REVIEW

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Recent advances in antineoplastic principles of Traditional Chinese Medicine

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Dedicated to Prof. Dr. Thorsten Beyrich, Ernst-Moritz-Arndt-University, Greifswald, Germany, on the occasion of his 70th birthday

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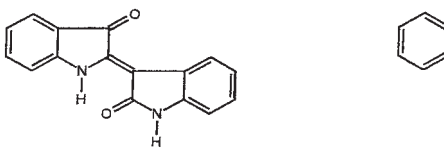
1. Introduction

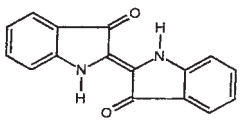
Traditional Chinese Medicine (TCM) is known to be a rich source of biologically active compounds. In the search of new antineoplastic agents, several compounds from TCM were found to be active in experimental and clinical studies. The cytotoxic and antineoplastic mechanisms of these compounds involve DNA intercalation; inhibition of DNA topoisomerases and protein kinases; induction of apoptosis; covalent binding with important enzymes; inactivation of ribosomes; immunostimulation and some unknown mechanisms. Compounds from TCM are relatively non-toxic in comparison with some synthetic agents. In the present paper, the highlights in study on cytotoxic and antineoplastic agents from TCM will be summarized.

2. Indirubin and related bisindoles

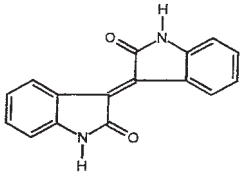
Indirubin is a minor constituent in Indigo naturalis (Qingdai), the dried mass obtained from the leaf of *Baphicacanthus cusia* (Nees) Bremek (Acanthaceae), *Polygonum tinctorium* Ait. (Polygonaceae) or *Isatis indigotica* Fort. (Brassicaceae). Indigo naturalis is listed in the Chinese Pharmacopoeia (Ed. 2000) and is used as an antipyretic, anti-inflammatory and hemostatic agent. Structurally, indirubin represents a bisindole with 3,2′-linkage, related to indigo with 2,2′-linkage and isoindigo with 3,3′-linkage.



Indirubin



Indigo



Isoindigo

2.1. Clinical trials

In the 1960s, Chinese scientists began with the identification of the active principle in a Chinese patent medicine, Danggui Longwei Wan, effectively used as an antileukemic agent [1]. It is listed in the Chinese Pharmacopoeia and is composed of 11 ingredients, including Indigo naturalis. Later, the antileukemic activity of Danggui Longwei Wan was found to be associated with indirubin. In a clinical study, treatment of 314 chronic myelocytic leukemia (CML) patients with indirubin at daily oral dosages of 300–450 mg per patient resulted in 82 cases (26%) of complete remission; 38 cases (12%) of partial remission and 87 cases (28%) of beneficial effect. The overall response rate was 87% [2]. Another clinical trial included 57 patients with CML, treatment with indirubin over a long period resulted in a median survival of 31.5 months. There were no obvious side effects over long-term use of indirubin [3]. A comparative clinical trial revealed that indirubin and busulfan exert similar efficacy. No cross-resistance between the two drugs was observed [4].

2.2 Experimental studies

Indirubin was reported to exert growth inhibition on human mammary carcinoma (MCF-7) and large cell lung carcinoma (LXFL529L) cells *in vitro* with IC_{50} of 4 μM and 11 μM, respectively. Growth inhibition of LXFL529L cells was also observed in nude mice treated orally with indirubin at a daily dosage of 100 mg/kg on days 1–5, 8 and 9 after tumor cell inoculation [5]. Furthermore, indirubin was found to inhibit DNA synthesis in several cell lines [6] and in a cell free assay [7]. In rats bearing W256 sarcoma, i.p. or s.c. administration of indirubin at a daily dosage of 200 mg/kg partially inhibited the incorporation of [^{3}H]thymidine into DNA of tumor tissue [8].

2.3. Mechanisms of action

Studies on antineoplastic mechanisms of indirubin showed that it significantly decreases DNA polymerase 1 activities in CML cells from the peripheral blood of patients [9]. Alterations were seen in the surface morphology of leukocytes and in endoplasmic reticulum, chromatin and nuclear-envelope structures of leukocytes from leukemia patients treated with indirubin [10]. Recently, we have found that indirubin and its derivatives are potent inhibitors of

cyclin-dependent kinases (CDKs). The crystal structure of CDK_2 in complex with indirubin derivatives showed that indirubin derivatives interact with the kinase's ATP-binding site through van der Waals interactions and three hydrogen bonds [11, 12]. Study on indirubin and indigo by electron spin resonance spectrometry demonstrated that their antitumor activities are originated from the C:C double bond [13].

2.4. Toxicity

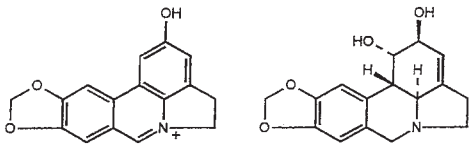
Indirubin is relatively non-toxic. Oral administration of indirubin at daily doses of 100–400 mg/kg to rats for 30 days did not show any effects on leukocyte count or on liver and renal functions. Long-term administration of high doses of indirubin did not affect hematopoietic stem cell production [14]. A subacute toxicity study of indirubin in dogs was reported. No adverse effect was shown at the low daily dosage of 20 mg/kg. At the middle daily dose of 100 mg/kg, mild diarrhea occurred within 10–30 days. Serum glutamic-pyruvic transaminase (SGPT) levels were slightly elevated after 5 months in one out of three treated dogs. At the high daily dose of 200 mg/kg, serious diarrhea and hematofecia occurred during 40–60 days and SGPT levels were elevated after 3 months of treatment [15]. The bone marrow and blood indexes, renal functions, and electrocardiogram were not affected by indirubin [16]. Indirubin is believed to be safe at clinical dosages. In human peripheral lymphocytes [17] and in bone marrow cells of CML patients [18], indirubin did not induce sister chromatid exchanges (SCE).

2.5. N-Methylisoindigo

Bisindole derivatives with 2,2′-, 3,3′- or 3,2′-linkages were compared for their effect on nucleic acid and protein synthesis. Indirubin, indigo and isoindigo were all found to inhibit nucleic acid and protein synthesis in W256 sarcoma cells *in vitro* and *in vivo*. Isoindigo derivatives were reported to be the most potent [19]. *N*-Methylisoindigo (meisoindigo) was more potent than indirubin against W256 sarcoma in rats [20]. The improved absorption of *N*-methylisoindigo, compared to indirubin, may be one of the major factors for the enhancement of antitumor activity. Studies on the mechanism of action of *N*-methylisoindigo indicated that it strongly inhibits DNA biosynthesis in L1210 cells and causes an arrest of S phase cells [21]. At a non-toxic concentration of 0.7 μg/ml, *N*-methylisoindigo induced differentiation of ML-1 human myeloblastic leukemic cells as the most pronounced effect accompanied by the down-regulation of c-*Myb* gene expression. *N*-Methylisoindigo as a second generation agent was chosen for clinical treatment of CML [22].

3. Phenanthridine and benzo[*c*]phenanthridine alkaloids

Lycobetaine (ungeremine, AT-1840) is a quaternary phenanthridinium alkaloid occurred in some amaryllidaceous plants as a minor constituent. It can be easily obtained by oxidation of lycorine, a major phenanthridine alkaloid in several amaryllidaceous plants [23].



Lycobetaine Lycorine

3.1. Clinical trials

In reviews and in meeting reports, lycobetaine was noted to be active in the treatment of cervical, ovarial, gastric and other cancers [24, 25]. The overall response in 233 cases of different cancers was reported to be about 35% [25], however, no detailed information is available.

3.2. Experimental studies

Lycobetaine was reported to exhibit growth inhibition against S180 [26] and KB [27] tumor cells *in vitro*. It exerted a cytocidal effect on gastric cancer cells *in vitro* even at low concentrations. The IC_{50} values of lycobetaine in the clonogenic assay against 21 human tumor xenografts were reported to range from 0.002 μM to 27.5 μM with a mean IC_{50} value of 0.8 μM. Lycobetaine significantly inhibited the proliferation of Ehrlich ascites carcinoma, ascites hepatoma, leukemias L1210 and P388, Lewis lung carcinoma and Yoshida ascites sarcoma in mice or in rats by i.p. injection. In nude mice bearing human gastric cancer xenografts, lycobetaine extended the survival time and decreased the tumor size [28]. Intraperitoneal administration of lycobetaine at a daily dosage of 30 mg/kg on days 1–5 and 8–12 to nude mice after inoculation of LXFL529L cells resulted in significant growth delay of the tumor [29, 30]. No significant myelotoxic, cardiotoxic and hepatotoxic effects of lycobetaine were observed [23].

3.3. Mechanisms of action

Studies on the cytotoxic mechanisms of lycobetaine showed that it intercalates in DNA base pairs, especially in GC-pairs [31]. After incubation of hepatoma cells with lycobetaine, the sensitivity of c-*Myc*, N-*Ras* and β_2-microglobulin genes of tumor cells to DNase I was significantly decreased [32]. Flow cytometrical study demonstrated a high accumulation of G_2/M phase cells in gastric carcinoma [28] and an accumulation of G_2 cells in mouse erythroleukemia [33] following incubation of the cells with lycobetaine. Recently, we have found that lycobetaine is an inhibitos of topoisomerases I and II. Lycobetaine was localized predominantly in the nucleus, competed with ethidium bromide for intercalation into calf thymus DNA and displaced the DNA minor groove binder Hoechst 33258. At growth inhibitory concentrations, lycobetaine inhibited topoisomerases I and II, stabilized the covalent DNA-topoisomerase I intermediate and induced apoptosis. Dose-dependent induction of DNA strand breaks by lycobetaine was detected by single cell gel electrophoresis (comet assay) [29, 30].

3.4. Structure-activity relationships

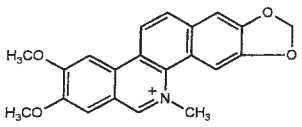
Study on structure-activity-relationship demonstrated that the calculated interaction energy of lycobetaine analogs with double-stranded oligonuclueotides paralleled with their anticancer potency [34, 35]. According to the 3-dimensional structure patterns of drug-oligonucleotide complex, the quaternary nitrogen atom in lycobetaine plays an important role in the formation of the hydrogen bonds between the compound and oligonucleotide [36]. Moreover, the betaine structure and methylenedioxy group in lycobetaine may be critical for its antitumor activity [23].

3.5. Lycorine

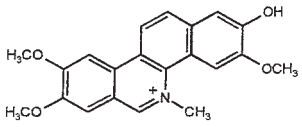
Lycorine was also reported to be cytotoxic [37]. We have found that lycorine is highly active in inhibiting a number of human tumor cell lines *in vitro*, including LXFL529L, Molt4, HL60, K562, U937 [38], GXF251L, and CXF94L [39]. In contrast to lycobetaine, lycorine did not compete with ethidium bromide for intercalation into calf thymus DNA and did not displace the DNA minor groove binder Hoechst 33258 [38, 39].

3.6. Benzo[c]phenanthridinium alkaloids nitidine and fagaronine

Lycobetaine related benzo[*c*]phenanthridinium alkaloids nitidine and fagaronine are major constituents in Radix Zanthoxyli (Liangmianzhen), the root of *Zanthoxylum nitidum* (Roxb.) DC. (Rutaceae) [40]. It is listed in the Chinese Pharmacopoeia. Nitidine chloride was noted to be effective in clinical treatment of CML [41].



Nitidine

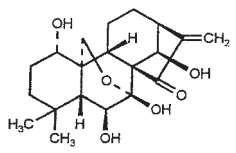


Fagaronine

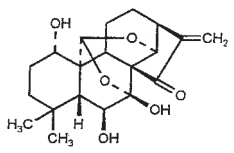
In experimental studies, nitidine was found to increase the life span of mice inoculated with Ehrlich ascites tumor; to cause a decrease in the mitotic index and size of the tumor cells; and to inhibit DNA and RNA synthesis of tumors [42]. Nitidine and fagaronine were reported to bind to calf thymus DNA by intercalation [43] and to be dual poisons of both topoisomerases I and II [44–46] as antitumor machanisms. Fagaronine is a DNA major groove intercalator, does not show any sequence specificity of DNA intercalation, but its highly electronegative oxygen of hydroxy group is shown to be an acceptor of the hydrogen bond with the NH_2 group of guanine base in DNA [47]. Nitidine exhibited strong stabilization of the covalent binary complex formed between topoisomerase I and DNA [40]. Unlike camptothecin as reference compound, nitidine and fagaronine bound directly to and mediated the unwinding of B-form DNA [48]. Inhibition of topoisomerase II by nitidine was observed at higher concentration in comparison to the inhibition of topoisomerase I [44, 49].

4. *Rabdosia* diterpene oridonin

The whole plant *Rabdosia rubescens* (Hemsl.) Hara (Lamiaceae) native to China has been used in folk medicine as antitumor or anti-inflammatory agent. Oridonin, ponicidin and related diterpenes are the cytotoxic principles in *R. rubescens* and other *Rabdosia* species [50].



Oridonin



Ponicidin

4.1. Clinical trails

Treatment of 115 patients suffering from inoperable esophageal carcinoma by chemotherapy alone or chemotherapy plus *R. rubescens* was reported. In a group, out of 31 patients, treated with chemotherapy alone, 10 patients (32.3%) responded to the treatment, including 2 partial response (greater than 50% tumor regression) and 8 minor response. In another group, out of 84 patients, treated with chemotherapy plus *R. rubescens*, 59 patients (70.2%) responded to the treatment, including 10 complete response (100% tumor regression), 16 partial response and 33 minor response. The one-year survival rates of the two groups were 13.6% and 41.3%, respectively. There was no significant difference in the side effects between the two groups [51]. From August 1974 to January 1987, 650 patients with moderately and advanced esophageal cancer were treated with a combination of chemotherapy plus *R. rubescens* or *R. rubescens* plus Chinese patent medicines. Forty patients survived for over 5 years (5-year survival rate 6.15%); 32 for over 6 years; 23 for more than 10 years; and 5 for more than 15 years [52]. In a review, it was noted that oridonin and ponicidin have also been tested in clinical trials for the treatment of esophageal cancer [53], however, no detailed information is available.

4.2. Experimental studies

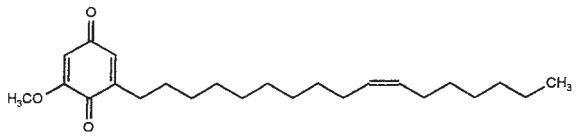
The extract of *R. rubescens* was reported to exert a cytotoxic effect on cisplatin-sensitive human ovarian cancer A2780 cells with an IC_{50} of about 0.6 mg/ml [54]. Oridonin was reported to exhibit proliferation inhibition on human gastric adenocarcinoma cell line MGc80–3 and human esophageal cancer cell line CaEs-17 at concentrations below 15 μg/ml [55]. Oridonin also inhibited Ehrlich ascites carcinoma [56] and L1210 leukemia [57] in mice by i.p. injection. The cell killing rates of oridonin at an i.p. dosage of 15 mg/kg to mice on day 5 and day 8 upon L1210 cells were 73% and 39%. The G_2 and S phases of L1210 cells were prolonged, while G_1 phase was unchanged [57]. Intraperitoneal administration of oridonin at a dose of 15 mg/kg to mice also inhibited the incorporation of [^{3}H]thymidine, [^{3}H]uridine, and [^{3}H]leucine into DNA, RNA, and protein of tumor cells [58, 59]. Oridonin was also found to inhibit DNA synthesis in cell-free system [60]. Oridonin was further reported to show synergistic effects with cisplatin [61] or bleomycin A_5 [62].

4.3. Mechanisms of action

The cytotoxic mechanism of oridonin was postulated to be caused by covalent binding to specific sites of essential enzymes in tumor cells [63]. Oridonin and related diterpenes bearing an α-methylenecyclopentanone structure are electrophilic and can be considered as weak alkylating agents [64]. Oridonin reacted with thiols easily under mild conditions to give the corresponding thioether adducts. The adduct with L-cysteine was formed smoothly and practically quantitatively. However, oridonin did not react with adenosine and cytidine under the same conditions [65].

5. Irisquinone A

Irisquinone A is a 1,4-benzoquinone derivative isolated from the seeds of *Iris pallasii* var. *chinensis* (Iridaceae) as



Irisquinone A

a cytotoxic and radio-sensitizing component [66]. The seed of *I. pallasii* var. *chinensis* is used in Chinese folk medicine as a fertility-regulating agent and for the treatment of malignant diseases.

5.1. Clinical trial

Irisquinone A given orally to 558 patients suffering from lung cancer, esophageal cancer, or superficial metastatic cancer during radiotherapy was noted to contribute significantly to the reduction of tumor size and to the prolongation of survival period of the patients [67].

5.2. Experimental studies

Irisquinone A was found to show growth inhibition against cervical cancer U_{14} and Ehrlich carcinoma in mice by i.p. administration and against lymphosarcoma by i.p. and oral administration [67]. Treatment of mice bearing U_{14} tumor with irisquinone A at an oral dosage of 100 mg/kg or at an i.v. dosage of 5 mg/kg once every other days for 5 times, starting 24 h after implantation, caused a tumor inhibition rate of 35–55% [83]. Radiosensitizing activities of irisquinone A were observed *in vitro* against U_{14} [68], S180 [69] and HeLa cells; in mice against Ma7373 breast cancer; and in nude mice against human intestinal mucoadenocarcinoma [70]. Irisquinone A significantly inhibited the respiration of P388 cells; and decreased the glutathione content in HeLa cells.

5.3. Toxicity

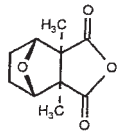
The LD_{50} of irisquinone A in mice was reported to be about 25.4 mg/kg by i.p. and about 2.8 g/kg by oral administration. The chemotherapeutic indices (LD_{50}/ED_{50}) of irisquinone A were estimated to be 5 by i.p. administration and 14 by oral administration. Subcutane toxicities in both rats and dogs were mild. No inhibition on bone marrow was observed [67].

5.4. Mechanisms of action

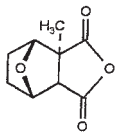
The radiosensitizing effect of oridonin was considered to be inhibition of oxygen consumption and depletion of glutathione in tumor cells [70].

6. Cantharidin and related compounds

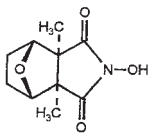
Cantharidin is an active component of mylabris [71], the brister beetle. It is the body of *Myrabris phalerata* Pallas or *M. cichorii* Linnaeus (Meloidae) and is listed in the Chinese Pharmacopoeia. Chemically, cantharidin is 3,6-epoxy-cyclohexan-1,2-dicarboxylic acid anhydride, a rather simple compound. Cantharidin was found to be antitumor active but highly toxic. Cantharidin disodium, the disodium salt of cantharidic acid [72], norcantharidin [73] and *N*-hydroxycantharidinimide [74] are synthetic derivatives of cantharidin.



Cantharidin



Norcantharidin



N-Hydroxycantharidinimide

6.1. Clinical trials

Treatment of 244 cases of primary hepatomas with norcantharidin was reported to result in an effective rate of 58.6%. The one-year survival rate was 30%. Reduction rate of α-fetoprotein and liver size were 39% and 37%, respectively. Norcantharidin did not cause bone marrow suppression. When the cumulative dose exceeded 500 mg, increased leukocyte count was observed [75]. Cantharidin disodium showed less urinary irritation than cantharidin, while norcantharidin showed little to no such irritation [76]. Norcantharidin was also noted for the treatment of esophageal and gastric cancers in China [77]. *N*-Hydroxycantharidinimde has also been recommended for clinical trials due to its low toxicity and broader spectrum of antineoplastic activity than cantharidin [74].

6.2. Experimental studies

Cantharidin, norcantharidin and *N*-hydroxycantharidinimide were reported to be cytotoxic aganist a series of tumor cell lines. Cantharidin exhibited growth inhibition against A2780, ADDP (ovarian cancer); 143B (osteosarcoma); HCT116 and HT29 (colon carcinoma) [78]; and Hep3B (hepatocellular carcinoma) cells [79]. The IC_{50} values of cantharidin on Hep3B cells and normal Chang liver cells were reported to be 2.2 and 30.2 μM [79]. Norcantharidin inhibited the proliferation of K562 cells *in vitro* [80]; and inhibited the growth of $HepG_2$ cells inoculated into nude mice. Intraperitoneal treatment of nude mice bearing $HepG_2$ tumors with norcantharidin at a daily dosage of 2 mg/kg for 12 days, the mean survival time of treated mice was 194 days compared to 129 days for control mice [81].

6.3. Mechanisms of action

The cytotoxic mechanism of cantharidin and its derivatives remains unclear. Cantharidin-treated Hep3B cells showed no evidence of major alterations in the cell cycle distribution within 1 h, but an accumulation of G_2/M phase after 36 h. Moreover, the treated Hep3B cells had a rounded and shrunken appearance. The microvilli of treated cells were reduced in number and replaced by numerous blebs. It was suggested that cantharidin can induce acute and lethal toxic effects on Hep3B cells by inhibiting the mitochondria energy system [79]. Norcantharidin also significantly inhibited the proliferation of HL60 cells, arrested the cells at S and G_2/M phases and induced apoptosis *in vitro* [82]. Cantharidin at a concentration of 2 μg/ml and norcantharidin at a concentration of 10 μg/ml induced apoptosis in K562 cells [83]. The cytotoxic activity of norcantharidin was suggested to be associated with endogenous p53 gene status, because norcantharidin was cytotoxic against RT-2 (wild-type p53) glioblastoma cell line, but not U251 (mutant p53) cell line. Restoring wild-type p53 gene function in the resistant U251 cells after adenoviral infections, the tumor cells become susceptible to norcantharidin [84]. In human hepatoma cells, norcantharidin at a concentration of 10 μg/ml induced apoptosis, which closely related with tumor cell M phase arrest and with the decrease of Bcl-2 expression [85]. It should be mentioned that cantharidin as a potent and specific inhibitor of protein phosphatases 1 and 2A [86] prevented all the apoptotic characteristics in human ML-1 cells induced by etoposide [87].

6.4. Structure-activity relationships

The stereochemistry of cantharidin derivatives may be an important factor that affects their biological activity. The 6-membered ring should possess boat conformation with the oxygen bridge and the 5-membered ring should be planar. One of the two short chain substituents at the joining points and the oxygen bridge are functional groups essential for the antineoplastic activity [53]. It appeared that the two methyl groups of cantharidin are associated with urinary irritation [76].

7. Arsenic trioxide

Arsenic trioxide (As_2O_3) was used in TCM in the past for the treatment of malaria, asthma and rheumatic diseases. The use of arsenic trioxide was declined in the last century on the base of its genotoxic and carcinogenic potentials. Arsenic trioxide was long recognized as a human carcinogen [88, 89]. By the mid 1990s, Chinese physicians reported the therapeutic effect of arsenic trioxide in the treatment of acute promyelocytic leukemia (APL) and the clinical trials have been begun in the 1970s.

7.1. Clinical trials

The first report included 15 APL patients at relapse after all-*trans*-retinoic acid treatment. Treatment with arsenic trioxide alone at a daily i.v. dosage of 10 mg per patient resulted in complete remission in 9 out of 10 patients [90]. Thereafter, a number of clinical studies using arsenic trioxide for the treatment of APL were reported [91–93]. A retrospective study on long-term survival in 120 APL patients treated with all-*trans*-retinoic acid, chemotherapy and arsenic trioxide revealed a median relapse-free survival of 26 months, an estimated 5-year relapse-free survival of 34% and an estimated 5-year median overall survival of 52.5% [94]. Randomized clinical trials in the USA led to FDA approval of arsenic trioxide for relapsed or refractory APL in September 2000 [95]. Besides APL, arsenic trioxide is used for clinical trials in hematologic malignancies, including acute and chronic myeloid leukemia, acute and chronic lymphocytic leukemia, non-Hodgkin's and Hodgkin's diseases, myelodysplastic syndrome, and multiple myeloma. Arsenic trioxide is also supporting research in solid tumors, such as advanced hormone-refractory prostate cancer, renal cell cancer, cervical cancer and refractory transitional cell carcinoma of the bladder [96].

7.2. Exyperimental studies

In vitro experiments showed that arsenic trioxide significantly inhibited the growth of Neuro-2a neuroblastoma cells at a concentration of 2 μM and induced cell apoptosis in Neuro-2a [97] and other neuroblastoma cell lines [98]. Induction of apoptosis by arsenic trioxide was also observed in human esophageal carcinoma cells [99]; in human MGC-803 gastric cancer cells [100]; and in human megakaryocytic leukemia cells [101] at concentrations of 0.01–1 μM. In HCE16/3 human cervical epithelial cells immortalized by human papillomavirus HPV16 DNA, arsenic trioxide reduced cell survival, induced apoptosis, arrested cells in G_1 phase and selectively inhibited the expression of viral early genes [102]. Apoptosis and growth inhibition in malignant lymphocytes after incubation with arsenic trioxide were observed at clinically achievable concentrations (1–2 μM) [103]. In *in vivo* experimental studies, arsenic trioxide given orally to mice at daily dosages of 2.0 and 3.5 mg/kg for 7 days inhibited the inoculated HepA solid and ascitic liver tumor. Some tumor cells showed the morphological characteristics of apoptosis [104]. Arsenic trioxide was also reported to cause selective necrosis in locally advanced methylcholanthrene-induced fibrosarcoma in BALB/c mice at a single i.p. dose of 10 mg/kg. Normal skin, muscle, and kidney were relatively unaffected by arsenic trioxide [105].

7.3. Toxicities

The toxic side effects of arsenic trioxide were reported to be relatively mild and included skin rash, hyperleukocytosis, APL differentiation syndrome, prolonged QT interval on electrocardiogram, hyperglycemia, fatigue, and musculoskeletal pain [91]. No bone marrow toxicity was observed [90]. Huang et al. have reported that the most common acute toxicity was fluid retention, including weight gains and pleuro-pericardial effusions. Evident polyneuropathy compatible with chronic arsenic toxicity was noted in some patients who received arsenic trioxide maintenance therapy [106]. In an APL patient, complete atrioventricular block was observed after arsenic trioxide treatment which seemed reversible and was not correlated to the leukemia status [107]. Niu et al. have reported the hepatotoxicity of arsenic trioxide, which was documented in 7 of 11 newly diagnosed APL cases including 2 deaths, in contrast to the mild liver dysfunction in one third of the relapsed patients [92]. Westervelt et al. have also reported 3 sudden deaths among 10 APL patients during the first cycle of arsenic trioxide treatment at a daily i.v. dosage of 0.1 mg/kg [93].

7.4. Mechanisms of action

APL accounts for about 10% of all acute myeloid leukemias and is characterized by the chromosomal translocation t(15;17), which fuses the retinoic acid receptor-(RAR) gene to the promyelocytic leukemia gene (PML). The PML/RAR fusion gene plays an important role in leukemogenesis through antagonizing retinoic acid signalling and the regulatory pathways mediated by PML. PML/RAR was proposed to block myeloid differentiation through inhibition of nuclear receptor response [108]. The action mechanisms of arsenic trioxide against APL were suggested to involve the induction of apoptosis and differentiation [109, 110] and the rapid modulation and degradation of PML/RAR proteins [111]. In a clinical study, 8 of 11 APL patients who initially tested positive for the PML/RAR fusion transcript by the reverse transcription polymerase chain reaction (RT-PCR) assay later tested negative; 3 other patients, who persistently tested positive, relapsed early [92].

8. Trichosanthin and related ribosome-inactivating proteins

Ribosome-inactivating proteins (RIP), widespread throughout the plant kingdom, are a group of proteins that are able to inactivate eukaryotic protein synthesis by attacking the 28S ribosomal RNA [112]. One of the first isolated, purified and sequenced RIP is trichosanthin from the root of *Trichosanthes kirilowii* Maxim. (Cucurbitaceae). Further RIPs from TCM are e.g. α-kirilowin, β-kirilowin

and trichokirin from the seeds of *T. kirilowii* [113, 114]; luffins from the fruits and seeds of *Luffa cylindrica* (L.) Roem. (Cucurbitaceae) [115, 116]; cochinchinin and momorcochin S from the seeds of *Momordica cochinchinensis* (Lour.) Spreng. (Cucurbitaceae) [117, 118]; cinnamomin and camphorin from the seeds of *Cinnamomum camphora* (L.) Sieb. (Lauraceae) [119–121]; pokeweed antiviral proteins from the leaves and seeds of *Phytolacca americana* L. (Phytolaccaceae) [122, 123]; ricin from the seeds of *Ricinus communis* L. (Euphorbiaceae) [124, 125]. Radix Trichosanthis (Tianhuafen), the root, Fructus Trichosanthis (Gualou), the ripe fruit, Pericarpum Trichosanthis (Gualoupi), the pericarp of the ripe fruits, and Semen Trichosanthis (Gualouzi), the ripe seed of *T. kirilowii* or *T. rosthornii*; Retinervus Luffae Fructus (Sigualuo), the fibrovascular bundle of the ripe fruits of *L. cylindrica*; Semen Momordicae (Mubiezi), the ripe seed of *M. cochinchinensis*; Semen Ricini (Bimazi), the ripe seed of *R. communis*; Radix Phytolaccae (Shanglu), the root of *P. americana* and *P. acinosa* are listed in the Chinese Pharmacopoeia.

Trichosanthin is a relatively simple linear polypeptide composed of 246(7) amino acid residues with a C-terminus of Asn-Asn-Met or Asn-Asn-Met-Ala. The molecular weight of trichosanthin is about 27 kDa.

```
1         10        20        30        40        50        60
DVSFRLSGATSSSYGVFISNLRKALPNERKLYDIPLLRSSLPGSQRYALIHLTNYADETI

          70        80        90        100       110       120
SVAIDVTNVYIMGYRAGDTSYFFNEASATEAAKYVFKDAMRKVTLPYSGNYERLQTAAGK

          130       140       150       160       170       180
IRENIPLGLPALDSAITTLFYYNANSAASALMVLIQSTSEAARYKFIEQQIGKRVDKTFL

          190       200       210       220       230       240
PSLAIISLENSWSALSKQIQIASTNNGQFESPVVLINAQNQRVTITNVDAGVVTSNIALL


LNRNNM(A)
```

8.1. Clinical trials

Trichosanthin was reported to be used for the treatment of abnormal growth of trichoblastic cells and choriocarcinomas [126]. Clinical trials using trichosanthin for the treatment of hydatidiform mole resulted in a success in 44 of 52 patients (85%) including 38 complete remissions (73%) and 6 partial remissions (12%) [127].

8.2. Experimental studies

Trichosanthin was found to selectively damage choriocarcinoma and melanoma cells *in vitro*. Cytotoxicity profiles of trichosanthin differed from those of anti-cancer drugs which interfere with DNA metabolism [128]. Trichosanthin was also used to form immunotoxins with monoclonal antibodies which were able to inhibit the growth of human melanoma and hepatpma cells *in vitro*. The cytotoxicity of the conjugate to M21 human melanoma cells was 2000-fold higher than that of a mixture composed of antibody and trichosanthin [129]. The cytotoxicity of the immunotoxin against hepatoma cells was 500-fold higher than that of free trichosanthin [130]. The *in vitro* cytotoxicity of trichosanthin conjugate with monoclonal antibody to human colon carcinoma (LoVo) cells was approximately 150-fold higher than that of free trichosanthin or 2000-fold higher that of the conjugate of trichosanthin with normal mouse immunoglobulin IgG. *In vivo* experiments showed that the immunotoxin also effectively inhibited human colon carcinoma xenografts in nude mice and prolonged the life span of tumor-bearing animals without obvious toxic effect to host mice [131]. Pokeweed antiviral proteins [132, 133] and ricin [134] were also used for preparation of immunotoxins with monoclonal antibodies. Ricin immunotoxins were reported to be entered in clinical trials mainly in the treatment of lymphomas [135–140].

8.3. Mechanisms of action

Trichosanthin as a ribosome-inactivating protein inactivated ribosomes and arrested protein synthesis by removing a specific adenine from 28S rRNA. The binding modes of trichosanthin were studied with oligonucleotides GAG, GAGA, and CGAGAG as substrates. All the oligoribonucleotides can dock into the active cleft of trichosanthin without unfavorable contacts [141, 142]. Position 120–123 of the native trichosanthin molecule may play a critical role in maintaining its inhibitory activity on protein synthesis [143, 144]. Fragments corresponding to amino acids 1–72 and 153–246 might be the antigenic sites [145]. Recently, trichosanthin was also reported to induce apoptosis in HeLa cells [146].

9. Polysaccharides

9.1. Fungal polysaccharides

A number of polysaccharides from fungi were reported to exhibit immunostimulating and antitumor effects [147, 148]. Lentinan from *Lentinus edodes* (Berk.) Sing. (Tricholomataceae) is one of the most studied fungal polysaccharides. It is a $(1 \rightarrow 3)$-β-glucan highly branched with $(1 \rightarrow 3)$-β- and $(1 \rightarrow 6)$-β-linked glucose residues exist mainly as linear triple-helical structures in aqueous solution. The molecular weight of lentinan was estimated to be about 500 kDa [149]. Krestin (PSK) [150] and PSP [151] are representative polysaccharide peptides from the CM-101 strain and the COV-1 strain, respectively, of *Coriolus versicolor* (Fr.) Quel. (Polyporaceae). Krestin is a protein-bound β-glucan containing approximately 25% protein. PSP is a polysaccharide peptide with a molecular weight of approximately 100 kDa. Glutamic and aspartic acids are abundant in the polypeptide component of PSP, whereas its polysaccharide component is composed of monosaccharides with α-$(1 \rightarrow 4)$- and β-$(1 \rightarrow 3)$-glucosidic linkages [147].

Further fungal polysaccharides with immunostimulating and antitumor activities were isolated from *Auricularia auricula* (L. ex Hook) Underw. (Auriculariaceae) [152]; *Cordyceps sinensis* (Berk.) Sacc. (Clavicipitaceae) [153], *Ganoderma lucidum* (Leys. ex Fr.) Karst. (Polyporaceae) [154, 155]; *Polyporus umbellatus* (Pers.) Fries (Polyporaceae) [156, 157]; *Poria cocos* (Schw.) Wolf (Polyporaceae) [158]; and *Tremella fuciformis* Berkely (Tremellaceae) [159, 160].

Cordyceps (Dongchongxiacao), the dried complex of the sclerotium of *C. sinensis* and the larve corpses of insects of the family Hepialidae; ganoderma (Lingzhi), the fruiting body of *G. lucidum*; polyporus (Zhuling), the fungal body of *P. umbellatus*; and poria (Fuling), the sclerotium of *P. cocos*, are all listed in the Chinese Pharmacopoeia, while tremella (Baimuer) and auricularia (Muer) are edible mushrooms.

9.1.1. Clinical trials

A multi-center prospective study on lentinan in patients with advanced unresectable and recurrent gastric cancer showed survival prolongation and improvement in life

quality when used in combination with other chemotherapeutic agents. Median survival time of patients treated with lentinan was significantly longer than those of patients without lentinan treatment (297 days *vs.* 199 days) [161]. Lentinan at a daily i.v. dosage of 2 mg per patient was effectively used for postoperative therapy of gastric cancer combined with 5′-deoxy-5-fluorouridine [162], cisplatin, 5-FU [163], and tegafur [164]. An increase of more than 50% in IL-1β production in the peripheral blood of cancer patients associated with lentinan was observed [165, 166]. An enhanced induction of lymphokine-activated killer (LAK) cell activity in patients with gastric carcinoma was determined after lentinan administration [167]. Krestin was reported to significantly extend the five-year survival rate of patients suffering from cancers of the stomach, colon-rectum, esophagus, nasopharynx, and lung (non-small cell) [147]. PSP was subjected to phase II and phase III trials in China. In double-blind studies, PSP significantly extended five-year survival in esophageal cancer patients. It improved life quality, provided substantial pain relief, and enhanced immune status in 70%–97% of cancer patients [147].

9.1.2. Experimental studies

Lentinan [168, 169], krestin [170, 171] and PSP [172–175] were all reported to exhibit significant immunostimulating effects in experimental animals, indicating that they act as biological response modifiers and can be used as adjuvants in tumor treatment.

9.2. Plant polysaccharides

A number of polysaccharides with immunostimulating and antitumor activities were isolated from Chinese medicinal herbs used as general tonic, such as Radix Astragali (Huangqi), the root of *Astragalus membranaceus* Bge. or *A. membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao (Fabaceae) [176–178]; Fructus Lycii (Gouqizi), the ripe fruits of *Lycium barbarum* L. (Solanaceae) [179–182]; and Radix Codonopsis Pilosulae (Dangshen), the root of *Codonopsis pilosula* (Franch.) Nannf., *C. pilosula* Nannf. var. *modesta* (Nannf.) L.T. Shen or *C. tangshen* Oliv. (Campanulaceae) [183].

9.2.1. Clinical trials

The root of *A. membranaceus* was reported to be used as clinical adjuvant in radiotherapy or chemotherapy of cancer, such as small cell lung cancer [184]. A significant immunorestorative activity of the polysaccharide fraction from the root of *A. membranaceus* were observed [185–187]. In a clinical trial, 79 advanced cancer patients were treated with LAK/IL-2 combined with *L. barbarum* polysaccharides. Results from 75 evaluable patients indicated an objective regression of cancer in patients with malignant melanoma, renal cell carcinoma, colorectal carcinoma, lung cancer, and nasopharyngeal carcinoma. The response rate of patients treated with LAK/IL-2 plus *L. barbarum* polysaccharide was 41% compared to 16% of patients treated with LAK/IL-2 alone. The mean remission periode in patients treated with LAK/IL-2 plus polysaccharides also lasted significantly longer. Treatment with LAK/IL-2 plus polysaccharides also led to a more markedly increase in natural killer (NK) cell and LAK cell activity treatment with LAK/IL-2 alone [188]. The polysaccharide significantly increased T lymphocyte blastogenetic rate and phagocytosis rate of macrophages in 171 cancer patients after radiotherapy [189]. The root of *C. pilosula* was reported to be used as an adjuvant in 76 cancer patients during radiotherapy and to reduce the immunosuppressive effect of radiation. However, it did not show influence on hemoglobin level and leukocyte count [190].

9.2.2. Experimental studies

The polysaccharides from the root of *A. membranaceus* [191–194]; the fruits of *L. barbarum* [195–197]; and the root of *C. pilosula* [198–200] were all reported to exhibit marked immunostimulating and antitumor effects in experimental animals. The antitumor effect of these plant polysaccharides were suggested to be mainly caused by their immunomodulating activities [201–204].

10. Conclusion

A series of compounds from TCM, which found to be active against malignant diseases both in experimental studies and clinical trials, have been summarized in the present paper. In contrast to the synthetic antineoplastic agents, these compounds are relatively low toxic. In recent years, a number of studies on their cytotoxic and antineoplastic mechanisms have been reported. They involve DNA intercalation; inhibition of DNA topoisomerases I and II; inhibition of protein kinases; induction of apoptosis; covalent binding with important enzymes; inactivation of ribosomes; and immunostimulation. Fungal and plant polysaccharides from TCM used as general tonic are useful as adjuvants in combination with other antineoplastic agents.

Acknowledgement: The author thanks Mrs. I. Hemm for her help during preparation of the manuscript.

References

1 Institute of Haematology, Chinese Academy of Medical Sciences: Chin. J. Intern. Med. **15**, 86 (1979)
2 Indirubin cooperative group: Chin. J. Hematol. **1**, 132 (1980)
3 Qian, L. S.; Xue, Y. P.; Zhang, X. M.; Yang, T. Y.; Yan, W. W.; Wang, Z. C.: Chin. J. Hematol. **12**, 125 (1991)
4 Zhang, Z. N.; Liu, E. K.; Zheng, T. L.; Li, D. G.: J. Trad. Chin. Med. **5**, 246 (1985)
5 Hoessel, R.: Thesis, University of Kaiserslautern, Germany (1999)
6 Wu, G. Y.; Fang, F. D.; Liu, J. Z.; Chang, A.; Ho, Y. H.: Chinese Med. J. **60**, 451 (1980)
7 Zhang, L.; Wu, G. Y.; Qiu, C. C.: Acta Acad. Med. Sin. **7**, 112 (1985)
8 Du, D. J.; Ceng, Q. T.: Chin. Trad. Herbal Drugs **12**, 406 (1981)
9 Gan, W. J.; Yang, T. Y.; Wang, Z. C.; Qian, L. S.; Ma, J.; Ge, Y. Q.; Cheng, B. J.; Li, Z. M.; Bo, H. Q.: Chin. Biochem. J. **3**, 225 (1987)
10 Lee, K.; Shih, C. Y.; Yang, T. Y.; Chen, L. S.; Chao, W. M.; Sun, C. S.; Wang, T. C.; Pien, S. K.; Sing, K. H.: Nat. Med. J. China **59**, 129 (1979)
11 Hoessel, R.; Leclerc, S.; Endicott, J. A.; Nobel, M. E.; Lawrie, A.; Tunnah, P.; Leost, M.; Damiens, E.; Marie, D.; Marko, D.; Niederberger, E.; Tang, W.; Eisenbrand, G.; Meijer, L.: Nat. Cell Biol. **1**, 60 (1999)
12 Marko, D.; Schaetzle, S.; Friedel, A.; Genzlinger, A.; Zankl, H.; Meijer, L.; Eisenbrand, G.: Br. J. Cancer **84**, 283 (2001)
13 Chen, K. Y.; Wang, Z. F.; Li, C. Y.; Li, W. X.: Chem. J. Chin. Univ. **10**, 869 (1989)
14 Wang, J. H.; You, Y. C.; Mi, J. X.; Ying, H. G.: Acta Pharmacol. Sinica **2**, 241 (1981)
15 Wen, Z. J.; Liu, Y.; Yi, Z. P.; Yang, Y. S.: Bull. Chin. Mater. Med. **13**, 306 (1988)
16 Sichuan Institute of Traditional Chinese Medicine: Chin. Trad. Herbal Drugs **12**, 27 (1981)
17 Cai, Y. Y.; Xu, C. L.; Li, S. H.; Liu, Y.: Acta Acad. Med. Sin. **5**, 161 (1983)

18 Feng, B. Z.: Chin. J. Oncol. **6**, 357 (1984)
19 Wu, K. M.; Zhang, M. Y.; Fang, Z.; Huang, L.: Acta Pharm. Sin. **20**, 821 (1985)
20 Gu, Y. C.; Li, G. L.; Yang, Y. P.; Fu, J. P.; Li, C. Z.: Acta Pharm. Sin. **24**, 629 (1989)
21 Ji, X. J.; Liu, X. M.; Li, K.; Chen, R. H.; Wang, L. G.: Biomed. Environ. Sci. **4**, 332 (1991)
22 Liu, X. M.; Wang, L. G.; Li, H. Y.; Ji, X. J.: Biochem. Pharmacol. **51**, 1545 (1996)
23 He, H. M.; Wenig, Z. Y.: Acta Pharm. Sin. **24**, 302 (1989)
24 Xu, B.: Mem. Inst. Oswaldo Cruz. **86** (Suppl 2), 51 (1991)
25 Xu, B.: Proceedings of Intern. Summit on Drugs from Natural Products, October 9–12, 1995, Beijing, China, Vol 1
26 Ghosal, S.; Singh, S. K.; Kumar, Y.; Unnikrishnan, S.; Chattopadhyay, S.: Planta Med. **54**, 114 (1988)
27 Wang, X. W.; Yu, W. J.; Shen, Z. M.; Yang, J. L.; Xu, B.: Acta Pharmacol. Sin. **8**, 86 (1987)
28 Wu, Y. L.; Wu, Y. X.; Yu, C. S.; Zhang, S. Y.; Su, Z. C.; Jiang, S. J.: Shanghai Med. J. **11**, 683 (1988)
29 Marko, D.; Niederberger, E.; Tang, W. C.; Spitzmueller, B.; Fiebig, H. H.; Eisenbrand, G.; Roth, T.: Proceedings of 89th Ann. Meet. of AACR, March 28-April 1, 1998, New Orleans, LA, #2871
30 Niederberger, E.; Roth, T.; Schulte, K.; Tang, W. C.; Genzlinger, A.; Zankl, H.; Fiebig, H. H.; Eisenbrand, G.; Marko, D.: Brit. J. Cancer **85**, 1585 (2001)
31 Liu, J.; Yang, S. L.; Xu, B.: Acta Pharmacol. Sin. **10**, 437 (1989)
32 Liu, J.; Yang, S. L.; Xu, B.: Sci. China **33B**, 1459 (1990)
33 Xu, B.: Am. J. Chin. Med. **9**, 268 (1981)
34 Wang, P.; Shi, G. B.; Song, G. Q.; Chen, K. X.; Ji, R. Y.: Acta Biochim. Biophys. Sin. **28**, 703 (1996)
35 Chen, J. Z.; Chen, K. X.; Jiang, H. L.; Lin, M. W.; Ji, R. Y.: Prog. Nat. Sci. **7**, 329 (1997)
36 Gan, L.; Liu, X. J.; Chen, K. L.; Ji, Y. Y.: Gaojishu Tongxun **2**, 30 (1992)
37 Campbell, W. E.; Nair, J. J.; Gammon, D. W.; Bastida, J.; Codina, C.; Viladomat, F.; Smith, P. J.; Albrecht, C. F.: Planta Med. **64**, 91 (1998)
38 Niederberger, E.: Thesis, University of Kaiserslautern, Germany (1998)
39 Schulte, K.: Thesis, University of Kaiserslautern, Germany (2000)
40 Fang, S. D.; Wang, L. K.; Hecht, S. M.: J. Org. Chem. **58**, 5025 (1993)
41 Zhu, D. Y.: Abstr. Chin. Med. (Hong Kong) **1**, 251 (1987)
42 Fan, Y. J.; Zhou, J.; Li, M.: Acta Pharmacol. Sin. **2**, 46 (1981)
43 Kubova, N.; Smekal, E.; Kleinwachter, V.; Cushman, M.: Stud. Biophys. **114**, 251 (1986)
44 Wang, L. K.; Johnson, R. K.; Hecht, S. M.: Chem. Res. Toxicol. **6**, 813 (1993)
45 Larsen, A. K.; Grondard, L.; Couprie, J.; Desoize, B.; Comoe, L.; Jardillier, J. C.; Riou, J. F.: Biochem. Pharmacol. **46**, 1403 (1993)
46 Holden, J. A.; Wall, M. E.; Wani, M. C.; Manikumar, G.: Arch. Biochem. Biophys. **370**, 66 (1999)
47 Fleury, F.; Sukhanova, A.; Ianoul, A.; Devy, J.; Kudelina, I.; Duval, O.; Alix, A. J.; Jardillier, J. C.; Nabiev, I.: J. Biol. Chem. **275**, 3501 (2000)
48 Del Poeta, M.; Chen, S. F.; Von Hoff, D.; Dykstra, C. C.; Wani, M. C.; Manikumar, G.; Heitman, J.; Wall, M. E.; Perfect, J. R.: Antimicrob. Agents Chemother. **43**, 2862 (1999)
49 Wang, X.; Henningfeld, K. A.; Hecht, S. M.: Biochemistry **37**, 2691 (1998)
50 Li, B. L.; Chen, S. N.; Shi, Z. X.; Chen, Y. Z.: Phytochemistry **53**, 855 (2000)
51 Wang, R. L.; Gao, B. L.; Xiong, M. L.; Mei, Q. D.; Fan, K. S.; Zuo, Z. K.; Lang, T. L.; Gao, G. Q.; Ji, Z. C.; Wie, D. C.: Chin. J. Oncol. **8**, 297 (1986)
52 Wang, R. L.: Chin. J. Oncol. **15**, 300 (1993)
53 Lou, F. C.; Ding, L. S.; Ma, Q. Y.; Du, F. L.: J. Nanjing Coll. Pharm. **17**, 152 (1986)
54 Yu, J. J.; Reed, E.: Oncol. Rep. **2**, 571 (1995)
55 Li, X. T.; Lin, C.; Li, P. Y.: Chin. J. Oncol. **8**, 184 (1986)
56 Fujita, T.; Takeda, Y.; Sun, H. D.; Minami, Y.; Marunaka, T.; Takeda, S.; Yamada, Y.; Togo, T.: Planta Med. **54**, 414 (1988)
57 Wang, M. Y.; Lin, C.; Zhang, T. M.: Acta Pharmacol. Sin. **6**, 195 (1985)
58 Wang, M. Y.; Lin, C.; Zhang, T. M.: Acta Pharmacol. Sin. **8**, 164 (1987)
59 Li, Y.; Zhang, T. M.: Acta Pharmacol. Sin. **8**, 271 (1987)
60 Li, Y.; Zhang, T. M.: Acta Pharmacol. Sin. **9**, 465 (1988)
61 Gao, Z. G.; Ye, Q. X.; Zhang, T. M.: Acta Pharmacol. Sin. **14**, 561 (1993)
62 Shou, M. G.; Wang, M. Y.; Wang, Q., Zhang, T. M.: Acta Pharmacol. Sin. **8**, 83 (1987)
63 Fujita, E.; Nagao, Y.; Node, M.; Kaneko, K.; Nakazawa, S.; Kuroda, H.: Experientia **32**, 203 (1976)
64 Zhai, J. K.; Han, W. C.; Ju, X. H.: Acta Chim. Sin. **51**, 854 (1993)
65 Fujita, E.; Nagao, Y.; Kaneko, K.; Nakazawa, S.; Kuroda, H.: Chem. Pharm. Bull. (Tokyo) **24**, 2118 (1976)
66 Wang, X. W.: Drugs Future **24**, 613 (1999)
67 Li, D. H.; Hao, X. G.; Zhang, S. K.; Wang, S. X., Liu, R. Y.; Ma, K. S.; Yu, S. P.; Jiang, H.; Guan, J. F.: Acta Pharmacol. Sin. **2**, 131 (1981)
68 Wang, S. X., Liu, M. F.; Yuan, L.; Zhang, W. L.; Li, D. H.: Chin. J. Clin. Oncol. **13**, 241 (1986)
69 Liang, J. P.; Wie, Z. Q.; Zhang, L., Jiang, Y. P.; Wang, J. F.; Zhang, X. W.; Guo, H. Y.; Li, W. J.: Fushe Yanjiu Yu Fushe Gongyi Xuebao **18**, 45 (2000)
70 Li, W. M.; Wang, S. H.; Kuang, P.; Qu, B. X.; Song, H. L.; Zhu, L. X.: Tumor **7**, 97 (1987)
71 Chen, G. F.: Chin. J. Pharm. Anal. **6**, 45 (1986)
72 Fu, N. W.; Zhang, L. S.; Quan, L. P.: Chin. J. Oncol. **2**, 96 (1980)
73 Liu, J. Y.; Zhang, B. X.; Sun, J. L.: Acta Pharm. Sin. **18**, 752 (1983)
74 Lou, F. C.; Ding, L. S.; Ma, Q. Y.; Du, F. L.: J. Nanjing Coll. Pharm. **17**, 152 (1986)
75 Wang, G. S.; Zhong, H. Y.; Huang, J. K.; Lu, F. X.; Yang, K. Z.; Liu, Z. C.; Yang, B. Y.; Huang, D. T.: Chin. Pharm. Bull. **21**, 90 (1986)
76 Wang, G. S.: J. Ethnopharmacol. **26**, 147 (1989)
77 Liu, X. H.; Bravo-Cuellar, A.; Breard, J.; Metzger, G.; Comisso, M.; Mathe, G.; Orbach-Arbouys, S.: Int. J. Immunother. **7**, 37 (1991)
78 McCluskey, A.; Bowyer, M. C.; Collins, E.; Sim, A. T. R.; Sakoff, J. A.; Baldwin, M. L.: Bioorg. Med. Chem. Lett. **10**, 1687 (2000)
79 Wang, C. C.; Wu, C. H.; Hsieh, K. J.; Yen, K. Y.; Yang, L. L.: Toxicology **147**, 77 (2000)
80 Yi, S. N.; Wass, J.; Vincent, P.; Iland, H.: Leuk. Res. **15**, 883 (1991)
81 Yang, E. B.; Tang, W. Y.; Zhang, K.; Cheng, L. Y.; Mack, P. O.: Cancer Lett. **117**, 93 (1997)
82 Liu, X. L.; Chen, J. X.; Liu, Y.: J. Beijing Univ. Trad. Chin. Med. **23**, 35 (2000)
83 Sun, Z. X.; Wie, Y. L.; Zhao, T. D.; Li, J. S.: Jiepou Xuebao **31**, 56 (2000)
84 Hong, C. Y.; Huang, S. C.; Lin, S. K.; Lee, J. J.; Chueh, L. L.; Lee, C. H.; Lin, J. H.; Hsiao, M.: Biochem. Biophys. Res. Commun. **276**, 278 (2000)
85 Sun, Z. X.; Ma, Q. W.; Zhao, T. D.; Wie, Y. L.; Wang, G. S.; Li, J. S.: World J. Gastroenterol. **6**, 263 (2000)
86 Pahan, K.; Sheikh, F. G.; Namboodiri, A. M.; Singh, I.: J. Biol. Chem. **273**, 12219 (1998)
87 Morana, S. J., Wolf, C. M.; Li, J.; Reynolds, J. E.; Brown, M. K.; Eastman, A.: J. Biol. Chem. **271**, 18263 (1996)
88 Bates, M. N.; Smith, A. H.; Cantor, K. P.: Am. J. Epidemiol. **141**, 523 (1995)
89 Ferreccio, C.; Gonzalez, C.; Milosavjlevic, V.; Marshall, G.; Sancha, A. M.; Smith, A. H.: Epidemiology **11**, 673 (2000)
90 Shen, Z. X.; Chen, G. Q.; Ni, J. H.; Li, X. S.; Xiong, S. M., Qiu, Q. Y.; Zhu, J.; Tang, W.; Sun, G. L.; Yang, K. Q.; Chen, Y.; Zhou, L.; Fang, Z. W.; Wang, Y. T.; Ma, J.; Zhang, P.; Zhang, T. D.; Chen, S. J.; Chen, Z.; Wang, Z. Y.: Blood **89**, 3354 (1997)
91 Soignet, S. L.; Maslak, P.; Wang, Z. G.; Jhanwar, S.; Calleja, E.; Dardashti, L. J.; Corso, D.; DeBlasio, A.; Gabrilove, J.; Scheinberg, D. A.; Pandolfi, P. P.; Warrell, R. P. Jr.: N. Engl. J. Med. **339**, 1341 (1998)
92 Niu, C.; Yan, H., Yu, T., Sun, H. P.; Liu, J. X.; Li, X. S.; Wu, W.; Zhang, F. Q.; Chen, Y.; Zhou, L.; Li, J. M.; Zeng, X. Y.; Yang, R. R.; Yuan, M. M.; Ren, M. Y.; Gu, F. Y.; Cao, Q.; Gu, B. W.; Su, X. Y.; Chen, G. Q.; Xiong, S. M.; Zhang, T. D.; Waxman, S.; Wang, Z. Y.; Chen, S. J.: Blood **94**, 3315 (1999)
93 Westervelt, P.; Brown, R. A.; Adkins, D. R.; Khoury, H.; Curtin, P.; Hurd, D.;. Luger, S. M.; Ma, M. K.; Ley, T. J.; DiPersio, J. F.: Blood **98**, 266 (2001)
94 Hu, J.; Shen, Z. X.; Sun, G. L.; Chen, S. J.; Wang, Z. Y.; Chen, Z.: Int. J. Hematol. **70**, 248 (1999)
95 Antman, K. H.: Oncologist **6** (Suppl 2), 1 (2001)
96 Murgo, A. J.: Oncologist **6** (Suppl 2), 22 (2001)
97 Wang, Z. H.; Yu, D.; Li, H. K.; Chow, V. W.; Ng, C. C.; Chan, H. B.; Cheng, S. B.; Chew, E. C.: Anticancer Res. **21A**, 493 (2001)
98 Akao, Y.; Yamada, H.; Nakagawa, Y.: Leuk. Lymphoma **37**, 53 (2000)
99 Shen, Z. Y.; Shen, J.; Cai, W. J.; Hong, C.; Zheng, M. H.: Int. J. Mol. Med. **5**, 155 (2000)
100 Zhang, T. C.; Cao, E. H.; Li, J. F.; Ma, W.; Qin, J. F.: Eur. J. Cancer **35**, 1258 (1999)
101 Lu, M.; Levin, J.; Sulpice, E.; Sequeira-Le Grand, A.; Alemany, M.; Caen, J. P.; Han, Z. C.: Exp. Hematol. **27**, 845 (1999)
102 Zheng, J.; Deng, Y. P.; Lin, C.; Fu, M.; Xiao, P. G.; Wu, M.: Int. J. Cancer **82**, 286 (1999)
103 Zhu, X. H.; Shen, Y. L.; Jing, Y. K.; Cai, X.; Jia, P. M.; Huang, Y.; Tang, W.; Shi, G. Y.; Sun, Y. P.; Dai, J.; Wang, Z. Y.; Chen, S. J.; Zhang, T. D.; Waxman, S.; Chen, Z.; Chen, G. Q.: J. Natl. Cancer Inst. **91**, 772 (1999)

104 Chen, H.; Qin, S.: Chung Hua Kan Tsang Ping Tsa Chih **8**, 27 (2000)
105 Lew, Y. S.; Brown, S. L.; Griffin, R. J.; Song, C. W.; Kim, J. H.: Cancer Res. **59**, 6033 (1999)
106 Huang, S. Y., Chang, C. S.; Tang, J. L.; Tien, H. F.; Kuo, T. L.; Huang, S. F.; Yao, Y. T.; Chou, W. C.; Chung, C. Y.; Wang, C. H.; Shen, M. C.; Chen, Y. C.: Br. J. Haematol. **103**, 1092 (1998)
107 Huang, C. H.; Chen, W. J.; Wu, C. C.; Chen, Y. C.; Lee, Y. T.: Pacing Clin. Electrophysiol. **22**, 965 (1999)
108 Andre, C.; Guillemin, M. C.; Zhu, J.; Koken, M. H.; Quignon, F.; Herve, L.; Chelbi-Alix, M. K.; Dhumeaux, D.; Wang, Z. Y.; Degos, L.; Chen, Z.; de The, H.: Exp. Cell Res. **229**, 253 (1996)
109 Zhang, P.: J. Biol. Regul. Homeost. Agents **13**, 195 (1999)
110 Kinjo, K.; Kizaki, M.; Muto, A.; Fukuchi, Y.; Umezawa, A.; Yamato, K.; Nishihara, T.; Hata, J.; Ito, M.; Ueyama, Y.; Ikeda, Y.: Leukemia **14**, 431 (2000)
111 Chen, G. Q.; Shi, X. G.; Tang, W.; Xiong, S. M.; Zhu, J.; Cai, X.; Han, Z. G.; Ni, J. H.; Shi, G. Y.; Jia, P. M.; Liu, M. M.; He, K. L.; Niu, C.; Ma, J.; Zhang, P.; Zhang, T. D.; Paul, P.; Naoe, T.; Kitamura, K.; Miller, W.; Waxman, S.; Wang, Z. Y.; de The, H.; Chen, S. J.; Chen, Z.: Blood **89**, 3345 (1997)
112 Wang, R. H.; Zheng, S.; Chen, X.; Shen, B. F.: Chin. Biochem. J. **8**, 395 (1992)
113 Dong, T. X.; Ng, T. B.; Yeung, H. W.; Wong, R. N. S.: Biochem. Biophys. Res. Commun. **199**, 387 (1994)
114 Wong, R. N. S.; Dong, T. X.; Ng, T. B.; Choi, W. T.; Yeung, H. W.: Int. J. Pept. Protein. Res. **47**, 103 (1996)
115 Poma, A.; Marcozzi, G.; Cesare, P.; Carmignani, M.; Spano, L.: Biochim. Biophys. Acta **1472(1–2)**, 197 (1999)
116 Poma, A.; Miranda, M.; Spano, L.: Melanoma Res. **8**, 465 (1998)
117 Huang, B.; Ng, T. B.; Fong, W. P.; Wan, C. C.; Yeung, H. W.: Int. J. Biochem. Cell. Biol. **31**, 707 (1999)
118 Hernandez, J. F.; Gagnon, J.; Chiche, L.; Nguyen, T. M.; Andrieu, J. P.; Heitz, A.; Trinh Hong, T.; Pham, T. T.; Le Nguyen, D.: Biochemistry **39**, 5722 (2000)
119 Li, X. D.; Chen, W. F.; Liu, W. Y.; Wang, G. H.: Protein Expr. Purif. **10**, 27 (1997)
120 Zhang, A. H.; Tang, S.; Liu, W.: J. Nat. Toxins. **10**, 119 (2001)
121 Xu, Y. Z.; Li, Y. J.; Hu, H. Y.; Hu, R.; Wu, H.; Liu, W. Y.: Biol. Chem. **381**, 447 (2000)
122 Kurinov, I. V.; Mao, C.; Irvin, J. D.; Uckun, F. M.: Biochem. Biophys. Res. Commun. **275**, 549 (2000)
123 Ferens, W. A.; Hovde, C. J.: Infect. Immun. **68**, 4462 (2000)
124 Despeyroux, D.; Walker, N.; Pearce, M.; Fisher, M.; McDonnell, M.; Bailey, S. C.; Griffiths, G. D.; Watts, P.: Anal. Biochem. **279**, 23 (2000)
125 Frigerio, L.; Vitale, A.; Lord, J. M.; Ceriotti, A.; Roberts, L. M.: J. Biol. Chem. **273**, 14194 (1998)
126 Shaw, P. C.; Chan, W. L.; Yeung, H. W.; Ng, T. B.: Life Sci. **55**, 253 (1994)
127 Lu, P. X.; Jin, Y. C.: Chin. Med. J. (Engl) **103**, 183 (1990)
128 Tsao, S. W.; Ng, T. B.; Yeung, H. W.: Toxicon **28**, 1183 (1990)
129 Zhang, R. P.; Xu, C. J.; Cao, H. T.; Ji, R. H.; Zhang, Z. C.: Chin. J. Immunol. **9**, 348 (1993)
130 Wang, Q. C.; Ying, W. B.; Xie, H.; Zhang, Z. C.; Yang, Z. H.; Ling, L. Q.: Cancer Res. **51**, 3353 (1991)
131 Gao, H. L.; Zhou, G. Y.; Lu, D. Y.; Zhang, W. Y.: Chin. J. Immunol. **8**, 300 (1992)
132 Schlick, J.; Dulieu, P.; Desvoyes, B.; Adami, P.; Radom, J.; Jouvenot, M.: FEBS Lett. **472**, 241 (2000)
133 Waurzyniak, B.; Schneider, E. A.; Tumer, N.; Yanishevski, Y.; Gunther, R.; Chelstrom, L. M.; Wendorf, H.; Myers, D. E.; Irvin, J. D.; Messinger, Y.; Ek, O.; Zeren, T.; Langlie, M. C.; Evans, W. E.; Uckun, F. M.: Clin. Cancer Res. **3**, 881 (1997)
134 Zhong, R. K.; van De Winkel, J. G.; Thepen, T.; Schultz, L. D.; Ball, E. D.: J. Hematother. Stem. Cell Res. **10**, 95 (2001)
135 van Oosterhout, Y. V.; van Emst, J. L.; Bakker, H. H.; Preijers, F. W.; Schattenberg, A. V.; Ruiter, D. J.; Evers, S.; Koopman, J. P.; de Witte, T.: Int. J. Pharm. **221**, 175 (2001)
136 Schindler, J.; Sausville, E.; Messmann, R.; Uhr, J. W.; Vitetta, E. S.: Clin. Cancer Res. **7**, 255 (2001)
137 Longo, D. L.; Duffey, P. L.; Gribben, J. G.; Jaffe, E. S.; Curti, B. D.; Gause, B. L.; Janik, J. E.; Braman, V. M.; Esseltine, D.; Wilson, W. H.; Kaufman, D.; Wittes, R. E.; Nadler, L. M.; Urba, W. J.: Cancer J. Sci. Am. **6**, 146 (2000)
138 Messmann, R. A.; Vitetta, E. S.; Headlee, D.; Senderowicz, A. M.; Figg, W. D.; Schindler, J.; Michiel, D. F.; Creekmore, S.; Steinberg, S. M.; Kohler, D.; Jaffe, E. S.; Stetler-Stevenson, M.; Chen, H.; Ghetie, V.; Sausville, E. A.: Clin. Cancer Res. **6**, 1302 (2000)
139 Schnell, R.; Vitetta, E.; Schindler, J.; Borchmann, P.; Barth, S.; Ghetie, V.; Hell, K.; Drillich, S.; Diehl, V.; Engert, A.: Leukemia **14**, 129 (2000)
140 Grossbard, M. L.; Multani, P. S.; Freedman, A. S.; O'Day, S.; Gribben, J. G.; Rhuda, C.; Neuberg, D.; Nadler, L. M.: Clin. Cancer Res. **5**, 2392 (1999)
141 Gu, Y.; Chen, W.; Xia, Z.: J. Protein Chem. **19**, 291 (2000)
142 Gu, Y. J.; Xia, Z. X.: Proteins **39**, 37 (2000)
143 Nie, H.; Cai, X.; He, X.; Xu, L.; Ke, X.; Ke, Y.; Tam, S. C.: Life Sci. **62**, 491 (1998)
144 Xi, Z. D.; Ma, B. L.; Yang, L. M.; Cao, H. N.; Wang, M.: Acta Pharmacol. Sin. **18**, 447 (1997)
145 Mulot, S.; Chung, K. K.; Li, X. B.; Wong, C. C.; Ng, T. B.; Shaw, P. C.: Life Sci. **61**, 2291 (1997)
146 Ru, Q. H.; Luo, G. A.; Liao, J. J.; Liu, Y.: J. Chromatogr. A **894**, 165 (2000)
147 Kidd, P. M.: Altern. Med. Rev. **5**, 4 (2000)
148 Ooi, V. E.; Liu, F.: Curr. Med. Chem. **7**, 715 (2000)
149 Shida, M.; Ushioda, Y.; Nakajima, T.; Matsuda, K.: J. Biochem. (Tokyo) **90**, 1093 (1981)
150 sukagoshi, S.; Hashimoto, Y.; Fujii, G.; Kobayashi, H.; Nomoto, K.; Orita, K.: Cancer Treat. Rev. **11**, 131 (1984)
151 Wang, H. X.; Ng, T. B.; Liu, W. K.; Ooi, V. E.; Chang, S. T.: Int. J. Biochem. Cell Biol. **28**, 601 (1996)
152 Misaki, A.; Kakuta, M.; Sasaki, T.; Tanaka, M.; Miyaji, H.: Carbohydr. Res. **92**, 115 (1981)
153 Zang, Q. Z.; He, G. X.; Zheng, Z. Y.; Xu, J. H.; Liu, J. Z.; Wang, S. Y.; Huang, J.Z.; Du, D. J.; Zeng, Q.T.: Chin. Trad. Herbal Drugs **16**, 301 (1985)
154 Lieu, C. W.; Lee, S. S.; Wang, S. Y.: Anticancer Res. **12**, 1211 (1992)
155 Lee, S. S.; Wie, Y. H.; Chen, C. F.; Wang, S. Y.; Chen, K. Y.: J. Chin. Med. **6**, 1 (1995)
156 Zhang, Y. H.; Liu, Y. L.; Yan, S. C.: Chin. J. Integr. Trad. West. Med. **11**, 225 (1991)
157 Li, J. F.; Guo, J. W.; Huang, X. F.: Chin. J. Integr. Trad. West. Med. **16**, 224 (1996)
158 Kanayama, H.; Togami, M.; Adachi, N.; Fukai, Y.; Okumoto, T.: Yakugaku Zasshi **106**, 307 (1986)
159 Ma, L.; Lin, Z. B.: Acta Pharm. Sin. **27**, 1 (1992)
160 Gao, Q.; Killie, M. K.; Chen, H.; Jiang, R.; Seljelid, R.: Planta Med. **63**, 457 (1997)
161 Nakano, H.; Namatame, K.; Nemoto, H.; Motohashi, H.; Nishiyama, K.; Kumada, K.: Hepatogastroenterology **46**, 2662 (1999)
162 Takita, M.; Onda, M.; Tokunaga, A.; Shirakawa, T.; Ikeda, K.; Hiramoto, Y.; Teramoto, T.; Oguri, T.; Fujita, I.; Okuda, T.; Mizutani, T.; Kiyama, T.; Yoshiyuki, T.; Matsukura, N.: Gan To Kagaku Ryoho **25**, 129 (1998)
163 Mio, H.; Terabe, K.: Gan To Kagaku Ryoho **24**, 337 (1997)
164 Taguchi, T.: Cancer Detect. Prev. **Suppl 1**, 333 (1987)
165 Takeshita, K.; Hayashi, S.; Tani, M.; Kando, F.; Saito, N.; Endo, M.: Surg. Oncol. **5**, 23 (1996)
166 Arinaga, S.; Karimine, N.; Takamuku, K.; Nanbara, S.; Nagamatsu, M.; Ueo, H.; Akiyoshi, T.: Int. J. Immunopharmacol. **14**, 43 (1992)
167 Arinaga, S.; Karimine, N.; Takamuku, K.; Nanbara, S.; Inoue, H.; Nagamatsu, M.; Ueo, H.; Akiyoshi, T.: Int. J. Immunopharmacol. **14**, 535 (1992)
168 Li, J. F.; Guo, J. W.; Huang, X. F.: Chin. J. Integr. Trad. West. Med. **16**, 224 (1996)
169 Liu, F.; Ooi, V. E.; Fung, M. C.: Life Sci. **64**, 1005 (1999)
170 Sakagami, H.; Sugaya, K.; Utsumi, A.; Fujinaga, S.; Sato, T.; Takeda, M.: Anticancer Res. **13**, 671 (1993)
171 Kohgo, Y.; Hirayama, Y.; Sakamaki, S.; Matsunaga, T.; Ohi, S.; Kuga, T.; Kato, J.; Niitsu, Y.: Acta Haematol. **92**, 130 (1994)
172 Qian, Z. M.; Xu, M. F.; Tang, P. L.: Am. J. Chin. Med. **25**, 27 (1997)
173 Lin, I. H.; Hau, D. M.; Chang, Y. H.: Acta Pharmacol. Sin. **17**, 102 (1996)
174 Li, X. Y.; Wang, J. F.; Zhu, P. P.; Liu, L.; Ge, J. B.; Yang, S. X.: Acta Pharmacol. Sin. **11**, 542 (1990)
175 Mao, X. W.; Archambeau, J. O.; Gridley, D. S.: Cancer Biother. Radiopharm. **11**, 393 (1996)
176 Huang, Q. S.; Lu, G. B.; Li, Y. C.; Guo, J. H.; Wang, R. X.: Acta Pharm. Sin. **17**, 200 (1982)
177 Tomoda, M.; Shimizu, N.; Ohara, N.; Gonda, R.; Ishii, S.; Otsuki, H.: Phytochemistry **31**, 63 (1991)
178 Shimizu, N.; Tomoda, M.; Kanari, M.; Gonda, R.: Chem. Pharm. Bull. (Tokyo) **39**, 2969 (1991)
179 He, J.; Zhang, S. H.: Chin. Pharm. J. (Beijing) **31**, 716 (1996)
180 Tian, G. Y.; Wang, C.; Feng, Y. C.: Acta Biochim. Biophys. Sin. **27**, 201 (1995)
181 Tian, G. Y.; Wang, C.: Acta Biochim. Biophys. Sin. **27**, 493 (1995)
182 Zhao, C. J.; He, Y. Q.; Li, R. Z.; Cui, G. H.: Chin. Chem. Lett. **7**, 1009 (1996)
183 Zhang, S. J.; Zhang, S. Y.: Chin. Trad. Herbal Drugs **18**, 98 (1987)
184 Cha, R. J.; Zeng, D. W.; Chang, Q. S.: Chin. J. Int. Med. **33**, 462 (1994)
185 Chu, D. T.; Sun, Y.; Lin, J. R.: Chin. J. Integr. Trad. West. Med. **9**, 351, 326 (1989)
186 Wang, D. C.: Chin. J. Oncol. **11**, 180 (1989)

187 Chu, D. T.; Wong, W. L.; Mavligit, G. M.: J. Clin. Lab. Immunol. **25**, 119 (1988)
188 Cao, G. W.; Yang, W. G.; Du, P.: Chin. J. Oncol. **16**, 428 (1994)
189 Liu, J. N.; Cheng, B. Q.; Zhang, J. R.; Tan, X. R.; Ji, Y. Z.: Zhonghua Fangshe Yixue Yu Fanghu Zazhi **16**, 18 (1996)
190 Zeng, X. L.; Li, X. A.; Zhang, B. Y.: Chin. J. Integr. Trad. West. Med. **12**, 607, 581 (1992)
191 Chen, L. J.; Shen, M. L.; Wang, M. Y.; Zhai, S. K., Liu, M. Z.: Acta Pharmacol. Sin. **2**, 200 (1981)
192 Chang, C. Y.; Hou, Y. D.; Xu, F. M.: Acta Acad. Med. Sin. **5**, 231 (1983)
193 Chu, D. T.; Wong, W. L.; Mavligit, G. M.: J. Clin. Lab. Immunol. **25**, 125 (1988)
194 Tu, W. W.; Yang, Y. Q.; Wang, L. J.; Zhang, Y. W.; Shen, J.: Chin. J. Immunol. **11**, 34 (1995)
195 Geng, C. S.; Wang, G. Y.; Lin, Y. D.; Xin, S. T.; Zhou, J. H.: Chin. Trad. Herbal Drugs **19**, 313 (1988)
196 Cao, G. W.; Du, P.: Chin. J. Microbiol. Immunol. **12**, 390 (1992)
197 Wang, B. K.; Xing, S. T.; Zhou, J. H.: Chin. J. Pharmacol. Toxicol. **4**, 39 (1990)
198 Mao, X. L.; Zhou, Y.: Chin. J. Integr. Trad. West. Med. **5**, 739 (1985)
199 Hu, S. K.: Chin. J. Integr. Trad. West. Med. **5**, 618 (1985)
200 Shan, B. E.; Yoshida, Y.; Sugiura, T.; Yamashita, U.: Int. J. Immunopharmacol. **21**, 149 (1999)
201 Lau, B. H.; Ruckle, H. C.; Botolazzo, T.; Lui, P. D.: Cancer Biother. **9**, 153 (1994)
202 Wang, B. K.; Xing, S. T.; Zhou, J. H.; Geng, C. S.: Chin. J. Pharmacol. Toxicol. **2**, 127 (1988)
203 Sun, W. J.; Xu, W. L.; Zhang, Y. X.; Huang, R. H.; Duan, G. S.: Chin. J. Clin. Oncol. **21**, 930 (1994)
204 Liu, J. L.; Zhang, L. H.; Qian, Y. K.: Chin. J. Immunol. **12**, 115 (1996)

Received September 5, 2001
Accepted October 15, 2001

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