

Therapeutic Effects of Ginseng on Psychotic Disorders

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Abstract : Ginseng, the root of *Panax* species, a well-known herbal medicine has been used as a traditional medicine for thousands of years and is now a popular and worldwide used natural medicine. Ginseng has been used primarily as a tonic to invigorate weak bodies to help the restoration of homeostasis in a wide range of pathological conditions such as cardiovascular diseases, cancer, immune deficiency and hepatotoxicity. Although conclusive clinical data in humans is still missing, recent research results have suggested that some of the active ingredients ginseng exert beneficial effects on central nervous system (CNS) disorders and neurodegenerative diseases, suggesting it could be used in treatment of psychotic disorders. Data from neural cell cultures and animal studies contribute to the understanding of these mechanisms that involve inhibitory effects on stress-induced corticosterone level increasing and modulating of neurotransmitters, reducing Ca^{2+} over-influx, scavenging of free radicals and counteracting excitotoxicity. In this review, we focused on recently reported medicinal effects of ginseng and summarized the possibility of its applications on psychotic disorders.

Key words: *Panax* ginseng; Ginsenoside; Psychotic disorders; Learning and memory; Anxiolytic effect; Sleep; Neurotransmitters.

INTRODUCTION

Psychotic disorders are mental disorders in which the personality is seriously disorganized and contact with reality is impaired. During psychotic disorders a person is confused about reality and often experiences delusions, anxiety or depression. Psychotic disorders include schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a specific general medical condition, substance-induced psychotic disorder and psychotic disorder unspecified. These disorders share many features and also have important features that set them apart from each other.¹⁾

Experts believe that many factors may play a role and there may be different causes for different illnesses within this group. Some researchers believe that individuals may inherited a tendency for developing a psychotic disorder for psychotic disorders tend to run in families.^{2,3)} The role of neurotransmitters is also under study.^{4,5)} On the other

hand, the cause of this disorder is also typically an extremely stressful event or trauma for environmental factors seem to play a role and stress seems to set off schizophrenia in certain susceptible individuals.⁶⁾

Severe stressful conditions are responsible for the etio-pathogenesis of various psychotic disorders. Mental homeostasis is controlled by various physiological mediators working in concert by interacting with receptors placed at various physiological levels and the functional identity of neurotransmitters is challenged during stressful conditions. Out of various neurotransmitters - noradrenaline (NA), dopamine (DA) and 5-hydroxy tryptamine (5-HT) are the important neurotransmitters which are widely distributed in brain and their functional role is well established during stressful conditions.⁷⁾ Recent neurobiological studies indicates that psychotic disorders may be induced by neurodevelopmental and progressive disorders with multiple biochemical abnormalities involving DA, 5-HT, glutamate and gamma-aminobutyric acid (GABA) ergic systems. Changes in their activity result in behavioral changes as well as a cascade of hormonal release from the hypothalamus-pituitary-adrenal (HPA) axis. Alternation of HPA axis and dysfunction of these neu-

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rotransmitters due to prolonged stressful conditions have been associated with a wide range of central and peripheral disorders like depression, anxiety, drug abuse, obsessive compulsive disorder, eating and sleeping disorders, hyperglycemia and decreased immune response.⁸⁻¹¹⁾ Due to increased physical and psychological demands in the present day life style and advent of various stress related disorders, there is an urgent need to develop agents to overcome these abnormalities.

The drugs of plant origin are gaining importance and being investigated for remedies of a number of psychotic disorders and other stress-related diseases. Since the introduction of adaptogen concept, several plants have been investigated, which were used earlier as tonics due to their adaptogenic and rejuvenating properties in traditional medicine.¹²⁾

Panax ginseng, one of the most popular herbal medicines, has been widely used for the therapy of stress related disorders.¹³⁾ In oriental medicine, ginseng is referred to as an agent that stimulates brain activity, invigorates mental capacity, improves vision, audition, power of thought and memory, thereby enhancing concentrations. In the early 1960s, scientists suggested that ginseng improved mental and intellectual performance in people. Ginseng extract and ginseng saponin improved memory acquisition, physical performance and learning disorders and confronted loss of memory in a memory-damaged animal model. Later, animal and clinical experiments carried out with ginseng as well as the active ingredients isolated from the ginseng have further supported the beneficial role of ginseng in brain activity.

EFFECTS OF GINSENG ON PSYCHOTIC DISORDERS

Improving learning and memory (Anti-dementia)

The specific mechanisms of learning and memory improving effects of ginseng are still unknown. Hyperglycemia has been shown to cause impairments in cognition and worsen the outcome of brain ischemia in several animal models. Some research work indicated that cognitive improvements may be related to the glycemic properties of ginseng because single doses of the ginseng have been shown to lower blood glucose levels and elicit cognitive improvements in healthy, overnight-fasted volunteers.¹⁴⁾ In a double-blind, placebo-controlled, balanced-crossover design, ginseng and glucose were proved to be effective in enhancing performance of a mental arithmetic task and ameliorated the increase in subjective feelings of

mental fatigue experienced by participants during the sustained, cognitively demanding task performance. Accuracy of performing the Rapid Visual Information Processing task was also improved following the glucose load. There was no evidence of a synergistic relationship between *Panax ginseng* and exogenous glucose ingestion on any cognitive outcome measure. *Panax ginseng* caused a reduction in blood glucose levels 1 hour following consumption when ingested without glucose. These data confirm that ginseng may possess glucoregulatory properties and enhance cognitive performance. It also suggest that there might be other mechanisms in the cognitive improving effects of ginseng.¹⁴⁾

Ginsenosides or ginseng saponins as the active ingredients have antioxidant, anti-inflammatory, anti-apoptotic and immunostimulant properties. Recent studies has revealed that ginsenosides possess neuroprotective and cognitive improving effects through activation of antioxidant enzymes, which raised speculations that these compounds could positively affect neurodegenerative disorders and delay neuronal aging. Although conclusive clinical data in humans are still missing, results from animal studies and neuronal cell culture experiments indicate that many ginsenosides, such as Rg₁, Rg₂, Rg₃, can counteract and attenuate factors promoting neuronal death as environmental toxins, excitotoxic action of glutamate and rises in intracellular calcium ([Ca²⁺]_i), excessive release of free radicals and apoptotic events. In cellular model of Alzheimer's disease established by amyloid-beta treated primary cultured cells, ginsenoside Rg₂ significantly attenuated [Ca²⁺]_i, lipid peroxidation and the protein expression levels of calpain II, caspase-3 increasing induced by amyloid-beta and increased cell viability.¹⁵⁾ Besides, ginsenosides Rb₁, Rb₂, Re and Rg₁ were also effective in reducing astrocytic death induced by oxidative stress, while Rb₁, Rb₂, Rd, Re and Rg₁ decreased formation of reactive oxygen species, ginsenoside Re being the most active compound.¹⁶⁾ Thus, researchers believe neuroprotective actions of ginsenosides could be an important reason for learning and memory improving effects of ginseng and come about as a valuable option to slow down neurodegenerative diseases such as Alzheimer's disease.

Anxiolytic and anti-depressive effects

Ginseng has also been widely used for the management of anxiety and emotional instability and studies have already proved that ginseng induces anxiolytic-like effects in the elevated plus-maze test.¹⁷⁾ Administration of red

ginseng and sun ginseng could increase significantly the number of open arm entries and the time spent on the open arm, sun ginseng was more potent than red ginseng in the elevated plus-maze model.¹⁸⁾ Ginseng powder and crude saponin fraction also significantly increased the frequency and duration of open arm entries. Among the ginsenoside Rb₁, Rg₁, and Ro, only ginsenoside Rb₁ significantly increased both the frequency and duration of open arm entries. Further investigation indicated that Ginsenoside Rg₁ and the Rg₅ and Rk mixture also significantly increased the number of open arm entries and the time spent on the open arm. However, ginsenosides Rg₃-R and Rg₃-S did not increase the number of open arm entries or the time spent on the open arm. On the other hand, ginsenoside Rb₁ and the Rg₅ and Rk mixture decreased locomotor activity in a manner similar to diazepam. These results indicated that ginseng saponins may play an important role in the anxiolytic effects of ginseng. Ginsenoside Rb₁, Rg₁, and the Rg₅ and Rk mixture are active anxiolytic components of ginseng root.¹⁹⁾ Since ginseng and ginsenosides, in contrast to traditional anxiolytic drugs, such as diazepam, had little effect on locomotion in these tests, its side-effect profile might be considered superior to the benzodiazepines.¹⁷⁾

Sleep

Insomnia has been considered as one of “syndrome” of supposed adverse effects of ginseng, which also include hypertension, nervousness and morning diarrhea. These symptoms occurred after use of high doses of products whose ginseng content was not well specified.

Recent studies on hypnotic activity of ginseng found that ginseng extract failed to affect pentobarbital sleep in psychologically stressed mice. On the other hand, Vietnamese ginseng extract, Vietnamese ginseng saponin and majonoside-R2 (a major ocotillol-type saponin constituent of Vietnamese ginseng) had no effect on pentobarbital sleep in unstressed control mice, but these drugs significantly recovered pentobarbital sleep decreased by psychological stress to the level of unstressed control animals.²⁰⁾ The reversing effects of majonoside-R2 and the decrease in pentobarbital sleep in isolated mice were significantly attenuated by pregnenolone sulfate, the steroidal negative allosteric modulator of the GABA_A receptor. In contrast, majonoside-R2 injection also significantly reversed the decrease in pentobarbital sleep induced by pregnenolone sulfate and corticotrophin-releasing factor (CRF) in mice. These results suggest that the reversing effect of Vietnamese ginseng saponin on the stress-induced decrease in

pentobarbital sleep is mediated by the neurosteroid site on the GABA_A receptor complex in mice.²¹⁾

Majonoside-R2 has not been isolated from *Panax ginseng*, American ginseng or Sanchi ginseng. It is still unclear about the exact effects of other ginseng saponins on sleeping behaviors. However, results already showed that ginseng extract stabilized sleeping in food-deprived rats, ginseng saponin prolonged pentobarbital sleeping time and even delayed the onset of convulsions in high doses.^{22,23)} Ginseng could lead to a significant shortening of the latency of the P300 component of the evoked potential, also lead to significant reductions in frontal “eyes closed” theta and beta activity, with additional reduction for ginseng in the alpha waveband on electroencephalograph (EEG) recordings. These findings demonstrate that ginseng can directly modulate cerebroelectrical activity and indicate that ginseng might also exert its effects on sleeping behaviors.²⁴⁾

Drug-induced psychosis

The intermittent administration of many CNS stimulants to animals produces changes in behavior, a phenomenon known as behavior sensitization (reverse tolerance). Single treatment with morphine in mice produces hyperactivity, and chronic treatment with morphine shows reinforcing effect, such as conditioned place preference (CPP). It is thought that this sensitization represents an animal model of drug-induced psychosis.²⁵⁾ The CPP paradigm has been used as a model for studying the reinforcing effects of drugs with dependence liability. Many of such drugs are known to induce CPP, including morphine, heroin, cocaine and amphetamine.^{26,27)}

Ginseng extract had an inhibitory activity on the development of the tolerance to the pharmacological actions of morphine. It had been found that ginseng extract had an inhibitory activity on the development of tolerance to the pharmacological actions of morphine. In addition, researches have shown that the standardized ginseng extract prevents the development of reverse tolerance to the ambulation-accelerating effect of methamphetamine.

Recently, it has been reported that ginseng total saponin (GTS) blocked the behavioral activation produced by drugs of abuse. For example, methamphetamine-, morphine- or cocaine-induced behavioral activities were blocked by pre-treatment with GTS.^{26,27)} Conditioned place preferences induced by methamphetamine were also antagonized by GTS.²⁷⁾ Since the reinforcing effects of DA release in the nucleus accumbens produced by drugs of abuse may be associated with a behavioral hyperactivity,

it seems possible that an inhibitory effect of GTS on behavioral activity might reflect blockade of dopaminergic transmission in nucleus accumbens.²⁸⁾

POSSIBLE MECHANISMS

Since ginseng extract has shown a significant improvement in symptoms such as memory loss, difficulties in concentration, fatigue, anxiety, and depressed mood in clinical trials, it is possible to be used as a good candidate for novel pharmacotherapy for psychotic disorders. Recent researches on the effect of ginseng on HPA axis and neurotransmitters which are closely related to occurrence of mood disturbance suggest further the possible effectiveness of ginseng supplementation on psychotic disorders.

HPA axis

Much interest has been focused on the effects of ginseng as an adaptogen, a substance which helps the body to resist the adverse influences of a wide range of physical, chemical and biological factors, and helps the restoration of homeostasis irrespective of the direction of altered physiological function.²⁹⁾ Some reports suggest that ginseng shows anti-stress activities in stressful circumstances such as footshock,¹²⁾ cold³⁰⁾ and heat.³¹⁾ The anti-stress activities of ginseng may account for its observed clinical efficacy in stress related disorders like depression and anxiety disorder.³²⁾

It is generally accepted that HPA axis functions to ensure the body adaptation and is one of the most important systems closely related to stress. Glucocorticoid secretion serves both to alert the organism to environmental or physiologic changes and to defend homeostasis under stressful conditions. Because administration of GTS and some individual ginsenosides including Rc increase plasma corticosterone and adrenocorticotrophic hormone (ACTH) level in basal state,³³⁻³⁶⁾ appropriately increased corticosteroids and ACTH might improve selectivity, discrimination, motivation, performance, arousal and vitality.³³⁾ Thus, it could be insisted that an appropriate stimulation of HPA axis by ginseng saponin may help healthy people to improve their ability to deal with stressful environmental situations.³³⁾ Ginseng saponin may be regarded as a kind of stressful agent and a mild activator of HPA axis in non-stressed state whose effect is superimposed on the basal level of HPA axis function.³⁴⁾

On the other hand, hypersecretion of glucocorticoids promoted the development of physiologic and psycholog-

ical dysfunction and inappropriate regulation of stress was implicated in the pathogenesis of stress related disorders.³⁷⁾ Suppressive drugs on the HPA axis are recommended as a new treatment strategy for the clinical and endocrine manifestations of mental disorders such as depression.^{38,39)} However, very interestingly, intracerebroventricular injection of GTS, ginsenosides Rc and Rg₃(S) attenuate the stress-induced and intraperitoneally injected ACTH-induced increase in plasma corticosterone level in rodents, indicate that the inhibitory effects of GTS and ginsenosides administered on stress-induced plasma corticosterone level appear to be mediated by blocking of ACTH action peripherally in the adrenal gland. It is showed that the effects of GTS on HPA axis was contrary in the presence of the stress, and these effects are blocked by co-administered L-NAME, an inhibitor of NOS, suggesting the involvement of NO in the brain.⁴⁰⁾ However, in other study, the inhibitory effect of GTS on the immobilization stress-induced increase in plasma corticosterone level was not affected by L-NAME, and Rg₃(S) did not affect the immobilization stress-induced increase in plasma corticosterone level. These results suggest that the inhibitory effects of GTS in the stress-induced increase in plasma corticosterone level are possibly mediated by different mechanisms according to the components of ginseng saponin, type of stress and routes of administration.⁴¹⁾ The exact mechanisms of homeostatic effects of ginseng saponin on HPA axis have not been explored until now.

DA systems

Dopaminergic neurons in the central nervous system play important roles in the psychotic behaviors and effects of related drugs. In 1929 Tatum and Seevers first reported that repeated cocaine administration induced enhancement of the motor-accelerating in dogs.⁴²⁾ It was later found that both of cocaine and methamphetamine administration produced hyperactivity, conditioned place preference (CPP) and supersensitivity to apomorphine in sensitized mice or rats as well as DA receptor supersensitivity.^{26,27)} Rodents sensitized to cocaine showed an enhanced response to direct DA receptor agonist apomorphine, suggesting the development of DA receptor supersensitivity.⁴³⁾ It has been demonstrated that the behavioral changes are attributable to the DAergic hyperfunction in the central nervous system.^{26,27)}

GTS was found useful for prevention and therapy of the adverse action of cocaine and methamphetamine. Administration of GTS inhibited the development of reverse tolerance to the ambulation-accelerating effect of cocaine

and the supersensitivity of DA receptors.⁴⁴⁾ Research work has shown that ginseng saponin also inhibited methamphetamine-induced hyperactivity, CPP and DA receptor supersensitivity in mice,^{28,45)} the ginsenosides Rb₁ and Rg₁ inhibited not only methamphetamine-induced hyperactivity but also CPP in mice following a single or repeated administration. DA receptor supersensitivity developed in methamphetamine-induced CPP mice was also inhibited by both Rb₁ and Rg₁, suggesting that Rb₁ and Rg₁ may be the active components of ginseng saponins in the modulation of DAergic behaviors such as hyperactivity and CPP, and ginseng saponin might modulate DA receptor dysfunction at both the pre- and postsynaptic DA receptors.^{46,47)}

Glutamate/NMDA systems

Glutamate is a major neurotransmitter in the mammalian nervous system. It plays an important role in many physiological functions including brain development and learning. Glutamate homeostasis is crucial to brain function.⁴⁸⁾ Fast removal of glutamate from the synaptic cleft by astrocytes guarantees short glutamate action on the postsynaptic target cell and thereby precise information signaling. Furthermore, high extracellular concentrations of glutamate damages cells and glutamate neurotoxicity plays a significant part in many neurological and psychiatric disorders.⁴⁹⁾

It is also generally accepted that the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors plays a key role in mediating at least a certain aspect of glutamate toxicity owing to its high Ca²⁺ permeability.⁵⁰⁾ Excessive Ca²⁺ loading exceeding the capacity of Ca²⁺ regulating mechanisms could activate several cell death-related genes and pathways.⁵¹⁾ These include Ca²⁺-dependent activation of nucleases, lipases, proteases and neuronal nitric oxide synthase thus increasing oxidative stress.^{52,53)} Physiologic concentrations of glutamate can also cause an excitotoxic influx of Ca²⁺ when reduced adenosine triphosphate (ATP) levels lead to disturbed cellular ion homeostasis, depolarized membrane potential and consequently release of the voltage-dependent Mg²⁺ blockade of the NMDA receptor. This mechanism might well contribute to the degeneration and damage of neurons.^{54,55)}

It had been proved that ginseng was effective in protecting against hypoxic damage and preserving structural integrity of neurons in neuronal cell culture. Using hypoxia reoxygenation neurodegenerative model, researchers reported that ginsenosides delay the breakdown of ATP in cultured neurons after hypoxia and accelerate the restoration of ATP

during reoxygenation.⁵⁶⁾ Wen and Lim concluded that ginsenoside Rb₁ protects hippocampus CA1 neurons against lethal ischaemia possibly by scavenging free radicals.^{57,58)} Additionally, Deng and Zhang reported that ginsenosides Rb₁ and Rg₁ inhibit lipid peroxidation within liver and brain by up-regulating catalases and glutathione peroxidase.⁵⁹⁾

More research works found that ginsenosides Rg₃ and to moderate extent, Rb₁ attenuated glutamate neurotoxicity in hippocampal slice culture through diminishing the activation of its receptors particularly, NMDA receptor.⁶⁰⁾ It has been further reported that ginsenosides Rb₁ and Rg₁ protected spinal cord neurons from excitotoxicity induced by glutamate and kainic acid, as well as oxidative stress induced by H₂O₂.⁶¹⁾ They also inhibited cell death in both CA1 and CA3 regions of rat hippocampus caused by kainic acid and protected hippocampal neurons from ischaemia.^{59,62)} It is found that both ginsenosides Rb₁ and Rg₁ partially promote the neurite lengths and the neurite numbers of neurons at the level of the surviving cells after glutamate exposure. The extension of axons and dendrites in neurons may compensate for and repair damaged neuronal networks in some neurodegenerative disease and thus may be the cause of the significant improvement in learning and memory observed in brain-damaged and aged rats after oral administration of ginseng powder.⁶³⁻⁶⁵⁾ Moreover, ginsenosides could reduce Ca²⁺ over-influx into the mitochondria of the surviving cells, thus lowering free radical production by depolarized mitochondria and increasing energy production crucial for cell surviving and neurite sprouting. The stimulatory effects of these ginsenosides on survival of neurons may be mediated through improving the energy metabolism and preserving the structural integrity of neurons.⁵⁶⁾ Induction of antioxidant enzymes by ginsenosides which are important for maintaining cell viability may equally contribute by lowering free radicals generated from intracellular metabolism either by neuronal or other cells in culture.^{66,67)}

GABA systems

GABA is an important inhibitory neurotransmitter that mediates the mammalian central nervous system.⁶⁸⁾ When GABA is released from the presynaptic site, it can bind to receptors or be taken up by cells and be metabolized. Two major subtypes of GABA receptors are well investigated. The GABA_A receptor activates a chloride channel,⁶⁹⁾ which consists of a heteromeric mixture of protein subunits forming a pentameric structure. GABA_B receptors couple to Ca²⁺ and K⁺ channels via G proteins and second

messengers.^{70,71)}

It has been shown that ginseng extract possessed a variety of effects on the activity of the central nervous system, promoting stimulation as well as inhibition of the cortical activity.⁷²⁾ It could not only stimulate the central nervous system in low doses, but also inhibit it. Effects of ginseng extracts on learning, memory and physical capacities have revealed that chronic intake of ginseng stabilized sleep and wakefulness,^{23,73,74)} GTS inhibited the development of reverse tolerance to the ambulatory-accelerating effect of morphine.^{25,44)}

Data from animal experiments showed that ginseng administration in animals caused behavioral changes which appeared to be related to the regulation of GABAergic transmission.⁷⁵⁾ Pretreatment with another species of ginseng, *Panax quinquefolium* L. significantly decreased the inhibitory effects induced by GABA_A agonist, indicating interactions of *Panax quinquefolium* L. with ligand-bindings of GABA_A receptors. This suggests that actions of ginseng might be mediated via the GABAergic system.⁷⁵⁾ This inference is supported by binding study which showed that total GTS decreased the affinity of specific [³H]muscimol binding, suggesting that the regulation of GABAergic neurotransmission may be important in the action of GTS.⁷⁶⁾ Ginsenoside Rh₂ induced up-regulation of [³H]muscimol binding in a region-specific manner after prolonged infusion into lateral ventricle. The levels of [³H]MK-801 binding were also highly decreased in almost all regions of frontal cortex and hippocampus by ginsenoside Rh₂. However, ginsenoside Rg₃ did not show the significant changes of ligand bindings. In addition, ginsenoside Rh₂ decreased the expression of nNOS in the hippocampus although Rg₃ decreased the expression in the cortex. These results suggest that ginsenoside Rh₂ could play an important role in the biological activities in the central nervous systems through GABAergic system.^{76,77)}

5-HT systems

5-HT is implicated in the pathophysiology of psychotic disorder and stress-related diseases.⁷⁸⁻⁸⁰⁾ A few studies investigated 5-HT levels and 5-HT receptors in patients found that 5-HT level was increased in patients with psychotic disorder,^{81,82)} and there was a significant relationship between psychotic symptoms,⁸³⁾ especially delusions, and 5-HT level in these patients.⁸⁴⁾ Further clinical research proved that 5-HT level was related to multiple psychotic symptoms^{85,86)} such as psychotic symptoms of depression,^{87,88)} delusions in dementia,⁸⁹⁾ aggression,⁹⁰⁾

impulsivity and violence,⁸⁵⁾ positive or paranoid symptoms of schizophrenia,^{91,92)} especially associated with depressive symptoms in post-traumatic stress disorder (PTSD) and aggression.^{90,93)} 5-HT alterations might contribute to the cognitive disturbances in PTSD⁹⁴⁾ and aggression.⁹⁰⁾ Administration of the 5-HT agonist meta-chlorophenylpiperazine provokes PTSD symptoms,⁹⁵⁾ 5-HT drugs (sertraline) show clinical efficacy in the treatment of PTSD.⁹⁶⁾

Researchers found that ginseng did not modify brain and hypothalamic 5-HT in unstressed rats.⁹⁷⁾ But it attenuated stress-induced elevation of brain and hypothalamic 5-HT.^{97,98)} Ginseng treatment inhibited stress-induced increases in 5-HT synthesis and tryptophan hydroxylase expression in the dorsal raphe and increased time to exhaustion for treadmill running in rats.⁹⁹⁾ These results suggest that the suppressive effect on 5-HT level during exercise is a possible anti-stress and ergogenic mechanism of ginseng.⁹⁹⁾ Anti-stress action of ginseng reflected by inhibition of stress-induced elevation of brain and hypothalamic content of 5-HT as also stress-induced concurrent elevation of plasma corticosterone were further diminished by diclofenac, a prostaglandin synthesis inhibitor, suggesting that mediatory action of 5-HT in anti-stress effects of ginseng may be modulated through prostaglandins.⁹⁷⁾ It has been demonstrated that 5-HT precursor pretreatment abolished the antagonism effect of GTS on selective kappa-opioid receptor agonist-induced antinociception.¹⁰⁰⁾ GTS and ginsenoside Rg₂ as well as ginsenoside metabolites were found to regulate human 5-HT_{3A} receptor channel activity in xenopus oocytes.^{101,102)} Further investigations found that ginsenoside Rg₃ could also regulate 5-HT_{3A} receptor channel activity in the open state at different sites; it inhibits 5-HT_{3A} receptor channel activity through interactions with residues in the channel gating region.¹⁰³⁾

CONCLUSION AND FUTURE PERSPECTIVES

Ginseng has been used in eastern Asia for more than 5,000 years and appears to be relatively safe. Regarding the adaptogenic property of ginseng and results from animal studies and neuronal cell culture experiments indicating that ginsenosides can counteract and attenuate factors promoting psychotic disorders, ginsenosides could be considered as a valuable option to treat psychotic disorders and it is possible to develop more efficacious ginseng-derived therapeutics for psychotic disorders. For

conclusive clinical data in humans is still missing, more research works will be needed to study the effects of ginseng on psychotic disorders.

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