

Research Advance on Chemical Constituents and Anti-tumor Effects of *Periplaneta americana* L.

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Abstract As a kind of traditional Chinese medicine with a long history , *Periplaneta americana* L. has a variety of pharmacological activities such as anti-virus , anti-tumor , improving immunity , promoting tissue repair , anti-inflammation , analgesia and protecting liver. In recent years , more and more people pay attention to the insect's development and utilization. There are a number of quasi-famous drug which main composition based on *P. americana* extracts have invested to the market (such as "Kangfuxin" , "Ganlong" , "Xinmailong") . All these show that *P. americana* have a huge medicinal potential. Moreover , highly reactive chemical substances have huge application prospects in anti-tumor. Based on the above , we review *P. americana* researches from the chemical composition and anti-tumor effect in recent years , which is aiming at providing theoretical support and help for the drug's further development and utilization.

Key words *Periplaneta americana* L. ; Chemical composition; Anti-tumor effects; Research and development

Periplaneta americana L. or called cockroach , one of the largest and the strongest vitality insect groups in genus *Periplaneta* , family Blattellidae , suborder Blattaria , order Dictyoptera , class Insecta , is first recorded in *Shen Nong's Herbal Classic* as a kind of traditional Chinese medicine^[1-2]. It has been shown by modern medical researches that its extracts and preparations have the effects of anti-virus (such as HBV) , anti-tumor , improving immunity , promoting tissue repair , anti-inflammation , analgesia and protecting liver^[3-7]. Prof. Li Shunan at Dali Medical College has devoted himself to studying this insect for a long time. Through unremitting efforts , the active constituents from *P. americana* has been successfully developed into drugs that have come into the market , which gradually changes the way people think about it^[8]. In recent years , more and more people pay attention to the preparations with their extensive application in clinic. Now the researches at home mainly focus on *P. americana* medicinal effects , while foreign scholars prefer to studying the species^[9] , part of chemical constituents including lipid , neuropeptide and pheromone^[10-13] , genes^[14-15] and how to kill cockroach^[16-17]. We review *P. americana* medicinal researches in recent years in terms of chemical composition and anti-tumor effects , so as to provide theoretical support and help for the drug's further development and utilization.

1 Study on chemical constituents

P. americana is rich in chemical substances , such as various amino acids (including human essential amino acids) ,

peptides (such as stress peptide) , proteins , oils and fats , chitin and mucopolysaccharide^[18-19]. It is reported by Yao Lian that *P. americana* contains more than 16 amino acids , including 7 human essential amino acids and 2 human semi-essential amino acids. And free amino acids and hydrolyzed amino acids occupy 5.679% and 75.487% of the total amount^[20]. A study from Zhou Qiong shows that *P. americana* contains a variety of amino acids such as ASP , Pro and Ser whose content is 52.86% in female adult , 60.21% in male adult and 52.93% in nymph. And the total content of essential amino acids including Thr , Val and Met is 21%^[21]. To sum up , *P. americana* can serve as high-quality protein resource that has high nutritional value. Xiao Xiao-qin has identified a lot of compounds from the oils and fats of *P. americana* , of which enols and eicosanoids represent 42.81% and alkanes accounts for about 50%. Out of fatty acids , the octadecenoic acid content is the highest at 13.86%^[22]. A total of 23 compounds are separated and identified from *P. americana* oils and fats by Meng Song-nian , of which the main chemical constituents are enols , olefine acids and alkanes^[23]. Through GC-MS analysis , 23 compounds are extracted by Luo Jian-rong^[24]. Of them , the content of 16-hydro-7-hexadecenoic acid lactone is the highest (35.98%) , followed by fatty acids and esters (26.62%) . In addition , stigmast-4-ene-3-one (5.96%) and little aliphatic aldehyde are isolated from *P. americana* oils and fats. The above difference may be connected with sample resource , experimental methods and other factors. Hu Chuan applied ion exchange column and polyacrylamide gel electrophoresis SDS-PAGE to study the allergen of *P. americana*. He discovered that the crude extracts contain 24 kinds of antigenic components , of which the 74 kDa protein is elucidated as the main allergen of *P. americana*^[25]. Zhang Yan-yan reported that the active site of *P. americana* resisting ulcerative colitis contain 20.03% amino acids. The combined amino acids are the mixture of polypeptides whose molecular

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weight is between 6 and 10 kDa^[26]. He Zheng-chun *et al.* pointed that a total of 50 neuropeptides have been identified from *P. americana*, including Procto lin, Corazonin and Pea-MIP^[27].

By means of normal and reverse phase silica gel, gel, ¹H-NMR and ¹³C-NMR, Luo Wan-ling has extracted 6 compounds from the methanol extracts of *P. americana*, of which 2 compounds are identified as 7-hydroxycotadecanoic acid and Bis (2-ethylhexyl) phthalate^[28]. Through elemental analysis by Zhou Qiong, *P. americana* is rich in constant and trace elements, especially Zn, Cu and K, which may be related to improving body's immunity^[21]. A study of compounds from Xiao Xiao-qin shows that polysaccharides from *P. americana* have typical absorption peaks, the configuration of carbohydrate chains may be pyran type and they have β -glycosidic bond^[22]. Dai Yun *et al.* used cockroach shells as raw materials for chitosan and carboxymethyl chitosan. Discoloring test showed that the both are good flocculating agents and chitosan can be recycled^[29]. Hu Yan-fen *et al.* reported the research situation of medicinal value and pointed that *P. americana* contains amino acids, octopamine, periplanone, tachykinin, and has various activities^[30].

2 Study on anti-tumor effects

Generally speaking, cockroaches live in messy environments, which carry plenty of pathogenic bacteria and viruses. They can remain survive even of facing various human kill means, which suggests that they contain some highly active materials to withstand pernicious invasion outside. The related extracts of *P. americana* have good anti-tumor effects, that is, they have inhibitory effects on many tumor cells.

Jiang Yong-xin *et al.* carried out a study of human gastric cancer cell BGC-823 apoptosis induced by "Kangfuxin" in vitro, the refined active constituents of *P. americana* extracts^[31]. After BGC-823 cells have been treated by different concentrations of "Kangfuxin" for 24, 48 and 72 h, IC_{50} is determined to be lower than 50 mg/ml in MTT tests. They show higher cytotoxic effects and time-dependent, concentration-dependent inhibitory effects. Flow cytometry test showed that BGC-823 cells appear obvious apoptosis peaks in the presence of "Kangfuxin", most of which block in G2/M phase. TUNEL detection showed that cell apoptosis and necrosis exist together. Based on in vitro tests, Jiang Yong-xin *et al.*^[32-33] studied the inhibitory effects of *P. americana* extracts on the 3LL lung cancer and Lewis lung cancer of C57BL/6J mice and their action mechanisms. Compared with N. S group, the tumor inhibition rate of high-, low-dose *P. americana* extracts is 41.24% and 81.08%, respectively. It is showed by flow cytometry test that the extract could induce apoptosis of 2 kinds of tumor cells and affect cell cycle (cells block in G₀/G₁ phase). Through HE staining, tumor cells have more necrosis compared with N. S group and capillaries are rarely seen in and around tumor tissue. Researchers believe that *P. americana* extracts have inhibitory effects on 3LL lung cancer, which may be associated with the expression of cell apoptosis-related genes such as p53 and Bcl-2. The killing effects of antimicrobial peptide from *Musca domestica* larvae

and antimicrobial peptide from *P. americana* nymph on human esophageal carcinoma cells Eca-109 and human leukemia cells K-562 were studied by Zhao Rui-jun *et al.*^[34]. The results showed that the above 2 kinds of antimicrobial peptides have obvious killing effects on Eca-109 and K-562. Meanwhile, the antimicrobial peptide from *P. americana* can promote the growth of 2 carcinoma cells. A total of 147 crude extracts are prepared by Hu Ming-hui, of which nearly 50 have activity and certain selectivity on tumor cell lines such as CNE (human nasopharyngeal carcinoma cells), Hela (cervix carcinoma cells), S-180 (mouse sarcoma cells), PC-3 (prostatic cancer cells), P388DI (mouse leukemia cells) and K-562. IC_{50} of some samples is less than 50 or 10 μ g/ml, from which we know that they have stronger inhibitory effects which are worth further studying^[35].

In recent years, the scholars at Dali University have done many studies on the anti-tumor effects of *P. americana* extracts. For example, Hu Yan-fen *et al.* studied *P. americana* extracts' inhibitory effects in vitro on NCI-H460 (human large lung carcinoma cell), NCI-H446 (human small lung carcinoma cell line) and A549 (human lung adenocarcinoma cell)^[36]. MTT test showed that *P. americana* extracts could inhibit the growth of the above 3 lung adenocarcinoma cells in dose-dependent and time-dependent manner to some extent. The inhibition rate of 300 μ g/ml *P. americana* extracts is 100%. Hu Yan-fen *et al.* also studied *P. americana* extracts' effects on the cell cycle of NCI-H446 and NCI-H460^[37]. MTT and flow cytometry tests showed that *P. americana* extracts not only have cytotoxicity but also affect cell apoptosis rate, cell necrosis rate and cell cycle distribution to some extent. He Zheng-chun *et al.* used MTT method to study the anti-tumor effects of *P. americana* extracts on 12 tumor cell lines, including K-562, HL-60, P388DI, CNE (nasopharyngeal carcinoma cells), KB (oral epithelium carcinoma cells), A-549, HO8910 (ovarian cancer cells), Hela, LS174T (colon cancer cells), Eca-109 and BGC-823^[38-41]. Experimental results showed that IC_{50} of the extracts from many parts of *P. americana* is less than 10 μ g/ml. Thus it can be seen that these extracts have good anti-tumor effects which are worth further studying. In addition, LV Xiao-man *et al.* studied *P. americana* extracts' anti-tumor effects on cell line K-562 in vivo and on S-180 solid tumor mice in vitro, as well as their action mechanisms^[42]. The results showed that the extract CII-3 has the dose-dependent anti-tumor activity in vitro, which is probably associated with inducing cell apoptosis and changing cell cycle. Prepared by Liu Guang-ming *et al.* through polyamide enrichment, reverse phase material preparation and macro porous adsorption resin preparation, the anti-tumor phases of *P. americana* have stronger cytotoxicity against KB, CNE and sarcome S-180, which are possible to be developed into new anti-tumor drugs^[43-45].

3 Conclusions and discussions

To sum up, *P. americana* contains many highly active chemical substances (such as ethanol extract, anti-tumor active constituent CII-3) that have huge application prospects in

anti-tumor. Although many scholars have done studies on chemical constituents and anti-tumor activity of *P. americana*, there are still some shortcomings. For example, it is difficult to separate and identify target components from *P. americana* because this insect contains plenty of proteins, peptides, fats and sterides. Aided by gel (Sepdex), ion change, SDS-PAG and membrane microfiltration, people can use column chromatography technology to separate target components with the purpose of overcoming the above problem^[46]. In addition, *P. americana* extracts have cytotoxicity against many tumor cells, but related mechanisms are not clear. Based on related reports, apart from flow cytometry, immunohistochemistry and Western blot can be used to study the apoptosis mechanism of tumor cells in molecular level, such as determination of cell apoptosis signal paths PI3K/AKT^[47] and MER/ERK^[48].

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