Utilization of Polislidae Wasp Venom as Potential New Insect Drugs in the R&D of Wellness Industry

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Abstract: The Polislidae wasp, one species of omnivorous social insects mainly living in the bush or under the leaves. The wasp has a venom sac in its tail, and the venom secreted by a sting can cause a series of body reactions and diseases. Multiple organ failure could be the outcome of wasp sting, if timely treatment or rescue has not been performed. Based on published reports on wasp sting related to medical concerns in recent years, this review summarizes the symptoms caused by wasp sting and corresponding mechanisms of actions. The medical application and relational utilization of the title insect is suggested derived from findings of the systematic review. Furthermore, we herewith sketch the perspectives of R&D on the venom of Polislidae wasp. It is expected to afford comprehensive references and be useful for broader study on the natural components and pharmacological effects of wasp venom.

Keywords: Polislidae wasp, wasp sting, clinical symptoms, insect drug, peptides, wasp venom.

1. INTRODUCTION

The Polislidae wasp is a kind of insects belonging to Polislidae, in Vespoidea, Hymenoptera. These rapidly flying social insects are ferocious predators and widely distributed in the world. Usually, they choose to build nests in the leafy bushes or under the eaves of human habitation. Polislidae wasp is rather aggressive and will attack any vulnerable animals approaching their hives. Untimely treatment after been stung can trigger the syndromes of pain, edema, local damage of the body and even death. The incidence of accidents and injuries caused by wasp stings is relatively high in China, due to the wide distribution of more than 20 species of Polislidae wasps scattered in the country [1,2]. In despite of the harmful results of wasp stings, wasp venom might merit further investigation and development as novel insect drugs according to the positive application of wasp venom’s pharmacological effects. However, comprehensive analysis concerning the comparisons among various clinical studies, reports of the pathogenic mechanisms, and the applicable clinical treatments are still missing. The aim of this work is to review the recently published papers regarding wasp venom and stings including many case report, with attempt to provide fundamental information and useful references for further research on venom constituents of Polislidae wasp and its pharmacological effects.

2. VENOM COMPOSITION AND PHARMACOLOGICAL EFFECTS OF POLISLIDA WASP

2.1. The Composition of Polislidae Wasp Venom

The wasp venom is a complex mixture of high degrees of physiological and pharmacological activities. Liang et al. found that fresh venom from Polistes olivaceus exhibited somewhat acidic with a pH value range from 6.0–6.5, which contains hyaluronic acid enzyme, cholinesterase, proteolytic enzymes, DNA enzymes, acid phosphatase, and alkaline phosphatase [3]. Murata et al. reported identification of four new peptides from Polistes rothneyi iwatai venom, which named Polistes-protonectin and Polistes-mastoparan-R1, 2, 3. Among them, Polistes-protonectin exhibited significant hemolytic activity while Polistes-mastoparan-R1, 2, 3 can induce the release of histamine which further led to occurrence of inflammation [4].

2.2. The Pharmacological Effects of Polislidae Wasp Venom

It is well known that melittin, the main component of the bee venom own certain efficacies such as anti-inflammatory, anti-bacterial, anti-tumor, and may also be used on the treatment of rheumatoid arthritis [5,6]. Furthermore, the Vespidae wasp venom peptide were reported to be composed of activated G protein, phosphatidic acid A2, and many other compounds, which exhibited a variety of biological functions such as to change the intracellular and extracellular concentration of Ca2+, to induce platelet aggregation, and to promote insulin secretion and corticotropin-
releasing [7]. However, though both Polisilidae wasp and Vespidae wasp belong to Vespoidea, the pharmacological studies on Polisilidae wasp venom are only at the very preliminary stage of exploration, which are comparable with the investigations upon Vespidae wasp venom.

2.2.1. Hemolytic Effect

Polisilidae wasp venom possesses a strong hemolytic activity with the HU$_{50}$ value of 17 $\mu$g/mL. Among the venom components, Phospholipase A$_2$ did not directly act on the cell wall lipids, but rely on the synergy of melittin. Another hemolytic mechanism maybe the Phospholipase A$_2$ form a complex with the substrate, while the combined-substrate approach to the cell while lying the membrane resulting in hemolysis. However, heparin may to some extent inhibit the hemolytic activity of on the venom of Polisilidae wasp [8].

2.2.2. Nerves and Muscle Tension

Crude Polisilidae wasp venom can completely block the nerve impulse transmission at the mice phrenic nerve-diaphragmatic muscle joint. The blocking effect is nearly irreversible, and the blocking of the phrenic nerve-diaphragmatic muscle nerve impulses passes prior to the blocking of diaphragmatic muscle contraction. A trace amount of crude Polisilidae wasp venom of $1 \times 10^{-4}$ g/mL can significantly inhibit the myocardial contractility of the ex-vivo heart of toad, while adding atropine may relieve the inhibition [3].

2.2.3. Anti-Tumor Effects

Sun et al. found that Polisilidae wasp venom exhibit clear cytotoxicity against S180 mouse sarcoma cells, and the cytotoxicity is dose-dependent and time-dependent. 1 mg/mL of the venom may 100% kill the S180 cells in half an hour. The possible mechanism might be the venom inhibiting the cell division thus prevented the tumor cells from replication [9]. Moreover, after treatment of the S180 tumor cells with Polisilidae wasp venom before inoculation to mice, the tumorigenic effect of the cells was lost. More interestingly, even a very low concentration (0.01 mg/mL) of venom treatment of tumor cells can significantly prolong the survival date of S180 tumor-bearing mice.

2.3. TOXICITY

The toxicity of Polisilidae wasp venom collected from Polistes olivaceus upon an insect model, Periplaneta americana was measured, and the LD$_{50}$ value is 7.45 $\mu$g/g, which is more toxic than the venom collected from Selenocosmia huwena (LD$_{50}$ value is 300 $\mu$g/g), and the LD$_{50}$ of the venom from Polistes olivaceus on mice was 5.54 mg/kg [3], which exhibited less toxic than the poison of Selenocosmia huwena (LD$_{50}$ = 1.16 mg/kg) [10], but more toxic than that of the centipede poison (LD$_{50}$ = 22.5 mg/kg) [11]. Schmidt et al. also reported the mild LD$_{50}$ values of Polistes rothneyi and P. olivaceus as 14.5 and 11.2 mg/kg on mice, respectively [12]. Furthermore, they indicated the Polisilidae wasp venom exhibited weak damaging potential to blood cells and low influences on phospholipase. Therefore, they indicated that these two venoms merit further pharmacological and medicinal analysis.

3. CLINICAL SYMPTOMS AFTER POLISLIDAE WASP STING AND CORRESPONDING TREATMENTS

3.1. Circulatory System

Zhu analyzed 53 cases of toxicosis caused by Polisilidae wasp sting and found that: The sting sites of the patients were redness, pain, heart palpitations. The examination revealed arrhythmia, myocardial enzymes mildly abnormal. Generally treatment of Polisilidae wasp sting is local irrigation using 5% sodium bicarbonate solution, iodine alcohol disinfection, and intravenous methylprednisolone sodium succinate. Most of the patients were recovered in three to five days. For those patient accompanied by occurrence of toxic myocarditis or neurological symptoms, bicarbonate dialysis is needed to perform once every other day, each time for four hours [13]. Another report concerning an Indian patient was the first case of delayed onset of Kounis syndrome following wasp sting, while the patient occurred simultaneously renal and cardiac complications of wasp bite together with the appearance of systemic multiple significant jaundice and pedal edema [14]. After received the treatment of injection of amiodarone and hemodialysis treatment for two months, the patient made full recovery from both the renal and cardiac toxicity.

3.2. Nervous System

3.2.1. Peripheral Nervous System

Báňovčin et al. reported the serious local reactions of a 10-years-old patient who was stung by wasp [15], the patient was given antihistamine therapy but found upper limb weakness, difficulty with walking after 28 h,
and continuous mild headache. After 32 h of stung the right-hand allergic swelling and the right lower extremity paresis, accompanied by fever, but with clear minds. Then sphincter disturbances lead to urinary incontinence while dexamethasone was given intravenously. After 72 h patient head and limbs were improved with the state of motion, mild headache completely disappeared [15]. Another two-years-old female patient was immediately given dexamethasone intravenous treatment after stung by wasp. After 12 h the patient exhibited orbital edema, and gradually extended to the whole body, accompany with the decreased urine output, and difficulty in breathing. Medical examination revealed the blood urea nitrogen, creatinine, creatine phosphokinase levels were increased. Hospitalized ten days, the patient suddenly suffered from serious ptosis and can not open her eyes, neostigmine and other acetylcholine receptor antibodies treatment were negative. Oral pyridostigmine treatment at 7 mg/kg/d giving pyridostigmine for eight weeks finally eliminated the symptoms [16].

3.2.2. Central Nervous System

Yang and Li reported one case of a 62-year-old patient was stung by Polisidae wasp and suffered from left limb weakness, unable to lift his left shoulder and left leg, and accompanied by left lower extremity pitting edema. B-ultrasound showed the presence of small amount of effusion in bilateral pleural and peritoneal. Head magnetic resonance imaging scan indicated that the right frontal and parietal cerebral infarction with a small amount of bleeding. The patient was diagnosed as hemorrhagic infarction and acute renal failure. The treatment was adopted to improve cerebral circulation, giving anti-infection, protecting liver functionality, and hemodialysis treatment. But the symptoms did not improving significantly and consciousness was lethargy liking after 2 weeks treatment [17]. Another symptoms of a clinical lacunar infarction patient arose from
Polisidae wasp sting was similar, electrocardiogram showed appearance of sinus rhythm, left ventricular surface of high voltage, the head CT showed the left internal capsule hind legs to see punctate hypodense lesions with a fuzzy boundary. The patient was orally taken “Yin Dang Xin Nao Tong” capsules and nifedipine after admission, giving defibrase brain protein hydrolyzate and pantoprazole to intravenous infusion, and using “Bu Yang Huan Wu Decoction” as complementary treatment. Three days later the patient was improved and discharged [18]. Crawley et al. reported that wasp stings patients displayed cerebral edema, encephalitis, cerebral infarction [19] while Sachdev et al. described that other symptoms appeared generally after stung for 30–96 h [20].

3.3. Digestive System

Tan and Wei reported a 1.5-year-old patient stung by the Polisidae wasp and induced toxic hepatitis symptom. The patient appeared local congestion and necrosis at the stung site. Next day symptom such as body skin and sclera stained yellow, dark yellow urine, decreased urine output, liver enlargement were appeared, no fever or vomiting. Clinical examination revealed total bilirubin was high, but hepatitis B and hepatitis C virus were negative, heart, lungs and nervous system was normal. After hepatoprotective, antiviral therapy treatment the patient’s jaundice significantly reduced, together with liver narrow, and the rest of the index close to normal [21]. Qiu et al. recorded two male cases of wasp-sting-induced multiple organ dysfunction and acute pancreatitis. The patients’ systemic multiple were stung, and successively symptom such as nausea, vomiting, oliguria, mild skin stained yellow were appeared, while lung breathe sounds and heart are normal. B-ultrasound showed that the gallbladder wall edema, liver and pancreas grow up in the patients. Give regular fasting, water deprivation, lifted spasm, analgesia, acid suppression, inhibition of pancreatic secretion, while rehydration to correct electrolyte and acid-base balance disorders. After treatment the acute pancreatitis symptoms was eliminated, and serum amylase returned to normal [22].

3.4. Urinary System

Cheng reported a case of acute renal failure arose from wasp sting happened to a 6-year-old patient. Edema appeared in a large area in the head, face and limbs of the patient, accompanied by the situation of lethargy, breathe difficulty, dark brown urine, percussion pain at the bilateral renal area. Routine urinalysis found Pro++, BLD++, BIL+, URO+. Immediate treatments such as peritoneal dialysis, blood dialysis, anti-inflammatory, and liver-protecting therapy were performed. The symptoms will eliminate after one month while the biochemical indices become normal [23]. D’Cruz described another patient was stung by wasp and associated with type 1 renal tubular acidosis [24]. After 9 h of stung, sudden onset weakness was happened, but no vomiting, rash and other symptoms could be seen. Intravenous chlorpheniramine and hydrocortisone treatment were given. Ammonium chloride test suggested the diagnosis of type I (distal) RTA. Furthermore, the metabolic acidosis was indicated by arterial blood gas analysis. Giving of potassium chloride and sodium bicarbonate therapy led to the attenuation of the symptoms [24]. Zhang and Chen recorded a 31-year-old male case being stung by Polisidae wasp which demonstrated oliguria and gross hematuria [25]. Biochemical check found that the patient’s serum K+ was significantly higher than normal, but blood pressure and heart rate were normal, no pathological murmur could be traced. ECG showed sinus rhythm, T-wave tip. After diuresis, hemodialysis treatments for one week the serum indicators and ECG T-wave returned to normal [25].

3.5. Immune System

Qu et al. recorded an anaphylactic shock case arose by Polisidae wasp sting. The 21-years-old male patient was stung at the head and immediately felt the symptoms of wound swelling, pain, blurred vision, palpitation, chest tightness, dizziness, sweating and fainting [26]. Medical analysis indicated his heart and liver function was normal. Giving epinephrine and promethazine intramuscular injection, intravenous infusion of dexamethasone, breath oxygen, the patient gradually awake and blood pressure returned to normal one hour latter [26]. Cai et al. described a case of immune hemolytic anemia resulting from Polisidae wasp sting. The 54-year-old male patient found oliguria and edema soon after been stung, and dark brown urine appeared at the 3rd day and less than 100 mL/day, accompanied by frequent nausea, vomiting, stool black, yellow sclera, lung breath sounds rough, whole abdominal tenderness, and percussion pain in kidney area. Examination revealed that the concentrations of hemoglobin, white blood cell count, and platelet counts were all lower than normal, reticulocytes 16.9%, while no red blood cell fragments was found. Routine urine examination found that direct
anti-human globulin is ++++, and indirect anti-human globulin is negative. The immunoglobulin in the normal range. Giving dexamethasone intravenous infusion once a day, while oral administration of sodium bicarbonate to alkalization of urine, use anisodous choline and prostaglandin E1 to improve microcirculation, together with the hepatoprotective and anti-infectious therapy. Following reexaminations found that the direct anti-human globulin decreased from +++ to ++ in 92 d, while to normal after 5 months [27].

3.6. Other Injuries

3.6.1. Corneal Injury

Li et al. mentioned a 28-year-old female case of corneal injury by Polislidae wasp sting. The patient was stung at left eye and immediately feel itching, blurred vision, photophobia, tearing, decreased visual acuity. After 4 d, the patient was found injured eye corneal edema, opacification, the real layer of gray muddy, normal anterior chamber depth, room observant and pupil shoen, light reflex is sensitive, eyes as clear diagnosis of keratitis. After intravenous antibiotics, oral administration of vitamin C, local subconjunctival injection of tobramycin, using tarivid eye drops water combination therapy the prognosis is better [28].

Moreover, Li et al. reported another 15-year-old female case being stung by for one month, they found the anterior chamber depth of the patient is middle, aqueous unclear, the pupil extremely dilated, less round, lens turbid white, the rest of the eye invisible. This case lack of timely treatment was finally diagnosed as secondary glaucoma and traumatic cataract [29].

3.6.2. Multiple Organ Dysfunction Syndromes (MODS)

Fan and Zhou analyzed 12 cases suffered from Polislidae wasp sting. After been stung the patients exhibited skin irritation, local wound purulent secretions, difficulty breathing, unconsciousness, oliguria, gross hematuria and melena. Checking liver function, renal function, myocardial enzymes and electrolytes disclosed that all these indices of patients were abnormal. All of the 12 cases were found accompanied with acute renal failure and MODS [30]. Furthermore, Yang analyzed 14 cases of Polislidae wasp sting patients and compared the different efficacies of the treatments. The author summarized the effective therapy is timely treatment hemodialysis once a day to correct the acidosis and electrolyte imbalance, intravenous infusion methylprednisolone of 1 or 2 times per day, intravenous infusion alprostadil, give glutathione reductase and omeprazole once per day. For infection patient used third generation of cephalosporin antibiotics in the anti-inflammatory treatment [31]. MODS is difficult to deal with, while clinicians should provide timely and symptomatic treatment base on the patient’s body condition and symptoms appeared. The four death cases in these two literature died of respiratory failure and ventricular arrhythmias caused by pump failure.

3.6.3. The Effect of Tumorigenic

Yang and Si mentioned a patient suffered from Polislidae wasp stung at the right earlobe four years ago, after being stung, the lump gradually grew up, anti-infective therapy failed to exhibit efficacy. The lump owns smooth surface and tough, no tenderness, no adhesion to the surface of the skin, patient can open mouth unlimited, no special exception, around the lump is not palpable lymph nodes. It is diagnosed the right parotid gland adenoma, while the pathological diagnosis indicated the presence of right parotid gland schwannoma with cystic degeneration. Surgical treatment easily removed this tumor [32]. This research was to some extent in agreement with other previously published work which found that the Polislidae wasp toxin induced pseudolymphoma by Sandbank et al. [33].

3.6.4. Limb Compartment Syndrome

Normally, the compartment syndrome of the hand is usually the result of trauma or burns happened to an uncommon entity in children. However, Sawyer et al. described the first case of a 5-year-old boy who developed a compartment syndrome of the hand after a single wasp sting that required emergent fasciotomy. After treatment, the patient healed uneventfully while at 5-month follow-up had full use of his hand, full range of motion, and normal 2-point discrimination in all the fingers [34].

4. WASP BITES AND MECHANISM OF ACTION

4.1. The Advantages and Disadvantages of the Polislidae Wasp

China is carrying out large-scale defarming-and-reafforestation project. With the progress of returning farmland to forest and ecological environment gradually improved, the events of wasp sting happened more frequently [2]. In city, firefighters often take actions in response to the residents’ request to destroy the invading wasps. However, to protect the biodiversity in
China and to keep the ecological balance, more nestles of wasps have been moved to the mountains or in the fields, while these wasp species demonstrated excellent predators to control pests. For example, feeding wasp in cotton fields suffered from serious pest in Hunan, and Jiangsu provinces of central China led to successfully bio-control of the pests [35].

4.2. Timely Processing of Polisilidae Wasp Bites

According to previously published research [2, 13-34], the dangers of wasp bites to human bodies demonstrated in various aspects. The local reaction exhibited as swelling and pain by wasp sting, whilst the influence to body exhibited mainly as arrhythmia, liver dysfunction, kidney dysfunction, anaphylactic shock, neuromuscular and movement disorders. Furthermore, we also noticed that the injured degrees of toxic reaction and allergic reaction are also quite different after getting stung of the victims because of their various physical status and different constitutions. Therefore, the patients being bitten should promptly go to hospital, while focusing on examination of functionalities of liver, renal, myocardial enzymes, and check of blood, etc. Especially, to those patients who are stung in a large area must subjected to protective treatments upon their heart, liver and kidney, to avoid the occurrences of a toxic reaction, organ damage, or MOSD caused by wasp venom entering into human body due to the delayed treatment.

4.3. Pharmacological Mechanisms of Polisilidae Wasp Bites Applicable to the Development of Insect Drugs

Though Polisilidae wasp sting is somewhat dangerous and sometimes fatal, for the local residents in southwestern China especially in Yunnan province, Polisilidae wasp has nevertheless been used historically as an alternative drug on treatment of rheumatic diseases [36]. Moreover, modern medical studies also have found that though bee venom also affects nervous system, cardiovascular system, respiratory system, endocrine system, immune function, inflammation, and other pathological processes, small doses of bee venom (such as bee sting) exhibited satisfactory effects on the treatment for certain diseases such as tumor, viral-infectious disease, heart disease, and HIV etc. [37]. However, because of a wasp sting may cause a series illnesses and appeared more serious symptoms than a bee sting, therefore a thorough understanding upon the pathogenic mechanism of the wasp venom is critical to future utilizing wasp venom for pharmacological interests. Based on the above reports, the pathogenic mechanisms of Polisilidae wasp sting might be categorized as follows according to the above-mentioned clinical cases.

4.3.1. Mechanism of Inducing Heart Damage

The wasp venom can cause myocarditis, arrhythmia and other heart damage, but the exact mechanism is unknown. These may be initiated by melittin’s inhibiting of mitochondrial and synaptic Na⁺-K⁺-ATP enzyme activity [38]. A report indicated that acute myocardial infarction caused by wasp sting may due to the wasp venom leading anaphylactic shock, which successively induced inadequate perfusion of coronary artery [39].

4.3.2. Mechanism of Inducing Brain Damage

The wasp venom can dilate blood vessels, thus having significant antihypertensive effect. After the blood pressure substantially declined, brain insufficiency might happened which will lead to cerebral infarction. A myasthenia gravis symptoms after wasp stung was reported [40], which was supposed to be initiated by venom allergens or toxic effects interfering with the synthesis and release of acetylcholine, thus resulting in the neuromuscular transmission disorders.

4.3.3. Mechanism of Inducing Liver Damage

The mechanism of wasp venom’s causing liver damage might attributable to melittin and its metabolites which inducing a large number of inflammatory mediators to form antigen-antibody complex, and to deposit in sinusoids surface of liver cells to damage them. It can also activate T cells, inducing CTL responses and antibody-dependent T cell mediated cytotoxicity, thus resulting in a large number of liver cell necrosis [41].

4.3.4. Mechanism of Inducing Renal Damage

The mechanism of wasp venom’s causing liver damage might attributable to melittin and its metabolites which inducing a large number of inflammatory mediators to form antigen-antibody complex, and to deposit in sinusoids surface of liver cells to damage them. It can also activate T cells, inducing CTL responses and antibody-dependent T cell mediated cytotoxicity, thus resulting in a large number of liver cell necrosis [41].
hyperemia, edema, exudation, and the decrease of effective circulating blood volume resulted in renal ischemia; (4) the venom possesses strong hemolytic activity, which can make lysis of erythrocytes, inducing haemoglobin to block the renal tubules, thus cause an acute renal tubular necrosis.

4.3.5. Mechanism of Influencing on Immunization

Wasp venom may cause allergic which belongs to a type I allergy. At the first time of wasp sting the body produces IgE. When repeated sting occurs, the venom, act as a allergen, will enter the sensitized body to combine mast cells and IgE of basophils cell membrane to release histamine, eosinophil chemotaxis chemotactic factor media cause smooth muscle spasm, vascular dilatation, increased microvascular permeability, and tissue edema [43]. Sometimes, there will be a delayed type allergy, which is considered as an immune-mediated type III allergic reactions and activation reaction upon immune complex deposition and complement system [44]. The reason of wasp venom's causing autoimmune hemolytic may be laid to that the causative agent acting on red blood cells to change the allergenicity of the membrane, to stimulate the formation of antibody, thus resulting in anti-erythrocyte antibody. In addition, patient's immune mechanisms might also have been destroyed and lost its recognizing function, leading to the production of the autoantibodies and their combination with the erythrocyte membrane antigen [45].

5. CONCLUSION AND FUTURE PERSPECTIVE

5.1. Future Perspectives of Polisilidae Wasp Venom Utilization And R&D

The Polisilidae wasp venom toxicity is serious harm of human, but using biologically active substances existing in the venom to treat human diseases will make this natural resource extremely valuable. However, the systematic investigations on chemical composition and pharmacological activities are rather lacking during the past decades, which urged our interest of further detailed research. Yunnan Province has rich resources of Polisilidae wasp with altogether 19 species [46], which may ensure the source origin of Polisilidae wasp venom.

Though preliminary chemical check indicated the most popular substances of the venom are peptidic [12], thorough components check of the Polisilidae wasp venom is essential to fully reveal its bioactive substances. Inspired by the findings of preliminary investigations on the pharmacological effects and toxicity of wasp venom [3, 8-12] as well as reported clinical symptoms after Polisilidae wasp stings [13-34], in-depth comprehensive pharmacological studies should be carried out with techniques including bioassay-guided extracts and pertinent bioactivity evaluation [47-54]. The to-be-determined pharmacological effects of Polisilidae wasp venom include but are not limited to those towards neuronal systems, cardiovascular and blood circulation systems, antibacterial and antifungal activities, anti-viral infections, anti-tumor effect, and therapeutic effects on autoimmune diseases, rheumatism, and rheumatoid.

In addition, Polisilidae wasp venom may dissolve muscle tissues, this natural venom or purified peptides from the venom merits further investigations and development to be the material base for the new inventions of health products on the treatment and control of obesity and the management of beauty and wellness. To fulfill its R&D, experiments against leptin receptor, ciliary neurotrophic factor, cannabinoid receptors, neuropeptide Y5 receptor, β3-adrenergic receptor, and fatty acid transport protein 4 should therefore be carefully performed.

5.2. Conclusion

Above all, in people’s impression, Polisilidae wasp belongs to pests of risky for human beings. But the double-sided nature of things enlightens us that we should make full use of this God-given resource, to overcome prejudices on it, and to optimally exploit the other nature of its beneficial to human health. This requires the joint efforts of worldwide scientists including entomologists, biochemists, pharmacologists, toxicologists, pharmacists, and so forth.

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