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Review Paper

Jiao Gu Lan (Gynostemma pentaphyllum): The Chinese Rasayan- Current Research Scenario

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ABSTRACT

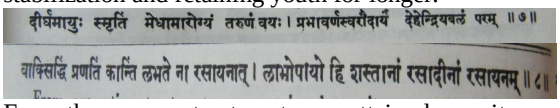
Jiaogulan (Gynostemma Pentaphyllum) is age old herb in traditional Chinese herbology. It has been widely researched. It is true Rasayan (Rejuvenator / Antiaging) herb as it is immunomodulator, adaptogen, antioxidant, anti-cancer, neuroprotective, nootropic and hepatoprotective. The only one Rasayan therapeutic activity about which there was no research reference is aphrodisiac.

Key words

Jiaogulan, Gynostemma Pentaphyllum, Rasayan, Anti aging, Anti oxidant, Immunomodulator

INTRODUCTION

The Rasayan branch of Ayurveda deals specifically with and Rasayan herbs and formulations that bestows upon the user, the longevity with age stabilization and retaining youth for longer.[1]


दीर्घमायुः स्मृतिं मेधामारोग्यं तरुणं वयः। प्रभावर्णस्वरौदार्यं देहेन्द्रियबलं परम् ॥७॥

वाक्सिद्धिं प्रणतिं कान्तिं लभते नरः रसायनात्। लाभोपायो हि शस्तानां रसादीनां रसायनम् ॥८॥

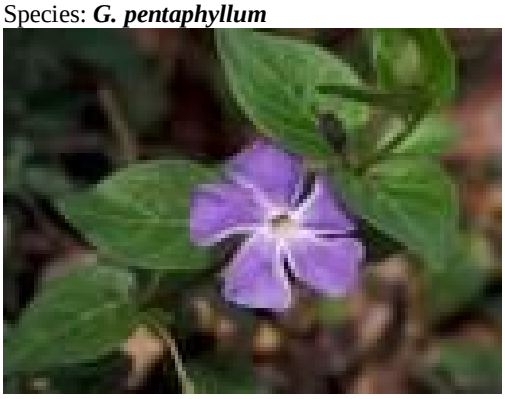
From the rasayan treatment, one attains longevity, memory, intelligence, freedom from disorders, youthful age, excellence of luster, complexion and voice, oratory, optimum strength of physique and sense organs, respectability and brilliance. It means the attaining the excellent Rasa etc.

These antiaging attributes will also incorporate being Adaptogen, Antioxidant and Immunomodulator

1.2 Scientific Classification:

Kingdom: Plantae

Order: Cucurbitales
Family: Cucurbitaceae
Subfamily: Zanonioideae Subtribe: Gomphogyninae
Genus: *Gynostemma*
Species: ***G. pentaphyllum***



1.3 Names in different languages:

Western languages such as English and German commonly refer to the plant as jiaogulan. Other names include.[2]

- Chinese: *xiancao* (仙草, literally "immortal grass"; more accurately "herb of immortality")
- English: five-leaf ginseng, poor man's ginseng, miracle grass, fairy herb, sweet tea vine, gospel herb, Southern Ginseng
- Japanese: *amachazuru* (kanji: 甘茶蔓; hiragana: あまちゃずる; literally 甘い*amai*=sweet, tasty 茶 *cha*=tea, 蔓 *zuru*=vine, creeping plant)
- Korean language: *dungkulcha* (덩굴차) or *dolwe* (돌외)

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- Latin: *Gynostemma pentaphyllum* or *Vitis pentaphyllum*
- Taiwanese: *sencauw*
- Tay language: *zan tong*
- Thai: *jiaogulan* (เจียวกู่หลาน)
- Vietnamese: *giảo cổ lam* or *bổ đắng* (*bổ*= nutritious, *đắng*=bitter)
- Portuguese: *cipó-doce*

1.4 Jiao gu lan in classical Chinese texts:

Although jiaogulan grows in many Asian countries, there does not seem to be any early historical documentation in existence other than in China. Jiaogulan is pronounced "jow-goo-lan". *Gynostemma pentaphyllum* is known as *Jiaogulan* (Chinese: 绞股蓝 "twisting-vine-orchid"[3]) in China. The plant was first described in 1406 CE by Zhu Xiao, who presented a description and sketch in the book *Materia Medica for Famine* as a survival food rather than a medicinal herb.[4] The earliest record of jiaogulan's use as a drug comes from herbalist Li Shi-Zhen's book *Compendium of Meteria Medica* published in 1578, identifying jiaogulan for treating various ailments such as hematuria, edema in the pharynx and neck, tumors, and trauma. While Li Shi-Zhen had confused jiaogulan with an analogous herb Wulianmei, in 1848 Wu Qi-Jun rectified this confusion in *Textual Investigation of Herbal Plants*, which also added more information on medicinal usage.[5]

Jiaogulan's traditional use has not been widespread in China. It was used as a folk herb in the local areas where it grew wild. Jiaogulan grows mostly in the mountainous regions of southern China, far from the central part of China, an area which has long been known as the "ancient domain of China". This central area of China is where the classical system that we call traditional Chinese medicine (TCM) evolved. For this reason, jiaogulan is not included in the standard pharmacopoeia of the TCM system, and therefore has not had as widespread use as TCM herbs. However, an experienced TCM practitioner in China has analyzed jiaogulan and described its qualities in terms of traditional Chinese medicine, as "sweet, slightly bitter, neutral, warm, enhancing 'Yin' and supporting 'Yang'", and suggested that "it would be used to increase the resistance to infection and for anti-inflammation."

Jiaogulan has been used by the people in the mountainous regions of Southern China as an energizing agent. They would take it as a tea before work to increase endurance and strength, and after work to relieve fatigue. It has also been taken for general health and has been recognized as a rejuvenating elixir. People also used it for treating common colds and other infectious diseases. Hence, the local Chinese people called jiaogulan, xiancao the "Immortality Herb," and described it thus: "Like ginseng but better than ginseng." Another story states that in a village near Fanjing Mountain in Guizhou province, the inhabitants would drink jiaogulan tea instead of the more common green tea and as a result many people there were living to 100 years of age.

The modern history of jiaogulan:

In 1972 the Research Group of Combined Traditional Chinese-Western Medicine of Qu Jing in Yunnan province did a study on the therapeutic effect of jiaogulan in 537 cases of chronic tracheo-bronchitis. This was the first report of medicinal usage of jiaogulan in modern Chinese medical literature.[6]Jiaogulan has since been included in the more recent Dictionary of Chinese Materia Medica, where it describes the traditional uses for jiaogulan as a medicine. There it is indicated for anti-inflammation, detoxification, cough remedy, as an expectorant and as a chronic bronchitis remedy.[7]Other traditional uses as a medicine have been anecdotally said to be for heart palpitation and for fatigue syndromes.

In Japan, jiaogulan is called Amachazuru[8] "Amacha" means "sweet" in Japanese, referring to the sweet component prevalent in the plant, "cha" means tea, and "zuru" means "vine". The name perfectly describes the jiaogulan plant, which grows as a climbing vine and produces a sweet tea from its leaves. Amachazuru has been recognized in Japan since the late 1970s, and its description and uses are included in the Japanese Colour Encyclopedia of Medicinal Herbs. Among other things, it is stated there: "Because of the sweet taste of the leaves, it has been used as a mountain vegetable" [9], similar to its use during the Ming Dynasty mentioned previously.

Perhaps one of the more significant revelations about jiaogulan came about in Japan in the mid-1970s. Previously unknown as a medicinal herb, jiaogulan's discovery in Japan came about like many of the world's great discoveries, partially through the hard labor of a dedicated scientist, and partially by accident. In the 1960s there was a trend amongst some research scientists to find an alternative sweetener to sugar. Although saccharin was in use for many years, they were still pursuing other sugar alternatives. In Japan, the government had prohibited the use of sodium cyclamate, a recently discovered artificial sweetener. Dr. Osama Tanaka, in the Dept. of Medicine of Hiroshima University, analyzing Amachzuru, found chemical compounds contained in amachazuru that are identical to some of the compounds found in Panax ginseng. He announced his findings at the twenty-

third Meeting of the Japanese Society of Pharmacognosy in 1976, at Hiroshima.[10] As it turned out, there was no further investigation of the herb for its sweetness. Another Japanese scientist, Dr. Tsunematsu Takemoto, whose specialty was herb medicine research, was seeking natural treatments for cancer and other ailments arising from stress, as well as a sugar alternative. His interest of study was in a Chinese fruit, botanical name Momordica grosvenori, a melon of the Cucurbitaceae (cucumber or gourd) family, known not only for its sweetness, but also for its medicinal uses. It is reputed as the "precious fruit of longevity" and as a popular Chinese medicine.[11] He learned of the research being done with amachazuru, an herb in the same family as the fruit he was studying and became very interested in studying it. Since the compounds in amachazuru were found to be similar to those in Panax ginseng, and because it was growing wild in the fields and mountains, Dr. Takemoto thought that he had possibly found, in an apparently insignificant perennial weed, an inexpensive and readily available health panacea, right in his native country.[12] Upon analyzing the amachazuru himself, Dr. Takemoto discovered that it contained four kinds of saponins exactly like those in Panax ginseng and seventeen other kinds of saponins very similar to those in Panax ginseng.[13] Over the next ten years he and his group of researchers identified and named eighty-two saponins from amachazuru, whereas Panax ginseng has been found to have up to 28 saponins.[14]
Although these two plants are not related, they contain the same major components: saponins, a substance that has the unique quality of dissolving both in water and oil, and when mixed with water and shaken, will foam up. In Panax ginseng the saponins are called ginsenosides, in jiaogulan, or amachazuru, they are called gypenosides. Throughout the 1980s, Dr. Takemoto, along with his staff, performed studies which isolated and identified eighty-two saponins, which they simply numbered 1-82.[15]

In 1984 they performed three experiments that began to demonstrate amachazuru's many health-supporting and medicinal qualities. They saw that amachazuru increased the activity and strength of mice in a swimming test, showing the herb's ability to improve endurance.[16] Another study on mice showed the herb's effectiveness as a neoplasm or tumor inhibitor,[17] and a third showed the herb's ability (adaptogenic) to prevent the unpleasant side effects of dexamethasone (hormone treatmen)[18] These studies used mice as subjects; nevertheless having been tested on mammals, they were a significant marker for the herb's possible effectiveness on humans. This was borne out by subsequent studies on humans. Jiaogulan would prove, in studies, to enhance endurance, inhibit tumors and help protect the cellular immunity in humans, as well as provide many other health-promoting benefits. Although the Japanese findings were significant, they were only the beginning of the extensive research that would be done on amachazuru. After death of Dr. Takemoto, the research significantly slowed in Japan.

However, interest in jiaogulan by Chinese researchers was growing rapidly, sparked by the results of a nationwide population census taken in the 1970s. The census revealed that, in small regions in the south central portion of China (some villages of Guangxi, Shicuan and other southern provinces), high rates of people per capita were living to 100 years of age. Cancer incidence was extremely low among the inhabitants as well. Scientists from the Chinese Academy of Medical Science in Beijing and other institutions began to research these regions and discovered that the people living there were regularly drinking a tea made from the herb jiaogulan.[19] Because of the significant results of the census taken in China during the 1970's, and then the boom of scientific interest in jiaogulan (amachazuru) in Japan during the 1980s, many research studies on jiaogulan were undertaken in China, and they have been continuing up to the present. Various pharmacological and therapeutic effects of jiaogulan were investigated and proven by tests on animals and human beings. Tonics and recipes made of jiaogulan have been developed and are being used in Chinese medical institutions. Surveys of the resources of jiaogulan in various portions of China have been made and cultivation techniques investigated.

Nearly 300 scientific papers on jiaogulan or its saponins have been published in respected journals, and information about the herb has been formally collected and published in the modern Dictionary of Chinese Materia Medica.[18] Jiaogulan has been recognized and accepted by ever-increasing numbers of Chinese people. From the time of the Qin Dynasty (221 B.C.), the Emperors of ancient China would send various envoys overseas to search for the "elixir of life", but their efforts were always fruitless. Perhaps, the "elixir" has been found by descendants of the Emperors, growing in their own homeland.

1.8 Botany:
Gynostemma pentaphyllum is a climbing, perennial vine native to China, Japan, and parts of southeast Asia. The plant is dioecious, that is, it carries male and female flowers on separate plants. While the plant grows abundantly and is harvested from the wild, it has been brought under cultivation and tissue culture has been achieved.[20, 21, 22]

Adulteration by Cayratia japonica has been noted.[23]

1.5 Traditional properties and products:

The jiaogulan plant has a history of folk use in the Guizhou province in China. Its properties are said to have been investigated when a Chinese census revealed a large number of elderly people in the province reported using the plant. Investigation as a potential sweetening agent stimulated chemical investigations in Japan. Commercialization and scientific study of the leaves have been promoted by provincial Chinese authorities, and the discovery that several ginseng saponins occur in the leaves has prompted aggressive promotion of the product as a substitute for ginseng.

Since the 16th century, Jiaogulan has been referred to in Chinese medical texts and the herb of immortality. Today, it is commonly used for a variety of ailments in China, Thailand and Japan.

Jiao gu Ian is an adaptogenic herb (normalizes body functions) and an antioxidant. In the southern Chinese mountains where the herb grows it is preferred to Ginseng. Chinese scientists surveyed demographics all over China to determine longevity and cancer rates. Those areas with unusual longevity (many people over 100) and low cancer rates all had only one thing in common. They all drank Jiao gu Ian tea on a regular basis.

It is an oriental medicinal herb for heat clearing, detoxification and expectorant for relieving cough in southern China, Japan, India, and Korea.[24] Jiaogulan is most often consumed as an herbal tea, and is also available as an alcohol extract and in capsule or pill form.

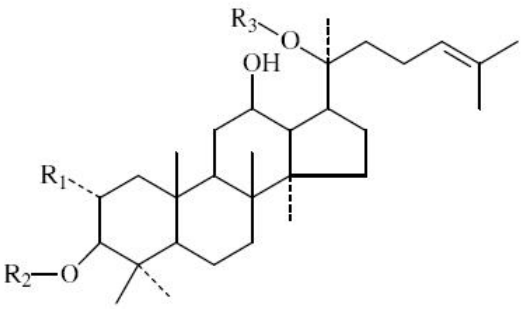
1.9 Chemical constituents:

A large series of dammarane triterpene saponins, gypenosides 1-82, have been isolated from the leaves, principally by Takemoto's group.[25, 26, 27, 28, 29 , 30 ,31, 32, 33]

Several of these saponins are identical to those found in ginseng. Specifically, gypenoside 3 is identical to ginsenoside Rb1, gypenoside 4 is identical to ginsenoside Rb3, gypenoside 8 is identical to ginsenoside Rd, and gypenoside 12 is identical to ginsenoside F2. Many of the other gypenosides are closely related structurally to the ginsenosides and include the 6′-malonyl derivatives characteristic of ginseng.[34] The content of saponins is comparable to that of ginseng roots. However, wide variation in the amount and nature of gypenosides has made production of a product standardized with specific gypenosides somewhat problematic. Most current products are standardized on total saponin content. The reasons for this variation have been investigated but have not been fully elucidated. Other constituents reported from Gynostemma pentaphyllum include sterols with the ergostane, cholestane, and stigmastane skeletons,[35, 36, 37, 38, 39] with several examples containing an acetylenic functionality, which is considered unusual in plants.[40] The flavonoid glycosides rutin, ombuoside,[41] and yixingensin[42, 43] have also been identified.

The related species G. compressum Chen and Liang have yielded dammarane saponins related to the gypenosides.[44]

In fact, four of the 85 saponins (called Gypenosides) in this herb are identical to those of Ginseng, but about four times as concentrated. Others are converted into Ginseng saponins but other saponins are unique to this herb. Ginseng has about 25 saponins.



General Structure of Dammarane-Type Gypenosides. Gypenoside consists of both the hydrophobic sapogenin part and the hydrophilic sugar part in the molecule (where R1 and R2 = glucose, rhamnose; R3 = glucose, xylose).

2 DOSAGE

The adaptogenic use of jiaogulan is standardized on an extract containing 85% gypenosides, with a daily dose of 60 to 180 mg gypenosides recommended; however, published studies to justify this dose are lacking.

3 TOXICITY / SAFETY

3.1LD50

The LD50 in mice for the aqueous extract has been reported as 2.8 g/kg IP. However, LD50 for the oral route could not be determined.[45] Another study found an oral LD50 of 49 g/kg for the crude extract with no organ toxicity at 4 g/kg daily for 90 days.[46] A third study of two different extracts found an LD50 of 1 to 2 g/kg IP in mice.[47] A rat LD50 of 1.9 g/kg IP has also been reported.[45]

3.2Chronictoxicity:

The effect of water extract of Gynostemma pentaphyllum was evaluated on 6-month chronic toxicity in Wistar rats. Control group received orally 10 ml kg(-1) day(-1). The extract was orally

given to the five treatment groups at the doses of 6, 30, 150, 750 and 750 mg kg(-1) day(-1) for 24 weeks. The last group served as the recovery group. The results showed that the extract did not produce any significant dose-related changes. Therefore, it is concluded that the extract of G. pentaphyllum at the given doses did not produce any significant toxic effect in rats during 6-month period of the treatment.[48]

3.3 Unlike most plants of the Cucurbitaceae family, jiaogulan does not show toxicity.[49]

3.4 *Gynostemma pentaphyllum* Makino (GP) is a herbal tea widely grown in Southeast Asia. However, this herbal tea can be contaminated with some heavy metals, especially cadmium (Cd), from agricultural areas, which may affect human health. The objective of this study is to evaluate the immunomodulatory effects of Cd contaminated in GP herbal tea and inorganic Cd on rat splenocytes. Rats were divided into groups and treated with drinking water (control), high $CdCl_2$ in drinking water (HCd; 0.05 mg/L), GP herbal tea containing 0.05 mg/L Cd (GP-HCd) for 4 months, low $CdCl_2$ in drinking water (LCd; 0.006 mg/L), and GP herbal tea containing 0.006 mg/L Cd (GP-LCd) for 6 months. After the treatments, Cd accumulation in organs and blood was detected by using a graphite furnace atomic absorption spectrophotometer. In spleen, HCd-treated rats had 4-fold higher Cd accumulations than GP-HCd-treated rats. Cd accumulation in liver and kidney in the HCd group also increased significantly. There were no significant changes in total leucocyte and lymphocyte counts; however, these parameters tended to decrease slightly in LCd, GP-LCd, and GP-HCd groups. The HCd group (ex vivo) significantly produced suppressive effects on T cell mitogen-induced splenocyte proliferation, with 1 μg/mL Con A and PHA-P. In addition, 0.5 μg/mL PWM-induced B cell proliferation, through T cell functions, was also significantly inhibited by HCd as compared to the control group, while GP-HCd had no effects. However, both GP-LCd- and LCd-treated rats had a slight increase in Con A-stimulated splenocyte proliferation. This study indicated that high Cd contamination in drinking water alone had suppressive effects on T cell functions, but these effects could not be found with the same Cd level contamination in GP herbal tea.[50]

4 PHARMACOLOGICAL AND CLINICAL PROPERTIES

4.1 Immunomodulation:

4.1.1 Water-soluble polysaccharide from Gynostemma pentaphyllum herb tea (PSGP) was isolated by hot-water extraction and ethanol precipitation. The chemical components and preliminary immunomodulating activity of PSGP were investigated both in vitro and in vivo. Capillary zone electrophoresis analysis showed that PSGP was a typical nonstarch heteropolysaccharide, with glucose being the main component monosaccharide (23.2%), followed by galactose (18.9%), arabinose (10.5%), rhamnose (7.7%), galacturonic acid (4.7%), xylose (3.9%), mannose (3.1%), and glucuronic acid (1.2%). PSGP could significantly stimulate peritoneal macrophages to release nitric oxide, reactive oxygen species, and tumor necrosis factor-alpha in a dose-dependent manner. This immunostimulating activity of PSGP was further demonstrated by its inhibition on the proliferation of human colon carcinoma HT-29 and SW-116 cells incubated with the supernatant of PSGP-stimulated macrophage culture. It is evident that PSGP is a very important ingredient responsible for at least in part the immunomodulating activity of G. pentaphyllum herb tea.[51]

4.1.2 Their previous report demonstrated that the oral administration of short-term high dose Gynostemma pentaphyllum extract (5 g/kg per day for 7days) decreased allergic reactions in ovalbumin (OVA)-sensitized mice. The aim of this study was to determine whether long-term oral administration of G. pentaphyllum attenuated airway inflammation in OVA-sensitized mice. Mice were sensitized and challenged with normal saline or OVA. OVA-sensitized mice were fed with 1.75 g/kg (low dose, GPL) or 5 g/kg (high dose, GPH) G. pentaphyllum extract, five days a week for 4 weeks. The airway hyperresponsiveness (AHR) and eosinophilia in bronchoalveolar lavage fluid (BALF) were examined. The cytokine levels or antibodies in BALF, serum and spleen cell culture supernatants were also determined. Both high and low dose extracts reduced AHR, serum OVA-IgE, and Th2-associated cytokine levels in spleen cell supernatants and BALF in OVA-sensitized mice. These results show that long-term orally administered G. pentaphyllum extract reduced allergic reactions in OVA-sensitized mice.[52]

4.1.3 The specimen of the total saponin for this experimental study was extracted from Gynostemma pentaphylla growing in Suining county in Hunan province. Weight of immune organs, content of anti-SRBC hemolysin, rate of special Ea-RFC formation and percentage of NK cell activity had been employed for the study as experimental indices, both the normal healthy mice and the mice with immunity impairment due to Cyclophosphamide (Cy) management as experimental models. The results of the study exhibited: (1) The total saponin of Gynostemma pentaphylla could markedly act against the

immunity inhibition due to Cy management in the experimental animals, showing a variant recovery in mice treated by Cy in weight of the immune organs, content of hemolysin, forming rate of Ea-RFC and unequivocally elevating NK cell activity, by significant difference in comparison with the Cy control groups (P less than 0.05-0.01). (2) The total saponin showed a definite of bidirective immunomodulatory action in normal healthy mice, recovering the immune indices to normal value from either originally lower or higher than the medium figure, by significant difference in comparison with the Cy control groups (P less than 0.05-0.01). (3) The total saponin had actions to prevent from fatigue and to tolerate hypoxia under usual atmospheric pressure. The above description indicates that the total saponin of Gynostemma pentaphylla is a better immunomodulator, seems to be like the actions of some Chinese drugs, for example, Panax ginseng, Astragalus membranaceus etc.[53]

4.1.4 Gynostemma pentaphyllum is a popular herbal tea in China and some Asian countries. The modulatory function of G. pentaphyllum total plant extracts on immune cells was evaluated in this study. The extract was intraperitoneally injected into mice for 5 consecutive days. The production of antibodies from B cells or cytokines from T cells was determined mainly with ELISA. After the treatment, serum IgM and IgG2a were significantly enhanced and showed dose-dependent effect. Moreover, serum IgA and IgG1 were also increased when received the extract at the doses of 0.05 or 0.50 g/kg/day. In addition to the serum levels, the injection of the extract enhanced the production of all antibodies from LPS-activated spleen cells. Furthermore, more cytokines were secreted from Con A-stimulated splenocytes of G. pentaphyllum-treated mice. Our results suggest that the extract of G. pentaphyllum might promote immune responses through the activation of T and B cells.[54]

4.1.5 Gynostemma pentaphyllum Makino (GP) is a herbal tea widely grown in Southeast Asia. However, this herbal tea can be contaminated with some heavy metals, especially cadmium (Cd), from agricultural areas, which may affect human health. The objective of this study is to evaluate the immunomodulatory effects of Cd contaminated in GP herbal tea and inorganic Cd on rat splenocytes. Rats were divided into groups and treated with drinking water (control), high CdCl 2 in drinking water (HCd; 0.05 mg/L), GP herbal tea containing 0.05 mg/L Cd (GP-HCd) for 4 months, low CdCl 2 in drinking water (LCd; 0.006 mg/L), and GP herbal tea containing 0.006 mg/L Cd (GP-LCd) for 6 months. After the treatments, Cd accumulation in organs and blood was detected by using a graphite furnace atomic absorption spectrophotometer. In spleen, HCd-treated rats had 4-fold higher Cd accumulations than GP-HCd-treated rats. Cd accumulation in liver and kidney in the HCd group also increased significantly. There were no significant changes in total leucocyte and lymphocyte counts; however, these parameters tended to decrease slightly in LCd, GP-LCd, and GP-HCd groups. The HCd group (ex vivo) significantly produced suppressive effects on T cell mitogen-induced splenocyte proliferation, with 1 mug/mL Con A and PHA-P. In addition, 0.5 mug/mL PWM-induced B cell proliferation, through T cell functions, was also significantly inhibited by HCd as compared to the control group, while GP-HCd had no effects. However, both GP-LCd- and LCd-treated rats had a slight increase in Con A-stimulated splenocyte proliferation. This study indicated that high Cd contamination in drinking water alone had suppressive effects on T cell functions, but these effects could not be found with the same Cd level contamination in GP herbal tea.[55]

4.1.6 An extract of Gynostemma inhibited the growth of a rectal adenocarcinoma cell line,[56] while total gypenosides inhibited growth of A549, Calu 1, and 592/9 carcinoma cells more potently (1 to 10 mg/L) than Hela and Colo 205 cells.[57] Both callus and field grown Gynostemma increased the lifespan of mice bearing Ehrlich's ascites carcinoma, an effect attributed to immune enhancement.[58] Crude gypenosides also had activity versus S-180 cells both in vitro and in vivo.[59] Gypenosides protected against cyclophosphamide-induced bone marrow and spermatozoal mutagenesis when given orally at 40 to 160 mg/kg to mice.[60] Similar treatments enhanced immune function in another report.[61]

4.1.7 Cancer patients given jiaogulan granules after chemotherapy showed improved immune function by several endpoints.[62]

4.2 Adaptogenic activity:

4.2.1 The action of gypenosides (GP, saponins of Gynostemma pentaphyllum, a Chinese medicinal herb) as an antioxidant was studied using various models of oxidant stress in phagocytes, liver microsomes and vascular endothelial cells. The results show that GP decreased superoxide anion and hydrogen peroxide content in human neutrophils and diminished chemiluminescent oxidative burst triggered by zymosan in human monocytes and murine macrophages. An increase of lipid peroxidation induced by Fe2+/cysteine, ascorbate/NADPH or hydrogen peroxide in liver microsomes and vascular endothelial cells was inhibited by GP. It was also found that GP protected biomembranes from oxidative injury by reversing the decreased membrane fluidity of liver microsomes and mitochondria, increasing mitochondrial enzyme activity in vascular

endothelial cells and decreasing intracellular lactate dehydrogenase leakage from these cells. The extensive antioxidant effect of GP may be valuable to the prevention and treatment of various diseases such as atherosclerosis, liver disease and inflammation.[63]

4.2.2 Jiaogulan is known as an adaptogen, which is an herb reputed to help the body to maintain optimal homeostasis[64] by balancing endocrine hormones, the immune system, the nervous system, and other biological functions.

4.2.3 Adaptogenic effects include regulating blood pressure and the immune system, improving stamina and endurance.[65]

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4.2.4 Jiaogulan is also believed to be useful in combination with codonopsis for jet lag and altitude sickness.[66]

4.2.5 Chen[67] found an increased tolerance to fatigue in forced swimming and hanging models in mice, and enhanced tolerance to anoxia, along with potentiation of pentobarbital hypnosis.[67]

4.3 Antioxidant activity:

4.3.1 An antioxidant effect of gypenosides was reported in phagocyte, endothelial cell, and liver microsome systems.[68]Further study by the same group[69] explored these effects in vascular endothelial cells injured by hydrogen peroxide. Rat microsome studies also have found similar effects for crude gypenosides.[70]

4.3.2 Jiaogulan has been found to increase superoxide dismutase (SOD), which is a powerful endogenous cellular antioxidant. Studies have found it increases the activities of macrophages, T lymphocytes and natural killer cells and that it acts as a tumor inhibitor.[71]

4.3.3 Five Gynostemma pentaphyllum (GP) samples were investigated and compared for their chemical compositions and their antioxidant, antiproliferative, and anti-inflammatory effects. Extracts (50% acetone, 75% ethanol, and 100% ethanol) of the five GP samples (GP1-5) differed in their total phenolic, saponin, and flavonoid contents and in their rutin and quercetin concentrations. The highest level of total flavonoids was 63.5 mg of rutin equiv/g in GP4, and the greatest total phenolic content was 44.3 mg of gallic acid equiv/g in GP1 with 50% acetone as the extraction solvent. GP2 had the highest total saponin content of 132.6 mg/g with 100% ethanol as the extraction solvent. These extracts also differed in their scavenging capacity against DPPH and hydroxyl radicals, although they all showed significant radical scavenging capacity. The 100% ethanol extracts also showed dose-dependently strong inhibition on IL-6 and Ptgs2 mRNA expression and weak inhibition on TNF-α mRNA expression. In addition, GP1 had the highest antiproliferative activity at 3.2 mg equiv/mL concentration in HT-29 human colon cancer cells. The results from this study will be used to promote the application of G. pentaphyllum for improving human health.[72]

4.3.4 Jiaogulan has been shown in tests to lower the amount of superoxide radical and hydrogen peroxide in certain white blood cells, an excellent indicator of antioxidant activity. Jiaogulan also has the remarkable property of increasing endogenous SOD (Superoxide Dismutase) in the body. SOD is one of the body‘s most important antioxidants and studies show that charting SOD levels in various animal species is a reliable indicator of their longevity. Trials in humans have shown that SOD levels returned to youthful levels after taking 20 mg of Gypenosides (active principle) daily for one month.[73]

4.3.5 Five Gynostemma pentaphyllum (GP) samples were investigated and compared for their chemical compositions and their antioxidant, antiproliferative, and anti-inflammatory effects. Extracts (50% acetone, 75% ethanol, and 100% ethanol) of the five GP samples (GP1-5) differed in their total phenolic, saponin, and flavonoid contents and in their rutin and quercetin concentrations. The highest level of total flavonoids was 63.5 mg of rutin equiv/g in GP4, and the greatest total phenolic content was 44.3 mg of gallic acid equiv/g in GP1 with 50% acetone as the extraction solvent. GP2 had the highest total saponin content of 132.6 mg/g with 100% ethanol as the extraction solvent. These extracts also differed in their scavenging capacity against DPPH and hydroxyl radicals, although they all showed significant radical scavenging capacity. The 100% ethanol extracts also showed dose-dependently strong inhibition on IL-6 and Ptgs2 mRNA expression and weak inhibition on TNF-α mRNA expression. In addition, GP1 had the highest antiproliferative activity at 3.2 mg equiv/mL concentration in HT-29 human colon cancer cells. The results from this study will be used to promote the application of G. pentaphyllum for improving human health.[74]

4.4Anticancer

4.4.1 Cancer patients given jiaogulan granules after chemotherapy showed improved immune function by several endpoints.[62]

4.4.2 GP1 had the highest antiproliferative activity at 3.2 mg equiv/mL concentration in HT-29 human colon cancer cells.[74]

4.4.3 An extract of Gynostemma inhibited the growth of a rectal adenocarcinoma cell line.[75] while total gypenosides inhibited growth of A549, Calu 1, and 592/9 carcinoma cells more potently (1 to 10 mg/L) than Hela and Colo 205 cells.[76] Both callus and field grown Gynostemma increased the lifespan of mice bearing Ehrlich's ascites carcinoma, an effect attributed to immune enhancement.[77] Crude gypenosides also had activity versus S-180 cells both in vitro and in vivo.[78] Gypenosides protected against cyclophosphamide-induced bone marrow and spermatozoal mutagenesis when given orally at 40 to 160 mg/kg to mice.[79] Similar treatments enhanced immune function in another report.[80]

4.4.4 A preparative column chromatographic method was developed to isolate flavonoids and saponins from Gynostemma pentaphyllum, a Chinese Medicinal herb, and evaluate their antiproliferation effect on hepatoma cell Hep3B, with the standards rutin and ginsenoside Rb(3) being used for comparison. Initially the powdered G. pentaphyllum was extracted with ethanol, followed by eluting flavonoids and saponins with ethanol-water (30:70, v/v) and 100% ethanol, respectively, in an open-column containing 5 g of Cosmosil 75C(18)-OPN, and then subjected to HPLC-MS analysis. The flavonoid fraction was mainly composed of quercetin- and kaempferol-glycosides, while in saponin fraction, both ginsenoside Rb(3) and ginsenoside Rd dominated. Both fractions were more effective against Hep3B cells than the standards rutin and ginsenoside Rb(3), with the cell cycle being arrested at G0/G1 phase for all the treatments. Additionally, the inhibition effect followed a dose-dependent increase for all the sample treatments. The result of this study may be used as a basis for possible phytopreparations in the future with G. pentaphyllum as raw material.[81]

4.4.5 The objectives of this study were to investigate the antiproliferation and apoptosis mechanism of saponin and flavonoid fractions from Gynostemma pentaphyllum (Thunb.) Makino on prostate cancer cell PC-3. Both flavonoid and saponin fractions were isolated by a column chromatographic method with cosmosil 75C¬18-OPN as adsorbent and elution solvents of ethanol-water (30:70, v/v) for the former and 100% ethanol for the latter, followed by HPLC-MS-MS analysis. Based on MTT assay, the saponin and flavonoid fraction were comparably effective in inhibiting growth of PC-3 cells, g/mL, respectively. Additionally,μwith the IC50 being 39.3 and 33.3 both fractions induced an arrest of PC-3 cell cycle at both S and G2/M phase, with both early and late apoptotic cell population showing a dose-dependent rise. The western blot assay indicated that the incorporation of flavonoid or saponin fraction could modulate the expression of G2 and M checkpoint regulators, cyclin A and B, as well as the anti-apoptotic proteins Bcl-2 and Bcl-xl, pro-apoptotic proteins Bad and Bax. The expression of the caspase-3 and its activated downstream substrate effectors, DFF45 and poly (ADP-ribose) polymerase-1 (PARP-1) was also increased and followed a dose-dependent manner. All these findings suggest that the apoptosis of PC-3 cells may proceed through the intrinsic mitochondria pathway.[82]

4.4.6 A preparative column chromatographic method for isolation of carotenoids and chlorophylls from Gynostemma pentaphyllum, a traditional Chinese herb, was developed to evaluate their antiproliferative effects on the hepatoma cell Hep3B. An open column containing 70 g of magnesium oxide-diatomaceous earth (1:2.5, wt/wt) was used to elute carotenoid with 2% ethanol in ethyl acetate and chlorophyll with 50% ethanol in acetone. After high-performance liquid chromatography-mass spectrometry analysis, the carotenoid fraction was composed of all-trans- and cis-isomers of lutein, α-carotene, and β-carotene as well as epoxy-containing carotenoids, while the chlorophyll fraction consisted of chlorophylls a and b and their derivatives. Both carotenoid and chlorophyll fractions as well as lutein and chlorophyll a standards at 50-100 μg/mL were effective against Hep3B cells with a dose-dependent response with the following order: carotenoid fraction > chlorophyll fraction > lutein > chlorophyll a. For all treatments, the cell cycle was arrested in the G_0/G_1 phase, with Hep3B cells undergoing necrosis or apoptosis.[83]

4.4.7 The hot water extract of the herbal tea, Gynostemma pentaphyllum Makino, was not found to be mutagenic in Salmonella mutation assay with or without metabolic activation. However, the extract had both DT-diaphorase inducing activity in the murine hepatoma (Hepa1c1c7) cell line and antimutagenic properties towards chemical-induced mutation in Salmonella typhimurium strains TA98 and TA100. Mutagenicity of aflatoxin B1 (AFB1), 2-amino-6-methyldipyrido 1, 2-a: 3', 2', 3-d. imidazole (Glu-P-1), 2-aminodipyrido 1, 2-a: 3', 2', 3-d. imidazole (GIu-P-2), 2-amino-1, 4-dimethyl-5H-pyrido 4, 3-b. indole (Trp-P-1), 3-amino-1-methyl-5H-pyrido 4, 3-b. indole (Trp-P-2), 2-amino-3-methylimidazo 4, 5-f. quinoline (IQ) and Benzo a. pyrene (Ba.P) was inhibited by the extract of Gynostemma pentaphyllum Makino in a dose-dependent manner, but no effect was found on the mutagenic activity of 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (AF-2). However, the extract enhanced the mutagenicity induced by 2-

aminoanthracene (2AA), and N-methyl-N-nitro-N-nitrosoguanidine (MNNG).[84]

4.4.8 Gypenosides (Gyp) are the major components of Gynostemma pentaphyllum Makino, a Chinese medical plant. Recently, Gyp has been shown to induce cell cycle arrest and apoptosis in many human cancer cell lines. However, there is no available information to address the effects of Gyp on DNA damage and DNA repair-associated gene expression in human oral cancer cells. Therefore, we investigated whether Gyp induced DNA damage and DNA repair gene expression in human oral cancer SAS cells. The results from flow cytometric assay indicated that Gyp-induced cytotoxic effects led to a decrease in the percentage of viable SAS cells. The results from comet assay revealed that the incubation of SAS cells with Gyp led to a longer DNA migration smear (comet tail) when compared with control and this effect was dose-dependent. The results from real-time PCR analysis indicated that treatment of SAS cells with 180 mug/ml of Gyp for 24 h led to a decrease in 14-3-3sigma, DNA-dependent serine/threonine protein kinase (DNAPK), p53, ataxia telangiectasia mutated (ATM), ataxia-telangiectasia and Rad3-related (ATR) and breast cancer gene 1 (BRCA1) mRNA expression. These observations may explain the cell death caused by Gyp in SAS cells. Taken together, Gyp induced DNA damage and inhibited DNA repair-associated gene expressions in human oral cancer SAS cells in vitro.[85]

4.4.9 Gypenosides (Gyp) are the major components of Gynostemma pentaphyllum Makino. The authors investigated the effects of Gyp on cell morphology, viability, cell cycle distribution, and induction of apoptosis in human oral cancer SAS cells and the determination of murine SAS xenograft model in vivo. Experimental design. Flow cytometry was used to quantify the percentage of viable cells; cell cycle distribution; sub-G1 phase (apoptosis); caspase-3, -8, and -9 activity; reactive oxygen species (ROS) production, intracellular Ca(2+) determination; and the level of mitochondrial membrane potential ($\Delta\Psi(m)$). Western blotting was used to examine levels of apoptosis-associated proteins, and confocal laser microscopy was used to examine the translocation of proteins in cells.[86]

4.4.10 The rate of cancer transformation in 1023 Recipe treated group was lower than that in the control group without treatment ($P<0.05$). Agglutinin receptors in the two groups were different significantly. 1023 Recipe is effective in treating hyperplasia, and can prevent its cancer transformation. The mechanism may be that 1023 Recipe can induce precancerous lesions to differentiate into normal tissues.[87]

4.4.11 Gyp inhibited the growth of WEHI-3 cells. These effects were associated with the induction of G0/G1 arrest, morphological changes, DNA fragmentation, and increased sub-G1 phase. Gyp promoted the production of reactive oxygen species, increased Ca(2+) levels, and induced the depolarization of the mitochondrial membrane potential. The effects of Gyp were dose and time dependent. Moreover, Gyp increased levels of the proapoptotic protein Bax, reduced levels of the antiapoptotic proteins Bcl-2, and stimulated release of cytochrome c, AIF (apoptosis-inducing factor), and Endo G (endonuclease G) from mitochondria. The levels of GADD153, GRP78, ATF6-α, and ATF4-α were increased by Gyp, resulting in ER (endoplasmic reticular) stress in WEHI-3 cells. Oral consumption of Gyp increased the survival rate of mice injected with WEHI-3 cells used as a mouse model of leukemia.

4.5 Neuroprotective activities:

4.5.1 Gypenosides (GP), the saponin extract derived from the Gynostemma pentaphyllum Makino, a widely reputed medicinal plant in China, has been reported to have some neuroprotective effects. We used a rat model of chronic cerebral hypoperfusion to investigate the protective effects of GP on the cortex and hippocampal CA1 region and the underlying mechanisms for its inhibition of cognitive decline. Daily doses of 100 and 200 mg/kg GP were orally administered to adult male Sprague-Dawley rats for 61 days after inducing cerebral hypoperfusion experimentally, and spatial learning and memory were assessed using the Morris water maze. Antioxidative capability was measured biochemically. The levels of lipid peroxidation and oxidative DNA damage were assessed by immunohistochemical staining for 4-hydroxynonenal and 8-hydroxy-2'-deoxyguanosine, respectively. Activated astrocytes were assessed by immunohistochemical staining and western blotting with GFAP antibodies. Rats receiving 200 mg/kg GP had better spatial learning and memory than saline-treated rats. GP 200 mg/kg/day were found to markedly enhance antioxidant abilities, decrease lipid peroxide products and oxidative DNA damage, and reduce the activation of inflammatory astrocytes. However, GP 100 mg/kg had no significant effects. GP may have therapeutic potential for the treatment of dementia induced by chronic cerebral hypoperfusion and further evaluation is warranted.[89]

4.5.2 Gypenosides (GPs) were tested for their ability to protect primary cultures of immature cortical cells against oxidative glutamate toxicity. In immature neural cells, glutamate cytotoxicity is known to be mediated by the inhibition of cystine uptake, leading to depletion of intracellular glutathione (GSH). The depletion of GSH impairs

cellular antioxidant defenses resulting in oxidative stress and cell death. We found that pretreatment with GPs (100-400 microg/ml) significantly protected cells from glutamate-induced cell death. It was therefore of interest to investigate whether GPs protect cortical cells against glutamate-induced oxidative injury through preventing GSH depletion. Results show that GPs significantly up-regulated mRNAs encoding gamma-glutamylcysteine synthetase (gamma-GCS) and glutathione reductase (GR) and enhanced their activities for GSH synthesis as well as recycle. Furthermore, GPs lowered the consumption of GSH through decreased accumulation of intracellular peroxides, leading to an increase in the intracellular GSH content. GPs were also found to prevent lipid peroxidation and reduce the influx of Ca(2+) which routinely follows glutamate oxidative challenge. GPs treatment significantly blocked glutamate-induced decrease in levels of Bcl-2 and increase in Bax, leading to a decrease in glutamate-induced apoptosis. Thus, we conclude that GPs protect cortical cells by multiple antioxidative actions via enhancing intracellular GSH, suppressing glutamate-induced cytosolic Ca(2+) elevation and blocking glutamate-induced apoptosis. The novel role of GPs implies their remarkable preventative and therapeutic potential in treatment of neurological diseases involving glutamate and oxidative stress.[90]

4.5.3 Oxidative injury has been implicated in the etiology of Parkinson's disease (PD). Gypenosides (GPs), the saponins extract derived from the Gynostemma pentaphyllum, has various bioactivities. In this study, GPs was investigated for its neuroprotective effects on the 1-methyl-4-phenylpyridinium ion (MPP(+))-induced oxidative injury of dopaminergic neurons in primary nigral culture. It was found that GPs pretreatment, cotreatment or posttreatment significantly and dose-dependently attenuated MPP(+)-induced oxidative damage, reduction of dopamine uptake, loss of tyrosine hydrolase (TH)-immunopositive neurons and degeneration of TH-immunopositive neurites. However, the preventive effect of GPs was more potential than its therapeutical effect. Most importantly, the neuroprotective effect of GPs may be attributed to GPs-induced strengthened antioxidation as manifested by significantly increased glutathione content and enhanced activity of glutathione peroxidase, catalyze and superoxide dismutase in nigral culture. The neuroprotective effects of GPs are specific for dopaminergic neurons and it may have therapeutic potential in the treatment of PD.[91]

4.5.4 6-Hydroxydopamine administration for 28 days (8 microg/2 microL) reduced the number of tyrosine hydroxylase (TH)-immunopositive neurons to 40.2% in the substantia nigra compared to the intact contralateral side. Dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid and norepinephrine levels were reduced to 19.1%, 52.3%, 47.1% and 67.4% in the striatum of 6-hydroxydopamine-lesioned rats compared to the control group, respectively. However, an oral administration of herbal ethanol extracts from Gynostemma pentaphyllum (GP-EX) (10 mg/kg and 30 mg/kg) starting on day 3 post-lesion for 28 days markedly ameliorated the reduction of TH-immunopositive neurons induced by 6-hydroxydopamine-lesioned rat brain from 40.2% to 67.4% and 75.8% in the substantia nigra. GP-EX administration (10 and 30 mg/kg) also recovered the levels of dopamine, 3,4-dihydroxyphenylacetic acid, homovanillic acid and norepinephrine in post-lesion striatum to 64.1% and 65.0%, 77.9% and 89.7%, 82.6% and 90.2%, and 88.1% and 89.2% of the control group. GP-EX at the given doses did not produce any sign of toxicity such as weight loss, diarrhea and vomiting in rats during the 28 day treatment period and four gypenoside derivatives, gynosaponin TN-1, gynosaponin TN-2, gypenoside XLV and gypenoside LXXIV were identified from GP-EX. These results suggest that GP-EX might be helpful in the prevention of Parkinson's disease.[92]

4.5.5 Oxidative injury has been implicated in the aetiology of Parkinson's disease (PD) and gypenosides (GP), which are saponins with various bioactivities, have shown antioxidative effects in vitro. The present study was designed to evaluate the effect of GP on a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model of PD. Acute administration of MPTP led to decreased glutathione content and reduced superoxide dismutase activity in the substantia nigra of the mice, which resulted in oxidative stress, loss of nigral dopaminergic neurons and motor dysfunction. Co-treatment with GP attenuated all the injuries induced by MPTP in a dose-dependent manner. The neuroprotective effect of GP may be attributed to increased antioxidation, as manifested by significantly increased glutathione content and enhanced superoxide dismutase activity in the substantia nigra. These results strongly indicate the possible therapeutic potential of GP as an antioxidant in PD.[93]

4.5.6 The memory-enhancing effects of TN-2 were evaluated using passive avoidance, Y-maze, and Morris water maze tests, and the protein expressions of brain-derived neurotrophic factor (BDNF), cAMP element binding protein (CREB), and p-CREB were determined by immunoblotting. TN-2 inhibited memory and learning deficits in scopolamine treated mice in the passive avoidance test. TN-2 (10, 20, and 40 mg/kg, p.o.) significantly inhibited memory and learning deficits in the

passive avoidance test by 40%, 96% and 78%, respectively, and exhibited significant memory-enhancing effects on the Y-maze test and the Morris water maze test. TN-2 also markedly increased BNDF expression and activated the transcription factor CREB in the hippocampi of scopolamine-treated mice. TN-2 may ameliorate memory and learning deficits by activating the CREB-BDNF pathway.[94]

4.5.7 Gypenoside LXXIV (G-74), a major constituent of GYNOSTEMMA PENTAPHYLLUM Makino (GP; family Cucurbitaceae), was isolated and its memory-enhancing effects were investigated in scopolamine-treated mice in passive-avoidance and Morris water maze tests. G-74 potently reversed memory impairment caused by scopolamine. G-74 also significantly shortened the scopolamine-prolonged escape latencies in the Morris water maze test ($p < 0.05$) and increased the scopolamine-shortened swimming time within the platform quadrant ($p < 0.05$). Based on these findings, G-74 might improve learning deficits.[95]

4.5.8 Experimental senility in mice induced by D-galactose was attenuated by intraperitoneal (IP) injection of Gynostemma aqueous extract.[96]

4.6 Cholesterol lowering activity (antihyperlipidemic):

4.6.1 Numerous clinical studies in Chinese medical literature have shown that jiagolan lowers serum cholesterol.[97]

4.6.2 Jiagolan lowers serum cholesterol, triglycerides, and LDL while raising HDL levels, with reported effectiveness rates ranging from 67% to 93%.[98]

4.6.3 Oral administration of a gynostemma decoction in combination with Nelumbo nucifera and Crataegus cuneata was found to lower triglycerides and cholesterol in rats and quail. However, a dose response was not demonstrated.[99]

4.6.4 Administration of an aqueous extract of the whole plant to rats in over 12 weeks resulted in a reduction in serum levels of total cholesterol and beta-lipoproteins.[100]

4.6.5 A second study in mice and rats given 200 mg/kg PO of the crude saponin demonstrated lower total cholesterol (TC) and VLDL but increased HDL/LDL.[101]

4.6.6 A clinical study of hyperlipoproteinemic subjects also found a decrease in TC with increased HDL/TC at a dose of 10 mg given 3 times daily for 30 days.[102] A study of 105 patients confirmed these effects.[103]

4.6.7 Preliminary studies indicate *Gynostemma* isolated triterpine glycosides lower cholesterol. These studies examine anti-hyperlipidemic effects of gypenosides. 1 g/kg P407 induced plasma triglyceride (25 fold), total cholesterol (6 fold), low density lipoprotein cholesterol (LDL) (7 fold), high density lipoprotein cholesterol (HDL) (1.6 fold), and nitrite (8 fold). After acute (4 days) and chronic (12 days) oral administration the gypenoside extract (250 mg/kg) reduced triglyceride (53% and 85%, respectively) and total cholesterol levels (10% and 44%, respectively). No significant effects on LDL or HDL cholesterol were observed. The gypenosides reduced nitrite ~80%. Similar results were obtained with atorvastatin (75 mg/kg for 4 days); except that LDL cholesterol was reduced (17%) and HDL cholesterol increased. 50% of lipoprotein lipase (LPL) plasma activity was inhibited by ~20 μM P407. Gynostemma had no effect on LL, however, it reversed the P407 inhibition of LPL activity in a concentration-dependent manner, with a 2-fold increase at ~10 μg/ml.

These studies demonstrate efficacy of *Gynostemma pentaphyllum* in lowering triglyceride, cholesterol and nitrite in acute hyperlipidemia. The results suggest further investigations of Gynostemma gypenosides are warranted to examine the mechanisms of this activity.[104]

4.7 Cardio and cerebrovascular effects:

4.7.1 Blood pressure- The adaptogenic nature of gypenosides have been found lower hypertension and raise hypotension, keeping blood pressure in a normal range. Laboratory tests demonstrate that jiaogulan stimulates the release of nitric oxide, causing blood vessels to relax; this is one proposed mechanism by which jiaogulan reduces high blood pressure.[105]

4.7.2 In a double-blind study, gypenosides administered to with Grade II hypertension showed 82% effectiveness in reducing hypertension, compared to 46% for ginseng and 93% for Indapamide (a hypertension medication).[106]

4.7.3 Cardiovascular functions: Animal studies as well as clinical testing on humans suggest that jiaogulan, when combined with other herbs, has beneficial effects on cardiovascular system, increasing heart stroke volume, coronary flow, and cardiac output while reducing the heart rate, without affecting arterial pressure.[107, 108]

4.7.4 The hot water extract of Gynostemma pentaphyllum was found to activate platelet

aggregation. However, the active principle was not elucidated.[109]

4.7.5 Gypenosides inhibited platelet aggregation in another study.[110]

4.7.6 In rabbits, crude gypenosides decreased heart rate, increased stroke volume, dilated blood vessels, and reduced blood pressure while slightly increasing cardiac output.[111]

4.7.7 Purified gypenosides 5 and 10 were found to lower systolic and diastolic blood pressure, decrease coronary, brain, and peripheral blood vessel resistance, raise coronary flow, and lower heart rate in dogs.[112]

4.7.8 Crude gypenosides protected against cerebral ischemic damage in a rabbit model.[113]

4.8 Antidiabetes activity:

4.8.1 Gynostemma pentaphyllum tea has been used in a Randomized Controlled Trial to treat type 2 diabetic patients.[114]

4.8.2 It has shown potential as a hypoglycemic treatment to reduce blood glucose.[115]

4.8.3 Extracts from *Gynostemma pentaphyllum* Makino (Cucurbitaceae), a Southeast Asian herb, has been reported to affect numerous activities resulting in antitumor, cholesterol-lowering, immunopotentiating, antioxidant, and hypoglycemic effects. We have isolated one active compound by ethanol extraction, distribution in *n*-butyl alcohol/water, solid phase extraction/separation, and several rounds of reverse phase high pressure liquid chromatography. We have shown by NMR and mass spectrometry that this active compound is a novel saponin, a gypenoside, which we have named phanoside (21-,23-epoxy-,3β-,20-,21-trihydroxydammar-24-ene-3-*O*-(α-d-rhamnopyranosyl(1→2).-β-d-glycopyranosyl(1→3).-β-d-lyxopyranoside)), with a molecular mass of 914.5 Da. Phanoside is a dammarane-type saponin, and four stereoisomers differing in configurations at positions 21 and 23 were identified, each of which were found to stimulate insulin release from isolated rat pancreatic islets. We have also found that the stereoisomers are interconvertible. Dose-dependent insulin-releasing activities at 3.3 and 16.7 mm glucose levels were determined for the racemic mixture containing all four stereoisomers. Phanoside at 500 μm stimulates insulin release *in vitro* 10-fold at 3.3 mm glucose and potentiates the release almost 4-fold at 16.7 mm glucose. At these glucose levels, 2 μm glibenclamide stimulates insulin release only 2-fold. Interestingly, β-cell sensitivity to phanoside is higher at 16.7 mm than at 3.3 mm glucose, although insulin responses were significantly increased by phanoside below 125 μm only at high glucose levels. Also when given orally to rats, phanoside (40 and 80 mg/ml) improved glucose tolerance and enhanced plasma insulin levels at hyperglycemia.[116]

4.8.4 The aim of the study was to investigate the antidiabetic effect of the traditional Vietnamese herb Gynostemma pentaphyllum in 24 drug-naïve type 2 diabetic patients. All patients were randomized to authenticated Gynostemma pentaphyllum tea or placebo tea, 6 g daily, during twelve weeks and received information regarding diet and exercise. Fasting plasma glucose, insulin levels, and glycosylated hemoglobin (HbA(1C)) were measured before, during, and after the treatment. Oral glucose tolerance tests were performed every four weeks. After 12-week treatment, fasting plasma glucose levels totally decreased to an extent of 3.0+/-1.8 mmol/l in the Gynostemma pentaphyllum tea group as compared to a decrease of 0.6+/-2.2 mmol/l in the control group ($p<0.01$). HbA(1C) levels after 12 weeks decreased approximately 2% units in the Gynostemma pentaphyllum group compared to 0.2% unit in the controls ($p<0.001$). Change in Homeostasis Model Assessment-Insulin Resistance between baseline and twelfth week indicated that insulin resistance decreased significantly in the Gynostemma pentaphyllum group (-2.1+/-3.0) compared with that (+1.1+/-3.3) in the control group ($p<0.05$). There were no hypoglycemias, or adverse effects regarding kidney and liver parameters or gastrointestinal function. In addition, lipid profiles, glucagon, cortisol levels, body measurements, and blood pressure were not different between the groups. This study shows a prompt improvement of glycemia and insulin sensitivity, and thereby provides a basis for a novel, effective, and safe approach, using Gynostemma pentaphyllum tea, to treat type 2 diabetic patients.[117]

4.8.5 This study was conducted to evaluate the antihyperglycemic effect of an extract of *Gynostemma pentaphyllum* Makino, containing standardized concentrations of gypenosides, in C57BL/KSJ-*db*/*db* mice. For 5 weeks, animals were provided a standard AIN-76 diet (normal control) with rosiglitazone (0.005%, wt/wt) or two different doses of *G. pentaphyllum* ethanol extract (GPE) of the plant leaves (0.0025% and 0.01%, wt/wt). After the experimental period, the blood glucose levels of the high-dose GPE- and rosiglitazone-supplemented groups were significantly lower than that of the control group. The plasma insulin concentrations of the GPE-supplemented mice were significantly elevated compared to the control group. The GPE and

rosiglitazone treatments profoundly affected the intraperitoneal insulin tolerance test compared to the control group, but not the intraperitoneal glucose tolerance test. In the evaluation of effects on hepatic glucose metabolism, the ratios of glucokinase/glucose-6-phosphatase activities in the high-dose GPE- and rosiglitazone-supplemented groups were prominently higher than that of the control group. The histology of the pancreatic islets revealed that the insulin-positive β-cell numbers were higher in the high-dose GPE- and rosiglitazone-supplemented groups than in the control group. These results suggest that the supplementation of high-dose GPE (0.01%) in the diet lowers the blood glucose level by altering the hepatic glucose metabolic enzyme activities.[118]

4.9 GIT and kidney protection:

4.9.1 In the present study, the phytoprotective effects of gypenosides from Gynostemma pentaphyllum throughout the gastrointestinal tract and kidney were examined in indomethacin-treated rats. Indomethacin induced gastric and intestinal damage as well as renal toxicity after a single toxicological dose (10 mg/kg) in rats. Acute oral administration of the gypenoside extract (200 mg/kg) significantly reduced gastric and intestinal toxicity induced by indomethacin as measured by ulceration, caecal haemoglobin and plasma haptoglobin. A significant decrease in small intestinal lactose fermenting enterobacteria was evident in animals treated with indomethacin and those pre-treated with G. pentaphyllum then indomethacin. In the renal system, kidney toxicity was evident after indomethacin and in animals pre-treated with indomethacin plus G. pentaphyllum with an increase in urinary N-acetyl-beta-glucosaminidase and a decrease in urinary sodium and chloride electrolyte output. However, a significant increase in urinary microprotein in indomethacin-treated animals was not present in indomethacin plus G. pentaphyllum-treated animals. These studies demonstrate the efficacy of Gynostemma pentaphyllum in lowering gastrointestinal damage induced by indomethacin. The results suggest further investigations of Gynostemma gypenosides are warranted to examine the mechanisms of this phytoprotective activity.[119]

4.9.2 GIT protection: Gynostemma pentaphyllum is an oriental medicinal herb reputed to have broad-spectrum activities. The plant's principal saponin components are structurally similar to those found in ginseng plants and this similarity is assumed to be responsible for the claimed activities. The present study was undertaken to evaluate a G. pentaphyllum butanol fraction (GPB) for its anti-gastric ulcer activity using experimental models. Oral administration of the GPB at 200 and 400 mg/kg body wt. significantly inhibited gastric ulcer formation induced by indomethacin, HCl/EtOH and water-immersion restraint stress in rats. In pylorus-ligated rats, pretreatment with the GPB had no effect on gastric volume, pH or acidity output, thus indicating a lack of anti-secretory effect. In ethanol-induced ulcerated rats, gastric wall mucus and hexosamine content were markedly preserved by GPB pretreatment. The findings indicate that the butanol fraction of G. pentaphyllum possesses gastroprotective potential related to the preservation of gastric mucus synthesis and secretion.[120]

4.9.3 Antigastric ulcer activity: *Gynostemma pentaphyllum* is an oriental medicinal herb reputed to have broad-spectrum activities. The plant's principal saponin components are structurally similar to those found in ginseng plants and this similarity is assumed to be responsible for the claimed activities. The present study was undertaken to evaluate a *G. pentaphyllum* butanol fraction (GPB) for its anti-gastric ulcer activity using experimental models. Oral administration of the GPB at 200 and 400 mg/kg body wt. significantly inhibited gastric ulcer formation induced by indomethacin, HCl/EtOH and water-immersion restraint stress in rats. In pylorus-ligated rats, pretreatment with the GPB had no effect on gastric volume, pH or acidity output, thus indicating a lack of anti-secretory effect. In ethanol-induced ulcerated rats, gastric wall mucus and hexosamine content were markedly preserved by GPB pretreatment. The findings indicate that the butanol fraction of *G. pentaphyllum* possesses gastroprotective potential related to the preservation of gastric mucus synthesis and secretion.[121]

4.10 Hepatoprotective activity:

4.10.1 Anoectochilus formosanus Hay and Gynostemma pentaphyllum Makino are popular folk medicines that have been used for treating hepatitis, hypertension and cancer in Taiwan. Our previous studies showed that these crude drugs exert antiinflammatory activity and hepatoprotective activity against CC14-induced liver damage. In this study, the antioxidant effect of these crude drugs and their hepatoprotective activity on acetaminophen-induced liver injury in rat was evaluated. Our results suggest that A. formosanus and G. pentaphyllum do have antioxidant effects. On acetaminophen-intoxicated model, the increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) by acetaminophen administration were reduced by treatment with these two herbs. In histological observation, gross necrosis in the centribular area, sinusoidal congestion, infiltration of the lymphocytes and

Kupffer cells around the hepatic central vein, and loss of cell boundaries and ballooning degeneration were reduced with herbal treatment. However, the effect of A. formosanus and G. pentaphyllum is biphasic. Methanol extract (100 and 300 mg/kg) and water extract (300 and 500 mg/kg) of A formosanus and water extract (100, 300 and 500 mg/kg) of G. pentaphyllum enhanced the recovery of liver injury while treatment with 500 mg/kg of A. formosanus methanol extract resulted in serious hepatic injury.[122]

4.10.2 Hepatoprotective and anticancer: Gynostemma pentaphyllum Makino is known in Asia for its effect on the treatment of hepatitis and cardiovascular diseases. Gypenosides (Gyp) are the major components extracted from Gynostemma pentaphyllum Makino. However, the molecular mechanism underlying the Gyp-induced cell cycle arrest and apoptotic process is unclear. In this study, the chemopreventive role of Gyp in human lung cancer (A549) cells in vitro was evaluated by studying the regulation of the cell cycle and apoptosis. Gyp induced GO/G1 arrest and apoptosis in the human lung cancer A549 cells. Investigation of the cyclin-dependent protein kinase inhibitors by Western blotting showed that p16, p21, p27 and p53 proteins were increased with the increasing time of incubation with Gyp in the A549 cells. This increase may be the major factor by which Gyp caused GO/G1 arrest in the examined cells. Flow cytometric assay and gel electrophoresis of DNA fragmentation also confirmed that Gyp induced apoptosis in the A549 cells. Our data demonstrated that Gyp-induced apoptotic cell death was accompanied by up-regulation of Bax, caspase-3 and caspase-9, but down-regulation of the Bcl-2 levels. Taken together, Gyp appears to exert its anticancer properties by inducing GO/GI-phase arrest and apoptosis via activation of caspase-3 in human lung A549 cancer cells.[123]

4.11 Bronchodilatory activity:

4.11.1 The bronchodilatory activity of the aqueous extract of Gynostemma pentaphyllum Makino leaves was investigated in anaesthetized guinea-pigs and compared with two of its isolated gypenosides (III and VIII). The results showed that the intravenous administration of the decoction of G. pentaphyllum (2.5, 5 or 10 mg kg(-1)) decreased bronchial resistance in basal conditions and significantly ($P < 0.01$) reduced (68% inhibition) the bronchoconstrictor action of histamine. Furthermore, the extract antagonized (80% inhibition) the bronchoconstrictor response induced by the antigen in sensitized guinea-pigs. Gypenosides III (0.7 mg kg(-1), i.v.) and VIII (0.3 mg kg(-1), i.v.) caused a similar protective effect in both experimental models used; however, the duration and the intensity of the action was less than that of the extract containing corresponding quantities of gypenosides III and VIII. This study confirmed the validity of the traditional use of this plant in the treatment of asthma and other respiratory disorders.[124]

4.12 Allergy asthma:

4.12.1 The increasing incidence of asthma in developing countries emphasizes the importance of identifying more effective treatments that have low cost. Gynostemma pentaphyllum (Thunb.) Makino (Cucurbitaceae), a common herbal tea in China, has been used to treat lung inflammation. Since the Th2 cytokines are the major mediators in the pathogenesis of asthma, Th1-biased immune responses caused by G. pentaphyllum might have the potential to relieve asthmatic symptoms. We hypothesized that oral administration of G. pentaphyllum extracts might suppress Th2 cytokine-induced airway inflammation responses in ovalbumin (OVA)-sensitive mice. BALB/c mice were sensitized with intraperitoneal injection and challenged 3 times with OVA inhalation (IH) (the IH3 model). G. pentaphyllum was orally administered for 7 consecutive days before the end of the OVA challenge. In the IH5 model, 2 more OVA challenges were administered to mimic the encounter with an allergen after drug treatment. G. pentaphyllum extracts significantly attenuated airway hyperresponsiveness (AHR) and inhibited eosinophil infiltration in mice in both models. Serum OVA-specific antibodies were also reduced with the treatment. Decreased Th2-type cytokines and increased IFN-gamma were detected in the cultures of OVA-activated splenocytes from treated mice. Our results suggest that G. pentaphyllum extracts might be beneficial for asthma airway inflammation through the suppression of Th2 activity.[125]

4.13 Exercise induced fatigue:

4.13.1 This study was designed to determine the effect of Gypenosides from *Gynostemma Pentaphyllum* (GGP) on exercise-induced fatigue in mice. Forty-eight mice were studied by being divided into three group (n = 16 per group) included the normal control group (NC), the low dose GGP group (LG) and the high dose GGP group (HG). The GGP groups were first administered different doses of GGP (50 and 100 mg/kg), while the NC group were force administered 1% arboxymethylcellulose for 28 days. The GGP groups showed a significant increase in swimming time to exhaustion as compared to the control group. Blood lactate concentration of the GGP groups was significantly lower and blood glucose concentration of the GGP groups was significantly higher than that in the NC group. In conclusion, GGP may have beneficial

effects on exercise-induced fatigue. GGP Supplementation can extend the swimming time for the mice, effectively delay the lowering of glucose in the blood, and prevent the increase in lactate.[126]

5. CONCLUSION: Jiaogulan (Gynostemma Pentaphyllum) is true Rasayan (Rejuvenator / Antiaging) herb as it is immunomodulator, adaptogen, antioxidant, anti-cancer, neuroprotective, nootropic and hepatoprotective. The only one Rasayan therapeutic activity about which we did not get research reference is aphrodisiac. As Jiaogulan

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