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PHARMACOLOGICAL ACTIONS OF *SINOMENIUM ACUTUM* : A BRIEF REVIEW

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Abstract

Sinomenine is an alkaloid, found in the roots of the *Sinomenium acutum*, which is a popular Chinese medicinal plant. It contains alkaloids, sterols, and phospholipids. Sinomenine have a great therapeutic benefit in rheumatic disease due to its analgesic, anti-arrhythmic and anti-inflammatory property. It is a morphinan derivative which is related to opioids such as levorphenol. It is reported to have activity against oligomeric Aβ protein, that support its neuroprotective potential, specifically to hippocampal cells. It also possesses anti-inflammatory effect against various neurological disorders. The current review mainly focuses on the action of sinomenine on immune system, cardiovascular system, and nervous system.

***Keywords*:** *Sinomenium acutum*, anti-inflammatory, sinomenine, neurologic disorders

Introduction

Sinomenium acutum was first recorded as a herbal medicine in Japan. Its main pharmacological actions are immunosuppression, arthritis amelioration, anti-inflammation, and protection against hepatitis induced by lipopolysaccharide (LPS). The plant was traditionally used in herbal medicine in Japan and China for rheumatism and arthritis. Sinomenine (SN) is the main alkaloid found in this plant. The main action of SN is neuroprotection, which has been demonstrated in brain injury models (Nishida and Satoh, 2006). Its anti-rheumatic effect was thought to be primarily mediated via release of histamine, but other effects such as inhibition of prostaglandin, leukotriene and nitric oxide synthesis may also be involved (Yang and Yang, 2003). It increases the chloride influx in the primary cultured hypothalamic neuronal cells. SN is a morphinan derivative, related to opioids such as levorphanol and the non-opioid cough suppressant dextromethorphan (Liu *et al.*, 2006). SN is mainly used for the clinical treatment of Rheumatoid arthritis (RA), due to its anti-inflammatory and immunomodulative actions (Liu *et al.*, 1994; Wang *et al.*, 2003; Wang *et al.*, 2004).

Climbing plant *Sinomenium acutum*

It impairs signalling through nuclear factor-kappaB (NF-b) (Sun *et al.*, 2009) and enhances the bioavailability of some compounds, at least in part through an inhibition of drug export by transporters like P-glycoprotein (Liu *et al.*, 2006; Kok *et al.*, 2005). SN inhibits the activity and production of Tumor necrosis factor-alpha and Necrosis factor-kappa. It suppresses adhesion, implantation, infiltration and growth of endometrial cells in the rat model of endometriosis. SN reduced the number of sleep wake cycles, and increased total sleep time and non-rapid eye movement (NREM) sleep. The Chinese medicinal herb *Sinomenium acutum*, is mainly used in china for the clinical treatment of rheumatoid arthritis and mesangial proliferative nephritis (Xu *et al.*, 2008; Cheng, 1982). It exerts neuroprotection in several CNS disease models, including cerebral ischemia (Kok *et al.*, 2005; Wang *et al.*, 2008) and intracerebral haemorrhage.

Chemical constituents

The chemical research has been conducted which lays the foundation for the pharmacological research. In previous phytochemical studies demonstrate that *Sinomenium acutum* contains alkaloids, sterols and lipids.

Many alkaloids such as SN, disinoimenine, sinactine, sinoactine, acutumine, and magnoflorine, as well as the lignin syringaresinol have been isolated from *Sinomenium acutum* (Wang *et al.*, 2007; Zhou *et al.*, 2008; Chang *et al.*, 1960). Among them, SN has been reported to have a variety of pharmacological effects including anti-rheumatism, immunomodulation and sedative effects (Ansari *et al.*, 2006; Zhou *et al.*, 2008). Recently, it was reported that *Sinomenium acutum*, has sedative and anxiolytic effects mediated by GABA-ergic systems. In addition, they reported that SN exerts considerable antinociceptive property for neuropathic pain via GABA-mediated mechanism, and it could be useful for the management of chronic painful conditions such as neuropathic pain (Min *et al.*, 2006). Based on previous studies, we focused on the hypnotic effect of SN as the ultimate goal of the experiment. We investigated the effects of different dosages of SN and muscimol in rodents with pentobarbital treatment and found that SN enhanced

pentobarbital induced sleep, similar to muscimol. It is suggested that potentiation of SN hypnotic effect can interact with GABA-ergic systems.

Many sterols and lipids such as paltimate, daucosterol, β-sitosterol, stigmasterol, aquilegiolide, aquilegiolide, syringaresinol, 3-methoxy-6-hydroxy-17-methylmorphinane, syringin1, 1,2,4/3, 5-cyclohexanepento have been isolated from *Sinomenium acutum* (Song *et al.*, 2007; Ban *et al.*, 2008; Li *et al.*, 2005).

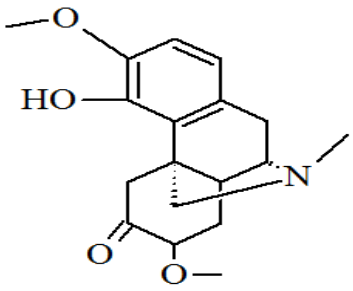

Fig. 1 : The structure of Sinomenine

Pharmacological actions of *Sinomenium acutum*

Effects on the CVS:

Effects on decompression : In the previous investigation they demonstrate that total alkali of *Sinomenium acutum* but also that SN has antianginal effects on decompression. If administered by I.V injection or oral route , application of the total alkaloid from *Sinomenium acutum* shows hypotensive effects in normal rodents, anesthesia cats and chronic renal hypertension dogs. Markedly, SN inhibits vascular smooth muscle cell proliferation and DNA synthesis in the dose-dependent manner (Mark *et al.*, 2006). In combination SN with low-dose, they targeted immunosupression T cell, associated with inhibition of intragraft expression of mediators involved in angiogenesis, vascular tone and remodeling of tissue (Nishida and Satoh, 2006). The mechanism action SN in the effect of decompression is caused vasorelaxation, which inhibitions of Ca^{2+} channel and K^+ channel activity and the activation of sodium oxide and prostaglandin synthesis in endothelium (Lee *et al.*, 2007). The vasorelaxation is also related to decreasing of Ca^{2+} caused by opening of ATP-sensitive K^+ channels (Sun *et al.*, 2009)

Effects on arrhythmia : The constituent of *Sinomenium acutum*, SN shows significant antagonism against arrhythmia induced by various experimental factors. The main action of SN in CVS, shorten the arrhythmia period, which induced by picrotoxin in rabbit and protect rodents against arrhythmia induced by $BaCl_2$. SN is used to recover the arrhythmia induced by $BaCl_2$. In addition, SN also revealed significant antagonism against ischemic arrhythmia (Huang *et al.*, 2000).

Effects on the nervous system

Effects on the central nervous system : Its proved that, SN have analgesic, sedative and anxiolytic effects since the 1960_s. The method is used, such as body-torison, hot-plate method, or electrical stimulation procedure. SN showed analgesic effects on laboratory mice. The mechanism action of SN in the nervous sytem, inhibit the synthesis and release PGE. SN can increase the mouse pain threshold induced by hot plate or electrical stimulation of the toes, and reduce the writhing times caused by glacial acetic acid.

Effects on neurotransmitters : SN has positive effects on morphine-dependent rodents, which relevant to monoamines neurotransmitters regulation disorders. If there increasing the doses of morphine in rats, will produce a physical dependence. SN can inhibit the withdrawal contracture of *in vitro* ileum from morphine-dependent guinea pigs (Li *et al.*, 2004) and has an effect on the NO/nNos system in the cerebellum and spinal cord, which may contribute to its alleviation of morphine-withdrawal symptoms (Dai *et al.*, 2008). SN action on the morphine dependent mice (Zhang *et al.*, 2009). Extracts of alcohol from the *Sinomenium acutum* and SN decrease the concenteration of neurotransmitters. Its elevate the intracellular calcium level and inhibit the decrease of Ca^{2+} induced by naloxonel (Lao *et al.*, 2000).

Effects on the immune system

SN can inhibit the proliferation of mouse lymphocytes induced by LPS *in vitro*. It reduce up-regulated CD^{4+}/CD^{8+} ratio of T lymphocyte subtype in adjuvant arthritis rat. In the same concenteration, they increased apoptosis ratio. It inhibit the immunological function and correct the imbalance of CD^{4+}/CD^{8+} ratio of T lymphocyte.

Effects on mononuclear cells : SN is the component of the plant, which has been used to treatment of autoimmune diseases, like rheumatoid arthritis. The therapeutic effect which are related to its impact on peripheral blood mononuclear cells. SNcan decrease the gene expression of IL-1β, IL-8 cytokines of peripheral blood mononuclear cells (Wang *et al.*, 2003). SN can reduce prostaglandin production in LPS stimulated human monocytes. Non stimulated human monocytes suggesting, SN inhibits the activity of (COX-2), which related to suppressing cyclooxygenase activity (Zhou *et al.*, 2009). SN observed to enhance the phagocytosis ability of macrophage through downregulating the expression of IL-6 and TNF-α in macrophages (Wang *et al.*, 2004).

Effect on T cells : T cells is effector cell, which regulate the immune responses, it also plays a important role in the pathogenesis of autoimmune diseases. An immunosuppressive role in rat renal allograft models through inhibiting CD^{4+} T-cell proliferation and down regulating the levels of INF-γ, TNF-α (Lao *et al.*, 2000; Chen *et al.*, 2008). SN which suppress the activation and proliferation of T lymphocytes blocking the cells at G0/G1 phase. Transferring receptor of T lymphocyte and the decrease of intake of iron by the cells (Cui *et al.*, 2009). SN has the potential counter the shift in the Th1/Th2 balance and thereby produces therapeutic effects on mesangial proliferative nephritis (Zhao *et al.*, 2007).

Effects on dendritic cells : Dendritic cells are the most powerful antigen presenting cells, which have completely effects on the immune system. SN inhibits the antigen presenting function of dendritic cell by decreasing their nuclear factor-κB activity involved in their maturation cascade and T-cell activation (Zhao *et al.*, 2009). SN can regulate the host immunological status by preventing the maturity of dendritic cells, which inhibit the activity of its presentation, and suppressing the secretion of its cytokine (Yu *et al.*, 2009). The mRNA and protein expressions of CCR5 and CCR7 on the surface of the dendritic cells and also decreased by SN. Similar results are observed in the expression of CXCL9 (MIG) and CXCL10 (IP-10), but not in CXC11 (Zhao *et al.*, 2006).

Effects on cytokines : In addition, SN suppresses the production of proinflammatory cytokines IL-1*β* and IL-6 in serum, inhibits protein expression and activities of MMP-2 and MMP-9, and elevates protein expression and activities of TIMP-1 and TIMP-3 in rat paw tissues (Our *et al*., 2009). The levels of CD147, MMP-2, and MMP-9 of A-THP-1 cells are markedly downregulated at the most notable concentrations of 0.25 mmol/L and 1.00 mmol/L of SN (Huang *et al.*, 2002). These results suggest a possible mechanism of the inhibitory effect of SN on cell invasion and migration ability. Recent study shows that SN can suppress IL-1*β*-induced mRNA and protein expressions of MMP-1, MMP-3, MMP-9, and MMP-13 in SW1353 cells and human osteoarthritic (OA) chondrocytes (Tranter *et al.*, 2008), suggesting that SN may act as an agent for pharmacological intervention in the process of OA. Heme oxygenase-1 (HO-1), a rate-limiting enzyme that oxidizes heme to biliverdin and carbon monoxide, has been proved to have anti-inflammatory properties in multiple inflammatory responses investigated the effect of SN on HO-1 induction and its hepatocellular protective effect (Song *et al*., 2009; Qian *et al*., 2007). The result showed that SN pretreatment is able to induce HO-1 expression in donor livers in a dose-dependent manner. The research on the effects of SN on the bone marrow-derived mast cell (BMMC) by reveals that SN inhibits the PMA plus A23187- induced production of IL-6, PGD(2), LTC4, *β*-Hex, and COX-2 protein indicating its potential for the treatment of allergy (Kubto *et al.*, 2001; Li *et al.*, 2003).

Effect on renal tubular epithelial cells

SN has potent immune regulatory properties. The mechanism action in renal tubular epithelial cells of SN is increase the recognition of the importance of renal tubular epithelial cells, in which they regulate the activity of tubular epithelial cells. In epithelial cells, raised the amount of urine which indicate infection or other health condition (Baron *et al*., 2002). If epithelial cells are increased in urine from the bladder and external urethra, they normally present in urine in small amount. The amount of epithelial cells in urine increases when someone has urinary tract infection or some other cause of inflammation (Bains *et al.*, 2012). Normal rat kidney proximal tubule epithelial cell cultures were obtained by collagenase digestion of cortex and studied for 10 days (Chan *et al.*, 2006). To assess the purity of the seeding suspension, histochemically demonstrated gamma-glutamyltranspeptidase in greater than 95% of the starting material. To identify cell types in cultures, we investigated several markers. Cells stained positively for lectin Arachishypogaea (rat proximal tubule) and negatively for Lotus tetragonolobus (rat distal tubule) (Chen *et al.*, 2005). Cells exhibited activities of two brush border enzymes, gamma-glutamyltranspeptidase and leucine aminopeptidase, and Na^+ dependent glucose transport activity. Multicellular domes were evident in the Week 2 of culture. Proliferation was studied by comparing growth factor-supplemented serum-free medium to cells grown in serum; growth enhancers included insulin, hydrocortisone, transferrin, glucose, bovine albumin, and epidermal growth factor (Johnson *et al.*, 2005). Cells proliferate best in medium with 5 or 10% serum and in serum-free medium supplemented with insulin, hydrocortisone, transferrin, glucose, and bovine albumin. By light microscopy, the cells were squamous with numerous mitochondria, a central nucleus, and a rather well-defined homogeneous ectoplasm. By electron microscopy, the cells were polarized with microvilli and cell junctions at the upper surface and a thin basal lamina toward the culture dish (Kato *et al.*, 2009). These data show that the proximal tubule epithelial cells retain a number of functional characteristics and that they represent an excellent model for studies of normal and abnormal biology of the renal proximal tubule epithelium (Wang *et al.*, 2008).

Effect on Ischaemic brain injury

Ischaemic brain injury is one of the leading causes of death and adult disability due to its high mortality rate in many countries. Calcium homeostasis may trigger different signalling pathways for cell death and they play critical role in ischaemic brain injury (Wang *et al.*, 2009; Waxham *et al.*, 1996). In ischaemic brain injury, they decreased brain infarction and theoveractivation of calcium-mediated events in rats subjected to 2 h ischaemia followed by 24 h reperfusion. Neuronal injury which are dependent on calcium is often thought to be related to ischaemic insults, including extracellular acidosis (Werling *et al.*, 2007; Zheng *et al.*, 2007; Zhen *et al.*, 2009). SN which has extracellular application, they inhibited the currents mediated by acid-sensing ion channel 1a and L-type voltage-gated calcium channels, in the rat cultured neurons, in a concenteration-dependent manner. Bioactive components from medicinal plants which exhibit particular anti-inflammation properties and to show neuroprotection against cerebral ischaemia; these include baicalein, tetrahydroxystilbeneglucoside and theaflavin (Zeng *et al.*, 2007; Wang *et al.*, 2006).

Effects on ankylosing spondylitis

Ankylosing spondylitis (AS), a common and unexplained chronic inflammatory-based autoimmune disease, is characterized by ankylosis, new bone formation, and inflammation of sacroiliac joints, hip, and spine (Wang *et al.*, 2006). The pathogenesis of AS is not yet completely clear and involves a variety of factors. SN treatment reduced the level of TNF-α, IL-1β, and IL-6 in a dose-dependent manner, and the levels of SOD, CAT, and GSH-PX were dose-dependent (Xu *et al.*, 2007). Many studies have shown that cytokine network abnormality is an important feature of AS pathology. The occurrence of AS is insidious and progressive, and the major clinical manifestations of the early stage are joint pain without apparent cause, which is easily ignored by patients, leading to missed diagnosis and delay in treatment. Advanced AS may lead to spinal deformity, loss of ability to work, and disability, seriously affecting the quality of life. The prevalence of AS in China is about 0.20% to 0.40%. Almost 80% of AS patients are young adults, and 5 years after diagnosis the disability rate reaches 40% to 60%. At present, there is no effective treatment for AS. SN has a beneficial role in AS through suppressing inflammatory mediators and by down-regulating oxidative stress via inhibiting the MAPKp38/NF-κB pathway and Cox-2 expression (Xu *et al.*, 2008).

Conclusion

The SA has been utilized to prevent and treat various diseases especially RA in Chinese medicine for over hundreds of years. SN, a natural compound from SA has shown the immunosuppressive, analgesic, sedative, and anxiolytic-like effects. With relatively few side effects and favourable therapeutical effects, SA has been used in the

treatment of RA, glomerular diseases, and ventricular arrhythmia in clinical trials. However, further studies are required for SA development. Although there are many investigations on SN, other known numerous compounds hardly investigate on their pharmacological effects and clinical applications. Moreover, toxicological data are imperfect, which has an adverse effect on the clinical applications of SA. Many of studies have suggested the potential to be an effective herbal remedy of SA. The investigations about the effects of SA on the immune system, cardiovascular system, and nervous system bring great benefits to human health. Nonetheless, the authors are looking forward to seeing further research of this extremely potential therapeutic agent.

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