CHAPTER 28

PHARMACOLOGY AND CLINICAL USES OF *GANODERMA*

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1. INTRODUCTION

Ganoderma is a medicinal fungus and has been treasured for this value in China for more than two thousand years. This fungus was described as a nontoxic medicine which was beneficial to viscera and could improve intelligence by enhancing memory, hearing, vision and smelling. If taken regularly for long periods, it would also retard aging and prolong life span (Li, 1978). In Chinese folk culture, *Ganoderma* has been regarded as a panacea, curing all kinds of diseases. Regardless of its medicinal value, wild *Ganoderma* were few and very expensive. We have succeeded in the mass cultivation of *Ganoderma* using solid-state-fermentation and submerged fermentation technologies. In practice, only the fruitbodies of *G. lucidum* and *G. japonicum* are used as a medicine, and the spores are discarded. Therefore, we carried out some pharmacological studies on the effects of the spore extracts of *G. lucidum* and mycelial extracts of *G. capense* on various diseases. Some promising results were obtained. This paper mainly reviews the results of our studies on the pharmacology and clinical uses of crude *Ganoderma* preparations.

2. PHARMACOLOGICAL ACTIVITIES OF THE ALCOHOL-WATER SOLUBLE FRACTION

Spores (SGL) and mycelium (MGC) were harvested from submerged cultures of *G. lucidum* and *G. capense*, respectively. Then, alcohol-water soluble and alcohol-ether soluble fractions of SGL and MGC were prepared. When the lipid-soluble fraction was used in aqueous medium, Tween 80 was added as a surfactant. The dosage of the preparations was calculated according to the raw material content.

2.1. Effects on the Central Nervous System in Mice

The following parameters in mice were monitored: spontaneous motor activity, sleeping time induced by barbiturates and salivation induced by pilocarpine and nicotine induced death rate (Liu *et al.*, 1977; 1979a, b; Leng & Liu, 1980a, b). The results are shown in Table 1.

TABLE 1. Effects of the alcohol-water soluble fractions of *Ganoderma lucidum* spores (SAW) and *G. capense* mycelium (MAW) on the central nervous system in mice.

	n	Control	SAW	MAW
Spontaneous motor activity	15	782.0±55	350.0±53*	306.0±62#
Sleeping time (min)				
Pentobarbital	1	51.0±3	69.0±6*	100.0±7#
Barbital	10	65.0±20	149.0±9#	156.0±2#
Nicotine induced death (%)	10	100.0	30.0#	0
Salivation (mg)	10	8.2±0.2	5.4±0.2*	2.6±0.2#

*, $P < 0.05$; #, $P < 0.01$.

For motor activity, adult male mice were injected intraperitoneally with 10gm SAW (from spores of *G. lucidum*) or 5gm MAW (from mycelium of *G. capense*) per kg biomass. Control mice received normal saline instead. The spontaneous motor activity in ten minutes following the injection was recorded by an electron-light apparatus. Both SAW and MAW significantly reduced the spontaneous motor activities in mice.

For sleeping time experiments, a dose of 20-30 gm SAW or MAW per kg biomass was injected subcutaneously to mice 20min before intraperitoneal injection of 50mg pentobarbital or 200mg sodium barbital per kg biomass. The disappearance and recovery of righting reflex was recorded as the sleeping time. SAW and MAW significantly prolonged sleeping time induced by the injection of barbiturates in mice.

For nicotine induced death test, prior to intravenous injection of nicotine (1mg/kg biomass) to the tail vein, 20gm SAW or 10gm MAW per kg biomass was intraperitoneally injected. The injection significantly protected the mice from convulsion and death induced by nicotine.

When SAW or MAW (20gm/kg) was administered subcutaneously 20 min prior to intravenous injection of 2.5mg/kg of pilocarpine to the tail vein, salivation was markedly reduced.

From the above results (Table 1), it shows that SAW and MAW have a sedative effect on the central nervous system in mice. MAW seems to be more potent than SAW.

When the culture broth of *G. capense* was dried and extracted to form the alcohol-water soluble portion (FAW), this portion also affected the central nervous system. FAW, 2.5 - 5gm per kg biomass, when injected intraperitoneally, significantly inhibited the spontaneous motor activities. FAW also potentiated the sedative effects of reserpine and chlorpromazine and antagonized the stimulating effect of amphetamine in mice. This effect was not observed with extract from *G. lucidum* culture broth. FAW, 20gm per kg biomass, when given intraperitoneally, prolonged sleeping time induced by pentobarbital and barbital. Pretreatment using FAW also reduced convulsion and death rate caused by nicotine. However, no such antagonistic effect was observed when convulsion and death were induced by strychnine and ammonium chloride. FAW also significantly inhibited salivation induced by pilocarpine.

In conclusion, the alcohol-water soluble portions of the spores of *G. lucidum*, the mycelium of *G. capense* and the culture broth of *G. capense* have similar sedative effects on the central nervous system in mice.

TABLE 2. Effects of the alcohol-water soluble fractions of *Ganoderma lucidum* spore (SAW) and *G. capense* mycelium (MAW) on cardio-cerebral vascular system on ten mice.

Dosage (gm/kg)	Tolerance to hypoxia (survival min)	Uptake of ^{86}Rb (cpm/g tissue)		Serum total cholesterol (mg/dl)
		Heart	Brain	
Control	47±4.8	3247±179	803±51	165±14
SAW 10	71±8*	3550±370	898±47	237±19
SAW 2	164±26#	2816±286	955±47*	173±10#
MAW	119±11	4271±440*	1223±70#	189±10#
MAW 20	141±19#	5343±649#	1440±87#	180±5#

*, $P < 0.05$; #, $P < 0.01$.

2.2. Effects on Cardio-Cerebral-Vascular System in Mice

The following parameters were examined: tolerance to hypoxia, uptake of ^{86}Rb by heart and brain, experimental hypercholesterolemia in mice and prostaglandin metabolism in ischemic brain of gerbils. Normal and isopropyl adrenaline treated-mice were administered subcutaneously a dose of 10 - 20 gm SAW or MAW 20 min before they were placed in a glass jar with a sealed cover. From Table 2, prior adminstration of MAW significantly prolonged the survival time of normal and isopropyl adrenaline treated-mice under hypoxia, while SAW showed effects only in normal mice but not in isopropyl adrenaline-treated mice under hypoxia (Bao *et al.*, 1988).

The uptake of ^{86}Rb by tissues may be used as an indication of the state of nutritional circulation in the organ. The higher the uptake, the higher the blood flow into the organ. A dose of 20 gm SAW per kg biomass was administered subcutaneously 20 min prior to intravenous injection of 10 uci/kg of ^{86}Rb. The radioactivities in heart and brain tissues were measured 20-30 sec after the injection. Table 2 shows that both SAW and MAW significantly promoted the uptake of ^{86}Rb by the brain, and only MAW increased the uptake by the heart.

Mice received a dose of 400mg triton WR1339 per kg tissue in the tail vein and a dose of 10 - 20 gm SAW or MAW subcutaneously at the same time. Then the mice was fasted for 5 hrs. Table 2 shows that total cholesterol in the serum was higher in the treated groups.

Prostaglandins play some role in the pathogenesis of brain ischemia. Therefore, the effect of *Ganoderma* on prostaglandins PGF1a and TXB_2 in ischemic brain was examined. Both cervical arteria of Mongolian gerbils were ligated 20 min after subcutaneous injection of SAW. 6-Keto-PGF1a and TXB_2 in ischemic cerebral cortex of gerbils were determined 5 min after the ligation. SAW significantly increased the content of 6-keto-PGF1a and decreased TXB_2, thereby increasing the ratio of $PGI2/TXA_2$. This effect of SAW seemed to be more potent than that of nootropil. The results indicate that the two alcohol-water soluble injections of *Ganoderma* have beneficial effects on cardio-cerebral-vascular system and may be useful for the treatment of heart and brain ischemia.

2.3. Effects on Immune Functions in Mice

The immune system is the specific defense mechanism against invaders. Our studies demonstrated that subcutaneous injection of the *Ganoderma* (SAW) once daily for 6 days significantly

TABLE 3. Effects of *Ganoderma* extract (SAW) on acid phosphatase and β-glucuronidase of mouse peritoneal macrophages and ^{3}H-TdR incorporation into spleen DNA in prednisolone treated-mice.

Enzyme	Control	SAW	Prednisolone
Acid phosphatase (u/ 5x10^6 cells)	1.7±0.35	7.5±0.5#	
Beta-glucuronidase (u/ 5x10^6 cells)	2.7±0.2	3.8±0.5*	
Spleen DNA (mg/gm tissues)	16.4±0.9	14.5±2.0*	13.4±1.3
^{3}H-TdR (cpm/gm spleen)	2985.0±447	3012.0±525*	2254.0±377

*, P < 0.05; #, P < 0.01.

increased the activity of acid phosphatase and β-glucuronidase of mouse peritoneal macrophages (Table 3) (Liu, 1989). In another test, SAW was given subcutaneously to mice once daily for 7 days, but on day 4 onwards, prednisolone acetate (5mg/kg) was also injected intraperitoneally once daily. Then each mouse received 10μci ^{3}H-TdR/kg tissues one day before the last dose of SAW. Then the spleen DNA content and the incorporation of ^{3}H-TdR into spleen DNA were measured. As shown in Table 3, prednisolone reduced spleen DNA and ^{3}H-TdR was incorporated into spleen DNA. Pretreatment with SAW did not affect prednisolone. It appears that *Ganoderma* extract has some effects on immune function in mice.

2.4. Anti-allergic Myositis in Rats

Serum and muscle creatine phosphokinase (SCPK, MCPK) were determined and served as biochemical parameters for evaluating the efficacy of *Ganoderma* since myopathic patients are usually associated with higher level of SCPK. Male Wistar rats were immunized with leg muscle homogenate of guinea-pig once a week for 4 weeks. One week after the last immunization, rats were killed and SCPK and MCPK were determined. The pathological changes of muscles of hind legs were

TABLE 4. Effects of *Ganoderma* (SAW) on serum and muscle creatine phophokinase (SCPK, MCPK) levels in rats with allergic myositis and mice with myotonia induced by 2,4-dichlorophenoxy acetic acid.

Animal	Group	SCPK	MCPK
Rat	Normal	34.3±3.7	136.0±10
	Immunization	60.6±6.9	91.0±15
	SAW 20gm/kg	43.3±7.9*	121.0±21*
Mice	Normal	25.8±0.4	120.0±12
	Immunization	45.5±10.2	69.6±11.3
	SAW 20gm/kg	30.0±4.8*	99.1±19.3*

*, P < 0.05.

observed by light microscopy. As shown in Table 4, SCPK increased and MCPK decreased significantly after immunization in rats. When the immunized rats were simultaneously injected with 20gm SAW per kg biomass subcutaneously once daily for 30 days, the elevation of SCPK and reduction of MCPK were significantly inhibited. The lesions of leg muscle were also ameliorated.

We have found that subcutaneous injection of 2,4-dichlorophenoxy acetic acid, a herbicide, not only caused myotonia but also induced elevation of SCPK and reduction of MCPK in mice. Therefore, we use this as a model system to evaluate the efficacy of *Ganoderma* extract. SAW was injected subcutaneously to mice after the mice were injected with 200mg herbicide per kg biomass. From Table 4, SAW significantly inhibited the elevation of SCPK and reduction of MCPK induced by the herbicide. However, SAW had no effect on normal mice.

2.5. Anti-oxidant Activity

In order test whether *Ganoderma* exerts its protective effect on experimental myositis through inhibition of lipid peroxidation, homogenates of mouse leg muscles were incubated with various concentrations of SAW for 30 - 60 min at 37°C. Malondialdehyde, a product of lipid peroxidation, initiated by addition of iron and cysteine was assayed. SAW inhibited malondialdehyde formation and the production of superoxide anion in xanthine/xanthine oxidase *in vitro*. These observations provide new evidence for the effects of SAW on several muscle diseases.

3. HEPATOPROTECTIVE ACTION OF THE ALCOHOL-ETHER SOLUBLE FRACTION OF *G. LUCIDUM* SPORES AND *G. CAPENSE* MYCELIUM IN MICE

3.1. Effect on Serum Transaminase

Only the alcohol-ether soluble fraction and not the water soluble fraction from *G. lucidum* spores and *G. capense* mycelium could reduce the elevated serum transaminase level induced by CCl_4 in mice (Liu *et al.*, 1979a, b).

3.2. Effect on Toxicity of Indomethacin and Digitoxin

Large doses of indomethacin induces ulceration and perforation of the gastrointestinal tract, and high doses of digitoxin causes cardio-toxicity which usually induces death in mice. When the *Ganoderma* extracts were administered simultaneously, the mortality rate of mice intoxicated with indomethacin and digitoxin decreased. Similar results were obtained with the lipid soluble extracts. In addition, the lipid soluble portion promoted regeneration of the liver in partially hepatectomized mice as revealed by the heavier weight of the liver in the treated group.

4. CLINICAL USAGE

The alcohol-water soluble protions of the *G. lucidum* spores (SAW) and the *G. capense* mycelium (MAW) were tested clinically. Two ml extracts from 400 mg spores/mycelium were administered intramuscularly once daily for a few days. From Table 5, both preparations were shown to have therapeutic effects on dermatosclerosis, dermatomyositis and multiple polymyositis,

TABLE 5. Clinical trials of the alcohol-water soluble preparations of *Ganoderma* on different diseases.

Disease	Preparation	Total cases	Effective rate (%)	Months of Treatment
Dermatosclerosis	MAW	173	79.1	3-6
Dermatomyositis & Multiple Polymyositis	MAW	55	96.4	3-6
Lupus erythromatosis	MAW	84	82.1	3
Alopecia areata	MAW	232	78.9	1-3
Atropic myotonia	MAW, SAW	35	74.3	3-6
Progressive muscular dystrophy	MAW, SAW	121	56.2	3-6

alopecia areata and other diseases.

4.1. Effects on Dermatomyositis and Multiple Myositis

Extracts of *G. capense* mycelium were used. Out of the 55 patients with different disease histories, 36 patients were treated with the *Ganoderma* injection in combination with prednisone. Among them, 53 patients showed improvement to different extents. Eight patients relapsed after the withdrawal of the *Ganoderma* treatment. In the treatment group, 2 patients died but without lung infection and perforation in the gastrointestinal tract. It appears that *Ganoderma* injection not only can arrest the development of the disease but also reduce the mortality rate among the patients.

4.2. Effect on Alopecia

232 patients with different disease histories were treated with *Ganoderma* injection for 3 months. The efficiacy rate was 78.9 - 86%. No side-effects were observed. Both extracts from *G. lucidum* spores and *G. capense* mycelium were effective.

4.3. Effect on Scleroderma

Scleroderma is a collagen disease and its cause is unknown. 173 patients with different disease histories were administered with *Ganoderma* injection or *Ganoderma* tablets for 3 - 6 months. The total rate of effectiveness was about 58-91%. Local injection of the *Ganoderma* extract for localized scleroderma seemed to be more effective than intramuscular injection of the *Ganoderma* for systemic scleroderma. Such local injection promoted blood circulation as revealed by laser instrumentation. Skin biopsy of several patients revealed that the pathological morphology, such as inflammatory infiltration, decreased or disappared. The collagen fibril became aeroses. Therefore, *Ganoderma* injection may have an anti-inflammatory function and loosen the connective tissues.

5. CONCLUSION

Ganoderma has been known as a panacea for thousands of years in China. However, modern studies on its biology, chemistry, pharmacology and clinical uses has only been carried out within the last two decades in China. From our experience, the different crude preparations of *Ganoderma* extracts have similar pharmacologic activities on animal models and therapeutic effects on patients suffering from different diseases. It is very important to know the action mechanism(s) of the *Ganoderma* extracts and identify the bioactive components. More efforts and co-operation between scientists are needed.

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