

RESEARCH PROGRESS ON *NIDUS VESPAE*, A TRADITIONAL CHINESE MEDICINE DERIVED FROM INSECTS

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ABSTRACT

Nidus vespae is a drug derived from insects that is commonly used in traditional Chinese medicine (TCM). No systematic review has previously been made about this drug. This paper summarizes previous investigations about the 49 identified chemical constituents and clinical application of *Nidus vespae*, and explores its pharmacological mechanism of treating disease. *Nidus vespae* has been reported to be effective in the treatment of rheumatoid arthritis and psoriatic arthritis, intractable skin diseases, dental disease, rhinitis, respiratory disorders, cervical erosion etc. *Nidus vespae* can be used alone or in combination with other drugs and compounds for a wide range of clinical applications. The objective of this review is to provide a comprehensive reference for further development and utilization of *Nidus vespae*.

Keywords: *Nidus vespae*; insect drug; structure; chemical composition; bioactivity; clinical application; review

INTRODUCTION

Nidus vespae (in Chinese: Lu Feng Fang) is the nest of the wasp species *Polistes olivaceous* (De Geer), *Polistes japonicus* Saussure, and *Parapolybia varia* Fabricius (family: Vespidae). These are three wasp species formally recorded in Chinese Pharmacopeia.¹ However, the local medicine of *Nidus vespae* utilized in China include more species belongs to Vespidae, such as Vespine wasp nests, *Polistes* wasp nests, and Stenogastridae wasp nests. *Nidus vespae* has a long history of use as a folk drug and was included in “Shen Nong’s Herbal Classic” two thousand years ago.² According to the Chinese pharmacopeia, it possesses the character of neutrality in nature, mild odor, sweet and acrid in taste, distributed to gastric meridian, and has efficacy of dispelling flatulence, detoxicating and destroying parasites, and analgesia. It is used for the treatment of skin and external diseases, edema and oncotic ulcer, mammary abscess, scrofula, stubborn dermatitis, and toothache¹. *Nidus vespae* is generally for external use, but can also be taken orally. Both methods of administration exhibit clear medicinal value and thus have obtained various clinical application. However, most investigations on the properties and clinical efficacy of *Nidus vespae* are reported in Chinese and no systematic review of this drug has been published previously. Since insect drugs are a critical part of traditional Chinese medicine, it is significant to introduce the recent investigations and clinical applications of this insect drug to the world. This review discusses the main chemical components, pharmacological efficacies, and clinical applications of this insect drug. The construction of a whole *Nidus vespae* nest is finished by the worker wasps by mixing of secreted oral fluid with plant fibers or wood pulps. For those species of wasps nesting in the trees or under the eaves, the shell of the *Nidus vespae* nestle adopts a huge pear-shaped structure with the height of 30–70 cm and 20–40 cm in width. For those digging species adopts cave-nesting style wasps, the diameter of nestle may be as wide as 100–200 cm (Figure 1). The internal structure of the *Nidus vespae* attributable to wasps nesting in the trees or under the eaves is mostly made of neat hexagonal holes of 4–10 mm

aperture with all the holes adown, in which every single room closely connected to each other and form an orderly arranged building.

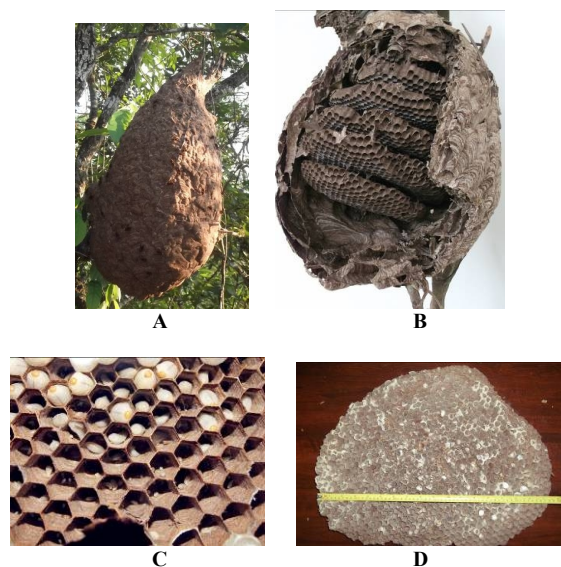


Figure 1: The external and internal wasp nests (A and B) and *Nidus vespae* (C and D)

As for the internal structure of the cave-nesting wasps, the obtained material of *Nidus vespae* demonstrated nearly the same structure with those nesting in the trees or under the eaves, except the diameter of each hexagonal hole attached to 8–16 mm. Both kinds of wasps nestles are made layer upon layer while the layers with different sizes, as well as gray white or taupe surfaces whose shapes are discoid, irregular flat discs or like lotus seedpod. These discs were locally called “wasp nestle cake”. Between the layers some small columns with diameters of 2–10 mm and 10–40 mm in height are constructed to support the distances reserved between the “wasp nestle cakes” (Figure 1). Wasp nests in-

tended for medicinal use are gathered mostly in autumn and winter. The collectors normally using the artificial method to collect the wasp nestle. All the worker wasps were captured, subsequently the pupae was removed, the shell was broken and got rid of, and the leaving the layers of wasp discs ("wasp nestle cakes") which is namely the raw material of *Nidus vespae*. The raw materials of this insect drug are light, pliable, slightly elastic, mild in smell, and acrid and light in taste.³ Dead wasps and pupae are removed from the freshly harvested *Nidus vespae*. The discs are air-dried to get rid of the impurities and preserved until use. When *Nidus vespae* is used clinically, the raw materials can be used directly or after processing. For direct use of *Nidus vespae*, the nest is simply cut into pieces. Traditional processing of *Nidus vespae* involves various preparative methods including, ustulation (broiling until coked with fire), broiling until yellow or red colour, Bran Frying, Lime Burning, and other methods recorded in "Classified Materia Medica".⁴ Furthermore, "Modern Chinese Materia Medica Identification" described three commonly-used methods of processing *Nidus vespae* as follows: (1) frying *Nidus vespae*: take clean pieces of *Nidus vespae* and fry them until yellowish; (2) honey-fried *Nidus vespae*: stir-fry the clean *Nidus vespae* pieces with honey, then fry them until pale yellowish, spray water and continue to fry until the raw materials yellow and not sticky; (3) charring *Nidus vespae*: place clean *Nidus vespae* in a can sealed with salt slurry. After charring the raw material, expose the processed product to air to diminish the fire-toxin before use.⁵

Chemical Constituents of *Nidus vespae*

The chemical components of *Nidus vespae* are rather complicated. Six compounds, *p*-dihydroxybenzene (1), protocatechuic acid (2), 4-hydroxybenzoic acid (3), 8-hydroxyquinoline (4), caffeic acid (5), and thymidine (6) (Figure 2), were separated and identified by Wang's group. Among them, 8-hydroxyquinoline (4) was first separated from natural resources and the other five were first separated from *Nidus vespae*.⁶ It was reported that the separation of 95 % ethanol extract of *Nidus vespae* resulted in eight compounds: fengfangin A (7), tutin (8), alnusone (9), centrololobol (10), (3*S*)-1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptan-3-ol (11), (3*S*)-1-(4-hydroxyphenyl)-(3,4-dihydroxyphenyl)heptan-3-ol (12), muricarpone (13), and 1-(3,4-dihydroxyphenyl)-7-(4-hydroxyphenyl)heptan-3-one (14) (Figure 2). Among these, fengfangin A (7) and

(3*S*)-1-(4-hydroxyphenyl)-(3,4-dihydroxyphenyl)heptan-3-ol (12) not been reported previously.⁷

Volatile Oils

Fan and Yu used diethyl ether to extract volatile chemical components at room temperature from *Nidus vespae* purchased from Guizhou Province, southwestern China, and isolated 68 components by gas chromatography (GC).⁸ They identified 28 components (15–42) by GC-MS technique and found that the identified components are mainly attributable to hydrocarbons (20 compounds), higher fatty acids and esters (seven compounds).⁸ Steam distillation at 70°C for 12 h to study the volatile oil in hives collected from northeastern China was adopted to disclose *p*-tert-butylcatechol (43), stearic acid (44), palmitic acid (35), and other components in the oil extract with the measurement of liquid chromatography-MS.⁹

Macromolecules

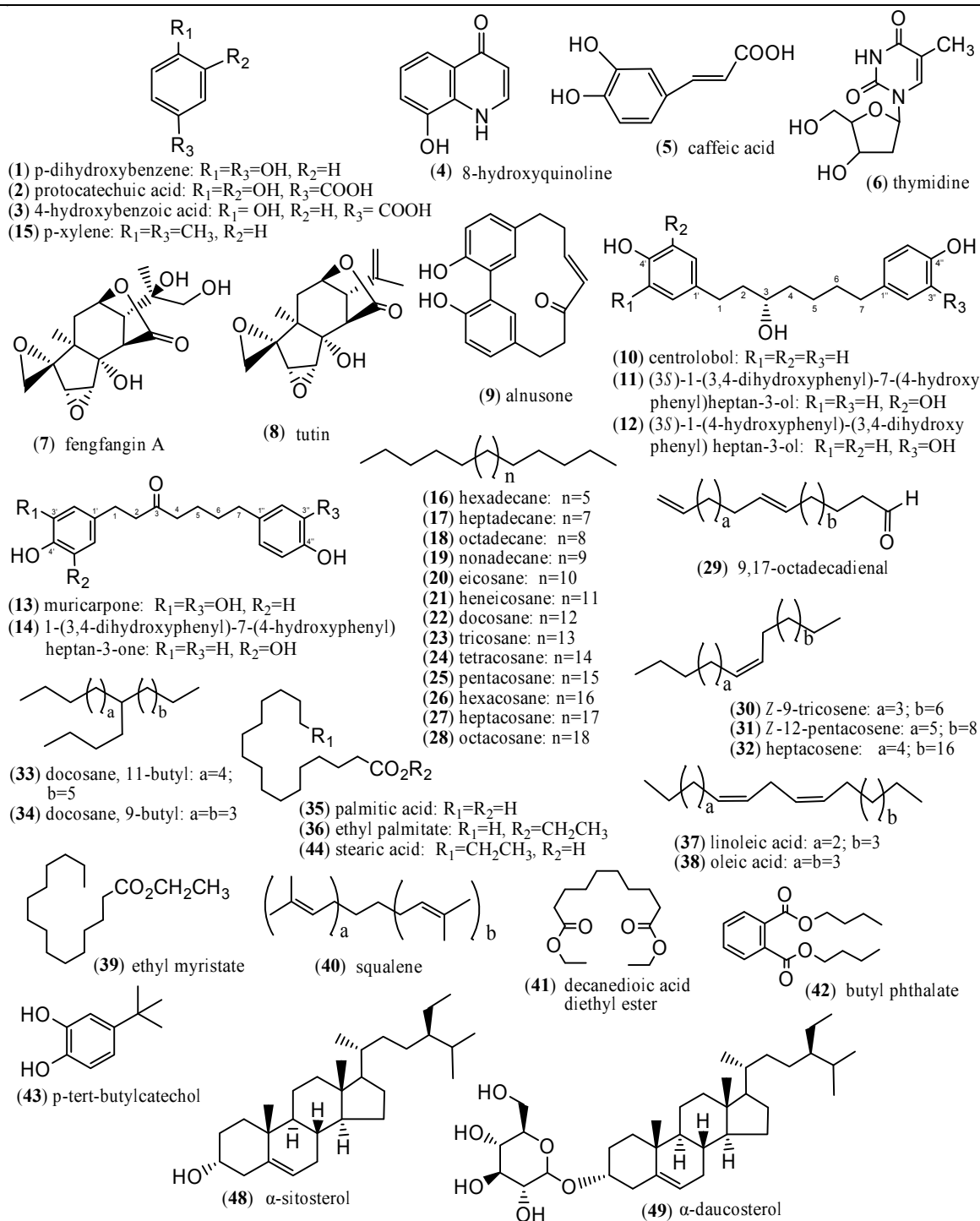
Li and Liu isolated an acidic peptide NV-PP-1 (45) from crude proteins and polypeptides part (5–7 KDa) of *Nidus vespae* and found that it contained 56 amino acid residues with molecular weight of 7.079 KDa.¹⁰ Wei and his co-workers further isolated an acidic protein from anti-inflammatory active part of *Nidus vespae* and named it as NV-PP-4 (46).¹¹ They found that that NV-PP-4 contained 87 amino acid residues with a molecular weight of 8.711 KDa. Both acidic peptides were found to have relatively high components of the amino acids glycine, proline, aspartic acid and glutamic acid.¹¹ Shi and his team described the purification of another protein (*Nidus vespae* protein-II, NVP-II, 47) from *Nidus vespae*, but lack of the characterization of the protein, whilst the authors interest are in the pharmacologically utilization of this protein on influence of HL-60 tumor cells.¹²

Steroids

The investigation of clinically used *Nidus vespae* extracts upon inhibiting oral cariogenic bacteria growth explored that the sterols such as α -sitosterol (48) and α -daucosterol (49) play an effective role on inhibiting of the dental caries based on their cariogenic bacteria-inhibiting effects.¹³

Trace Element

In addition to the above-mentioned substances, *Nidus vespae* also contains ammonia, iron, calcium and rich trace elements such as zinc, silicon, manganese and copper.¹⁴

Figure 2: The main chemical components of *Nidus vespae*

Pharmacology and Clinical Application

"Compendium of Materia Medica", a classical Chinese pharmacopeia, recorded that *Nidus vespae* is a sort of intense Yang drug which has effects of treating the virulent pathogen with poisonous agents and anthelmintic.¹⁵ *Nidus vespae* could release pains caused by osteomyelitis of dental alveoli and cavities; malignant sore caused by gingival abscess; scrofula; mouthpiece edema pain; rubella pruritus; refractory dermatosis. The *Nidus vespae* contains various chemical constituents which possess various kinds of pharmacological activities such as anti-inflammatory, analgesic, antitumor and so on. The broad clinical application is mainly concentrated on the treatment of rheumatoid arthritis, intractable skin dis-

eases and a variety of pulmonary diseases. The main pharmacological effects and clinical application of *Nidus vespae* are described as follows.

Treatment of Arthralgia

Treatment of Rheumatoid Arthritis

Li reported the self-made "decoction of strengthening body resistance and arthralgia diminishing" to treat 100 cases of rheumatoid arthritis patients, its main constituents are *Nidus vespae*, *Nux vomica* (*Strychnos nux-vomica* L.), common threewingednut Root (*Tripterygium wilfordii* Hook. f.), and raw milkvetch root (*Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao), two months as one course of

treatment.¹⁶ After taking averagely 61 days of treatment, the total effective rate was found to be 97 %, which shows the remarkable efficiency in the treatment of rheumatoid arthritis. The efficacy was evaluated according to the Curative Effect Standard for RA Formulated in 1988 First National Academic Conference of Treatment of Rheumatic Disease With Combination of TCM and Western Medicine in China.¹⁶ Among the treated 100 cases of rheumatoid arthritis patients, those in short-term control were 38 cases, those conspicuous effective were 36 cases, and those effective were 23 cases, while those invalid were only three cases. Meanwhile, the control treatment of 30 cases of rheumatoid arthritis patients using both ibuprofen (0.4 g, thrice per day) and prednisone (10 mg, thrice per day) for two courses of treatment (30 d as one course) exhibited no short-term control cases, and only 19 cases were effective resulting in a total effective rate of 63.3 %. The “*Nidus vespae* granules” which was made mainly of *Nidus vespae* with adjuvant species such as common threewinged nut root (*Tripterygium wilfordii* Hook.f.), north Radix Saposhnikovia, aconite root (*Aconitum carmichaeli* Debx.), and other traditional Chinese herbal medicines (20 g, thrice per day) was used to treat 96 cases of patients suffering from rheumatoid arthritis, an obvious efficacy on joint swelling was found with less side effects, while the total effective rate was 96.8 %, and the 39 cases were conspicuous effective, the comparing was based on the differences between before and after administration.¹⁷ Another research group indicated that, *Nidus vespae* mixed with *Asarum* (*Asarum heterotropoides* Fr. Schmidt var. *mandshuricum* (Maxim.) Kitag.) displayed also curative effect on rheumatoid arthritis in swelling and pain of facet joint by a mechanism of subduing swelling, eliminating stagnation, and activating meridian to stop pain.¹⁸

Psoriatic Arthritis

Psoriatic arthritis is an arthropathy associated with psoriasis. The symptoms are psoriatic lesions and arthralgia. The disease is liable to recurrence and forms ankylosis or joint distortion leading to disability in its late stage. Psoriasis is more common in patients of arthritis. Xia described a therapeutic method of removing cold and dehumidification method in the treatment of psoriatic arthritis, which is specifically suitable against the anemofrigid-damp arthralgia type patients of psoriatic arthritis.¹⁹ The basic prescription includes *Nidus vespae*, aconite root (*Aconitum carmichaeli* Debx.), Chinese angelica (*Angelica sinensis* (Oliv.) Diels), safflower (*Carthamus tinctorius* L.), Szechwan lovage rhizome (*Ligusticum chuanxiong* Hort.), dense fruit pittany root-bark (*Dictamnus daeyparpus* Turcz.) and other TCM materials, after the treatment, the patient's skin lesions and arthralgia were apparently eliminated, whilst the symptom of dysarthrosis were significantly relieved.

Other Arthralgia

By the TCM theory, *Nidus vespae* has effects of pyretic tonification of renal Yang, dispelling Wind and removing obstruction in the meridians, analgesic and promoting blood circulation. It is thus suggested that this insect drug also demonstrated to be a good remedy on lumbocrural pain caused by senile weakness, hepatorenal asthenia, and over-strained injury. Wei *et al.* reported the treatment of 150 patients suffering from biceps brachii myotendinitis with “me-

ridian-activating decoction” made of *Nidus vespae*, lobed kudzu vine root (*Pueraria lobata* (Willd.) Ohwi), radix rhizoma notoginseng (*Panax notoginseng* (Burk.) F.H. Chen), mulberry twig (*Morus alba* L.), net cliffbean (*Millettia reticulata* Benth), Radix Saposhnikovia, Radix clematidis, caulis Ionicerae (*Lonicera japonica* Thunb.), Chinese wolfberry root-bark (*Cortex Lycii*), white peony root (*Paeonia lactiflora* Pall.), etc. After 1–3 periods of treatment, the total effective rate reached 96.7 % and the pathologic part of pain was obviously attenuated which suggested that a satisfactory therapeutic efficacy was achieved.¹¹ Chen reported the treatment of lumbago, blood stasis, and rheumatism with “lumbar vertebrae rehabilitation pill” composed of *Nidus vespae*, hairy antler (*Cervus Nippon* Temminck), malaytea scurfpea fruit (*Psoralea corylifolia* L.), Eucommia bark (*Eucommia ulmoides* Oliv.), walnut meat (*Juglans regia* L.), ground beetle (*Eupolyphaga seu Steleophaga*), ginger (*Zingiber officinale* Rosc.), barbary wolfberry fruit (*Lycium barbarum* L.), zaocys dhumnades, and prepared rhizome of adhesive *Rehmannia* (*Rehmannia glutinosa* (Gdertn) Iibosch. ex Fisch. et Mey.), and the symptoms of lumbago was significantly reduced after treatment.²⁰

Treatment of Skin Diseases

Psoriasis vulgaris is a common chronic dermatosis, which will bring patients great physical pain and mental disorder due to the fact that it may attack repeatedly. Zhang and Li treated 108 cases of psoriasis with self-made “*Nidus vespae* psoriasis-diminishing decoction”, after treatment, the skin lesions were found to be recovered up to a range of 50 % – 80 %, and the skin rashes were significantly disappeared after the remedy.²¹ Furthermore, once it was cured, the recurrence rate was as low as 21.6 %, besides the advantages of safety and little side effects of this drug. It was reported that the treatment of psoriasis with “three-shell plus decoction” according to basic theory of TCM, which was made of “cooling the blood” drugs of “reducing the hot toxicity in blood” *Nidus vespae*, periostracum cicadae (*Cryptotympana pustulata* Fabricius), buffalo horn, and dried rehmannia root (*Rehmannia glutinosa* (Gaertn.) Li-bosch.) obtained satisfactory therapeutic effect in one case of clinic patient.²² Moreover, rhagades of hands and feet is a common skin disease in which the skin and soft tissue of the hand and foot is drying and rhagadia because of varied reasons, it is also called “rhagades sore” in TCM theory and is quite common in winter. Liu *et al.* released a liquid decoction prescription composed of *Nidus vespae*, malaytea scurfpea fruit (*Psoralea corylifolia* L.), radix paeoniae rubra (*Paeonia lactiflora* Pall.), fructus kochiae (*Kochia scoparia* (L.) Schrad.), and Chinese wolfberry root-bark (*Cortex Lycii*). Immersed the afflicted part of hands or feet into the liquid decoction for 20 minutes each day, while the effect on rhagades sore was quite clear after 10-days treatment.²³

Antitumor Effect

Historically, *Nidus vespae* is a Chinese anticancer drug of little side-effect and high curative efficacy.²⁴ It has been recorded in ancient literature that *Nidus vespae* was used to treat carbuncle ulcer and malignant sore, and today it is used to treat breast cancer, lung cancer and nasopharyngeal carcinoma in clinical practice.²⁵ Either using the single *Nidus vespae* or using it accompany with other TCM drugs in

plus-minus according the “syndrome differentiation” will both achieve curative effect on treating tumor diseases. For example, “Chinese tumor-diminishing pills” made of equal proportions of *Nidus vespae*, stiff silkworm (*Bombyx mori* L.), Scorpion (*Buthus martensii* Karsch) and gecko (*Gekko japonicus* Dumeril et Bibron) was proved to exhibit remarkable curative effects on laryngeal carcinoma and nasopharyngeal carcinoma.²⁶ It was found that the apoptosis of leukemia cells (HL-60) was induced by the purified *Nidus vespae* protein II (NVP-II), and the quantity of leukemia cells treated by NVP-II decreased significantly with cell debris, which suggested that NVP-II possesses a significant effect of inducing the apoptosis and inhibiting the proliferation of leukemia cells in both dose- and time-dependent manners.¹² Dai’s group investigated the cytotoxicity against HepG2 cells using the extracts of different solvent extracts of *Nidus vespae*. The results implied that both the petroleum ether extract and the ethyl acetate extract of the alcoholic extract of *Nidus vespae* exhibited significant cytotoxicity against the growth of HepG2 cells, which suggested that *Nidus vespae* extract possess somewhat potential as an antitumor drug candidate.²⁷

Antimicrobial Effect

Nidus vespae was also recorded to own efficacies of antibacterial *in vitro* and anti allergic. It was reported that *Nidus vespae* extract plays strong inhibition on the growth of *Streptococcus mutans*, *Actinomyces viscosus* and lactobacillus in oral cavity.¹³ Zhuang’s group performed an antibacterial experiment *in vitro* on resistance *Pseudomonas aeruginosa* ATCC 27853 with the alcohol extract of *Nidus vespae*, and carried out a preliminary research on the drug-resistant mechanism.²⁸ Negative results were found after 5 days administration of drug for all the expressions of the drug-resistant genes, i.e., TEM, SHV, DHA, CTX-M-1, CTX-M-2, CTX-M-9, OXA-2, OXA-10, oprD2 via PCR detection of their mRNAs. It suggested that though the drug-resistant genes still exist in the bacteria after the drug treatment, the transcription product RNA could be inhibited. This implied that one of the mechanisms of *Nidus vespae* reverse bacterial drug-resistance may be attributable to inhibiting the transcription of bacterial drug-resistant gene, which prevents the drug-resistance enzyme from expressing.²⁸

Treatment of Dental Disease

Treatment of Periodontitis

Periodontitis is a chronic inflammation that invades gingival and periodontium, which is also called "gingival abscess" and "osteomyelitis of dental alveoli" in TCM theory. The main clinical manifestation consist of that painful gum and pyorrhea appear, then forms periodontal pocket, as the disease progresses the tooth will loosen gradually that mainly lead to teeth loss of patients. Huang and Xiao prescribed the composite of Chinese goldthread (*Coptis chinensis* Franch.), dried rehmannia root (*Rehmannia glutinosa* (Gaertn.) Li-bosch.), plaster stone, tree peony bark (*Paeonia suffruticosa* Andr.), radix scrophulariae, rhizoma cimicifugae (*Cimicifuga heracleifolia* Kom.), rhubarb (*Rheum palmatum* L.), and liquorice root (*Glycyrrhiza uralensis* Fisch.) to treat patients with symptoms of painful gingiva, bitter taste of mouth, and halitosis of periodontitis. It was found that the

painful gingival attenuated slightly after 3 days’ treatment. Then *Nidus vespae* and lophatherum gracile Brongn were added into the compound drug due to their efficiencies of attacking counteracting toxic substances, tumescence, and analgesia. The painful gingival and other symptoms were significantly disappeared, which showed that *Nidus vespae* had a good effect on periodontitis.²⁹ Furthermore, *Nidus vespae* also demonstrated a good efficacy against pyogenic infection of soft tissues, Dong and Chen treated three cases of gingival red and swollen with prescription composed of *Nidus vespae* powder, plaster stone, dried rehmannia root (*Rehmannia glutinosa* (Gaertn.) Li-bosch.), Chinese goldthread (*Coptis chinensis* Franch.), Chinese angelica (*Angelica sinensis* (Oliv.) Diels), and capejasmine (*Gardenia jasminoides* Ellis), patients’ redness and swollen faded away, and the symptoms disappeared after taking twice medications.³⁰

Treatment of Dental Caries

Modern medical research disclosed that, the oral cavity contains simultaneously cariogenic bacteria and beneficial bacteria species in the dental plaque. When the bacteria ratio changed and pushed the non-cariogenic bacteria into cariogenic species, it may eventually lead to the oral cavity loss balance which will cause dental caries.³¹ Huang and Xiao studied the effect of hive crude extracts on the growth of cariogenic bacteria, and found that they can effectively inhibit the growth of *Streptococcus mutans*, *Streptococcus sanguis* and *Actinomyces viscosus*. The MIC values against these three pathogens are 4.0, 0.125 and 0.5 mg/mL, respectively. It was inferred that the anti caries effective ingredients in the hive crude extracts can reduce the occurrence of caries to a certain extent.²⁹ Furthermore, Zuo and colleagues disclosed that the *Nidus vespae* extracts can inhibit oral cariogenic bacteria growth, while the sterols such as α -sitosterol and α -daucosterol play an effective role on inhibiting of the dental caries.¹³

Treatment of Respiratory Disorders

Treatment of Rhinitis

Nidus vespae has a reliable effect on rhinitis with few toxicity and side effects. Sinusitis is the nonspecific inflammation of sinus mucosa and is a common frequently encountered disease in rhinology, which is clinically treated by TCM therapy such as heat-clearing and detoxifying, damp-eliminating and dissipating stasis, apocenos and inducing resuscitation. The prescription composed of *Nidus vespae*, dandelion (*Taraxacum mongolicum* Hand.), *Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. f.), asarum (*Asarum heterotropoides* Fr. Schmidt var. *mandshuricum* (Maxim.) Kitag.), Fructus forsythia (*Forsythia suspense* (Thunb.) Vahl), rhizoma cimicifugae (*Cimicifuga heracleifolia* Kom.), wrinkled gianthyssop (*Agastache rugosa* (Fisch. et Mey.) O. Ktze.), blackberrylily rhizome (*Belamcandae chinensis* (L.) DC.), and Chinese honeylocust spine (*Gleditsia sinensis* Lam. (G. horrid Willd.) could achieve an obvious clinical efficacy in the treatment of sinusitis.³² Jia treated 60 patients suffering from chronic rhinitis with self-made prescription composed of *Nidus vespae*, cocklebur (*Xanthium sibiricum* Patr.), flos magnoliae (*Magnolia biondii* Pamp.), baical skullcap root (*Scutellaria baicalensis* Georgi), asarum (*Asarum heterotropoides* Fr.

Schmidt var. *mandshuricum* (Maxim.) Kitag.), radix saposhnikoviae, and fructus forsythia (*Forsythia suspense* (Thunb.) Vahl). After administration of drug for six weeks, it was observed that the nasal obstruction, rhinalgia and other symptoms of rhinitis of patients were completely disappeared, and the total effective rate of the treatment group is 90.8 %, whilst the total effective rate of chronic simple rhinitis is significantly higher than that of chronic hypertrophic rhinitis.³³

Treatment of Respiratory Disease

It is recognized that *Nidus vespae* possesses an effect of relieving cough and asthma, based on the summary from long-term clinical practice. The *Nidus vespae* can decrease trachea's tense, and remit tracheospasm.³⁴ Based on the finding of *Nidus vespae* capable to invigorate the kidney to promote inspiration, relieving cough and asthma, the composite of *Nidus vespae*, roast herba ephedrae, asarum, *Schisandra chinensis*, and *Vitex negundo* L. was prescribed and proven to be effective in treating senile chronic bronchitis, emphysema with non-stop cough, and asthma and white phlegm.³⁵ Liu treated chronic bronchitis with prescription composed by *Nidus vespae*, medicinal ephedra, zhejiang fritillary, cicada skin, almond, dry earthworm, glycyrrhiza, radix peucedani, and heartleaf houttuynia. The body temperature of two cases immediately dropped after one medication, while other cases dropped after twice intakes. Furthermore, other symptoms of chronic bronchitis apparently attenuated after taking thrice medications.³⁶ Mao treated 82 cases of mild and moderate asthma patients with "asthma-pacifying decoction" which composed by *Nidus vespae*, roast herba ephedrae, *descurainia sophia* (L.) Webb ex Prantl, bitter almond, perilla seed, seeds of brassica alba, peach kernel, and earthworm.³⁷ Clinical observation showed that the curative (*viz.* all clinical syndromes of asthma were diminished) rate of the compound drug group was 75.6 %, comparable to that of the first-line positive chemical drugs (salbutamol sulphate aerosol, ketotifen, predenison, aminophylline) group (76.2 % cured) in treating acute asthma. Meanwhile, the total effective rates of the compound drug group and chemical drug group were 89.0 and 91.2 %, respectively, which also showed similar efficacy for the compound drug and positive control. However, the treatment group showed superior to the positive controls in terms of adverse effects. Four cases of nausea and vomiting, one case of mild palpitations, and one case of mild headache made the rate of adverse reactions to be 7.3 % in the treatment group, whilst the control group had seven cases of nausea and vomiting, five of mild palpitations, eight of lethargy, three of light degree of headache, and one case of trembling fingers which made the adverse reaction reached 30.0 %.³⁷ This disclosed that the side-effect of the compound drug is obviously less than the positive chemical drug, which exhibit the advantage of this decoction drug.

Strengthening Yang Action

Nidus vespae was also reported to have a tonic effect due to its aphrodisiac kidney function. Ancient "Qian Jin Yao Fang" recorded that *Nidus vespae* possess curative efficacy against erectile dysfunction.³⁸ "Compendium of Materia Medica" again narrated that *Nidus vespae* therapy on ED patients caused by flaccidity with Yin asthenia. Applying the ash of

Nidus vespae to the penis of patients for overnight was described to heat Qi and effective to ED patients.¹⁵ It was found that the aqueous extract of *Nidus vespae* (6 g/kg, once per day for 14 days) can increase the weights of young Sprague-Dawley rats' (body weight 90–120 g) accessory sex organs when compared with those of the negative controls (preputial gland 50.0 vs. 24.6 mg/100 g; levator ani muscle 23.3 vs 18.0 mg/100 g; seminal vesicle prostate 43.4 vs 29.0 mg/100 g; thymus 294.6 vs 341.8 mg/100 g; adrenal 66.4 vs 33.4 mg/100 g; respectively), which suggested *Nidus vespae* extract owns androgenic function. It was further disclosed that the water-soluble and alcohol soluble parts of *Nidus vespae* are the main effective parts of invigorating kidney and strengthening Yang, both in dose-dependent manners.³⁹

Treatment of Cervical Erosion

The cervical erosion is one of the most common inflammatory diseases occurred upon female reproductive system. The gynecologic disease cervical erosion was treated with self-made "Tiger-wasp electuary" composed of *Nidus vespae*, *Bletilla* (*Bletilla striata* (Thunb.) Reichb. f.), and rhizoma polygoni cuspidati (*Polygonum cuspidatum* Sieb. et Zucc.), 14 cases were cured in the first period of treatment of 10 days (once per night), 22 cases were cured in the second, while six cases were cured in the third period of treatment. 14 cases were improved, and 2 cases were invalid.⁴⁰ Besides the above-mentioned pharmacological efficacies, *Nidus vespae* was also reported to possess additional pharmacological effects on analgesic, lowering the body temperature, blood clotting, and diuresis.⁴¹ All of these information implied that this insect drug has outstanding medicinal value and extensive clinical application which worth further research and development.

Mechanism Discussions

From the above-mentioned information, it could be seen that *Nidus vespae* has a long history of medicinal application, as well as extensive in clinical application, either used as single remedy or in compatible application with other TCM drugs. It has the advantages of both showing few adverse-effect and exhibits rapid onset. This urged our interest to categorize also its action mechanisms. In a mechanistic sight of view, the pharmacological mechanism of *Nidus vespae* might be as-sorted as follows.

Mechanism of Action on Anti-inflammatory and Immune Regulations

When *Nidus vespae* treats joint pain, skin diseases and respiratory infections and other diseases, the active substances in this insect drug may exhibit the effects of both anti-inflammation and enhancing the immunologic function by inhibiting the expression of various kinds of cytokines. For example, rheumatoid arthritis has a definite relationship with all kinds of osteoarthritis and inflammation. The mechanism that *Nidus vespae* treats arthralgia may lie on that the active substances inhibited the activity of peanut arachidonic acid cyclooxygenase or COX-2, or they inhibited the synthesis and release of thromboxane A₂ (TXA₂), and simultaneously inhibit the expression of inflammatory cytokines such as TNF- α , IL-1- β , and ICAM-1.⁴² Now it is generally believed that psoriasis is an autoimmune disease mediated by T cell, and in its pathogenesis exceptions occurs in the expression of

Th cytokines and result in helper T (Th) cell balance disorders.⁴³ Hive can be very effective against this disease, the reason may be that during the treatment of the disease hive inhibits the expression and transcription of some Th cytokines in the patients' skin lesions, and corrects Th cells' balance disorders in the skin lesions of psoriasis. Furthermore, the reason that *Nidus vespae* can treat respiratory diseases might be attributable to the active substances in the hive can enhance the immunologic function and, meanwhile it can also reduce the contents of oxyphil cells, lymphocyte and reduce tumor necrosis factor (TNF- α), interleukin-6 (IL-6), and interleukin-10 (IL-10). This is useful to control the development of inflammation which led to the significant curative effect of treating respiratory diseases.⁴⁴

Mechanism of Action on Antibacterial and Antiviral Effects

It is known that the antimicrobial efficacies and effects against drug-resistant bacteria of drugs demonstrated *via* various paths.⁴⁵⁻⁴⁹ It could be summarized the antibacterial mechanism of TCM were classified to five directions: (1) direct bactericidal; (2) modulation of immune and enhance the antibacterial ability of the body; (3) sensitizing effect which may improve efficiency of antibiotics, thereby improving the sensitivity of bacteria to antibiotics; (4) eliminating bacterial plasmids in particular to eliminate the R plasmid (R factor), thus reduce the drug-resistant characteristics; (5) reversing of drug-resistance of bacteria including inhibition of β -lactamase and inhibition of drug-resistant antibiotic efflux pump.⁵⁰ *Nidus vespae* demonstrating strong inhibitory effects on many kinds of bacteria, the mechanism of action should be attributable to its damage of the drug-resistant gene of bacteria, thus, inhibiting the transcription of drug-resistant genes, which made the drug-resistant enzymes cannot be expressed and finally lowering the drug resistance.^{28,50} More interestingly, the *Nidus vespae* extract is supposed to display a post antibiotics effect thus making an antibacterial effect becomes operative, while balancing normal oral flora and adjusting eubiosis of oral cavity can led to the treatment of dental caries with the *Nidus vespae* extract.¹³ As for the anti-viral effect, no body systematically describes the anti-viruses effects of *Nidus vespae*. However, it is well known that cervical erosions was related to infected HSV-2, and active part from insect drug has already proved to demonstrate significant anti-HSV effect,⁵¹⁻⁵² therefore we suppose the curative capability of *Nidus vespae* against cervical erosion reported in reference 40 partially lies on inhibition of HSV-2 virus. This deduction is in accordance with the above-mentioned records that *Nidus vespae* possess efficacies upon pyocutaneous disease oncotoc ulcer, detoxifying and promoting tissue reproduction.

Mechanism of Action on Antitumor Activity

The pharmacological mechanism of antitumor activity of *Nidus vespae* could be summarized as follows: the biosynthesis of cancer cells is influenced by this insect drug, while the proliferation of cancer cells may be impeded mainly by interfering the replication and irreversible rupture of cell genes; the transduction of signal paths in cancer cells is influenced, the initiating genes of apoptosis are intensified and the expression of apoptosis genes is promoted so that the proliferation of cancer cells is inhibited. By enhancing the activ-

ity of B-cells, T-cells in the body, their synergy effect on monocyte is reinforced, the secretion of cytokines of biological regulatory function is promoted, tumor cells are thereby suppressed or damaged, whilst the immunologic function of the organ is improved as well.⁵³⁻⁵⁴ Furthermore, we have described that the antioxidant capability of the natural products play an important role of many diseases including anti-tumor and anti-virus.⁵⁵⁻⁵⁷ Meanwhile, the free radical scavenging ability is closely related to anti-inflammatory effect of the crude parts of TCM.⁵⁸⁻⁵⁹ Phenolic compounds are also proved to demonstrate various kinds of biological activities,⁶⁰⁻⁶¹ it is obvious more detailed and comprehensive pharmacological mechanism studies of *Nidus vespae* still await further detailed research.

Outlook of the Investigation Directions upon *Nidus vespae*

Structure-Activity Relationship (SAR) of the Chemical Substances of *Nidus vespae*. Though many of pharmacological and chemical investigations on *Nidus vespae* have been reported as we reviewed herewith, the SAR detection of *Nidus vespae* regarding the active substances and their antibacterial, anti-inflammatory, immunoregulatory, anti-viral and antitumor properties still remains nearly blank. Based on the review, it could be found out that the chemical constituents of *Nidus vespae* is very complicated, including but are not limited to free amino acids, free alcohols, higher fatty acids, esters, saccharides, tannins, macromolecular substances like acidic peptides, cadmium, irons, manganese, silicon and other trace elements. Among these substances, many demonstrated various pharmacological effects, for example, the volatile substances found in *Nidus vespae* are reported to possess anticancer activity, while the polypeptides exhibit an effect of anti-inflammation and inhibiting the growth of tumor cells. Sterols, which are the main active substances in treating dental caries, were proven to own a strong bactericidal property. Therefore, sound SAR investigations are of need for further research and development the title species.

Preparation-Activity Relationship (PAR) of *Nidus vespae*

The activity of *Nidus vespae* is influenced, to a great extent, by various processing methods and the subsequently obtained components. Alcoholic extract are apparently different with that soaked in acidic solution, while the calcinations of *Nidus vespae* produce chemical substances differing from its solvent extract. A clear relationship between the different preparation methods of *Nidus vespae* and their corresponding pharmacological activities should be emphasized and thoroughly detected in future investigations. The different quality control protocols concerning corresponding preparation methods also merit detailed studies to provide standardization strategies.

Scientific and Systematic Pharmacological Research and Clinical Study Are Needed

Though tens of research papers regarding the chemical constituents and bioactivities of *Nidus vespae* are available, the investigation of its clinical applications is still at a preliminary stage. In China, the clinical applications of *Nidus vespae* are mainly based on the records of ancient medical books and folk remedies, which need to be validated with the systematic modern techniques. Research on pharmacological mecha-

nisms of anti-tumor, antiviral, anti-inflammation, and immuno-regulation is far from comprehensive, which severely limited further development of clinical application of *Nidus vespae*. Therefore, in addition to systematic search for the pharmaceutical active substances from *Nidus vespae*, the employment of advance modern *in vitro* and *in vivo* pharmacological studies to detect the experimental use scope upon this insect drug in future investigations.

CONCLUSION

China has a long history of applying *Nidus vespae* as TCM more than 15 centuries. The insect is widely distributed in China, especially in Southeastern China including Yunnan Province, which guarantee the material sources supplement for the research concerning both of the bioactive components purification and pharmacological investigations. For better exploitation of this medicinal resources, it is essential to perform systematic and detailed studies based on the molecular level pharmacology of the antitumor, antiviral, antibacterial, anti-inflammatory and immuno-regulation effects of *Nidus vespae* and its isolated pure components, to investigate thorough SAR to lay the foundation for verifying the pharmacological and clinical value of *Nidus vespae* and providing technical supports for the further development of the insect drugs as well. Moreover, the computer-aided drug design (CADD) technique should be also of merit to future research upon *Nidus vespae* to afford docking status and other molecule-enzyme complex diagrams for efficiently developing chemical agents towards pertinent targets. Part of above-mentioned study plans has been undertaking by our research teams at the Yunnan Provincial Key Laboratory.

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