

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Traditional Chinese Medicine Active Ingredient-Metal Based Anticancer Agents

Zhen-Feng Chen, Hong Liang and Yan-Cheng Liu
Guangxi Normal University,
China

1. Introduction

Traditional Chinese medicine (TCM) possesses a rich and ancient history, tracing its roots back several thousand years. The practice of TCM, highly influenced by the development of Chinese culture, involves physical therapy using acupuncture, moxibustion (application of heat to the acupuncture point by burning a piece of the Chinese plant *Artemisia moxa* on the skin or the acupuncture needle), and chemical therapy. TCM natural products are isolated as decoctions of animal, mineral and herbal materials (Chan, 1995; Shibata, 1985;). The objective of the system of TCM is on the patient rather than disease, which fundamentally intention to promote health and enhance the quality of life, with therapeutic strategies for treatment of specific disease or symptoms in holistic fashion. TCM represents an old Chinese philosophical thinking, where the human is considered the centre of the universe and acts as an antenna between celestial and earthly elements of the world. The world is a single unit and its movement affords yin and yang, the two main antithetic aspects. Moreover, Chinese believe that yin and yang are not absolute but relative. Consistent with the modern view of homeostasis, yin and yang are interchanged to meet the view that yang decline and yin rises? Or yang is raised to produce a decline of yin? The four bodily humors (qi, blood, moisture and essence) and internal organ systems (zang fu) play an important role in balancing the yin and yang in human body. Proper formation, maintenance and circulation of these energies are essential for health. When the two energies fall out of harmony, and the balance is broken, disease develops (Patwardhan et al., 2005). The physician takes into account this concept while treating patients. Drugs or herbs are used to correct this imbalance of yin-yang in the human body (Cheng, 2000; Gibert, 1998).

Different from TCM, western science and medicine are focused on the mechanism, which belongs to reductionism. Rather than addressing the overall well being of a patient, it is only the disease that is analyzed at the cellular, molecular, and pharmacological level. The history, philosophy, theory and practice of TCM can be seen in recent reviews (Liu, 1988), herein, we do not give unnecessary details.

Although medicinal herbs have played an important role in Western medicine from ancient to modern times, medicinal plants gradually lost their importance as synthetic pharmaceuticals advanced in Western countries during the 20th century. Currently, there is a revival of interest in bioactive natural products as chemical lead compounds for the generation of semi-synthetic derivatives, namely regression nature.

Traditional Chinese medicine (TCM) has held, and still holds, an important position in primary health care over vast rural areas of China and is appreciated in urban and well-developed areas because of its 5000-year-old tradition. Recently, the Chinese government has undertaken enormous efforts to modernize TCM by investing capital in scientific research, technology programs, and in the economic development of TCM therapies. In the Western world, interest in TCM is increasing due to the belief that it may lead to novel TCM-Western hybrid medicines and treatments.

Since the discovery of cisplatin (**1**, Fig. 1) in 1969, great progress has been made expanding the diversity of platinum anticancer drugs and the conditions they treat (Alt et al., 2007; Clark et al., 1999; Giandomenico, 1999; Jung & Lippard, 2007; Orvig & Abrams, 1999; Rosenberg et al., 1969; Wataru et al., 2008; Wong & Jamieson & Lippard, 1999; Zutphen & Reedijk, 2005). Cisplatin is currently used to treat bladder, non-small cell lung, head and neck, ovarian, cervical, and other cancers, being curative in nearly all cases of testicular cancers. Several similar platinum complexes with fewer toxic side effects, carboplatin (**2**, Fig.1) and oxaliplatin (**3**, Fig.1) were approved as a first-line treatment for colorectal cancer. Nedaplatin (**4**, Fig. 1) was approved for use in Japan, and lobaplatin (**5**, Fig.1) was approved for use in China (Lovejoy & Lippard, 2009). During the past three decades, medicinal chemists have investigated many approaches to enhance antitumor activity, reduce side effects, and overcome drug resistances. To data, thousands of platinum compounds have been synthesized, characterized, and their antitumor activity investigated; however, only 30 platinum compounds have entered clinical trials. Moreover, none have exceeded the anticancer activity of cisplatin. Obviously, current synthetic strategies for development of metal-based anticancer are inefficient (Kelland, 2007). Although non-platinum antitumor metal complexes exhibit different action mechanisms and structural characteristics compared to platinum drugs, the antitumor activity of these non-platinum compounds needs to be determined and their action mechanisms await further investigation. Recent research has shown that metal complexes based on TCMS afforded a novel approach to a potential (pro-) drugs (Chen et al., 2009; Ho et al., 2001; Liu et al., 2009).

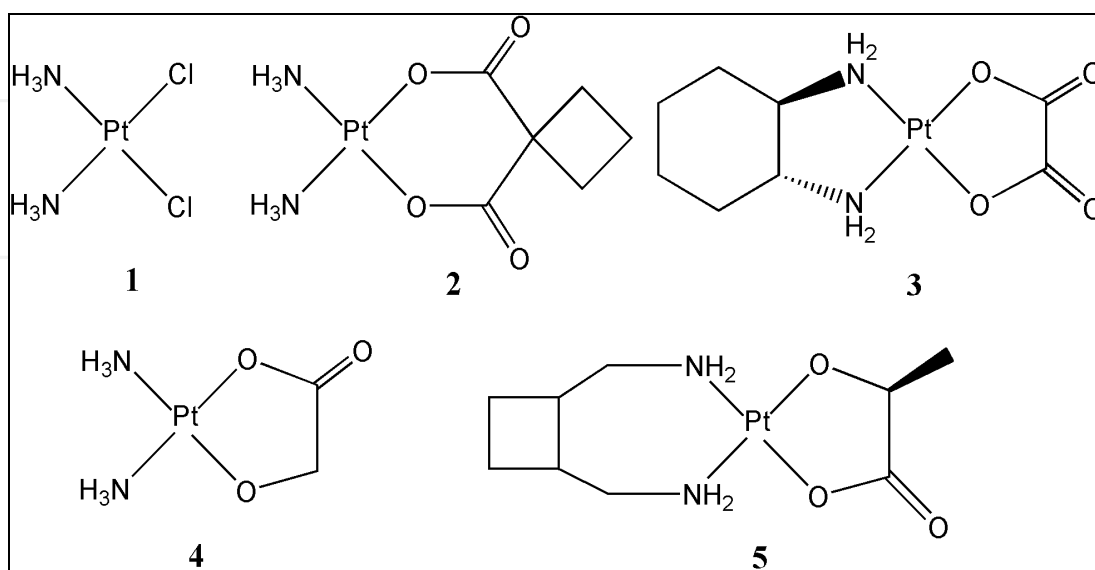


Fig. 1. Structures of platinum compounds currently in clinical use. 1: cisplatin, 2: carboplatin, 3: oxaliplatin, 4: nedaplatin, 5: lobaplatin.

2. The anticancer metal-based agents based on TCM active ingredients

Considering the low success rate of current metal-based anticancer synthetic strategies, some bioinorganic chemists have shifted focus to TCM derivatives. There are many successful examples of TCM-derived anticancer agents through organic modification of the active TCM constituents, which is considered a shortcut to discover new anticancer drugs, however, the TCM-metal based anticancer agents are still lack of enough attention, which represent another approach of modification. It is well known that metals and metal complexes can make significant contributions to drug development, but are not receiving the attention they merit. Metal complexes are relative easy to prepare, and the additional geometric possibilities resulting from the use of six-coordinate metal centres (compared to four-coordinate carbon) make this an attractive approach for the rapid development of new species, either as drugs or as probes of the geometric requirements of active sites (Hambley, 2007). Along with the TCM coordination chemistry theory springs up, it is convinced of that metal ion existence plays important role in TCM. Moreover, due to many active compounds containing hydroxyl, carboxylic acid, and amine groups, they are excellent donor atoms that may easily form coordination bonds. Developing TCM coordination complexes may lead to novel therapies that synergistically combine the functions of TCM and metals, generating a novel strategy that bridges traditional Chinese medicine to rational cancer therapy. This concept has attracted increased interest in TCM-metal based antitumor agents. Herein, we review the progress in TCM-metal based anticancer agents according to the TCM active gradient category.

2.1 Alkaloid-metal based anticancer agents

Alkaloids, which are generally defined as nitrogen-containing natural molecules independently of the basic character of the nitrogen, are abundant secondary metabolites in plants and represent one of the most widespread class of compounds endowed with multiple, varied pharmacological properties, including anticancer, antibacterial, anti-fungi, and even anti-virus activities. Up to now, the alkaloid-metal based anticancer agents mainly include oxoaporphine, matrine, β -carboline alkaloid-metal based anticancer agents.

2.1.1 Liriodenine-metal based anticancer agents

Among alkaloids, the aporphinoids constitute a broad subgroup of benzyloquinoline compounds, with more than 500 alkaloids isolated up to now. They are widely distributed in a large number of plant families including *Annonaceae*, *Magnoliaceae*, *Monimiaceae*, *Menispermaceae*, *Hernandiaceae*, *Renunculaceae*. Our group has widely carried out a series of investigations on oxoaporphine-metal based anticancer agents. Liriodenine (**6**, Fig. 2), as an oxoaporphine alkaloid, was isolated for the first time from *Liriodendron tulipifera* L. and was subsequently found mainly in the family of *Annonaceae*, *Rutaceae*, *Magnoliaceae*, *Monimiaceae*, *Menispermaceae*, ect. (Bentley, 2001; Lan et al., 2003; Lin et al., 1994; Hsien et al., 2005; Nissanka et al., 2001; Woo et al., 1997; Wu et al., 1990). Liriodenine has a wide range of pharmacological activities, such as anti-bacterial, anti-fungi, antitumour and even anti-virus activities. Due to its planar aromatic structure, liriodenine can intercalate into the neighbouring base pairs of DNA double helix, to which its significant antitumor activity can be primarily attributed. Moreover, it also catalytically inhibits topoisomerase to block DNA synthesis and increase p53 and iNOS expression to induce cell cycle G1 arrest (Chang et al, 2004). Liriodenine has been isolated by our group from a classical Chinese herb richly yield

in Guangxi Province of China, *Zanthoxylum nitidum* Var. *Fastuosum*, known for its significant anticancer properties. Based on the planar character of liriodenine and its N-7/O-8 donor sites, it can ligate metal ions (M^{n+}) to form metal-based bifunctional compounds with potential synergistic effects on antitumor activity.

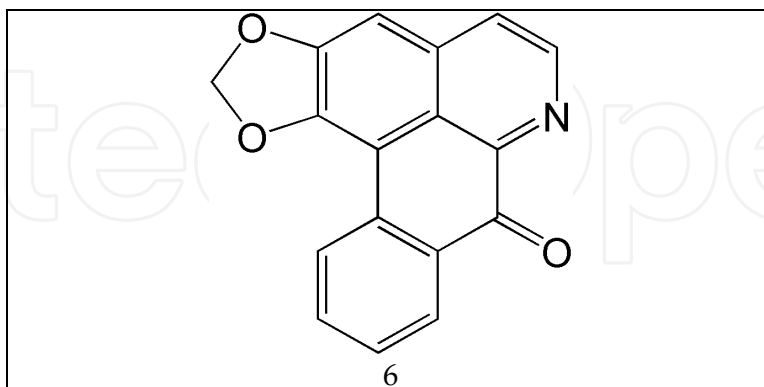


Fig. 2. Structure of liriodenine.

Reaction of liriodenine (L) with Pt(II), Ru(II), Mn(II), Fe(II), and Zn(II) as well as a series of lanthanides afforded a series of metal complexes. The crystal structures of *cis*-[Pt(L)(DMSO)Cl₂] (7), *cis*-[Ru(L)(DMSO)Cl₂] \cdot 1.5H₂O (8) (Chen et al., 2009); [MnCl₂(L)₂] (9), [FeCl₂(L)₂] (10), [Zn₂(L)₂(μ_2 -Cl)₂Cl₂] (11) (Fig.3) (Liu et al., 2009); [Ce(L)₂(NO₃)₃] (12), [Pr(L)₂(NO₃)₃] (13), [Sm(L)₂(NO₃)₃] (14), [Eu(L)₂(NO₃)₃] (15) (Fig. 4) (Chen et al., 2011), were determined by single crystal X-ray diffraction methods. These complexes were fully characterized by elemental analysis, IR, ¹H and ¹³C NMR spectroscopy, and ESI-MS spectrometry.

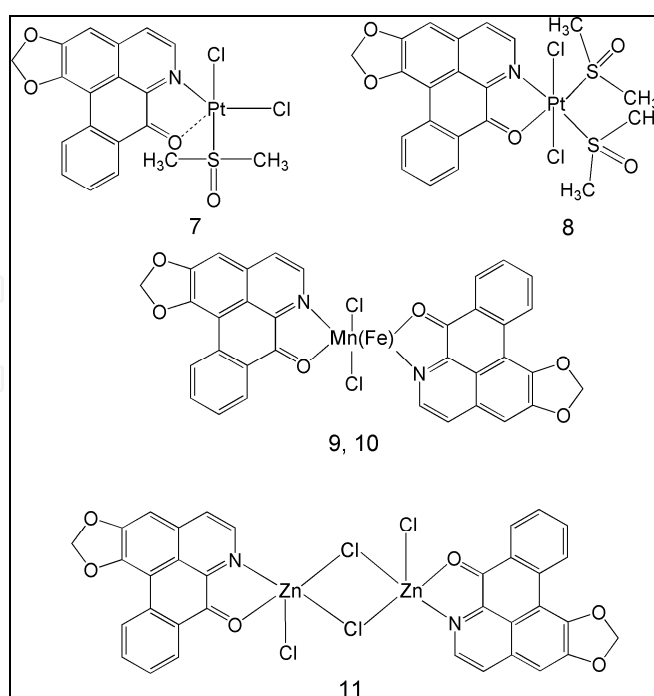


Fig. 3. Crystal structures of *cis*-[PtCl₂(L)(DMSO)] (7), *cis*-[RuCl₂(L)(DMSO)₂] (8), MnCl₂(L)₂ (9), [FeCl₂(L)₂] (10), and [Zn₂(L)₂(μ_2 -Cl)₂Cl₂] (11).

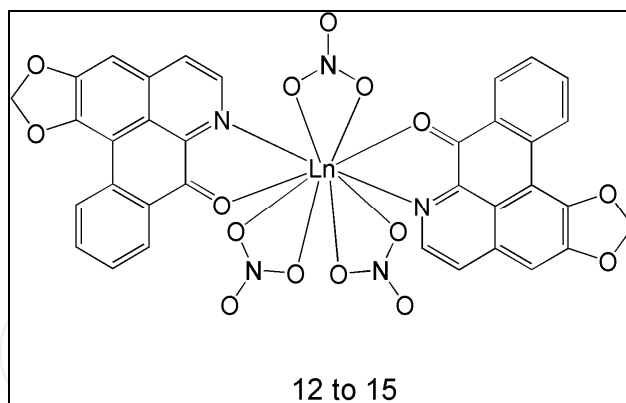


Fig. 4. Structures of four lanthanide complexes (**12 to 15**) with liriodenine.

The *in vitro* cytotoxicity of L and a series of its metal complexes against a panel of tumour cell lines have been evaluated by MTT method. The results show that these liriodenine metal-based compounds exhibit enhanced cytotoxicity *vs.* free L in most cases, and the IC₅₀ values are in range of μM , suggesting that these compounds display synergic effect in the combination of metal ions and liriodenine. Although there is some evidence to suggest that other biological targets, including RNA or proteins, may be important in the cisplatin action mechanism, it is generally accepted that DNA is the primary target. Similarly, interactions between small molecules and DNA rank among the primary action mechanisms of anticancer activity. DNA replication in tumour cells will be blocked by the small molecule intercalation of the neighboring base pairs of DNA. On the other hand, topoisomerases are ubiquitous molecules that relieve the torsional stress in the DNA helix generated as a result of replication, transcription, and other nuclear processes; they are also specific targets for a number of anticancer agents (Baraldi et al., 2004), including the camptothecins, indolocarbazoles, and indenoisoquinolines. These compounds bind to a transient topoisomerase I (TOPO I)-DNA covalent complex and inhibit the resealing of a single-strand nick that the enzyme creates to relieve superhelical tension in duplex DNA (Holfalnd et al, 2000; Staker et al., 2005). Therefore, in our researches, we investigated the interactions of these compounds with DNA and TOPO I. The interactions between ct-DNA and L or its Pt(II) and Ru(II) complexes through UV-Vis, fluorescence, EB competition binding, CD spectra, viscosity and agarose gel electrophoretic experiments reveal that these compounds mostly adopted a classical intercalation mode with DNA, but the metal complexes may bind covalently to DNA simultaneously because they easily hydrolyze to give coordinate active sites. Based on quantitative analysis of spectral titration experiments, it can conclude that the Pt(II) and Ru(II) complexes have higher binding ability than L itself does, suggesting that the metal complexes of planar L reinforce the binding ability. Although these results do not display a good coherence with what has been revealed in quantitative spectral analysis, however, it still confirms that DNA is an important target in cellular systems for these metal-based compounds derived from TCM. To introduce a TCM as a ligand to form bifunctional metal-based anticancer compounds (Herein, bifunction means TCM moiety intercalation and complex covalent binding to DNA, and differs from the meaning appearing in previous literature (Song et al., 2002; Wu et al., 2005) is a new effective strategy to achieve promising potential metal-based anticancer drug.

The *in vitro* cytotoxicity of three divalent transition metal (Mn(II), Fe(II), Zn(II)) complexes against 10 human tumor cell lines shows that most of these metal complexes exhibit higher cytotoxicity than L or cisplatin does, suggesting a probable synergistic effect upon

liriodenine (L) coordinated to metal ions. The interactions between ct-DNA and L or its four divalent later transition metal complexes studied by UV-Vis, fluorescence, EB competition binding and CD spectra, as well as viscosity measurements and gel mobility shift assay experiments, reveal that these compounds mostly adopted an intercalation mode with DNA. Complexes **9**, **10** have higher binding affinity than L itself, suggesting that the metal complexes of planar L reinforce the binding ability. But it is lower than that of typical metallointercalator, which could be attributed to dichloride complex species (neutral) without chloride ligand exchange for water in short incubation period. In contrast, for biological assay on tumor cell lines, the long period incubation could allow (inside the cell) the conversion to diaqua species (dicationic) with a better interaction with NDA, and exhibit satisfied cytotoxicity. The electrostatic interactions between complex **11** and the polyanionic backbone of DNA helix should be considered simultaneously. Complex **11** tends to hydrolyze to form coordination unsaturated species, $[\text{Zn(L)}]^{2+}$, which can covalently bound to DNA. In addition, complexes **9–11** exhibit significant topoisomerase I inhibition ability at lower concentrations in contrast to L, implying topoisomerase I may be another molecular target. Although the exact molecular mechanism (including the real complex species in these metal complexes interacting with ct-DNA and tumour cell lines) needs further more detailed investigation, anyway, the three synthesized divalent later transition metal complexes of liriodenine exhibit significant enhanced cytotoxicity, offering a new effective strategy to achieve promising potential dual targeting cytotoxic agents by combining bioactive non-cytotoxic metal ions with cytotoxic active components from TCM.

The *in vitro* cytotoxicity of the lanthanide complexes **12–15** of liriodenine against four selected cell lines (7702, SK-OV-3, 7404, NCI-H460) were tested using MTT colorimetric method. The results indicate that the metal complexes exhibit enhanced cytotoxicity against the four selected cell lines than that of liriodenine, which display the synergistic effects. All the complexes exhibit higher cytotoxicity to the tested tumor cells than ligand and cisplatin does. Remarkably, among these complexes, complexes **13** and **14** exhibit the highest cytotoxicity to tumour cells SK-OV-3, with IC_{50} values of 0.22 ± 0.09 and 0.23 ± 0.05 μM . The interactions between the liriodenine, its complexes and DNA were investigated by using various spectroscopic methods such as UV-Vis, fluorescence, CD, as well as viscosity and agarose gel electrophoresis experiments. The results indicate that liriodenine and its metal complexes interacted with DNA in an intercalation binding mode due to the liriodenine having good planarity and the π cyclic conjugated system. DNA has negative charge, there exist electrostatic interactions between liriodenine, its complexes. The interaction of complexes and DNA are stronger than that of liriodenine, it is agreed well with the results of antitumor activity tests. Overall, these liriodenine-metal complexes interact with DNA mainly by intercalation and electrostatic interaction, which blocks DNA synthesis and replication and induces cytotoxicity.

2.1.2 Oxoglauanine-metal based anticancer agents

Oxoglauanine (OG, **16**, Fig. 5) is an oxoaporphine alkaloid that has been isolated from overground parts of plants belonging to different families such as *Annonaceae* (Chang et al., 1998; Chen et al., 1996), *Lauraceae* (Chen et al., 1998), *Magnoliaceae* (Chen et al., 1976), *Fumariaceae* (Blanco et al., 1993; Tojo et al., 1991), *Menispermaceae* (Ohiri et al., 1982) and *Papveraceae* (Sari, 1999), which is also found widely exist in many traditional Chinese medicine, such as *aquilegia ecalcarata Maxim* (*Ranunculaceae*) mainly distributed in Sichuan

and Yunnan Provinces of China and used for the treatment of necrotic boils, pustulosis and other infections (Wu et al., 1998). The primary screening results reveal that oxoglaucine possesses strong anticancer activity, such as against HCT-8 ($ED_{50} = 1.00 \mu\text{g/ml}$) and K_B ($ED_{50} = 2.00 \mu\text{g/ml}$) (Chang et al., 2002; Chen et al., 2002; Wu et al., 1989). In addition, oxoglaucine exhibits other important pharmacological activities including antiplatelet aggregation (Chang et al., 1998; Jantan et al., 2006), immunomodulatory activity (Ivanovska et al., 1997 and 2000), treatment of adjuvant arthritis (Ivanovska & Hristova, 2000), anti-inflammatory (Remichkova et al., 2009), antifungal activity (Clark et al., 1987).

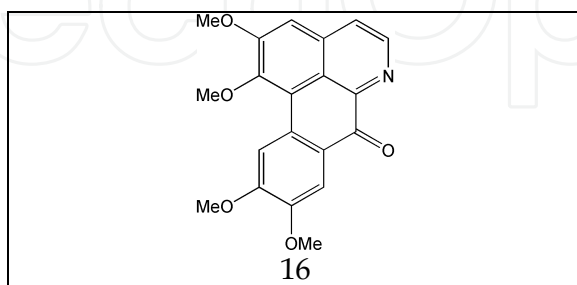


Fig. 5. Structure of oxoglaucine (16).

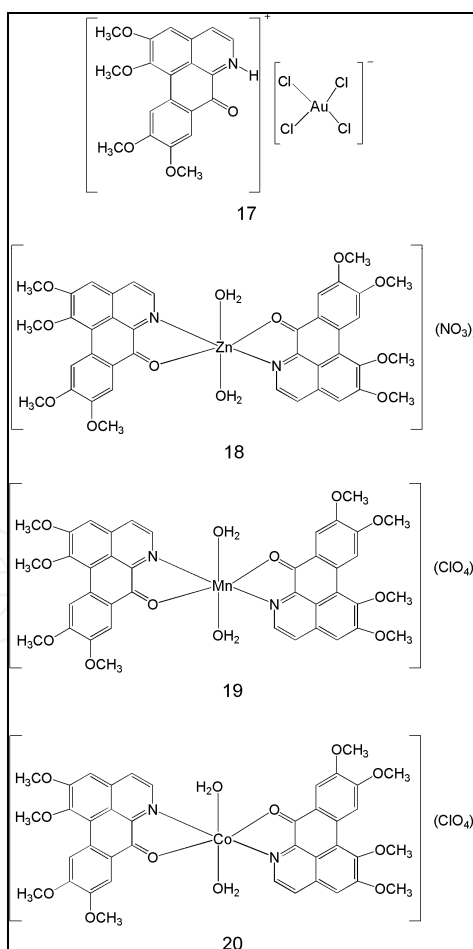


Fig. 6. Structures of $[\text{OGH}][\text{AuCl}_4]$ (17), $[\text{Zn}(\text{OG})_2(\text{H}_2\text{O})_2](\text{NO}_3)_2$ (18), $[\text{Mn}(\text{OG})_2(\text{H}_2\text{O})_2](\text{ClO}_4)_2$ (19), $[\text{Mn}(\text{OG})_2(\text{H}_2\text{O})_2](\text{ClO}_4)_2$ (20).

Oxoglaucine alkaloid (OG) was synthesized via a two-step reaction route. Using OG as ligand to react with corresponding transition metal salts gave rise to four metal-based compounds: $[\text{OGH}][\text{AuCl}_4] \cdot \text{DMSO}$ (**17**), $[\text{Zn}(\text{OG})_2(\text{H}_2\text{O})_2](\text{NO}_3)_2$ (**18**), $[\text{Mn}(\text{OG})_2(\text{H}_2\text{O})_2](\text{ClO}_4)_2$ (**19**), $[\text{Co}(\text{OG})_2(\text{H}_2\text{O})_2](\text{ClO}_4)_2$ (**20**, Fig. 6), whose structures were determined by X-ray single crystal diffraction analysis. The *in vitro* cytotoxicity of **17–20** against various tumour cell lines was assayed by MTT method. The results show that most of these metal-based compounds of oxoglaucine exhibit enhanced cytotoxicity *vs.* oxoglaucine and corresponding metal salts, with IC_{50} values ranging from 1.4 to 32.7 μM for sensitive cancer cells, implying a positive synergistic effect. Moreover, these complexes seem to be selectively active against certain cell lines. The interactions of oxoglaucine and its metal complexes with DNA and topoisomerase I were investigated by spectroscopic, viscosity and agarose gel electrophoresis measurements, which indicate that these OG metal-based compounds interact with DNA mainly *via* intercalation mode. Of special note, these metal-based compounds effectively inhibit Topoisomerase I even at low concentration, implying topoisomerase I may be another molecular target. However, the exact molecular mechanism requires further detailed investigation. Cell-cycle analysis revealed that these OG-metal complexes cause S-phase cell arrest.

2.1.3 Matrine-metal based anticancer agents

Matrine, a quinolizidine alkaloid matrine (MT), a main component found in roots of the Chinese herb *Sophora* including *Sophora flavescens* and *Sophora tonkinensis*, was selected as an active ligand. Matrine has been extensively used in China for the treatment of viral hepatitis and cardiac diseases (Liu et al., 2007). Matrine also exhibits inhibition activity toward many tumour cells (such as HeLa cell and gastric cancer MKN45 cell) (Galasso et al., 2006; Luo et al., 2007; Ruan et al., 2006; Zhang et al., 2001 & 2007).

Three TCM-metal compounds of Ga(III), Au(III), with Sn(IV) and matrine (MT), $[\text{H-MT}][\text{GaCl}_4]$ (**21**), $[\text{H-MT}][\text{AuCl}_4]$ (**22**) and $[\text{SnCl}_5(\text{H-MT})]$ (**23**, Fig. 7), have been synthesized and characterized. The crystal structure analyses reveal that **21** and **22** are ionic compounds, while **23** is a coordination compound formed by monodentate MT *via* its carbonyl O (Fig.7). But the ESI-MS results show that they may exist with ionic species: $[\text{H-MT}]^+$, $[\text{GaCl}_4]^-$, $[\text{AuCl}_4]^-$ and $[\text{SnCl}_5]^-$ in water solution. The *in vitro* cytotoxicities of **21**, **22** and **23** against eight selected human tumour cell lines are different. In some case, they exhibit significant enhanced antitumour activity, such as **21** to SW480, **22** to HeLa, HepG2 and MCF-7, which exceed matrine and cisplatin, and display synergistic contribution of their components. However, in the case of **23**, such synergistic effect could not be observed due to the electronic structure alteration of lactam group of matrinium, thus **23** exhibits lower antitumour activity than that of compounds **21** and **22**. Although the spectroscopic and agarose gel electrophoresis assay show that these compounds bind to DNA inducing only small structural changes in the duplex, it could lead to a different cellular response. The cell cycle analyses show that compounds **21**, **23** and MT exhibit cell cycle arrest at the G2/M phase. Their interactions with ct-DNA indicate that these metal-matrine compounds may be act mainly *via* intercalation mode of H-MT. In addition, **21** and **22** exhibit potent TOPO I inhibition ability, implying topoisomerase I may be another molecular target. However, the exact molecular mechanism requires further detailed investigation (Chen et al., 2011).

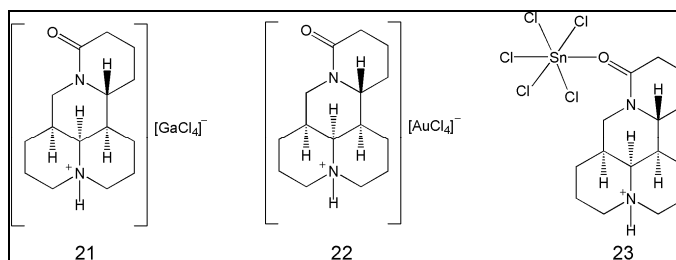


Fig. 7. Structures of [H-MT][GaCl₄] (**21**), [H-MT][AuCl₄] (**22**) and [SnCl₅(H-MT)] (**23**).

2.1.4 β-Carboline alkaloid-metal based anticancer agents

β-Carboline alkaloids, naturally occurring nitrogen-containing ligands, for example, harmaline (4,9-dihydro-7-methyl-3H-pyrido[3,4-b]indole), harmalol (4,9-dihydro-1-methyl-3H-pyrido[3,4-b] indole-7-ol), harmine (7-methoxy-1-methyl-9H-pyrido[3,4-b]indole), and harmane (1-methyl-9H-pyrido[3,4-b]indole), are extremely effective as antituberculosis, analgesic, and antimicrobial agents. Al-Allaf and co-worker reported the synthesis and cytotoxic evaluation of a series of novel biologically active platinum(II) (**24**, **26**, **28**, **30**) and palladium(II) (**25**, **27**, **29**, **31**, **32**, Fig. 8) complex of some β-carboline alkaloids (harmaline, harmine, and harmane). These complexes exhibited promising antitumour activity. The IC₅₀ of the complexes varied from 0.2 to 2.0 μg/mL in the antiproliferative assays against three tumour cell lines, and the calculated therapeutic index varied again from 10 to 20 μg/mL (Al-Allaf et al., 1990; Al-Allaf & Rashan, 1998).

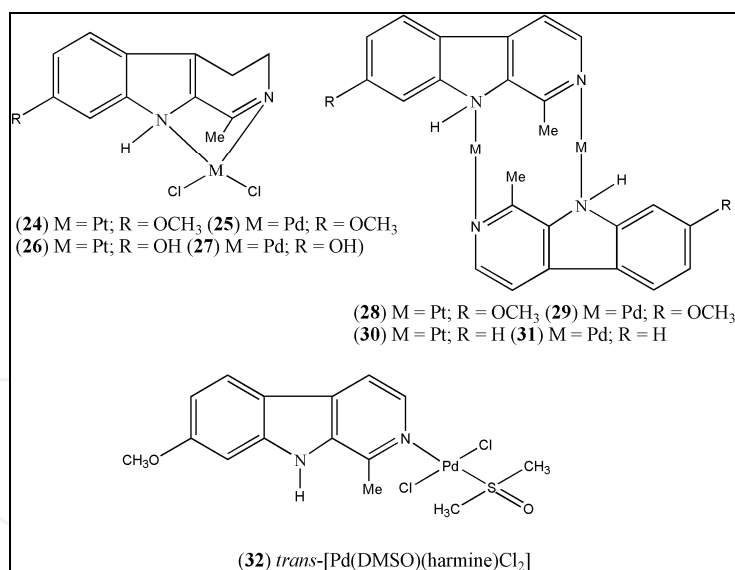


Fig. 8. Structures of β-carboline alkaloid-metal complexes (**24-32**).

2.2 Flavonoid-metal based anticancer agents

Flavonoids are found in many plants and belong to a group of natural substances occurring in TCM with variable phenolic structures. Their therapeutic effects were known long before they were isolated (Nijveldt et al., 2001). Flavonoids display many important biological effects including antitumour, antioxidative, anti-inflammatory (inhibition of cyclooxygenase and lipoxygenase), antiviral, antibacterial, and antifungal actions. They also were shown to be effective inhibitors of platelet aggregation (Narayana et al., 2001; Nijhoff et al., 1995).

2.2.1 Chrysin, morin-metal based anticancer agents

Chrysin (5, 7-di-OH-flavone) is one flavonoid occurring in TCM, a natural ligand for benzodiazepine receptors with anticonvulsant properties. Complexes with Co(II), Ni(II), Cu(II), Pb(II), Fe(III) and Y(III) etc., have been synthesized and characterized. [Ansari, 2008; Engelmann et al., 2005; Pusz et al., 1997, 2000] Recently, Tang et al. reported chrysin-La(III) complex, $\text{La}(\text{chrysin})_2(\text{OAc}) \cdot 7\text{H}_2\text{O}$ (**33**, Fig. 9), which exhibited high inhibition rate (*in vitro*) to A549 and P388 with 74.5% and 42.4 at $10\mu\text{M}$, respectively; and higher too much than that of chrysin (4.9% and 16.7%). The intrinsic binding constants of La(III) complex and chrysin are 1.29×10^6 and $5.44 \times 10^5 \text{M}^{-1}$, respectively, which are considered both them bind to DNA by intercalation (Zeng et al., 2003).

Morin (2', 3, 4', 5, 7-pentahydroxyflavone) occurs in TCM and has antitumour activity (Alldrick et al., 1986). Wang et al. synthesized and characterized two complexes, $\text{Zn}(\text{morin})_2 \cdot 3\text{H}_2\text{O}$ (**34**, Fig. 9) and $\text{Cu}(\text{morin})_2 \cdot 2\text{H}_2\text{O}$ (**35**, Fig. 9) The two complexes exhibit higher *in vitro* antitumour activity to Hep-2, BBHK-2, BHK21 and HL-60 than morin alone, but the antitumour activity of the cobalt(II) complex (**36**, Fig. 9) is lower than morin (Zhang et al., 1996). Song and co-worker investigated the Zn(II) and Co(II) complexes of morin bound to ct-DNA by spectroscopic and voltammetric methods. The results indicate that they have different spectral characteristics and electrochemical behaviour, which suggests that the mode and affinity of Zn(II) and Co(II) complexes of morin bound to ct-DNA, may be responsible to their different antitumor activity (Song et al., 2003).

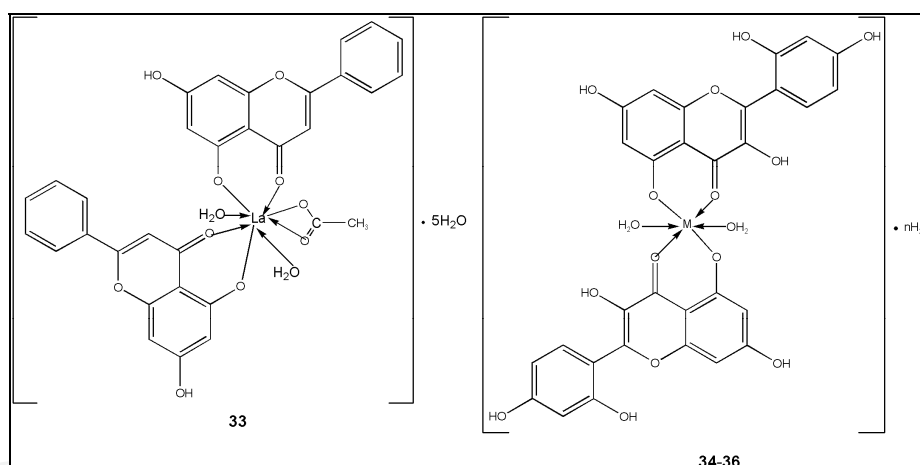


Fig. 9. Structure of $\text{La}(\text{chrysin})_2(\text{OAc}) \cdot 7\text{H}_2\text{O}$ (**33**) and the possible structure of the complexes. M = Zn(II) (**34**), Cu(II) (**35**), Co(II) (**36**), n = 0, or 1.

2.2.2 Hesperetin, naringenin, and apigenin-metal based anticancer agents

Hesperetin (5, 7, 3-trihydroxy-4-methoxy-flavanone), naringenin (4, 5, 7-trihydroxyflavanone) and apigenin (4, 5, 7-trihydroxyflavone), are biologically active flavonoids, commonly found in TCM (Tripoli et al., 2007). They have been reported to exhibit antitumour effects against breast cancer and hepatoma HepG2 cell lines (Korkina & Afanasev, 1997; Pereira et al., 2007). In addition, some metal complexes of hesperetin and naringenin have been found to exhibit antioxidant and anticancer activity (Chiang et al., 2006; So et al., 1996). The Naringenin Schiff base La(III) complex is more potent against the A-549 cell line than cisplatin under reasonable experimental concentrations (Li et al., 2008; Wang et al., 2006). Copper(II) complex of naringenin Schiff base possesses potent antioxidant activity, better than standard antioxidants

like vitamin C and mannitol (Li et al., 2007). Our group reported three new copper(II) complexes of hesperetin, naringenin, and apigenin of general composition $[\text{CuL}_2(\text{H}_2\text{O})_2] \cdot n\text{H}_2\text{O}$ (37–39, Fig. 10). The *in vitro* antitumor activity of the copper(II) complexes *vs* free ligand against human cancer cell lines HepG-2, SGC-7901, and HeLa have been assayed. Hesperetin-Cu(II) and apigenin-Cu(II) complexes were found to exhibit growth inhibition of SGC-7901 and HepG2 cell lines with respect to the free ligands; the inhibitory rate of hesperetin-Cu(II) complex is 43.2% and 43.8%, while apigenin-Cu(II) complex is 46% and 36%, respectively. Both hesperetin-Cu(II) complex and hesperetin were found to bind DNA in intercalation modes, and the binding affinity of the complex was stronger than that of free hesperetin (Tan et al., 2009).

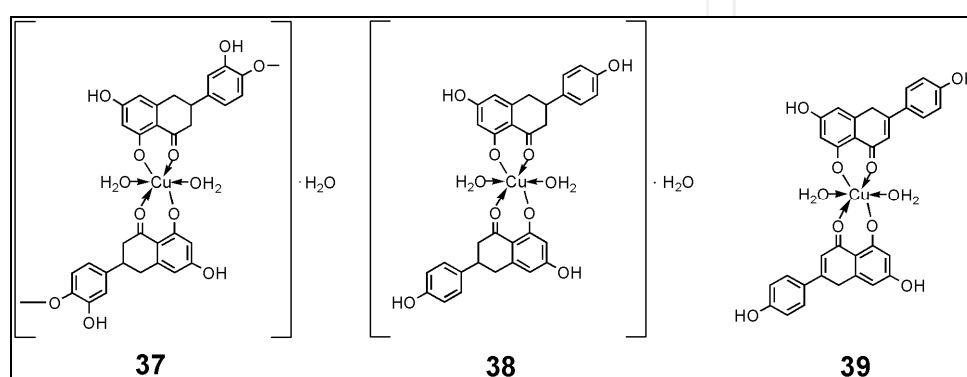


Fig. 10. The possible structure of the hesperetin-Cu(II) (37), naringenin-Cu(II) (38) and apigenin-Cu(II) (39) complexes.

2.2.3 Quercetin-metal based anticancer agents

Quercetin (3, 5, 7, 3', 4'-pentahydroxyflavone), a widely occurring compound in TCM, protects DNA from damage induced by reactive oxygen species (ROS) (Russo et al., 2000). Quercetin can chelate metal ions to form metal complexes that have better antioxidation and antitumour activity than quercetin alone (Zhou et al., 2001). Williams and co-worker reported the synthesis, characterization, antitumoural and osteogenic activities of quercetin vanadyl(IV) complexes. It was found that the free ligand quercetin might be a good candidate to be further evaluated in the treatment of bone tissue tumours because its effect has been more deleterious for tumoural osteoblasts than for the normal cells. However, the complexation of quercetin with vanadium center does not improve its potential anticarcinogenic properties. On the other hand, quercetin vanadyl(IV) complex seems to be a promising compound because it activates type I collagen production and shows a slight inhibitory effect on ALP specific activity, two markers of osteoblastic differentiation. It was believed that the activation of ERK pathways seems to be involved at least as one possible mechanism in the biological effects of quercetin vanadyl(IV) complex (Ferrer et al., 2006). Wang et al. investigated in detail the DNA binding, cytotoxicity, apoptotic inducing activity, and potential molecular mechanism of quercetin zinc(II) (46, Fig. 11) and copper(II) (47, Fig. 11) complexes. The quercetin zinc(II) complex exhibits significant cytotoxicity against three tumour cell lines (HepG2, SMMC7721, and A549), which might be related to its intercalation into DNA (Tan et al., 2009). The quercetin zinc(II) complex displays strong DNA hydrolytic cleavage activity, which successfully promotes the cleavage of plasmid DNA, producing single and double DNA strand breaks, supported by evidence from free radical quenching, thiobarbituric acid-reactive substances (TBARS) assay, and T4 ligase ligation (Tan et al.,

2007). Tan et al. systematically investigated the mode of DNA binding, oxidative DNA cleavage activity, and apoptosis-inducing activity of the quercetin copper(II) complex. The results showed that the antitumour mechanism of the quercetin copper(II) complex involves not only its oxidative DNA damage with generation of ROS but also its specific interaction with DNA (Tan et al., 2009).

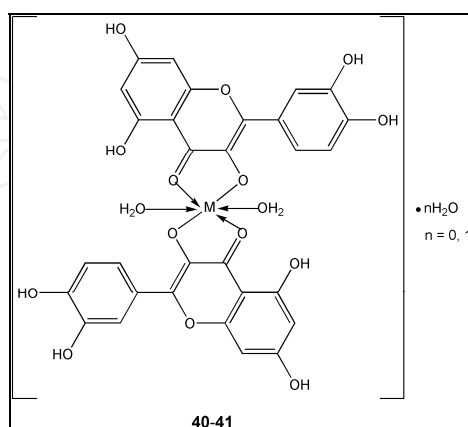


Fig. 11. The possible structures of quercetin metal complexes (M = Zn(II) (40), Cu(II)(41)).

In conclusion, flavonoids possess many potential pharmacological activity, represent a large type of TCM ligands, but because the flavonoids contain rich phenolic and carbonyl groups, chelate to metal ion, very easily to form polymeric structures, resulting in poor solubility, that limit the actual applications. Therefore, investigation of flavonoid metal-based antitumour agents, the excellent synthetic and characterized techniques is required, the good choice of flavonoids is very important.

2.3 Other TCM active ingredient-metal based anticancer agents

2.3.1 Coumarin-metal based anticancer agents

It is well documented that coumarin and a variety of coumarin derivatives have antitumour and antiproliferative activity. They have been shown to inhibit proliferation of particular human malignant cell lines *in vitro*, as well as affecting tumour activity against several *in vitro* tumour types (Kostova & Momekov, 2006). Kostova et al. synthesized a series of new zirconium(V) complexes with bis-coumarin ligands containing pyrazole or pyridine rings. The cytotoxic screening by MTT assay to HL-60 and the chronic myeloid leukemia LAMA-84 indicates that the zirconium(V) complexes of coumarins proved to be less potent than the corresponding free ligands (Kostova & Momekov, 2006). Egan and coworker investigated *in vitro* antitumour and cytoselective effects of coumarin-3-carboxylic acid and three of its hydroxylated derivatives, along with their silver-based complexes using human epithelial carcinoma cell lines (A-498 and Hep-G2). The *in vitro* antitumour assay results indicated that all of the ligands and their silver complexes induced a concentration-dependent cytotoxic effect. Hydroxylation of C-3-COOH and its subsequent complexation with silver led to the production of a series of compounds with dramatically enhanced cytotoxicity, with 6-OH-C-3-COO-Ag having the greatest activity, and all of the metal-based complexes were selectively cytotoxic to both carcinoma-derived cell lines, relative to normal renal and hepatic cells. The IC_{50} values obtained with Hep-G2 cells were between 2 and 5.5 times more cytotoxic than cisplatin. All of the coumarin-silver complexes inhibited the DNA synthesis, which did not appear to be mediated *via* intercalation. These findings suggest that both

hydroxylation, particularly in the 6th position, and complexation with silver give rise to a cytotoxic-selective agent that significantly targets cancer cells, relative to normal cells (Thati et al., 2007). In addition, Kostova and co-worker investigated the cytotoxic activity of new lanthanum (III) and cerium (III) complexes of bis-coumarins. Their findings suggest that the coumarin-lanthanide complexes exhibited cytotoxic activity in micromolar contractions. Their *in vitro* effects are clearly expressed (Kostova et al., 2005, 2006). Recently, Creaven et al. reported the antibacterial and anticancer activities, coordination modes of copper(II) complexes of Schiff based-derived coumarin ligands (Creaven et al., 2010). Therefore, these coumarin-metal compounds have potential to develop as anticancer drugs, which provides hope for the pursuit of non-platinum anticancer drugs.

2.3.2 Cantharidin-metal based anticancer agents

Cantharidin is the active principle of *Epicanta gorhami* or *Mylabris* ("blister beetles"), which has long been applied as a TCM treatment for liver, lung, intestinal and digestive tract tumours (Wang, 1989). Cantharidin has severe side effects such as dysphagia, hematemesis, and dysuria (Wang, 1989). Cantharidin and its derivatives have been reported to have strong affinity and specificity for a protein phosphatase 2A (Li & Casida, 1992). Demethylcantharidin (norcantharidin, DMC) is a synthetic analogue of cantharidin and has potent antitumour activity but without the latter's adverse effects (Wang, 1989). Ho and coworker have carried out systematic, innovative research on the combination of demethylcantharidin with a platinum moiety to give a series of TCM-based platinum compounds $[\text{Pt}(\text{C}_8\text{H}_8\text{O}_5)(\text{NH}_2\text{R})_2]$ (**42-46**, Fig. 12). These platinum complexes exhibit selective cytotoxicity toward SK-Hep-1 (human liver cell line), and circumvention of cross-resistance. They may possess a novel dual mechanism of antitumour action: inhibition of PP2A and platination of DNA (Ho et al., 2001 & 2003; To et al., 2004). Ho et al. determined the release of hydrolyzed demethylcantharidin from norcantharidin-Pt(II) compounds with anticancer activity by gas chromatography, in which the TCM component was slowly released from the norcantharidin-Pt(II) compounds over 24h, leading to PP2A inhibition. These complexes may prove to be new anticancer agents with novel mechanisms of cytotoxic action (To et al., 2002). The *in vitro* anti-proliferative activity of compounds **42-46** was investigated in human hepatocellular carcinoma (HCC) cell lines using MTT assay, which showed that compounds **42-46** were approximately 2-20 and 20-200 times more potent than cisplatin and carboplatin, respectively, in SK-Hep1 and HepG2 cells. The *in vivo* antitumour efficacies of **42-46** were evaluated in a s.c. inoculated SK-Hep1 xenograft model in nude mice. Compounds **42-46** exhibited definite *in vivo* activity without undue toxicity, contrasting the lack of activity of cisplatin and carboplatin. For *in vivo* cisplatin resistance model of human HCC, compounds **42-46** performed the same level of tumour growth suppression as in the control tumours, indicating the circumvention of cisplatin (To et al., 2005). Further studies indicated that compounds **42-46** were considerably less reactive to sulfur-containing nucleophiles than cisplatin, implying that they had reduced toxicity when compared with cisplatin, but the antitumour activity still remained (To et al., 2006). In order to determine the influence of the isomers on their anticancer activity, a series of platinum complexes integrating demethylcantharidin (CMC) with isomers of 1, 2-diaminocyclohexane (DACH) have been synthesized. These compounds exhibit superior *in vitro* anticancer activity against colorectal and human hepatocellular cancer cell lines comparing with oxaliplatin, cisplatin, and carboplatin. The flow cytometric analysis results showed that the *trans*-DACH-Pt-DMC analogues presented similar behaviour to oxaplatin on affecting the

cell cycle of the HCT116 colorectal cancer cells, but different from that of cisplatin or carboplatin. The DACH component obviously dictates the *trans*-DACH-Pt-DMC complexes to act similar to oxaliplatin, whereas the DMC ligand enhanced the compounds' overall anticancer activity. It was speculated these compounds accelerated the cell cycle from G1 to S-phase with subsequent onset of G2/M arrest and accompanying apoptosis (Yu et al., 2006). Ho's group also studied the pharmacokinetics and tissue distribution of these DMC-Pt anticancer agents in rats. Their findings suggested that the novel DMC-Pt compounds might afford higher clinical efficacy and reduced systemic side effects in contrast to cisplatin (Wang et al., 2007).

Moreover, the synergistic interaction between platinum-based antitumour agents and demethylcantharidin were investigated *in vitro* and *in vivo*, which demonstrated that synergistic effects occurred by combining demethylcantharidin with platinum-based antitumour agents. The demethylcantharidin might play a role in enhancing the efficacy of cisplatin in the treatment of various solid human tumours such as HCC, and overcoming cisplatin resistance. The demethylcantharidin has considerable promise as an adjuvant to chemotherapy (To et al., 2005).

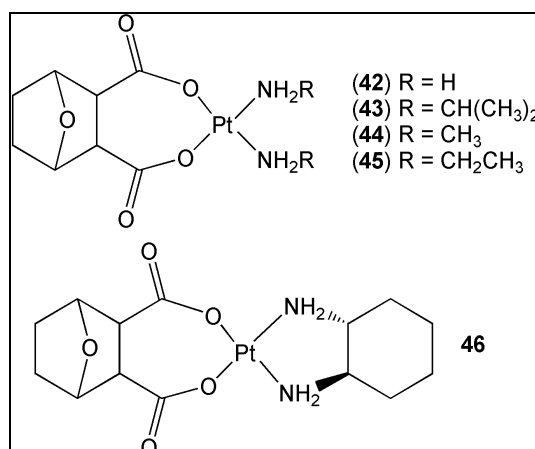


Fig. 12. Structures of $[Pt(C_8H_8O_5)(NH_2R)_2]$ (42-46) .

The systematic work carried out by Ho's group on cis-DMC-Pt anticancer agents provides a successful paradigm for future research of TCM metal-based anticancer agents by utilization of multi-targets and multi-mechanisms of TCM-metal based compounds. Their achievement make us to believe that innovative metal-based anticancer drugs enable to develop by integration of the multiple advantages of metals and metal complexes with TCM's multi-target and multi-mechanism features.

2.3.3 Plumbagin-metal based anticancer agents

Plumbagin (PLN) is a potent toxic natural product extracted from TCM *Plumbago Zeylanica* L. (*Plumbaginaceae*), which has been used in China as well as other Asian countries for the treatment of rheumatoid arthritis, dysmenorrhea, injury by bumping, and even cancer. The anticancer property of PLN against HeLa, P388 lymphocytic, leukemia, colon cancer and hepatoma has been reported (Aziz et al., 2008; Kuo et al., 2006; Lin et al., 2003; Olagunju et al., 1999; Srinivas et al., 2004). Our group carried out the studies on plumbagin metal-based antitumour agents. The anticancer TCM, plumbagin (PLN), was isolated from *Plumbago Zeylanica*. Reaction of plumbagin with Cu(II) salt, afforded $[Cu(PLN)_2] \cdot 2H_2O$ (47, Fig.13).

With 2,2'-bipyridine (bipy) as a co-ligand, PLN reacts with Cu(II) to give rise to $[\text{Cu}(\text{PLN})(\text{bipy})(\text{H}_2\text{O})]_2(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ (**48**, Fig. 13). The two complexes were characterized by elemental analysis, IR, and ESI-MS. Their crystal structures were determined by single crystal X-ray diffraction methods (Fig. 13). And the *in vitro* cytotoxicity of PLN and the two copper complexes against seven human tumour cell lines was assayed. The metal-based compounds exhibit enhanced cytotoxicity vs. that of PLN, suggesting that these compounds display synergy in the combination of metal ions with PLN. The binding properties of PLN and the two copper complexes to DNA were investigated with UV-vis, fluorescence, CD spectroscopy, and gel mobility shift assay, which indicated that the two copper complexes of plumbagin were non-covalently binding and mainly intercalated in the neighboring base pairs of DNA. PLN and its copper complexes exhibit inhibition activity to topoisomerase I (TOPO I), but the metal complexes were more effective than PLN (Chen et al., 2009).

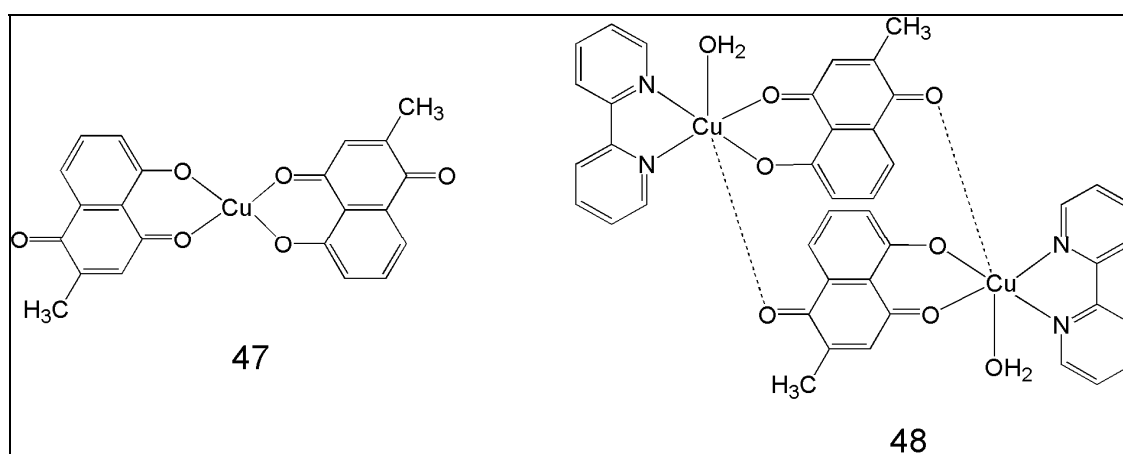


Fig. 13. Crystal structures of $[\text{Cu}(\text{PLN})_2]$ (**47**) and $[\text{Cu}(\text{PLN})(\text{bpy})(\text{H}_2\text{O})](\text{NO}_3)_2$ (**48**).

This work has recently been reviewed by Professor Roy Planalp. He thought that this work is very exciting with regards to the enhanced antitumour properties of a natural substance by complexation with a common biometal (Saxton, 2010).

In order to investigate the cytotoxicity of plumbaginate lanthanide complexes, five new lanthanide(III) complexes of deprotonated plumbagin: $[\text{Y}(\text{PLN})_3(\text{H}_2\text{O})_2]$ (**49**), $[\text{La}(\text{PLN})_3(\text{H}_2\text{O})_2]$ (**50**), $[\text{Sm}(\text{PLN})_3(\text{H}_2\text{O})_2] \cdot \text{H}_2\text{O}$ (**51**), $[\text{Gd}(\text{PLN})_3(\text{H}_2\text{O})_2]$ (**52**), and $[\text{Dy}(\text{PLN})_3(\text{H}_2\text{O})_2]$ (**53**, Fig. 14) were synthesized by the reaction of plumbagin with the corresponding lanthanide salts, in amounts equal to ligand/metal molar ration of 3:1. The PLN-lanthanide(III) complexes were characterized by different physicochemical methods: elemental analyses, UV-visible, IR and ^1H NMR and ESI-MS as well as TGA. The plumbagin and its lanthanide(III) complexes **49–53**, were tested for their *in vitro* cytotoxicity against BEL7404 (liver cancer) cell lines by MTT assay. The five PLN-lanthanide (III) complexes **49–53** effectively inhibited BEL7404 cell lines growth with IC_{50} values of 11.0 ± 3.5 , 5.1 ± 1.3 , 6.1 ± 1.1 , 6.4 ± 1.3 , and $9.8 \pm 1.5 \mu\text{M}$, respectively, and exhibited a significantly enhanced cytotoxicity compared to plumbagin and the corresponding lanthanide salts, suggesting a synergistic effect upon plumbagin coordination to the Ln(III) ion. The lanthanide complexes under investigation also exerted dose- and time-dependent cytotoxic activity. $[\text{La}(\text{PLN})_3(\text{H}_2\text{O})_2]$ (**50**) and plumbagin interact with calf thymus DNA (ct-DNA) mainly via intercalation mode, but for $[\text{La}(\text{PLN})_3(\text{H}_2\text{O})_2]$ (**50**), the electrostatic interaction should not be

excluded; the binding affinity of $[\text{La}(\text{PLN})_3(\text{H}_2\text{O})_2]$ (**50**) to DNA is stronger than that of free plumbagin, which may correlate with the enhanced cytotoxicity of the PLN-lanthanide(III) complexes (Chen et al. 2011).

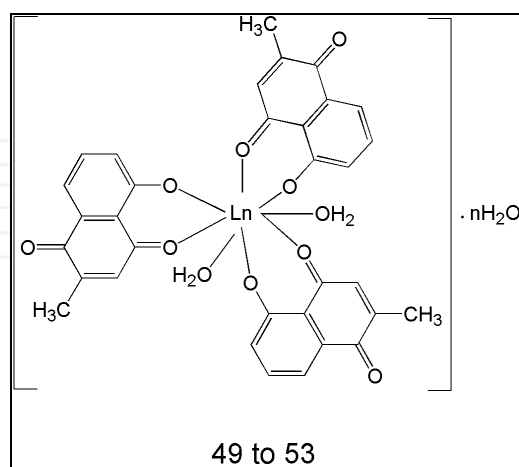


Fig. 14. The possible structure of complexes **49–53** ($n=0$, $\text{Ln} = \text{Y(III)}$ (**49**), La(III) (**50**), Gd(III) (**52**), Dy(III) (**53**); $n = 1$, $\text{Ln} = \text{Sm(III)}$ (**51**)).

2.3.4 Curcumin-metal based anticancer agents

Curcumin, an extract of turmeric, *Curcuma longa* L., has been used for centuries in variety of TCM pharmaceutical applications (Sharma, 1976), including treatment of arthritis (Deodhar et al., 1980), as an anti-inflammatory agent (Rao et al., 1982; Srimal & Dhawan, 1973) and as an orally available treatment for diabetes (Arun & Nalini, 2002). Thompson and co-worker synthesized a novel vanadyl curcumin complex ($\text{VO}(\text{cur})_2$) (**54**, Fig. 15) and studied its anticancer potential in inhibiting mouse lymphoma cell growth. The complex was more effective than uncoordinated curcumin (Thompson et al., 2004).

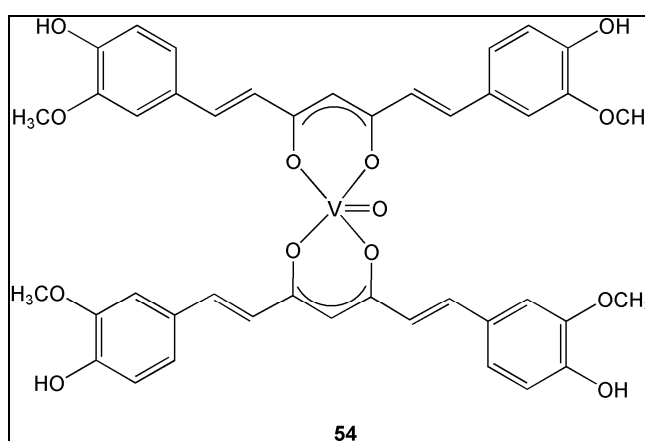


Fig. 15. Structure of vanadyl curcumin complex ($\text{VO}(\text{cur})_2$ **54**).

2.3.5 Camphorato-metal based anticancer agents

Camphor has long been used as TCM to relieve pain, stop tickle, anti-inflammation, cure ulcers and sores, dental caries, and kill worms and acariasis as early as the Ming Dynasty. Camphoric acid can be obtained by the oxidation of camphor and is used in

pharmaceuticals as exciting centre and respiration analeptic agent. Gou and coworker synthesized eight new camphorato platinum complexes (**55**, Fig. 16) and evaluated their *in vitro* cytotoxicity against HL-60, 2AO, BEL-7402 and A549 cells. The results show that most complexes exhibited good cytotoxic activity against the selected cell lines. One complex displayed not only higher *in vivo* antitumour activity, but also less toxicity than oxaliplatin when it was administered intravenously at a dose of 6 mg/Kg three times. Gou and coworkers research provides a new selection to find chiral leaving groups from TCM (Wang et al., 2005).

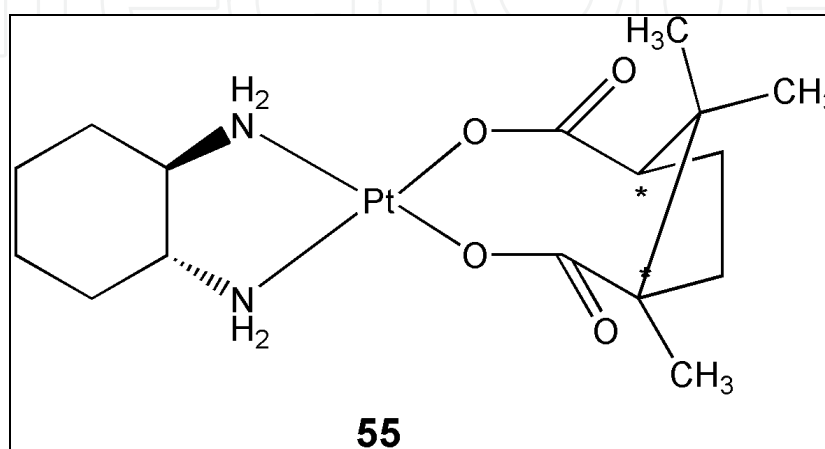


Fig. 16. *trans*-1R, 2R-Diaminocyclohexane camphorate-Pt complex (**55**).

3. Conclusion

TCM is a natural “combination chemical resources armoury”, which has undergone several thousands years worth of clinical practice and screening. TCM possess multi-component, multi-target and co-regulatory features which meet the view points of multi-target drugs through the network approach (Csermely et al., 2005) and robustness-based approach to systems-oriented drug design (Kitano, 2007). TCM metal-based antitumor agents have at least two remarkable advantages: either TCM playing key role or metal complex making multiple contributions in development of drugs. In this review, the alkaloids, flavonoids, cantharidin, coumarins, plumbagin, curcumin and camphoric acid metal-based compounds with antitumor activity were summarized. Generally, TCM-metal based compounds formed *via* metal ions coordinating to TCM with O, N donors, exhibiting enhanced activity and synergistic effect with multi-targets and multi-mechanisms. With the Chinese government promotion of the modernization of TCM (Normile, 2003) and carrying out the *herbalome* (Stone, 2008), as well as the advancements of genome, proteome, metabolome, there is the possibility to design new TCM metal-based anticancer drugs and develop modern TCM, which will benefit to overcoming multidrug resistance (MDR). The promising trends have been supported by great potential of TCM metal-based antitumor agents mentioned above. We believe that innovative metal-based anticancer drugs enable to develop by integration of the multiple advantages of metals and metal complexes with TCM’s multi-target and multi-mechanism features. But the action species and multi-target and multi-mechanism in cell and *in vivo* of the TCM metal-based antitumor agents still need to be widely and deeply investigated by adopting modern genome, proteome, metabolome technologies.

4. Acknowledgment

This work was supported National Basic Research Program of China (Nos. 2009CB526503, 2010CB534911), the National Natural Science Foundation of China (20861002), and Natural Science Foundation of Guangxi Province of China (Nos. 0991012Z, 0991003, and 2010GXNSFF013001).

5. References

- Al-Allaf, T. A. K.; Ayoub, M. T.; Rashan, L. J. (1990). Synthesis and characterization of novel biologically active platinum(II) and palladium(II) complexes of some β -carboline alkaloids. *J. Inorg. Biochem.*, Vol.38, No.1, (January 1990), pp. 47-56, ISSN 0162-0134.
- Al-Allaf, T. A. K.; Rashan, L. J. (1998). Synthesis and cytotoxic evaluation of the first trans-palladium(II) complex with naturally occurring alkaloid harmine. *Eur. J. Med. Chem.*, Vol.33, No.10, (October 1998), pp. 817-820, ISSN 0223-5234.
- Alldrick, A. J.; Flynn J.; Rowland, I. R. (1986). Effects of plant-derived flavonoids and polyphenolic acids on the activity of mutagens from cooked food. *Mutat. Res.*, Vol.163, No.3, (December 1986), pp. 225-232, ISSN 0027-5107.
- Alt, A.; Lammens, K.; Chiocchini, C.; Alfred Lammens, A.; Pieck, J. C.; Kuch, D.; Karl-Peter Hopfner, K.-P.; Carell, T. (2007). Bypass of DNA lesions generated during anticancer treatment with cisplatin by DNA polymerase ϵ . *Science*, Vol. 318, No.5852, (November, 2007), pp. 967-970, ISSN 0036-8075.
- Ansari, A. A. (2008). ^1H NMR and spectroscopic studies of biologically active yttrium (III)-flavonoid complexes. *Main Group Chem.*, Vol.7, No.2, (February 2008), pp. 133-145, ISSN 1024-1221.
- Arun, N.; Nalini, N. (2002). Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. *Plant Foods Hum. Nutr.*, Vol.57, No.1, (January 2002), pp. 41-52, ISSN 0921-9668.
- Aziz, M. H.; Dreckschmidt, N. E.; Verma, A. K. (2008). Plumbagin, a medicinal plant-derived naphthoquinone, is a novel inhibitor of the growth and invasion of hormone-refractory prostate cancer. *Cancer Res.*, Vol.68, No.21, (November 2008), pp. 9024-9032, ISSN 0008-5472.
- Baraldi, P. G.; Bovero, A.; Fruttarolo, F.; Preti, D.; Tabrizi, M. A.; Pavani, M. G.; Romagnoli, R. (2004). *Med. Res. Rev.*, Vol.24, No.4, (April 2004), pp. 475-496, ISSN 0198-6325.
- Bentley, K. W. (2001). β -Phenylethylamines and the isoquinoline alkaloids. *Nat. Prod. Rep.*, Vol.18, No.2, (February 2001), pp. 148-170, ISSN 0265-0568.
- Blanco, O. M.; Castedo, L.; Villaverde, M. C. (1993). *Phytochemistry*, Vol.32, No.4, (March 1993), pp. 1055-1057, ISSN 0031-9422.
- Chan, K. (1995). Progresses in traditional Chinese medicine. *Trends Pharmacol. Sci.*, Vol.16, No.6, (June 1995), pp. 182-187, ISSN 0165-6147.
- Chang, F.-R.; Hsieh, T.-J.; Huang, T.-L.; Chen, C.-Y.; Kuo, R.-Y.; Chang, Y.-C.; Chiu, H.-F.; Wu, Y.-C. (2002). Cytotoxic constituents of the stem bark of *Neolitsea acuminatissima*. *J. Nat. Prod.*, Vol.65, No.3, (March 2002), pp. 255-258, ISSN 0163-3864.
- Chang, H. C.; Chang, F. R.; Wu, Y. C.; Lai, Y. H. (2004). Anti-cancer effect of liriodenine on human lung cancer cells. *Kaohsiung J. Med. Sci.*, Vol.20, No.8, (August 2004), pp. 365-371, ISSN 1607-551X.

- Chen, C.-L.; Chang, H.-M.; Cowling, E. B.; Huang Hsu, C.-Y.; Gates, R. P. (1976). *Phytochemistry*, Vol.15, No.7, (July 1976), pp. 1161–1167, ISSN 0031-9422.
- Chen, K.-S.; Chang, F.-R.; Chia, Y.-C.; Wu, T.-S.; Wu, Y.-C. (1998). Chemical constituents of *Neolitsea parvigemma* and *Neolitsea konishii*. *J. Chin. Chem. Soc.*, Vol.45, No.1, (January 1998), pp. 103–110, ISSN 0009-4536.
- Chen, S.-B.; Gao, G.-Y.; Yu, S.-C.; Xiao, P.-G. (2002). Cytotoxic Constituents from *Aquilegia ecalcarata*. *Planta Med.*, Vol.68, No.6, (June 2002), pp. 554–556, ISSN 0032-0943.
- Chen, Z.-F.; Liu, Y.-C.; Liu, L.-M.; Wang, H.-S.; Qin, S.-H.; Wang, B.-L.; Bian, H.-D.; Yang, B.; Fun, H.-K.; Liu, H.-G.; Liang, H.; Orvig, C. (2009). Potential new inorganic antitumour agents from combining the anticancer traditional Chinese medicine (TCM) liriodenine with metal ions, and DNA binding studies. *Dalton Trans.*, Vol.38, No.2, (January 2009), pp. 262–272, ISSN 1477-9226.
- Chen, Z.-F.; Mao, L.; Liu, L.-M.; Liu, Y.-C.; Peng, Y.; Hong, X.; Wang, H.-H.; Liu, H.-G.; Liang, H. (2011). Potential new inorganic antitumour agents from combining the anticancer traditional Chinese medicine (TCM) matrine with Ga(III), Au(III), Sn(IV) ions, and DNA binding studies. *J. Inorg. Biochem.*, Vol.105, No.2, (February 2011), pp.171–180, ISSN 0162-0134.
- Chen, Z.-F.; Shi, Y.-F.; Liu, Y.-C.; Hong, X.; Geng, B.; Peng, Y.; Liang H. (2011). Unpublish results.
- Chen, Z.-F.; Tan, M.-X.; Liu, L.-M.; Liu, Y.-C.; Wang, H.-S.; Yang, B.; Peng, Y.; Liu, H.-G.; Liang H. and Orvig, C. (2009). Cytotoxicity of the traditional Chinese medicine (TCM) plumbagin in its copper chemistry. *Dalton Trans.*, Vol.38, No.48, (December 2009), pp. 10824–10833, ISSN 1477-9226.
- Chen, Z.-F.; Tan, M.-X.; Liu, Y.-C.; Peng, Y.; Wang, H.-H.; Liu, H.-G.; Liang, H. (2011). Synthesis, characterization and preliminary cytotoxicity evaluation of five lanthanide-plumbagin complexes. *J. Inorg. Biochem.*, Vol.105, No.2, (February 2011), pp. 308–316, ISSN 0162-0134.
- Chen, Z.-F.; Tao, L.; Liu, Y.-C.; Liang, H. (2011), unpublish results.
- Cheng, J. T. (2000). Review: drug therapy in Chinese traditional medicine. *J. Clin. Pharmacol.*, Vol.40, No.5, (May, 2000), pp. 445–450, ISSN 0091-2700.
- Chiang, L.-C.; Ng, L. T.; Lin, I.-C.; Kuo, P.-L.; Lin, C.-C. (2006). Anti-proliferative effect of apigenin and its apoptotic induction in human Hep G2 cells. *Cancer Lett.*, Vol.237, No.2, (June 2006), pp. 207–214, ISSN 0304-3835.
- Clark, A. M.; Watson, E. S.; Ashfaq, M. K.; Hufford, C. D. (1987). *In vivo* efficacy of antifungal oxoaporphine alkaloids in experimental disseminated candidiasis. *Pharmaceutical Res.*, Vol.4, No.6, (December 1987), pp. 495–498, ISSN 0724-8741.
- Clarke, M. J.; Zhu, F.; Frasca, D. R. (1999). Non-platinum chemotherapeutic metallopharmceuticals. *Chem. Rev.*, Vol.99, No.9, (August 1999), pp. 2511–2533, ISSN 0009-2665.
- Creaven, B. S.; Czegledi, E.; Devereux, M.; Enyedy, E. A.; Kia, A. F.-A.; Karcz, D.; Kellett, A.; McClean, S.; Nagy, N. V.; Noble, A.; Rockenbauer, A.; Szabo-Planka, T.; Walsh, M. (2010). Biological activity and coordination modes of copper(II) complexes of Schiff based-derived coumarin ligands. *Dalton Trans.*, Vol.39, No.45, (December 2010), pp. 10854–10865, ISSN 1477-9226.

- Csermely, P.; Ágoston, V.; Pongor, S. (2005). The efficiency of multi-target drugs: the network approach might help drug design. *Trends Pharmacol. Sci.*, Vol.26, No.4, (April 2005), pp. 178-182, ISSN 0165-6147.
- Deodhar, S. D.; Sethi, R.; Srimal, R.C. (1980). Preliminary study on antirheumatic activity of curcumin (diferuloyl methane). *Indian J. Med. Res.*, Vol.71, No.4, (April 1980), pp. 632-634, ISSN 0971-5916.
- Engelmann, M. D.; Hutcheson, R.; Cheng, I. F. (2005). Stability of ferric complexes with 3-hydroxyflavone (flavonol), 5,7-dihydroxyflavone (chrysin), and 3',4'-dihydroxyflavone. *J. Agric. Food Chem.*, Vol.53, No.8, (March 2005), pp. 2953-2960, ISSN 0021-8561.
- Ferrer, E. G.; Salinas, M. V.; Correa, M. J.; Naso, L.; Barrio, D. A.; Etcheverry, S. B.; Lezama, L.; Rojo, T.; Williams, P. A. M. (2006). Synthesis, characterization, antitumoral and osteogenic activities of quercetin vanadyl(IV) complexes. *J. Biol. Inorg. Chem.*, Vol.11, No.6, (October 2006), pp. 791-801, ISSN 0949-8257.
- Galasso, V.; Asaro, F.; Berti, F.; Pergolese, B.; Kovac, B.; Pichierri, F. (2006). On the molecular and electronic structure of matrine-type alkaloids. *Chem. Phys.*, Vol.330, No.3, (November 2006), pp. 457-468, ISSN 0301-0104.
- Gibert, T. F. (1998). Thought on traditional Chinese medicine and its pharmacopeia. *Ann. Pharm. Fr.*, Vol.56, No.6, (November 1998), pp. 282-285, ISSN 0003-4509.
- Hambley, T. W. (2007). Metal-based therapeutics. *Science*, Vol.318, No.5855, (November 2007), pp. 1392-1393, ISSN 0036-8075.
- Hofland, K.; Petersen, B. O.; Falck, J.; Helin, K.; Jensen, P. B.; Sehested, M. (2000). Differential cytotoxic pathways of topoisomerase I and II anticancer agents after overexpression of the E2F-1/DP-1 transcription factor complex. *Clin. Cancer Res.*, Vol.6, No.4, (April 2000), pp. 1488-1498, ISSN 1078-0432.
- Ho, Y.-P.; Au-Yeung, S. C. F.; To, K. K. W. (2003). Platinum-based anticancer agents: innovative design strategies and biological perspectives. *Med. Res. Rev.*, Vol.23, No.5, (September 2003), pp. 633-655, ISSN 0198-6325.
- Ho, Y.-P.; To, K. K. W.; Au-Yeung, S. C. F.; Wang, X.; Lin, G.; Han, X. Potential new antitumor agents from an innovative combination of demethylcantharidin, a modified traditional Chinese medicine, with a platinum moiety. *J. Med. Chem.*, Vol.44, No.13, (June, 2001), pp. 2065-2068, ISSN 0022-2623.
- Hsieh, T. J.; Liu, T. Z.; Chern, C. L.; Tsao, D. A.; Lu, F. J.; Syu, Y. H.; Hsien, P. Y.; Hu, H. S.; Chang, T. T.; Chen, C. H. (2005). Liriodenine inhibits the proliferation of human hepatoma cell lines by blocking cell cycle progressesession and nitric oxide-mediated activation of p53 expression. *Food and Chem. Toxicol.*, Vol.43, No.7, (July 2005), pp. 1117-1126, ISSN 0278-6915.
- Ivanovska, N.; Hristova, M.; Philipov, S. (2000). Immunosuppression and recovery of drug-impaired host resistance against *Candida albicans* infection by oxoglaucine. *Pharmacol. Res.*, Vol.41, No.1, (January 2000), pp. 101-107, ISSN 1043-6618.
- Ivanovska, N.; Hristova, M. (2000). Treatment with oxoglaucine can enhance host resistance to *Candida albicans* infection of mice with adjuvant arthritis. *Diagnostic Microbiology and Infectious Disease*, Vol.38, No.1, (September 2000), pp. 17-20, ISSN 0732-8893.
- Ivanovska, N.; Philipov, S.; Georgieva, P. (1997). *Pharmacol. Res.*, Vol.35, No.4, (April 1997), pp. 267-272, ISSN 1043-6618.

- Jamieson, E. R.; Lippard, S. J. (1999). Structure, recognition, and processing of cisplatin-DNA adducts. *Chem. Rev.*, Vol.99, No.9, (August, 1999), pp. 2467-2498, ISSN 0009-2665.
- Jantan, I.; Raweh, S. M.; Yasin, Y. H. M.; Murad, S. (2006). Antiplatelet activity of aporphine and phenanthrenoid alkaloids from *Aromadendron elegans* Blume. *Phytother. Res.*, Vol.20, No.6, (June 2006), pp. 493–496, ISSN 0951-418X.
- Jung, Y.; Lippard, S. J. (2007). Direct cellular responses to platinum-induced DNA damage. *Chem. Rev.*, Vol.107, No. 5, (May, 2007), pp. 1387-1407, ISSN 0009-2665.
- Kelland, L. (2007). The resurgence of platinum-based cancer chemotherapy. *Nature Rev.*, Vol.7, No.8, (August 2007), pp. 573-584, ISSN 1474-175X.
- Kitano, H. (2007). A robustness-based approach to systems-oriented drug design. *Nature Rev. Drug Discovery*, Vol.6, No. 3, (March 2007), pp. 202-210, ISSN 1474-1776.
- Korkina, L. G. & Afanasev, I. B. (1997). Antioxidant and chelating properties of flavonoids. *Adv. Pharmacol.*, Vol.38, No.2, (February 1997), pp. 151–163, ISSN 1054-3589.
- Kostova, I.; Manolov, I.; Momekov, G.; Tzanova, T.; Konstantinov, S.; Karaivanova, M. (2005). Cytotoxic activity of new cerium (III) complexes of bis-coumarins. *Eur. J. Med. Chem.*, Vol.40, No.12, (December 2005), pp. 1246-1254, ISSN 0223-5234.
- Kostova, I.; Momekov, G. (2006). New zirconium (IV) complexes of coumarin with cytotoxic activity. *Eur. J. Med. Chem.*, Vol.41, No.6, (June 2006), pp. 717-726, ISSN 0223-5234.
- Kostova, I.; Momekov, G.; Zaharieva, M.; Karaivanova, M. (2005). Cytotoxic activity of new lanthanum (III) complexes of bis-coumarins. *Eur. J. Med. Chem.*, Vol.40, No.6, (June 2005). pp. 542-551, ISSN 0223-5234.
- Kostova, I.; Momekov, G.; Tzanova, T.; Karaivanova, M. (2006). Synthesis, characterization, and cytotoxic activity of new lanthanum (III) complexes of bis-coumarins. *Bioinorg. Chem. Appl.*, Doi 10.1155/BCA?2006/25651, ISSN 1687-479X.
- Kuo, P.-L.; Hsu, Y.-L.; Cho, C.-Y. (2006). Plumbagin induces G2-M arrest and autophagy by inhibiting the AKT/mammalian target of rapamycin pathway in breast cancer cells. *Mol. Cancer Ther.*, Vol.5, No.12, (December 2006), pp. 3209-3221, ISSN 1535-7163.
- Lan, Y. H.; Chang, F. R.; Yu, J. H.; Yang, Y. L.; Chang, Lee, Y. L.; S. J.; Wu, Y. C. (2003). Cytotoxic styrylpyrones from *Goniolthalamus amuyon*. *J. Nat. Prod.*, Vol.66, No.4, (April 2003), pp.487-490, ISSN 0163-3864.
- Li, T.-R.; Yang, Z.-Y.; Wang, B.-D. (2007). Synthesis, characterization and antioxidant activity of naringenin Schiff base and its Cu(II), Ni(II), Zn(II) complexes. *Chem. Pharm. Bull.*, Vol.55, No.1, (January 2007), pp. 26-28, ISSN 0009-2363.
- Li, T.-R.; Yang, Z.-Y.; Wang, B.-D. Qin, D.-D. (2008). Synthesis, characterization, antioxidant activity and DNA-binding studies of two rare earth(III) complexes with naringenin-2-hydroxy benzoyl hydrazone ligand. *Eur. J. Med. Chem.*, Vol.43, No.8, (August 2008), pp. 1688–1695, ISSN 0223-5234.
- Li, Y. M.; Casida, J. E. (1992). Cantharidin-binding protein: identification as protein phosphatase 2A. *Proc. Natl. Acad. Sci. USA*, Vol.89, No.24, (December 1992), pp. 11867-11870, ISSN 1091-6490.
- Lin, C. H.; Chang, G. J.; Su, M. J.; Wu, Y. C.; Teng, C. M.; Ko, F. N. (1994). Pharmacological characteristics of liriodenine, isolated from *Fissistigma glaucescens*, a novel muscarinic receptor antagonist in guinea-pigs. *Br. J. Pharmacol.*, Vol.113, No.1, (September 1994), pp. 275-281, ISSN 0007-1188.

- Lin, L. C.; Yang L. L. and Chou C. J. (2003). Cytotoxic naphthoquinones and plumbagic acid glucosides from *Plumbago zeylanica*. *Phytochemistry*, Vol.62, No.4, (February 2003), pp. 619-622, ISSN 0031-9422.
- Liu, Y.-C.; Chen, Z.-F.; Liu, L.-M.; Peng, Y.; Hong, X.; Yang, B.; Liu, H.-G.; Liang, H. and Orvig, C. (2009). Divalent later transition metal complexes of the traditional chinese medicine (TCM) liriodenine: coordination chemistry, cytotoxicity and DNA binding studies. *Dalton Trans.*, Vol.38, No.48, (December 2009), pp. 10813-10823, ISSN 1477-9226.
- Liu, J. Y.; Hu, J. H.; Zhu, Q. G.; Li, F. Q.; Wang, J.; Sun, H. J. (2007). Effect of matrine on the expression of substance P receptor and inflammatory cytokines production in human skin keratinocytes and fibroblasts. *International Immunopharmacol.*, Vol.7, No.6, (June 2007), pp. 816-823, ISSN 1567-5769.
- Liu, Y. C. (1988). *The essential book of traditional Chinese medicine: theory, clinical practice*, Columbia University Press.
- Lovejoy, K. S. and Lippard, S. J. (2009). Non-traditional platinum compounds for improved accumulation, oral bioavailability, and tumor targeting. *Dalton Trans.*, Vol.38, No.48, (December 2009), pp. 10651-10659, ISSN 1477-9226.
- Luo, C.; Zhu, Y. L.; Jiang, T. J.; Lu, X. Y.; Huang, J. (2007). Matrine induced gastric cancer MKN45 cells apoptosis via increasing pro-apoptotic molecules of Bcl-2 family. *Toxicology*, Vol.229, No.3, (January 2007), pp. 245-252, ISSN 0300-483X.
- Narayana, K. R.; Reddy, M. S.; Chaluvadi, M. R.; Krishna, D. R. (2001). Bioflavonoids classification, pharmacological, biochemical effects and therapeutic potential. *Indian J. Pharmacol.*, Vol.33, No.1, (February 2001), pp. 2-16, ISSN 0253-7613.
- Nijveldt, R. J.; van Nood, E.; Hoorn, D. E. C.; Norren, K.; Leeuwen, P. A. M. (2001). Flavonoids: a review of probable mechanisms of action and potential applications. *Am. J. Clin. Nutr.*, Vol.74, No.4, (October 2001), pp. 418-425, ISSN 0002-9165.
- Nijhoff, W. A.; Bosboom, M. A.; Smidt, M. H.; Peters, W. H. M. (1995). Enhancement of rat hepatic and gastrointestinal glutathione and glutathione S-transferases by alpha-angelicalactone and flavone. *Carcinogenesis*, Vol.16, No.3, (March 1995), pp. 607-612, ISSN 0143-3334.
- Nissanka, A. P. K.; Karunaratne, V.; Bandara, B. M. R.; Kumar, V.; Nakanishi, T.; Nishi, M.; Inada, A.; Tillekeratne, L. M. V.; Wijesundara, D. S. A.; Gunatilaka, A. A. L. (2001). Antimicrobial alkaloids from *Zanthoxylum tetraspermum*. and *caudatum*. *Phytochemistry*, Vol.56, No.8, (April 2001), pp. 857-861, ISSN 0031-9422.
- Normile, D. (2003). The new face of traditional Chinese medicine. *Science*, Vol.299, No.5604, (October 2003), pp. 188-190, ISSN 0036-8075.
- Ohiri, F. C.; Verpoorte, R.; Baerheim Svendsen, A. (1982). Alkaloids from *Chasmanthera dependens*. *Planta Med.* Vol.46, No.12, (December 1982), pp. 228-230, ISSN 0032-0943.
- Olagunju, J. A.; Jobi, A. A.; Oyedapo, O. O. (1999). An investigation into the biochemical basis of the observed hyperglycaemia in rats treated with ethanol root extract of *plumbago zeylanica*. *Phytother. Res.*, Vol.13, No.4, (June 1999), pp. 346-348, ISSN 0951-418X.
- Orvig, C.; Abrams, M. J. (1999). Medicinal inorganic chemistry: introduction. *Chem. Rev.*, Vol.99, No.9, (August 1999), pp. 2201-2203, ISSN 0009-2665.

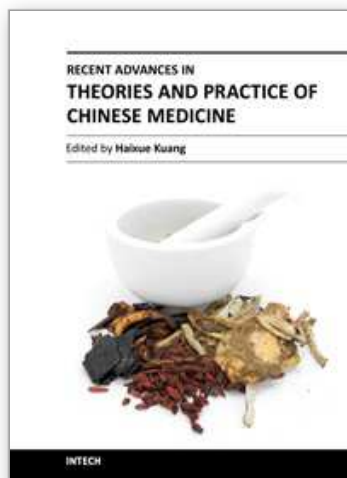
- Patwardhan, B.; Warude, D.; Pushpangadan, P. and Bhatt, N. (2005). Ayurveda and traditional Chinese medicine: a comparative overview. *Evid. Based Complement. Altern. Med.*, Vol.2, No.4, (December 2005), pp. 465-473, ISSN 1741-427X.
- Pereira, R. M. S.; Andrades, N. E. D.; Paulino, N. Sawaya, A.C. H.; Eberlin, M. N.; Marcucci, M. C.; Favero, G. M.; Novak, E. M.; Bydlowski, S. P. (2007). Synthesis and characterization of a metal complex containing naringin and Cu, and its antioxidant, antimicrobial, antiinflammatory and tumor cell cytotoxicity. *Molecules*, Vol.12, No.7, (July 2007), pp. 1352-1366, ISSN 1420-3049.
- Pusz, J.; Nitka, B. (1997). Synthesis and physicochemical properties of the complexes of Co(II), Ni(II), and Cu(II) with chrysin. *Microchem. J.*, Vol.56, No.3, (July 1997), pp. 373-381, ISSN 0026-256x.
- Pusz, J.; Nitka, B.; Zieliska, A.; Wawer, I. (2000). Synthesis and physicochemical properties of the Al(III), Ga(III) and In(III) complexes with chrysin. *Microchem. J.*, Vol.65, No.3, (October 2000), pp. 245-253, ISSN 0026-265X.
- Rao, T. S.; Basu, N.; Siddiqui, H. H. (1982). Anti-inflammatory activity of curcumin analogues. *Indian J. Med. Res.*, Vol.75, No.2, (April 1982), pp. 574-578, ISSN 0971-5916.
- Remichkova, M.; Dimitrova, P.; Philipov, S.; Ivanovska, N. (2009). Toll-like receptor-mediated anti-inflammatory action of glaucine and oxoglaucine *Fitoterapia*, Vol.80, No.7, (July 2009), pp. 411-414, ISSN 0367-326X.
- Rosenberg, B.; VanCamp, L. V.; Trosko, J. E.; Mansour, V. H. (1969). Platinum compounds: a new class of potent antitumour agents. *Nature*, Vol.222, No.5191, (April 1969), pp. 385-386, ISSN 0028-0836.
- Ruan, L.-P.; Chen, S.; Yu, B.-Y.; Zhu, D.-N.; Cordell, G. A.; Qiu, S. X. (2006). Prediction of human absorption of natural compounds by the non-everted rat intestinal sac model. *Eur. J. Med. Chem.*, Vol.41, No.5, (May 2006), pp. 605-610, ISSN 0223-5234.
- Russo, A.; Acquaviva, R.; Campisi, A.; Sorrenti, V.; Di Giacomo, C.; Virgata, G.; Barcellona, M. L.; Vanella, A. (2000). Bioflavonoids as antiradicals, antioxidants and DNA cleavage protectors. *Cell Biol. Toxicol.*, Vol.16, No.2, (April 2000), pp. 91-98, ISSN 0742-2091.
- Sakai, W.; Swisher, E. M.; Karlan, B. Y.; Agarwal, M. K.; Higgins, J.; Friedman, C.; Villegas, E.; Jacquemont, C.; Farrugia, D. J.; Couch, F. J.; Nicole Urban, N.; Taniguchi, T. (2008). Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. *Nature*, Vol.451, No.7182, (February 2008), pp. 1116-1120, ISSN 1476-4687.
- Sari, A. (1999). Alkaloids from *Glaucium leiocarpum*. *Planta Med.*, Vol.65, No.5, (June 1999), pp. 492, ISSN 0032-0943.
- Saxton, C. (2010). Natural remedy shows anticancer activity. *Highlights in Chemical Science*, 01.
- Sharma, O. P. (1976). Antioxidant activity of curcumin and related compounds. *Biochem. Pharmacol.*, Vol.25, No.5, (August 1976), pp. 1811-1812, ISSN 0006-2952.
- Shibata, S. (1985). In *Advances in Chinese Medicinal Materials Research* (Chang, H. M.; Yeung, H. W.; Tso, W. W. and Koo, A.; eds), pp3-16, World Scientific Publishing.
- So, F. V.; Guthrie, N.; Chambers, A. F.; Moussa, M. and Carroll, K. K. (1996). Inhibition of human breast cancer cell proliferation and delay of mammary tumorigenesis by

- flavonoids and citrus juices. *Nutr. Cancer*, Vol.26, No.2, (August 1996), pp. 167-181, ISSN 0163-5581.
- Song, Y.; Kang, J.; Wang, Z.; Lu, X.; Gao, J.; Wang, L. (2002). Study on the interactions between CuL2 and Morin with DNA. *J. Inorg. Biochem.*, Vol.91, No.3, (August 2002), pp. 470-474, ISSN 0162-0134.
- Song, Y.; Yang, P.; Yang, M.; Kang, J.; Qin, S.; Lü, B. (2003). Spectroscopic and voltammetric studies of the cobalt(II) complex of morin bound to calf thymus DNA. *Transition Met. Chem.*, Vol.28, No.6, (June 2003), pp. 712-716, ISSN 0340-4285.
- Srimal, R. C.; Dhawan, B.N. (1973). Pharmacology of diferuloyl methane (curcumin) a non-steroidal anti-inflammatory agent. *J. Pharm. Pharmacol.*, Vol.25, No.6, (June 1973), pp. 447-452, ISSN 0022-3573.
- Srinivas, P.; Gopinath, G.; Banerji, A.; Dinakar, A.; Srinivas, G. (2004). Plumbagin induces reactive oxygen species, which mediate apoptosis in human cervical cancer cells. *Mol. Carcinogen.*, Vol.40, No.4, (August 2004), pp. 201-211, ISSN 1098-2744.
- Staker, B. L.; Feese, M. D.; Cushman, M.; Pommier, Y.; Zembower, D.; Stewart, L.; Burgin, A. B. (2005). Structures of three classes of anticancer agents bound to the human topoisomerase I-DNA covalent complex. *J. Med. Chem.*, Vol.48, No.7, (February, 2005), pp. 2336-2346, ISSN 0022-2623.
- Stone, R. (2008). Lifting the veil on traditional Chinese medicine. *Science*, Vol.319, No.5864, (February 2008), pp. 709-710, ISSN 0036-8075.
- Tan, M.-X.; Zhu, J.-C.; Pan, Y.M.; Chen, Z.-F.; Liang, H.; Liu, H.-G.; Wang, H.-S. (2009). Synthesis, cytotoxic activity, and DNA binding properties of copper (II) complexes with hesperetin, naringenin and apigenin. *Bioinorg. Chem. Appl.*, doi:10.115/2009/347872, ISSN 1687-479X.
- Tan, J.; Wang, B. C.; Zhu, L. C. (2007). Hydrolytic cleavage of DNA by quercetin zinc(II) complex. *Bioorg. Med. Chem. Lett.*, Vol.17, No.5, (March 2007), pp. 1197-1199, ISSN 0960-894X.
- Tan, J.; Wang, B. C.; Zhu, L. C. (2009). DNA binding and oxidative DNA damage induced by a quercetin copper(II) complex: potential mechanism of its antitumor properties. *J. Biol. Inorg. Chem.*, Vol.14, No.5, (June 2009), pp. 727-739, ISSN 0949-8257.
- Tan, J.; Wang, B. C.; Zhu, L. C. (2009). DNA binding, cytotoxicity, apoptotic inducing activity, and molecular modeling study of quercetin zinc(II) complex. *Bioorg. Med. Chem.*, Vol.17, No.2, (January 2009), pp. 614-620, ISSN 0968-0896.
- Thati, B.; Noble, A.; Creaven, B. S.; Walsh, M.; McCann, M.; Kavanagh, K.; Devereux, M.; Egan, D. A. (2007). In vitro anti-tumour and cyto-selective effects of coumarin-3-carboxylic acid and three of its hydroxylated derivatives, along with their silver-based complexes, using human epithelial carcinoma cell lines. *Cancer Lett.*, Vol.248, No.2, (April 2007), pp. 321-331, ISSN.
- Thompson, K. H.; Böhmerle, K.; Polishchuk, E.; Martins, C.; Toleikis, P.; Tse, J.; Yuen, V.; McNeill, J. H.; Orvig, C. (2004). Complementary inhibition of synovioyte, smooth muscle cell or mouse lymphoma cell proliferation by a vanadyl curcumin complex compared to curcumin alone. *J. Inorg. Biochem.*, Vol.98, No.12, (December 2004), pp. 2063-2070, ISSN 0162-0134.
- To, K. K. W.; Wang, X.; Yu, C.-W.; Ho, Y.-P.; Au-Yeung, S. C. F. (2004). Protein phosphatase 2A inhibition and circumvention of cisplatin cross-resistance by novel TCM-

- platinum anticancer agents containing demethylcantharidin. *Bioorg. Med. Chem.*, Vol.12, No.17, (September 2004), pp. 4565-4573, ISSN 0968-0896.
- To, K. K. W.; Ho, Y.-P.; Au-Yeung, S. C. F. (2002). Determination of the release of hydrolyzed demethylcantharidin from novel traditional Chinese medicine-platinum compounds with anticancer activity by gas chromatography. *J. Chromatogr. A*, Vol.947, No.2, (February 2002), pp. 319-326, ISSN 0021-9673.
- To, K. K. W.; Ho, Y.-P.; Au-Yeung, S. C. F. (2005). *In vitro* and *in vivo* suppression of growth of hepatocellular carcinoma cells by novel traditional Chinese medicine-platinum anti-cancer agents. *Anti-cancer Drugs*, Vol.16, No.8, (September 2005), pp. 825-835, ISSN 0959-4973.
- To, K. K. W.; Au-Yeung, S. C. F.; Ho, Y.-P. (2006). Differential nephrotoxicity of cis-platin and a novel series of traditional Chinese medicine-platinum anticancer agents correlates with their chemical reactivity towards sulfur-containing nucleophiles. *Anti-cancer Drugs*, Vol.17, No.6, (July 2006), pp. 673-683, ISSN 0959-4973.
- To, K. K. W.; Ho, Y.-P.; Au-Yeung, S. C. F. (2005). Synergistic interaction between platinum-based antitumor agents and demethylcantharidin. *Cancer Lett.*, Vol.223, No.2, (June 2005), pp. 227-237, ISSN 0304-3835.
- Tojo, E.; Dominguez, D.; Castedo, L. (1991). *Phytochemistry*, Vol.30, No.3, (March 1991), pp. 1005-1010, ISSN 0031-9422.
- Tripoli, E.; Guardia, M. L.; Giammanco, S.; Majo, D. D. and Giammanco, M. (2007). Citrus flavonoids: Molecular structure, biological activity and nutritional properties: A review. *Food Chem.*, Vol.104, No.2, (September 2007), pp. 466-479, ISSN 0308-8146.
- Wang, B.-D.; Yang, Z.-Y.; Wang, Q.; Cai, T.-K.; Crewdson, P. (2006). Synthesis, characterization, cytotoxic activities, and DNA-binding properties of the La(III) complex with naringenin Schiff-base. *Bioorg. Med. Chem.*, Vol.14, No.6, (March 2006), pp. 1880-1888, ISSN 0968-0896.
- Wang, G. S. (1989). Medical uses of mylabris in ancient China and recent studies. *J. Ethnopharm.*, Vol.26, No.2, (September 1989), pp. 147-162, ISSN 0378-8741.
- Wang, L.; Gou, S.; Chen, Y., Liu, Y. (2005). Potential new antitumour agents from an innovative combination of camphorato, a ramification of traditional Chinese medicine, with a platinum moiety. *Bioorg. Med. Chem. Lett.*, Vol.15, No.14, (July 2005), pp. 3417-3422, ISSN 0960-894X.
- Wang, X.; Au-Yeung, S. C. F.; Ho, Y.-P. (2007). Pharmacokinetics and tissue distribution of novel traditional Chinese medicine-platinum anticancer agents in rats. *J. Inorg. Biochem.*, Vol.101, No.6, (June 2007), pp. 909-917, ISSN 0162-0134.
- Wong, E.; Giandomenico, C. M. (1999). Current status of platinum-based antitumor drugs. *Chem. Rev.*, Vol.99, No. 9, (August 1999), pp. 2451-2466, ISSN 0009-2665.
- Woo, S. H.; Reynolds, M. C.; Sun, N. J.; Cassady, J. M.; Snapka, R. M. (1997). Inhibition of topoisomerase II by liriodenine. *Biochem. Pharmacol.*, Vol.54, No.4, (August 1997), pp. 467-473, ISSN 0006-2952.
- Wu, J.-Z.; Yuan, L.; Wu, J.-F. (2005). Synthesis and DNA binding of \square -[2,9-bis(2-imidazo[4,5-f][1,10]phenanthroline)-1,10-phenanthroline]bis[1,10-phenanthroline-copper(II)]. *J. Inorg. Biochem.*, Vol.99, No.11, (November 2005), pp. 2211-2216, ISSN 0162-0134.
- Wu, Y. C.; Duh, C. Y.; Wang, S. K.; Chen, K. S.; Yang, T. H. (1990). Two new natural azafluorene alkaloids and a cytotoxic aporphine alkaloid from *Polyalthia longifolia*. *J. Nat. Prod.*, Vol.53, No.5, (September 1990), pp. 1327-1331, ISSN 0163-3864.

- Wu, Y.-C.; Liou, Y.-F.; Lu, S.-T.; Chen, C.-H.; Chang, J.-J.; Lee, K.-H. (1989). *Planta Med.*, Vol.55, No.2, (April 1989), pp. 163–165, ISSN 0032-0943.
- Wu, Z. Y.; Zhou, T. Y.; Xiao, P. G. (1998). *Xin Hua Compendium of Materia Medica (I)*, Shanghai: Shanghai Science & Technology Press, 1998: pp. 113–117.
- Yu, C.-W.; Li, K. K. W.; Pang, S.-K. ; Au-Yeung, S. C. F.; Ho, Y.-P. (2006). Anticancer activity of a series of platinum complexes integrating demethylcantharidin with isomers of 1, 2-diaminocyclohexane. *Bioorg. Med. Chem. Lett.*, Vol.16, No.6, (March 2006), pp 1686-1691, ISSN 0960-894X.
- Zeng, Y.-B.; Yang, N.; Liu, W.-S.; Tang, N. (2003). Synthesis, characterization and DNA-binding properties of La(III) complex of chrysin. *J. Inorg. Biochem.*, Vol.97, No.3, (November 2003), pp. 258-264, ISSN 0162-0134
- Zhang, Q.; Wang, L.; Liu X. (1996). Synthesis, characterization and antitumour properties of metal(II) solid complexes with morin. *Transition Met. Chem.*, Vol.21, No.1, (January 1996), pp. 23-27, ISSN 0340-4285.
- Zhang, L. J.; Wang, T. T.; Wen, X. M.; Wei, Y.; Peng, X. C.; Li, H.; Wei, L. (2007). Effect of matrine on HeLa cell adhesion and migration. *Eur. J. Pharmacol.*, Vol.563, No.1-3, (June 2007), pp. 69-76, ISSN 0014-4285.
- Zhang, L. P.; Jiang, J. K.; Tam, J. W. O.; Zhang, Y.; Liu, X. S.; Xu, X. R.; Liu, B. Z.; He, Y. J. (2001). Effects of Matrine on proliferation and differentiation in K-562 cells. *Leuk. Res.*, Vol.25, No.9, (September 2001), pp. 793-800, ISSN 0145-2126.
- Zhou, J.; Wang, L.; Wang, J.; Tang, N. (2001). Antioxidative and anti-tumour activities of solid quercetin metal(II) complexes. *Transition Met. Chem.*, Vol.26, No.1-2, (January 2001), pp. 57-63, ISSN 0340-4285.
- Zutphen, S.; Reedijk, J. (2005). Targeting platinum anti-tumour drugs: Overview of strategies employed to reduce systemic toxicity. *Coord. Chem. Rev.*, Vol.249, No.24, (December 2005), pp. 2845-2853, ISSN 0010-8545.

IntechOpen



Recent Advances in Theories and Practice of Chinese Medicine

Edited by Prof. Haixue Kuang

ISBN 978-953-307-903-5

Hard cover, 504 pages

Publisher InTech

Published online 18, January, 2012

Published in print edition January, 2012

During the recent years, traditional Chinese medicine (TCM) has attracted the attention of researchers all over the world. It is looked upon not only as a bright pearl, but also a treasure house of ancient Chinese culture. Nowadays, TCM has become a subject area with high potential and the possibility for original innovation. This book titled Recent Advances in Theories and Practice of Chinese Medicine provides an authoritative and cutting-edge insight into TCM research, including its basic theories, diagnostic approach, current clinical applications, latest advances, and more. It discusses many often neglected important issues, such as the theory of TCM property, and how to carry out TCM research in the direction of TCM property theory using modern scientific technology. The authors of this book comprise an international group of recognized researchers who possess abundant clinical knowledge and research background due to their years of practicing TCM. Hopefully, this book will help our readers gain a deeper understanding of the unique characteristics of Chinese medicine.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Zhen-Feng Chen, Hong Liang and Yan-Cheng Liu (2012). Traditional Chinese Medicine Active Ingredient-Metal Based Anticancer Agents, Recent Advances in Theories and Practice of Chinese Medicine, Prof. Haixue Kuang (Ed.), ISBN: 978-953-307-903-5, InTech, Available from: <http://www.intechopen.com/books/recent-advances-in-theories-and-practice-of-chinese-medicine/traditional-chinese-medicine-active-ingredient-metal-based-anticancer-agents>

INTeCH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen