are also related to the rate of change in synaptic levels of dopamine, a key neurotransmitter involved in reinforcement in the nucleus accumbens. The chronic effects of abused drugs include tolerance and sensitization as well as the neurobiologic substrate for withdrawal symptoms.

Chronic administration of opioids and psychostimulants has been shown to alter the activity or expression of diverse types of cellular proteins in specific target neurons within the CNS. Prominent

examples include signaling proteins, such as receptors, G proteins, second messenger synthetic enzymes, and protein kinase. It is now increasingly possible to relate particular molecular adaptations to specific behavioral actions of drugs of abuse in animal models of addiction. The best-established mechanism of dependence at the level of an individual cell involves up-regulation of the cAMP pathway (Collier and Francis, 1975; Sharma, et al., 1975; Nestler, 1993). An increase in functional D1 receptor sensitivity also is related to drug-induced up-regulation of the cAMP pathway after long-term treatment of those drugs. Whereas acute opiate exposure inhibits the cAMP pathway in at least a subset up-regulation in many types of neurons in the brain, chronic abuse drugs exposure leads to a compensatory up-regulation of the cAMP pathway in at least a subset of neurons. This up-regulation involves increased levels of specific subtypes of adenylyl cyclase, cAMP-dependent protein kinase, and other components of this signaling pathway. Up-regulation of the cAMP pathway opposes acute opioid inhibition of the pathway, which represents a form of tolerance and dependence (Self and Nestler, 1995; Nestler, 1997). Immediate early genes such as *c-fos* and *c-jun* are activated followed by regulation of other genes with more sustained effects on protein transcription that may lead to the observed down-regulation of receptor number and up-regulation of second messenger systems. For each of the classes of abused drugs a complex molecular biology has been described, including specific neuroanatomic substrate linked to different neurotransmitters during acute intoxication and during withdrawal after dependence is established. Much has been learned about these neurobiologic substrates for withdrawal in opioid dependence, including the activation of adrenergic brain systems such as the locus ceruleus during withdrawal (Figure 2) (Weeks, 1962; Nestler, et al., 2001). A reduction of central dopaminergic function attenuates psychostimulants-induced rewarding effects and withdrawal of opiates (Lyness et al., 1979; Spyraki et al., 1983; Wise and Bonarth, 1987; Bonarth and Wise, 1989). For hundreds of years, efforts have been made to help people with drug addictions. Nevertheless, the body of knowledge regarding the nature of addictions and how to treat them is still incomplete. There are many alternative and widely divergent points of view about many treatment issues. Much treatment is either not evaluated or poorly evaluated, which makes it difficult to make global recommendation. However, medications may be used in drug treatment to accomplish various goals. Therapeutic drugs sometimes are helpful in minimizing the severity of withdrawal symptoms; examples are benzodiazepines and multivitamins. Use of narcotic antagonist is rational therapy because blocking the action of self-administered opioids should eventually distinguish the habit. Naltrexone, a long-acting orally active pure opioid antagonist, has been extensively studied. Narcotic antagonists may be also useful for other psychostimulants (Kosten and Hollister, 2001). The recent findings have important treatment implications, such as the use of clonidine for opioid withdrawals. Even though physical withdrawal is often mild, an addict knows that any discomfort can be relieved in minutes simply by taking a dose of abused drug. Medications for withdrawal control can be helpful in the short run for discouraging relapse.

On the other hand, a folk medicine composed of seven herbal drugs including *Panax ginseng* has been used as antidote in the treatment of morphine tolerant-dependent patients. Traditional prescription for the treatment of morphine tolerant-dependent patient consists 7 kinds natural products such as *Ginseng Radix*, *Euphobiae Pekinensis*, *Manis squama*, *Zizyphi Spinosi Semen*, *Angeliacae Gigantis Radix*, *Cnidii Rhizoma* and *Paeonia Radix*. Kim et al. (1987a) were interested in the anti-narcotic of ginseng. They reported that *Panax ginseng* inhibited analgesic tolerance and physical dependence-induced

by morphine. In addition, GTS inhibited the hyperactivity, reverse tolerance and psychological dependence-induced by abuse drugs. Here, we review current knowledge about the behavioral and biochemical neurobiology of abuse drugs, and the effects of ginseng on the prevention and therapy of the adverse actions of each class of dependent-liable drugs.

### **Anti-narcotic effects of ginseng on opioids**

It was well reported that saponin fraction, major component of ginseng antagonized the analgesia in mice induced by morphine. The antagonisms of total saponins, and protopanaxadiol and protopanaxatriol saponins were compared, respectively (Kim et al., 1986; Kim et al., 1990a).

On the other hand, some investigators have revealed the analgesic effects of GTS (Nabata et al., 1973; Saito et al., 1973). Watanabe et al. (1988a; 1988b) demonstrated a non-opioid mechanism in the inhibitory effect of GTS on electrically evoked contractions of guinea-pig ileum and mouse vas deferens. Moreover, GTS inhibited the exogenous ATP-elicited contraction of mouse vas deferens, by inhibiting the action of ATP, which was released from sympathetic nerve terminal via P2-purinoceptors (Kim et al., 1993c; Kim et al., 1993d). However, recently it was reported that GTS have the affinity on opioid receptors in CNS. GTS inhibited opioid bindings in some regions of the brain. Especially, specific [<sup>3</sup>H]DAGO bindings was decreased without changes of *B<sub>max</sub>* in the frontal cortex (Oh et al., 2002). In addition, the antinociception of U-50-488H, a selective  $\kappa$ -agonist, was prevented by GTS in the tail flick test, presumed that the antagonism of U-50488H-induced antinociception by GTS is dependent on serotonergic mechanisms (Kim et al., 1992a). Interestingly, the antagonistic activities of ginseng against a variety of pharmacological effects induced in the brain also reported (Ramarao and Bhargava, 1990; Bhargava and Ramarao, 1991; Takahashi and Tokuyama, 1998). Ginsenosides injected intrathecally or intracerebroventricularly antagonized morphine-induced antinociception (Suh et al., 1997). GTS and ginsenosides may modulate morphine-induced antinociception by modulating the GABA receptors. We reported that ginsenosides decrease the binding affinity of GABAA and GABAB receptors without changing the number of binding sites (Kimura et al., 1994). Ginsenoside-R2 from Vietnamese ginseng attenuates the opioid-induced antinociception by acting the spinal and supraspinal levels, suggesting GABA receptor complex at the supraspinal level may be involved (Huong et al., 1997). In addition, systemic administration of GTS decreased pentazocine-induced analgesia, dose-dependently and inhibited the development of analgesic tolerance to pentazocine (Kim et al., 1992c).

### **Inhibition by ginseng of the development of analgesic tolerance to and physical dependence on morphine.**

In addition, they also determined the inhibitory effects of GTS on the development of analgesic tolerance to and physical dependence on morphine, and presumed that these effects were associated with increased hepatic glutathione level by ginseng administration (Schole, 1978; Kim et al., 1987a; Kim et al., 1987b; Kim et al., 1989). An aliquot of morphinone, a toxic metabolite of morphine, conjugated with glutathione was closely related to the detoxication process and other aliquot of morphinone was metabolized into morphinone-protein SH conjugate concerned with the development of morphine induced analgesic tolerance and dependence by covalent binding to the sulfhydryl group of opioid receptors (Nagamatsu et al., 1982; Nagamatsu et al., 1983; Yamamoto et al., 1985). Moreover, morphine

6-dehydrogenase catalyzes the production of morphinone from morphine. GTS inhibited morphine-6-dehydrogenase, dose dependently (Kim et al., 1987b). Indeed, we reported that cholane compounds inhibited morphine-induced analgesic tolerance and physical dependence (Kim et al., 1990c)

Meanwhile, it was reported that the antagonistic effects of morphine 10 mg/kg was observed in mice pretreated with reserpine 2.5 mg/kg, being accompanied with reductions of brain biogenic monoamines (Takagi et al., 1964; Verri et al., 1967). Several neurotransmitters such as dopamine and noradrenaline, and cAMP have been implicated in the abstinence syndromes (Di Chiara, and Imperato, 1988b). The symptoms of withdrawal are associated with increased dopamine level and cAMP in brain (Iwamoto et al., 1973; Collier et al., 1975). Most of the studies shows that the level of noradrenaline, dopamine and cAMP were increased in GTS treated animals (Joo, 1984; Park, 1984; Kim et al., 1985). However, the brain levels of noradrenaline, dopamine and serotonin were not changed after administration of GTS, a single dose of 100 mg/kg, and inhibited locomotor activity, showing depressive effects by GTS in mice. These experimental results were consistent with studies by Kaneto and Kihara (1982), reported that daily treatment with a small dose of reserpine 0.1mg/kg, which did not affect any appreciable changes in brain levels of catecholamines, could effectively block the development of morphine-induced analgesic tolerance. Therefore, it is suggested that the adrenergic systems play an important role on the inhibition of the development of analgesic tolerance to and physical dependence on morphine. On the other hand, the development of analgesic tolerance of U-50,488H and pentazocine was inhibited by GTS. In addition, the inhibition by GTS was dependent on serotonergic mechanism (Kim et al., 1992a; Kim et al., 1993a). However, Watanabe et al. (1988b) reported that the inhibitory effect of GTS in isolated guinea pig ileum and mouse vas deferens showed the direct action of GTS on smooth muscle preparation without the involvement of cholinergic and/or serotonergic mechanisms on the opioid receptors.

Concurrent administration of GTS significantly diminished jumping, teeth chattering and weight loss precipitated by naloxone, in rat was infused with morphine via osmotic minipump into lateral cerebral ventricle (Kim et al., 1992b). GTS also inhibited the development of physical dependence on nalbuphine and pentazocine, most frequently abused in Korea (Kim et al., 1992c; Kim and Oh, 1994).

### **Inhibition of psychostimulants-induced psychosis by ginseng**

Repeated administration of psychostimulants such as methamphetamine, cocaine and morphine results in a complex multiphasic spectrum of behavioral changes including a progressive behavioral augmentation or sensitization to the drug challenge that persists after prolonged periods of abstinence. This phenomenon is referred to as "sensitization" or "reverse tolerance" and also is a model studying the psychotoxicity of dependent-liable drugs (Hirabayashi and Alam, 1981; Segal et al., 1981; Robinson and Becker, 1986). Neuropharmacological investigations demonstrate that repeated administration of psychostimulants lead to increase in ambulatory activity and rewarding properties and that dopaminergic systems play important roles in mediating the ambulatory and rewarding activities of psychostimulants (Scheel-Kruger et al., 1977; Roy et al., 1978). This response results, at least in part, as a consequence of the neurotoxicity associated with continuous exposure to psychostimulants (Segal et al., 1981; Segal and Geyer 1985; Robinson and Becker, 1986). Investigators have suggested that continuous exposure may stimulate more closely at least some patterns of self-administration in stimulant abuser (Ellison, 1978;

Nielsen et al., 1980; King et al., 1992). It has been also reported that rats sensitized to psychostimulants show an enhanced response to apomorphine, a direct dopamine receptor agonist, suggesting the development of dopamine receptor supersensitivity (Hunt et al., 1974).

After pretreatment with ginseng extract for 5 days, concomitant injections of methamphetamine and ginseng extract suppressed the development of reverse tolerance to the effect of methamphetamine, although ginseng extract did not affect the spontaneous activity of the naive mice (Tokuyama et al., 1992). In addition, G115 (standardized ginseng extract) also significantly inhibited the development of morphine-induced analgesic tolerance and reverse tolerance to the locomotor-accelerating effect of morphine (Kim et al., 1990b). On the other hand, GTS from ginseng extract more significantly inhibited the development of reverse tolerance to morphine, methamphetamine and cocaine and inhibited the dopamine receptor supersensitivity induced by those drugs. It is presumed that ginseng inhibited dopamine receptor activation (Kim et al., 1994; Kim et al., 1995a; Kim et al., 1995b; Kim et al., 1995c; Tokuyama et al., 1996; Kim et al., 1996a; Kim et al., 1996b). In addition, pseudoginsenoside-F-11 from American ginseng also protects methamphetamine-induced neurotoxicity (Wu et al., 2003). Therefore, these results provide an evidence that ginseng may be useful for prevention and therapy of drug-induced psychotoxicity or psychosis.

Amphetamine-like compounds facilitate the release of dopamine from the synaptosomes and cocaine inhibited dopamine uptake by the presynaptic neurons (Heikkila et al., 1975; Heikkila et al., 1979; Hadfield and Mott, 1980; Butcher et al., 1988). These enhanced neurotransmitter activities, particularly at the dopamine receptors, have been implicated in the locomotor and stereotyped behaviors, as well as rewarding properties of psychostimulants such as amphetamine and cocaine. On the other hand, multiple dose of amphetamines cause substantial and long-lasting depletions of striatal dopamine and its metabolites (Kuczenski, 1977; Wagner et al., 1980a). The neuropathological alterations, which occur in response to high dose of methamphetamine parallel, in part, the pathology observed in Parkinson's disease (Wagner et al., 1980b; Wagner et al., 1980c).

A single administration of methamphetamine increased the concentration of dopamine with concomitant decrease in the concentration of 3,4-dihydroxyphenylacetic acid (DOPAC) in the mouse striatum. Pretreatment with GTS caused a significant reduction in the methamphetamine-induced dopamine increase (Oh et al., 1997). Moreover, GTS significantly restored the methamphetamine-induced DOPAC decrease. In addition, the four injections of methamphetamine resulted in significant depletions of striatal dopamine, DOPAC and homovanillic acid (HVA). Pretreatment with two injections of GTS reduced the magnitude of the methamphetamine-induced dopamine, DOPAC, and HVA depletions. It is suggested that GTS prevent the methamphetamine-induced striatal dopaminergic neurotoxicity (Oh et al., 1997). It has been reported that ginsenosides exerted powerful inhibitory actions on catecholamines secretion, suggesting GTS has the ability to modulation dopaminergic activity preferentially at the presynaptic sites (Takahashi et al., 1993).

### **Inhibition of psychostimulants-induced psychological dependence by ginseng**

In addition to sensitization, repeated exposure to psychostimulants induces profound cellular and molecular changes within neurons of the brain reward circuit, which in turn are believed to cause the



alternations in reinforcement (psychological dependence) mechanisms that contribute to addiction. A reinforcing stimulus is one that increases the probability that behaviors paired with it will be repeated. It appears that addictive drugs rewarding and reinforcing because they act in brain reward pathways to enhance either dopamine release or the effects of dopamine in the nucleus accumbens or related structures, or because they produce effects similar to dopamine (Lakoski et al., 1992; Koob, 1992). Drug-induced pleasurable states are important motivators of initial drug use. Drug actions that produce these states also produce associated, but ultimately undesirable, changes in brain reward circuitry that promote future drug use. In addition, it has been hypothesized that recently that addictive drugs derive their reinforcing quality by stimulating the same neurochemical system that modulates psychomotor activity. The conditioned place preference (CPP) has been used as a model for studying the psychological dependence of abuse drugs. In this type of experiment, animals learn to associate a particular environment with passive drug exposure. This paradigm is believed to demonstrate the strong cue-conditioned effects of addictive drugs and to provide indirect measure of drug reward. The paradigm used to investigate drug-induced psychological dependence in animal research is well known as conditioned place preference (Van der Kooy, 1987).

It is also important to know that ginseng inhibits the hyperactivity induced by psychomotor-stimulants. Addictive drugs such as psychostimulants derive their reinforcing quality by stimulating the same neurochemical system that mediates psychomotor activity (Van der Kooy, 1987). GTS from the extract of *Panax ginseng* suppressed the development of cocaine, methamphetamine and morphine-induced conditioned place preference (Figure 3) (Tokuyama et al., 1996). Ginseng also inhibited dopamine receptor activation. In CPP model, repeated administration of psychostimulants also develops dopamine receptor supersensitivity (Figure 4) (Kim et al., 1996a; Kim et al., 1996b; Kim et al., 1998a; Kim et al., 1998b; Kim et al., 1998c; Kim et al., 1999c; Kim et al., 1999e). Ginsenosides inhibited tyrosine hydroxylase activity. These inhibitory effects of ginsenosides on tyrosine hydroxylase may be partially responsible for the antidoaminergic action (Kim et al., 1999e).

GTS also inhibited nicotine-induced hyperactivity and conditioned place preference in mice (Kim et al., 1999b; Kim et al., 1999d). In addition, GTS inhibited nicotine-induced *c-fos* and *c-jun* mRNA level ventral tegmental area and nucleus accumbens (Shim et al., 2000).

Pharmacological manipulations yielded the first evidence to support the idea that dopaminergic system are important for the manifestation of drug-induced reward. GTS attenuated drug-induced CPP by inhibiting the same neurochemical system that mediates psychostimulant-induced hyperactivity and the development of dopaminergic receptor supersensitivity induced by psychostimulant. Therefore, it is suggested that GTS inhibition of the psychostimulant-induced hyperactivity and CPP may be closely related with the inhibition of dopaminergic activation. From molecular studies, it is reported that ginsenosides antagonized morphine-induced intracellular cAMP production (Li et al., 2001).

The study on the prevention and therapy of the adverse actions of dependent-liable drugs of GTS has been continued. Ginsenosides such as Rb1 and Rg1 from GTS also inhibited the development of reverse tolerance and psychological dependence-induced by methamphetamine and cocaine (Figure 5) (Kim et al., 1998a).

The responsibility to point the way toward adequate rehabilitation and restoration to a more normal life likewise fell on physician as well as on other health professionals. One of main problems associated with drug abuse is high incidence of relapse or return to drug use after a period of abstinence. Much work

has been made to seek a remedy that inhibits the psychological dependence. When the desire to continue taking the drug becomes a psychic craving or compulsion and the user becomes preoccupied with drug taking, there exists the basis for compulsive drug use (Jaffe, 1975).

The primary goals of addiction treatment are the facilitation of abstinence and prevention of relapse. Such goals have been proven difficult to attain in the treatment of many forms of addiction. Pharmacological treatment often is used to reduce withdrawal symptoms and involves complex mechanisms that include associative learning. Yet, it remains a theoretical possibility that medications that block the reinforcing effects of drugs or drug-induced plasticity might reduce drug craving and the likelihood of relapse. Unfortunately, with the exception of naltrexone for the treatment of alcoholism, no reward-reducing treatment has yet been developed for the clinical use.

Ginseng inhibited analgesic effect of morphine and the development of analgesic tolerance to and dependence on morphine, simultaneously. Ginseng also inhibited hyperactivity, reverse tolerance and CPP induced by psychostimulants (Table 1). The compounds derived from traditional herbs or natural products may have a possible therapeutic relevance in the treatment of drug abuse (Kim and Lim, 1999a). We suggest that ginseng may be useful for the prevention and therapy of the adverse actions of dependent-liability drugs.

### Acknowledgement

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Table 1. Representative publications on the beneficial effects of abused drugs by ginseng.

Psychotropic drugs	Ginseng	Effects	Authors
Morphine	Panax ginseng	Inhibition of tolerance	Bhargava et al., 1991
Morphine	Ginseng total saponin	Inhibition of reverse tolerance	Kim et al., 1992 Morphine
Morphine	Ginseng total saponin	Inhibition of reverse tolerance	Kim et al., 1995c
Morphine	Ginsenosides	Inhibition of antinociception	Suh et al., 1997
Opioids	Ginseng total saponin	Inhibition of CPP	Kim et al., 1998b
Opioid	Majonoside-R2	Inhibition of antinociception	Huong et al., 1997
U-50,488H	Ginsenosides	Inhibition of tolerance	Choi et al., 2000
Cocaine	Ginseng total saponin	Inhibition of antinociception	Kim et al., 1992a
Cocaine	Ginseng total saponin	Inhibition of CPP	Kim et al., 1996a
Cocaine	Ginseng total saponin	Inhibition of reverse tolerance	Kim et al., 1995a
Methamphetamine	Ginsenosides Rb1 and Rg1	Inhibition of CPP	Kim et al., 1999a
Methamphetamine	Pseudoginsenosides-F11	Inhibition of neurotoxicity	Wu et al., 2003
Methamphetamine	Ginsenosides Rb1 and Rg1	Inhibition of CPP	Kim et al., 1998a
Methamphetamine	Ginseng total saponin	Inhibition of CPP	Kim et al., 1996b

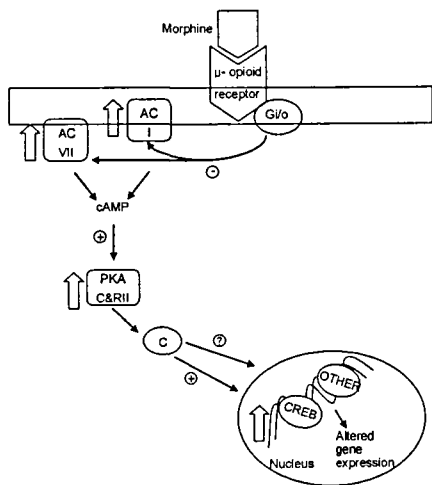
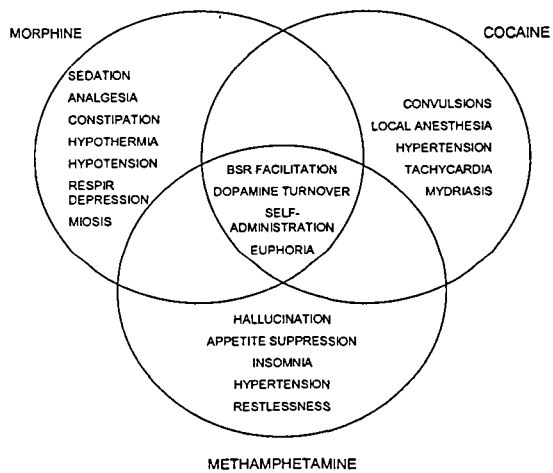


Figure 2.

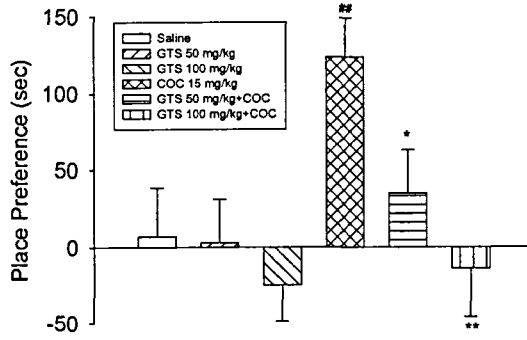


Figure 3.

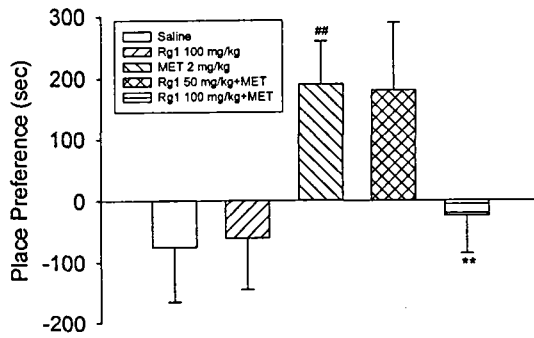


Figure 4.

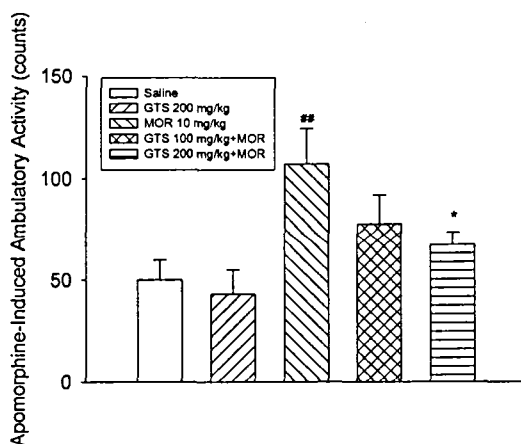


Figure 5.

## Legends

Figure 1. The area of overlap represents the common effects produced by cocaine, methamphetamine and morphine.

Figure 2. Scheme illustrating opiate actions in locus coeruleus.

Figure 3. Inhibitory effects of GTS on cocaine (COC)-induced conditioned place preference (CPP). ## $P < 0.01$ , compared with that of the saline group. \* $P < 0.05$ , \*\* $P < 0.01$ , compared with that of morphine control.

Figure 4. Inhibitory effects of ginsenosides Rg1 on methamphetamine (MAT)-induced CPP. ## $P < 0.01$ , compared with that of the saline group. \*\* $P < 0.01$ , compared with that of morphine control.

Figure 5. Effects of ginseng total saponin (GTS) on the enhanced activity of apomorphine in mice with morphine (MOR) for 7 days. ## $P < 0.01$ , compared with that of the saline group. \* $P < 0.05$ , compared with that of morphine control.

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