

TRADITIONAL CHINESE MEDICINE AND TREATMENT OF NEONATAL JAUNDICE

N K Ho

ABSTRACT

Objective: Treatment with herbs may increase the risk of neonatal jaundice (NNJ). It is logical to look into the current practice in some hospitals in China where herbs are being used in the treatment of NNJ. It is also the purpose of this study to find out the chemical constituents and actions of the herbs, and the rationale of the treatment.

Methods: Twenty reports, from 1973 to 1989, from different parts of China, come in a published book and the paediatric journals written in the Chinese language. The *Zhong Yao Da Zi Dian*, an encyclopedia of Chinese materia medica, and other books on the pharmacology and applications of Chinese materia medica were also referred to in the study.

Findings: Yin-chen (oriental wormwood or *Artemisia*) was the most commonly used herbs for NNJ (95%). Others were Da-huang (rhubarb or *Rheum officinale*), Huang-qin (skullcap root or *Scutellaria*), Gan-cao (licorice or glycyrrhiza) and Huang-lian (goldthread rhizome or *Coptis chinensis*). Huang-lian, which contains the alkaloid berberine, was used in 4 centres (20%). Berberine can cause severe acute hemolysis in babies with G6PD deficiency. Currently, Yin-chen comes as a decoction *Artemisia composita* and an intravenous preparation. These preparations have potential central nervous system and cardiovascular toxicities.

Conclusions: Chinese herbs have many pharmacological substances and therefore multiple actions. In recent years, Chinese herbs are used in conjunction with "Western" drugs, rendering the study of the effects of herbs on NNJ extremely difficult.

The efficacy and safety of phototherapy for NNJ have been firmly established, thus diminishing the need for drug treatment. What is the present day role, therefore, of herbal medicine for NNJ? Is there a place for further research of these herbal medicines?

Keywords: corticosteroids, Huang-lian (berberine), Gan-cao (licorice), neonatal jaundice, traditional Chinese medicine (TCM), Yin-chen (*Artemisia*)

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INTRODUCTION

The use of herbs, medication derived from herbs, or traditional medicine is prevalent in many countries, including China, Egypt, Greece, India, Mexico, Ethiopia⁽¹⁾, Cuba⁽²⁾, Turkey⁽³⁾, etc. Hundreds of medicinal plants were known in India before the Christian era, and the Chinese have a compilation of more than 1,000 ancient herbals. Even the Greeks had written accounts. Hippocrates (460-377 BC), Galen (129-199 AD), and Dioscorides (40-90 AD) employed spices and herbs in the treatment of diseases. Many Chinese, whether residing in China or overseas, resort to traditional Chinese medicine for various ailments and illnesses. Traditional medicine or herbs have been used in the management of NNJ. In our country, the Malays use *Teluk Lawa* (from the root of ginger) and sunflower seeds and the Chinese use many herbs for treatment of NNJ.

It has been well documented that the Chinese use herbs for various diseases. There were hundreds of works as well as major imperial compilations of drugs referred to as *Ben-cao* or knowledge of drugs and herbs (pharmacology). A book called *Shen Nong Ben Cao Jing* or The Herbal was produced in the West Han Dynasty (206 BC-24 AD). It compiled the knowledge of drugs and herbs used before the West Han Dynasty, and was

written by physicians of many generations. Three hundred and sixty-five types of medicine, the majority of which were medicinal plants, were described. This book had been lost in the early Tang Dynasty (618-907). Only some of the contents could still be found in other books on materia medica⁽⁴⁾. Li Shi-zhen (1518-93) began to write the *Ben-cao Gang-mu* or the Compendium of Materia Medica in 1552⁽⁵⁾. The book was completed in 1580, after 27 years of research. It took him another 10 years to make numerous amendments and to append about 1,000 illustrations of the medicinal plants. The book was sent to print in 1590 and was completed in 1596, 3 years after his death⁽⁶⁾. He had referred to more than 800 publications on drugs and herbs. The Compendium listed 1,892 drugs and about 10,000 prescriptions⁽⁵⁾.

NNJ is very common in babies of Chinese origin⁽⁷⁾. It is a clinically recognisable condition of the newborn, with yellow discolouration of the skin, sclera and other organs as a result of an accumulation of bilirubin. Jaundice becomes apparent at serum bilirubin levels of approximately 85-120 $\mu\text{mol/L}$ (5-7 mg/dL)⁽⁸⁾. In ancient days, the diagnosis and treatment of NNJ were most probably based on clinical observation. It was known as 'tai-huang' or 'tai-dan'⁽⁹⁻¹¹⁾. In the Chinese language, the word 'tai' means 'fetus', 'huang', 'yellow'; and 'dan', 'bile'. Is the severity of NNJ aggravated by consumption of herbs by the pregnant mother and by the newborn baby? Such relationship between herbs, intended for the treatment of NNJ or otherwise, and the occurrence of severe NNJ in Oriental infants have been raised by many workers⁽⁷⁾.

A search for the various commonly used herbs for NNJ in China was done and the constituents are studied, by referring to the *Zhong Yao Da Zi Dian* or the Encyclopedia of Chinese materia medica⁽¹²⁾. The rationale of the use of these herbs was studied. It is hoped that one can gain an insight of traditional Chinese medicine (TCM) with a history of many thousand years, and to

Department of Neonatology 1
Kandang Kerbau Hospital
Hampshire Road
Singapore 219428

N K Ho, M Med (Paed), FAMS, FRACP
Senior Consultant Paediatrician and Head

learn from the wisdom of the physicians of the past.

Physicians of modern medicine are mostly educated in the English or non-Chinese languages. They are not familiar with, or know very little about traditional Chinese medicine, because they do not understand the texts written in modern or classical Chinese language. Nevertheless, medical schools in China include traditional Chinese medicine in the training syllabi.

In recent years, the use of herbs in the treatment of NNJ has been complicated by the combined use of "Western" drugs. The use of phenobarbitals, plasma and steroidal drugs, as well as the use of phototherapy renders the study of the effects of herbs for NNJ extremely difficult.

MATERIAL AND METHODS

In order to understand the treatment of NNJ with traditional Chinese medicine, referral to documented reports in medical literature is very useful. Unfortunately, searching for these referenced reports was extremely difficult. Such reports are usually not found in the *Medline* or the *Index Medicus*. A book, written in the Chinese language, was published in the Hunan Province, China. It collected 6,470 publications on paediatric topics from 700 medical journals and from data compilations in China⁽¹³⁾. There were 20 reports, from 1973 to 1989, on the treatment of NNJ. These reports come mainly from the southern parts of China, in particular, the Guangdong Province. Nineteen reports were written in the Chinese language. The selection of referenced reports could be biased because findings from other provinces may not be available for inclusion in the book. The commonly used herbs for NNJ were noted. Generally, these

reports reflected the current clinical practice in the use of herbs for NNJ. The current uses of the herbs are also in line with ancient recommendations^(14,15), except that estimations of serum bilirubin are usually done. *Zhong Yao Da Zi Dian*, an Encyclopedia of Chinese materia medica, written in the Chinese language, was referred to in the study⁽¹²⁾. Other publications on the pharmacology and applications of Chinese materia medica, in the English language, were also referred to in the study⁽¹⁶⁾.

FINDINGS

A variety of herbs have been used for the treatment of NNJ. The following herbs: Yin-chen (Oriental wormwood or *Artemisia*), Huang-lian (goldthread rhizome or *Coptis chinensis*), Da-huang (rhubarb or *Rheum officinale*), Huang-qin (skullcap root or *Scutellaria*), and Gan-cao (licorice or *glycyrrhiza*) were commonly used for NNJ. Huang-lian, also known as Chuen-jin is commonly used by people in Hong Kong⁽¹⁷⁾ and Singapore⁽¹⁸⁾. However, huang-lian, which contains the alkaloid berberine, was only used in 4 centres in China (20%) (Table I).

Yin-chen (Oriental wormwood or *Artemisia capillaris*)

The 20 reports recorded that Yin-chen was the most commonly used herbs for the treatment of NNJ. It was used in all except one centre (95%) in China^(19,20-38).

The herb comes from the plant *Artemisia capillaris* which can be found growing in most areas in China. Other species such as *Artemisia scoparia*, *Artemisia frigida*, and *Artemisia stricta* have also been used as Yin-chen. It is also pertinent to mention the herb Qing-hao or Ching-hao (sweet wormwood) here. For

Table 1 - Treatment of Neonatal Jaundice in China 1973-89

No.	Ref	Locality	Year	No. cases	Huang-lian	Da-huang	Huang-qin	Yin-chen	Gan-cao	Others	Plasma	Steroids	Pheno	Px	Ex	Outcome
1	19	Guangdong	1973	12						Aureo-herbs	+	+				
2	20	Guangdong	1973	14*			+	+		other herbs	+					1 died, 14 kern
3	21	Guangdong	1974	31**	+	+	+	+		Aureo/genta	+	19				8 died, 10 kern
4	22	Shanghai	1976	38	+	+	+	+		other herbs						
5	23	Jiangxi	1977	?			+	+		other herbs						
6	24	Guangdong	1977	100				+		other herbs						no deaths
7	25	Guangdong	1977	120				+	+	other herbs		+				94.2% 'recovered'
8	26	Guangxi	1977	13		+	+	+	+	+	+	+	+	+	+	no deaths
9	27	Shanghai	1977	91	+	+	+	+		other herbs		+	+	+	+	8 died
10	28	Jilin	1978	1		+	+	+	+	other herbs	+	+				alive
11	29	Nanjing	1978	?		+	+	+	+	other herbs						?
12	30	Guangdong	1978	39 (G6PDdef)				+		other herbs		+		+		9 died, 1 seque, 14 kern
13	31	Beijing	1979	30				+		other herbs					+	no deaths
14	32	Shanghai	1979	15		+	+	+	+	other herbs						no deaths
15	33	Shanghai	1979	90		+	+	+	+	other herbs					+	no deaths
16	34	Hunan	1979	2		+	+	+	+	other herbs						no deaths
17	35	Jinan	1980	1				+		other herbs						no deaths
18	36	Guangdong	1980	109 (G6PDdef)	+	+	+	+		other herbs					+	8 kern
19	37	Shanghai	1987	111		+	+	+	+						+	
20	38	Guangdong	1989	390(@66)		+	+	+		other herbs	+	+	+	+	+	

Legend: pheno=phenobarbital, Px=phototherapy, Ex=exchange transfusion, kern=kernicterus, aureo-aureomycin, seque=sequele, genta=gentamicin
* admitted kernicteric, **=12 steroids & herbs, 19 only steroids, @=G6PD deficient

some time it has been confused with *Artemisia annua*. Qing-hao comes from this plant and not from *Artemisia apiacea* or daisy-leaf blue wormwood^(39,40). Qing-hao is used for the treatment of malaria. It should not be confused with Yin-chen.

Yin-chen, also known as Yin-chen-hao contains scoparone (6,7 dimethoxycoumarin), chlorogenic acid, caffeic acid, capillin, capillone, capillene, capillarin and fatty acids like arachidic acid, linoleic acid, palmitic acid, etc. Other substances include 4 hydroxyacet phenone which has cholerectic action, and choline, salicylic acid, etc⁽⁴¹⁾. Yin-chen also has anti-bacterial activity^(41,42) and anti-helminthic activity⁽⁴¹⁾.

Scoparone, the active principle of Yin-chen exhibits vasorelaxant and immunosuppressive effects^(42,43). Huang et al⁽⁴³⁾ demonstrated that scoparone could suppress the responses of human mononuclear cells to phytohemagglutinin and mixed lymphocyte reaction. It also has some diuretic effects. It is important to note that there are many species of *Artemisia*, which are known by different names and have different chemical substances and therapeutic actions. *Artemisia vulgaris* is known as Ai or moxa, which is used for moxibustion. *Artemisia argyi* is known as Ai-hao or Chinese mugwort. It is used for abdominal colic. A flavonone, 7-O-methylerythrodityol, isolated from a folk medicine *Artemisia monosperma* was also found to have antispasmodic effects in animals⁽⁴⁴⁾. The chemical contents of the plants also vary according to the particular parts of the plant. Production of cholerectic substances in the capitulum, leaf and stem of *Artemisia capillaris* changes at different plant cycle⁽⁴⁵⁾. The chemical concentrations also have seasonal variations. The highest content of scoparone was found before flowering, 1.52% during the pre-flowering period as contrast to 0.46% during the flowering period^(41,46). Similar observations have been noted in *Artemisia annua*. The yield of this anti-malarial drug artemisinin (qinghaosu) was highest in the leaves just before flowering⁽⁴⁷⁾. These findings have important therapeutic relevance because the dosages can vary⁽⁴¹⁾. It therefore appears that a physician who uses herbs has not only to know the pharmacology of the herbs well but also to be a good botanist or phytochemist!

Artemisia decoction is conducive to bile flow and ultrasonic examination shows that the decoction given intravenously has remarkable effect on the contractility of gall bladder⁽⁴⁸⁾.

Yin-chen is the most commonly used drug. However, no centre used this herb singly. Other herbs commonly used in conjunction with Yin-chen include Huang-lian, Da-huang and Huang-qin (together known as the three 'huangs' or three 'yellows'). Gan-cao or licorice is another herb used. It is noted that there is no standard formula or consistency for treatment of NNJ. Different combinations of herbs had been used in different centres in China for NNJ. Other herbs include Che-qian or plantain (*Plantago asiatica*),⁽⁴⁹⁾ La-mei-hua or wintersweet (*Chimonanthus praecox*),⁽⁵⁰⁾ Yu-mi-xu or corn stigma (*Zea mays*)^(51,52) Gou-teng or uncaria stem (*uncaria rhynchophylla*),⁽⁵³⁾ Zhi-zi or Cape-jasmine fruit (*Gardenia jasminoides*),⁽⁵⁴⁾ Da-ye-she-zong-guan, a plant from the Guangxi Province, China (*Isodon nervosus*)^(19,55) and Chan-tui, the exuviate of the insect (cicada) *Cryptotympana*⁽⁵⁶⁾, and many others. These drugs also contain multiple chemical substances.

In recent years, Shanghai has prepared a decoction *Artemisia composita* or the 'Huangdan (jaundice) Yin-chen Decoction'. The decoction contains Yin-chen 15g, Da-huang 3g, Huang-qin 9g, and Gan-cao (licorice) 1.5g. The decoction is dissolved in 60 mL of sweetened water and 20 to 30 mL is given to the baby three times daily for 3 to 4 days. Chen⁽³⁷⁾ in Shanghai demonstrated that the decoction was effective in ABO, or even the Rh-incompatible haemolytic jaundice because of the immunosuppression of anti-A, anti-B, and anti-D actions. However, Yin-chen (*Artemisia capillaris*) alone did not show

any immunosuppressive effect against anti-A, B and D. It could only work well in conjunction with Da-huang, Huang-qin and Gan-cao. It has been mentioned earlier that Huang et al⁽⁴³⁾ have also shown that scoparone exhibited vasorelaxant and immunosuppressive effects.

An intravenous preparation of *Artemisia scoparia* for the treatment of NNJ came from Beijing. It is distributed widely for use in various parts of China. Twenty-five to 50 mL of the extract is to be given to a term infant over 15-20 minutes⁽⁵⁷⁾. There was also some concern over the use of the intravenous preparation of *Artemisia scoparia*. It has been shown that the herb is highly effective in displacing bilirubin from its protein binding⁽⁵⁷⁾. The oral preparation of Yin-chen might exert its effect after going through various metabolic pathways. However, the intravenous form of Yin-chen may exert its effect immediately and strongly. Bilirubin could be cleared from the circulation and the baby may subsequently appear less jaundice. Unfortunately, the displaced bilirubin could have found its way to the brain. The sulfisoxazole experience should be a good lesson to remember⁽⁵⁸⁾. It is imperative to exclude interference with bilirubin binding whenever lowering of the plasma bilirubin concentration is attributed to the action of a drug.

In many Chinese medical records, Yin-chen is known for its role in the treatment of jaundice^(14,15). However, it is not without toxicity. Two patients had cardiac complications manifested as conduction defect, cardiac arrhythmia, cardiopulmonary arrest and Stokes-Adams syndrome^(40,41).

Huang-lian (*Coptis chinensis*)

Huang-lian, which contains the alkaloid berberine as the major ingredient, was not widely used in the hospitals in China^(19,38). Only 4 centres (20%) had used it. However, a Hong Kong survey in 1982 revealed that 28% of the newborn infants were given Huang-lian. It was 50.9% in 1972⁽¹⁷⁾. It is believed that many mothers gave the herbs to their babies on their own accord.

Like all other Chinese herbs, Huang-lian has many pharmacological substances and therefore multiple actions. It has been reported to have a broad spectrum of activity against some bacteria, including *Vibrio cholerae*, *shigella*, *pseudomonas*, *diplococcus* and *protozoa*, etc^(59,63). It also has action on the circulatory system⁽⁶⁴⁾. Though the alkaloids have relaxant property on the smooth muscle of the blood vessels, the alkaloids (palmatine, jatrorrhizine) also have excitatory action on smooth muscle of the gut and uterus^(59,65,66). Such action may enhance peristalsis and increase the passage of meconium and sequestration of bilirubin in the gut. Enterohepatic circulation of bilirubin will then be interrupted⁽⁶⁷⁾. The Chinese physicians believe that it is necessary to get rid of the "tai-du" or "toxic substances in the fetus" by herbs that enhance the gut movement.

Other contents of Huang-lian include berbamine, coptisine, worenine, palmatine, jatrorrhizine, etc⁽⁶⁵⁾.

Perhaps the important action of berberine is its cholerectic action. It increases bile excretion and renders bile juice more dilute⁽⁵⁹⁾. Berberine can displace bilirubin from the protein binding sites resulting in a significant decrease in mean bilirubin serum binding. Elevation of both unbound and total serum bilirubin, possibly due to inhibition of metabolism, may ensue⁽⁶⁸⁾. The use of berberine can be harmful when given to a newborn baby who has glucose 6 phosphate dehydrogenase (G6PD) deficiency. This disorder, known only a few decades ago, and the potential toxicity of berberine were unfamiliar to many people. Also the incidence of G6PD deficiency is low in northern parts of China⁽¹⁸⁾. This alkaloid can trigger acute haemolysis giving rise to severe NNJ. Kernicterus may occur resulting in brain damage. Its use for the treatment of NNJ has been discouraged^(38,38a).

Huang-qin (*Scutellaria viscidula*)

Huang-qin contains baicalein, wongonoside, scutellarin, etc. It has a number of pharmacological functions including anti-inflammatory and anti-bacterial actions. Other than antipyretic, anti-hypertensive and diuretic effects, Huang-qin is also a cholagogue, which is useful in the treatment of jaundice⁽⁶⁹⁾.

Huang-qin was shown to have some immunosuppressive effect on antiserum D, as demonstrated by Chen⁽³⁷⁾.

Da-huang (*Rheum officinale*)

Da-huang, however, has cathartic effect because of the presence of chrysophanol, emodin, aloce-emodin, sennoside A, rhein, etc⁽⁷⁰⁻⁷²⁾. It has bacteriostatic effect against *Staphylococcus aureus*. It also has choleric effect. Its role in the treatment of NNJ may be due to the laxative property so that the enterohepatic circulation of bilirubin is interrupted. It should be noted that the main cathartic component of Da-huang is sennoside A, which has to be transformed to sennidine by the colonic bacteria for laxative effect⁽⁷⁰⁾. One wonders whether the drug effect occurs in the newborn babies, because newborns have no significant gut flora during the first few days of life.

Similarly, Da-huang also has some inhibitory effect on the A, B and D antisera⁽³⁷⁾.

Gan-cao (*licorice or glycyrrhiza*)

This herb is used in 45% (9/20) of the centres in China. It comes from the plant *Glycyrrhiza uralensis*. The main components are glycyrrhizic acid and its hydrolysed compound glycyrrhetic acid, as well as glycyrrhizin, the water soluble uralenic acid, liquiritin, and many other chemicals^(73,74).

Gan-cao also has multiple pharmacological actions. It has adrenocorticosteroid-like actions because the chemical structure of glycyrrhetic acid is similar to that of adrenocorticosteroids⁽⁷⁵⁾. Recent study revealed that glycyrrhizin induced mineralocorticoid activity through alterations in cortisol metabolism in the human kidney⁽⁷⁶⁾. It inhibits the enzyme 11-beta-hydroxysteroid dehydrogenase causing a defect in the conversion of cortisol to cortisone. Cortisol, which occurs in much larger amounts than aldosterone, binds with the same affinity as aldosterone to the mineralocorticoid receptors. As a result, hypermineralocorticoid effect of cortisol appears^(77,78). Glycyrrhizin also has immunological⁽⁷⁹⁾ as well as anti-viral actions⁽⁸⁰⁾.

It appears that Gan-cao plays only a minor role in treatment of NNJ. However, steroid hormones are generally considered to have an inhibitory effect on heme oxygenase activity experimentally. The inhibitory effect observed may be a general metabolic response to steroid administration⁽⁸¹⁻⁸³⁾. It is not known whether Gan-cao was used because of its steroidal effect, probably acting as a heme oxygenase inhibitor.

Chen⁽³⁷⁾ also found that Gan-cao had inhibitory effect on antisera D. Its other pharmacological actions include, in experimental animals, antispasmodic, anti-inflammatory, choleric, cough suppressant, diuretic, etc. It does not appear that the herb has beneficial effect on NNJ in the human⁽⁷³⁾.

The use of steroidal drugs

It is observed that many centres in China used steroidal drugs for the treatment of NNJ^(38,84,85). These include hydrocortisone, dexamethasone and cortisone. Eight centres (40%) had used steroids for treatment of NNJ^(18,20,24,25,29-31,37). Steroidal drugs are not known to be used for NNJ in other parts of the world. The rationale of using steroids in NNJ is not clear. It is surmised that the inhibitory effect of steroids on heme oxygenase may play a role in decreasing bilirubin production⁽⁸³⁾. But what are the side effects or complications of the drugs? Both Huang⁽⁸⁵⁾, from

Beijing and Fan⁽⁸⁶⁾, from Shanghai, discouraged the use of steroids for NNJ.

Orange peels and the bilirubin degrading enzyme

Many plant products have been used for the treatment of NNJ. One wonders why the use of orange peels escaped the attention of the older generations of the Chinese physicians. A bilirubin degrading enzyme, bilirubin oxidase, isolated from orange peels was found by Wu and Li in 1988⁽⁸⁷⁾. The enzyme, extracted from the peels of edible oranges, catalyzes the degradation of unconjugated bilirubin. This enzyme however is poorly soluble in water. Its clinical use is being investigated.

DISCUSSION

One of the most important goals in medicine is to continue searching for better treatment. Even in modern medicine, better and more effective treatment is replacing the older forms of treatment. Traditional medicine has played its role in the past. With emergence of better treatment, what further role can traditional medicine play in the advancement of medicine?

For instance, Yin-chen (*Artemisia*) has remained the mainstay of treatment for NNJ since 207 AD^(14,15). The current use of this herb is still in line with ancient recommendations. If Yin-chen is the panacea for NNJ, many parts of the world should be using it for NNJ and there should be no reports of kernicterus. Since Yin-chen has been there for many centuries, there may be a place for further research, in order to gain more information and to discover more beneficial effects of the plant.

Generally, the optimal form of medical treatment, such as treatment of NNJ, should be:

- (a) Non-invasive, which is neither oral nor parenteral
Both oral *Artemisia composita* decoctions or intravenous *Artemisia scoparis* are less ideal than phototherapy that is non-invasive. Phototherapy, as an alternative treatment of NNJ, has gained general acceptance, and its efficacy and safety have been firmly established. The need for the management of neonatal jaundice with drugs has greatly diminished. In treatment with traditional medicine, 20 to 30 mL of the decoction has to be given to the baby three times daily for 3 to 4 days. This volume of fluid is too much for a premature baby and is also not suitable for a baby who is not able to suck well. With more babies successfully treated with phototherapy, less exchange blood transfusion is required. We have done 2 exchange blood transfusions in the past 6 years (a total of 49,919 births).
- (b) Low cost, for example, short hospitalisation, inexpensive and easily available, etc
For babies treated with traditional medicine, the therapeutic course takes 3-4 days to complete⁽³⁷⁾. Other types of herbal treatment may take as long as 7-10 days. The baby has to remain in the hospital during that period of herbal treatment, separated from the mother, and bonding problems arise. It is not clear whether the herbs are costly. It depends on the availability of the herbs that are on sale in some traditional drug stores. It is also important to take note that:
- (c) The action, metabolism, pharmacokinetics of the medicine should be known
In modern medicine, the pharmacokinetics of a drug is and has to be known in great details. Studying of herbal medicine however is extremely difficult because of the multiple pharmacological agents in the herbs. One plant product is considered as single item of the herbal medicine prescribed. This plant product actually contains many chemical

compounds. Prescribing a concoction or decoction amounts to administering a large variety of chemical substances to a baby. For the treatment of NNJ, many types of herbs are prescribed. This amounts to giving the newborn baby as many as 50 chemicals. Would the relatively immature organs of the newborn baby be able to handle these drugs? In addition, some of these compounds may act on the non-target organs or systems. The effect of these substances may not be desirable.

When herbs are prescribed in the crude form, pharmacokinetic study of the various components is difficult. It has been pointed out that the chemical contents vary in different plant cycle^(41,46,47). It is also not known whether these ingredients have complementary, synergistic or antagonistic effect in the body. The actions of a herb are many, for example, anti-microbial, hypotensive, cholerectic, diuretic, and even sedative. Are these effects beneficial or undesirable, or even harmful. Some herbs have opposite effect when given in different dosages. Da-huang, for example, if given in larger dose (1-5 gm of sennoside A) will cause catharsis. However, if smaller dose is prescribed (0.05 to 0.3 gm), constipation can occur⁽⁷⁰⁾.

The older way of preparing the decoction was done at home by the family members. Quantitative and qualitative control could be a problem. As a result, the patient received different dosages of medicine each time.

- (d) The drugs should be free from short-term and long-term complications.

Some reports claimed success in treatment of NNJ with herbs. However, what is the definition of success? Does one accept clinical disappearance of jaundice as success? Most reports took clinical disappearance of jaundice as marker of success of treatment. Unfortunately, kernicterus or even deaths had occurred^(20,21,27,30,33).

Glucose-6-phosphate-dehydrogenase (G6PD) deficiency is prevalent in South China⁽⁴⁸⁾. The safety of the herbs has to be ensured before consumption. Herbs may contain alkaloids that can precipitate acute haemolysis. One report of 39 newborn babies with G6PD deficiency showed that there was no obvious advantage in the use of herbs for NNJ. In the same report however, there were 14 cases of kernicterus, 9 deaths and 1 with sequelae⁽³⁰⁾. In another report of 109 cases of G6PD deficiency, there were 8 cases (7.3%) of kernicterus⁽³⁶⁾. In our country, we have not seen a single case of kernicterus for more than a decade⁽¹⁸⁾.

- (e) The drugs should also be safe for premature or sick babies. Very few reports mentioned the safety of the herbal medicine for the high risk babies such as the premature babies and the very sick newborns.

Chinese herbs have many pharmacological substances and therefore multiple actions. The study of the pharmacokinetics of these herbs is difficult. In recent years, the use of Chinese herbs in the treatment of NNJ has been complicated by the combined use of "Western" drugs^(38,36a). The use of phenobarbitals^(30,31,38,38a) plasma^(19,21,30,32,85) and steroids^(19,21,25,30,37,85) as well as the use of phototherapy and exchange blood transfusion^(27,30,31,37,38,38a) renders the study of the effects of herbal treatment of NNJ extremely difficult.

For the use of traditional drugs, De Smet has put it very aptly: 'No patient deserves to be treated with a remedy that is more than the disease. It is essential, however, that traditional drug therapies are submitted to an appropriate benefit/risk analysis.' He further mentioned that the drug should be looked at '... not only the pharmacological efficiency -- but also the social utility of the drug in its cultural

context'⁽⁶⁸⁾.

REFERENCES

1. Desta B. Ethiopian traditional herbal drugs. Part II: Antimicrobial activity of 63 medicinal plants. *J Ethnopharmacol* 1993; 39: 129-39.
2. Carbajal D, Casaco A, Arruzazabala F, Gonzalez R, Fuentes V. Pharmacological screening of plant decoctions commonly used in Cuban folk medicine. *J Ethnopharmacol* 1991; 33: 21-4.
3. Sezik E, Tabata M, Yesilada E, Honda G, Goto K, Ikeshiro Y. Traditional medicine in Turkey. I. Folk medicine in north-east Anatolia. *J Ethnopharmacol* 1991; 35: 191-6.
4. Institute of Chinese Medicine of Beijing. The development of materia medica in the feudal society in: *Notes on History of Chinese Medicine*. Hong Kong: Medicine and Health Publishers 1968: 23.
5. Li Shi-zhen. *Ben-cao Gang-mu* (A Compendium of Materia Medica). Chinese Encyclopedia, reprinted. Shanghai: the Commercial Press Ltd, 1930 (in the Chinese language).
6. Yuan-Liu Encyclopedia Editorial Board. Li Shi-zhen. Physicians of Ancient China. Taipei, Taiwan: Yuan-Liu Publisher, 1978; 139-54.
7. Brown WR, Wong HB. Ethnic group differences in plasma bilirubin levels of full term, healthy Singapore newborns. *Pediatrics* 1965; 36: 745-51.
8. Maisels MJ. Neonatal jaundice. Neonatology - pathophysiology and management of the newborn. In: Avery GB, eds. (3rd ed). Philadelphia: Lippincott 1987: 534-629.
9. Chao YF. *Zhu Bing Yuan Hou Zong Lun* (General treatise on the etiology and symptomatology of diseases. China 610 (in classical Chinese language).
10. Yan JZ. *Qian Yi's Xiao Er Yao Zheng Zhi Jue* (Key to therapeutics of children's diseases) China, 1119 (in classical Chinese language).
11. Ding X. *You Ke Tie Jing* (Iron Mirror of Pediatrics) China, 1695 (in classical Chinese language).
12. Jiangsu College of New Medicine. *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers, 1977.
13. Integrated group of Chinese and Western physicians of Hunan Province. A collection of publications of Chinese Paediatrics. In: Chang BL, Ling SS, eds. Hunan, China: Hunan Science and Technology Publishers 1991 (in the Chinese language).
14. Wang SH, editor. *Zhang Zhongjing's Shang Han Lun* (Treatise on febrile diseases). China 207 (in the classical Chinese language).
15. Zhang L. *Zhang Shi Yi Tong* (Zhang's Treatise on General Medicine) China 1695. (In the classical Chinese language).
16. Chang HM, But PPH, editors. *Pharmacology and applications of Chinese materia medica*. Philadelphia: World Scientific Publishing Co Pte Ltd, 1986.
17. Yeung CY. Bilirubin metabolism in Chinese newborn infants. Proceedings of Centennial Scientific Conference. Faculty of Medicine, University of Hong Kong, 1987: 261-8.
18. Ho NK. Neonatal jaundice in Asia. In: Fleming AF, eds. *Bailliere's Clinical Haematology - Epidemiology of Haematological Disease: Part I*. London: Bailliere Tindall 1992; 5: 131-42.
19. People's Hospital of Guangdong. Treatment of hyperbilirubinemia by combined Chinese and Western methods. *Medical Science Data of Guangdong* 1973; 3:11. (In the Chinese language).
20. First People's Hospital of Zhaoqing. Treatment of kernicterus of the newborn by combined Chinese and Western medicine: a report of 14 cases. *The New Chinese Medicine* 1973; 2: 6. (In the Chinese language).
21. First People's Hospital of Foshan Region. Treatment of hyperbilirubinemia by combined Chinese and Western methods: a report of 12 cases. *Medical Data of Guangdong* 1974; 10:14. (In the Chinese language).
22. Shanghai Children's Hospital. Treatment of hyperbilirubinemia by Chinese medicine - the "three-huang" mixtures: a report of 38 cases. *Chinese Med J* 1976; 56: 749. (In the Chinese language).
23. Zeng MZ. Neonatal hyperbilirubinemia. *Medical Data of Jiangxi* 1973; 52. (In the Chinese language).

24. People's Hospital of Guangdong. Treatment of neonatal jaundice by *bai tou weng* mixtures: a report of 100 cases. Medical Data of Guangdong 1977; 7: 36. (In the Chinese language).
25. People's Hospital of Guangdong. Prevention of hyperbilirubinemia by combined Chinese and Western methods. Medical and Health Data of Zhaoqing, Guangdong 1977; 3: 42. (In the Chinese language).
26. Guangxi Medical College Hospital. Treatment of hyperbilirubinemia by combined Chinese and Western methods. Guangxi: Medical Information Exchange of Guangxi Province 1977; 6: 24. (In the Chinese language).
27. Shanghai Children's Hospital. Neonatal haemolytic diseases: An analysis of 91 cases. Chinese Med J 1977; 57: 171. (In the Chinese language).
28. Liu JH. Treatment of neonatal haemolytic diseases by combined Chinese and Western medicine. Medical Data of the First Jilin Hospital 1977; 4: 58. (In the Chinese language).
29. Nanjing Children's Hospital. Neonatal jaundice. Medical Academic Data of Nanjing 1978; 23:1. (In the Chinese language).
30. First People's Hospital of Foshan, Guangdong. Neonatal hyperbilirubinemia due to erythrocytic G6PD deficiency: Clinical analysis of 39 cases. Chinese Pediatric Journal 1978; 16: 62. (In the Chinese language).
31. Treatment of Neonatal Jaundice by combined Chinese and Western methods. Data (the West learns from the Chinese) from the Military General Hospital of Beijing 1979. (In the Chinese language).
32. Chen HY. Treatment of neonatal jaundice by Chinese medicine. Journal of the Bare-footed doctors 1979, 4: 8 (In the Chinese language).
33. Liu XG. Neonatal haemolytic diseases. Middle Medical Journal 1979; 3: 50. (In the Chinese language).
34. No. 167 People's Liberation Army Hospital. Treatment of neonatal haemolytic diseases by combined Chinese and Western medicine: 2 case reports. Hunan Medical Journal 1979; 4: 1. (In the Chinese language).
35. Ding CE. Treatment of neonatal haemolytic diseases by Chinese medicine (ABO Incompatibility): report of a case. Jinan Medicine 1980; 4: 62. (In the Chinese language).
36. Wu ZL. A clinical study of neonatal hyperbilirubinemia due to erythrocytic G6PD deficiency. Chinese Pediatric Journal 1980; 18:9. (In the Chinese language).
37. Chen HY. Artemisia composita for the prevention and treatment of neonatal hemolysis and hyperbilirubinemia. J Trad Chin Med 1987; 7: 105-8.
38. Guan XJ, Yu SJ, Chen XT. Study on prevention and treatment of G6PD deficiency of the neonates' erythrocytes in perinatal period. Chinese Pediatric Journal 1989; 27: 14-5. (In the Chinese language).
- 38.a Guan XJ. Prenatal prevention of hyperbilirubinemia in erythrocyte glucose-6-phosphate dehydrogenase deficiency in neonates. (English version) In: Abstracts of Scientific Presentation XVIII. International Congress of Pediatrics; 1986 July 7-12; Honolulu, Hawaii, 1986: No. 500.
39. Jiangsu College of New Medicine. *Qing hao*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers, 1977; 2: 1228-9.
40. Bi CS. *Qing hao*. In: Chang HM, But PPH, editors. Pharmacology and applications of Chinese materia medica. Philadelphia: World Scientific Publishing Co Pte Ltd, 1986; 1: 685-93.
41. Jiangsu College of New Medicine. *Yin chen hao*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 2: 1588-91.
42. Nagy JG, Tengerdy RP. Antibacterial action of essential oils of Artemisia as an ecological factor. I. antibacterial action of the volatile oils of Artemisia tridentata and Artemisia nova on aerobic bacteria. Appl Microbiol 1967; 15: 819-21.
43. Huang HC, Chu SH, Chao PD. Vasorelaxants from Chinese herbs, emodin and scoparone, possess immunosuppressive properties. Eur J Pharmacol 1991; 198: 211-3.
44. Abu Niaaj L, Abu Zarga M, Sabri S, Abdalla S. Isolation and biological effect of 7 O methylerythroidiol, a flavanone isolated from Artemisia monosperma, on rat isolated smooth muscle. Plant Med 1993; 59: 42-5.
45. Ikenaga T, Hizako M, Tajima M, Nakashima K. Production of choleric substances in the capitulum, leaf and stem of Artemisia capillaris during the plant growth cycle. Biol Pharm Bull 1994; 17: 150-1.
46. Zhang LH, Wang JZ, Zhou XB, Wu BJ. A comparative study on chologogic effect of artemisia. Chung Kuo Chung Yao Tsa Chih Journal of the Chinese Medicine 1993; 18: 560-1.
47. Laughlin JC. Agricultural production of artemisin - a review. Trans R Soc Trop Med Hyg 1994; 88 suppl 1: S21-2.
48. Yu ZF, Wu XS. Ultrasonic studies of the effect of artemisia decoction on the volume and dynamics of gallbladder. Chin Med J (Engl) 1993; 106: 145-8.
49. Jiangsu College of New Medicine. *Che-qian*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 1: 401-3.
50. Jiangsu College of New Medicine. *La-mei-hua*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 2: 2552-3.
51. Jiangsu College of New Medicine. *Yu-mi-xu*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 1: 555-6.
52. Bi CS. *Yu-mi-xu*. In: Chang HM, But PPH, editors. Pharmacology and applications of Chinese materia medica. Philadelphia: World Scientific Publishing Co Pte Ltd 1986; 1: 293-7.
53. Jiangsu College of New Medicine. *Gou-teng*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 2: 1668-70.
54. Jiangsu College of New Medicine. *Zhi-zi*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 2: 1984-7.
55. Jiangsu College of New Medicine. *Da-ye-she-zong-guan*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 1: 159.
56. Jiangsu College of New Medicine. *Chan-tui*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 2: 2558-9.
57. Yeung CY, Leung CS, Chen YZ. An old traditional herbal remedy for neonatal jaundice with a newly identified risk. J Paediatr Child Health 1993; 29: 292-4.
58. Silverman W, Anderson D, Blanc W, Crozier DN. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. Pediatrics 18: 614-25.
59. Deng WL. *Sankezhen*. In: Chang HM, But PPH, editors. Pharmacology and applications of Chinese materia medica. Philadelphia: World Scientific Publishing Co Pte Ltd, 1986; 1: 62-71.
60. Sharma R, Joshi CK, Goyal RK. Berberine tannate in acute diarrhoea. Indian Pediatr 1970; 7: 496-501.
61. Desai AB, Shah KM, Shah DM. Berberine in the treatment of diarrhoea. Indian Pediatr 1971; 8: 462-5.
62. Khin MU, Myo-khin, Nyunt NW, Aye-kyaw, tin U. Clinical trials of berberine in acute watery diarrhoea. Br Med J 1985; 291: 1601-5.
63. Chang WH. In-vitro antibacterial activity of some common Chinese herbs on gram-positive aerobic bacteria. Chinese Med J 1949; 67: 648-56.
64. Maroko PR, Ruzyllo W. Improved left ventricular performance after berberine infusion. Circulation 1983; 68 suppl 3: III-374.
65. Jiangsu College of New Medicine. *Huang-tian*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 2: 2022-30.
66. Shin DH, Yu H, Hsu WH. A paradoxical stimulatory effect of berberine on guinea pig ileum contractility: possible involvement of acetylcholine release from the postganglionic parasympathetic nerve and cholinesterase inhibition. Life Sci 1993; 53: 1495-500.
67. Poland RL, Odell GB. Physiologic jaundice: The enterohepatic circulation of bilirubin. N Engl J Med 1971; 284: 1.
68. Chan E. Displacement of bilirubin from albumin by berberine. Biol Neonate 1993; 63: 201-8.

69. Jiangsu College of New Medicine. *Huang-qin*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 2:2017-21.
70. Jiangsu College of New Medicine. *Da Huang*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 1: 102-8.
71. Drill VA, editor. *Pharmacology in medicine: a collaborative textbook*. 2nd ed. New York: McGraw-Hill, 1958; 676.
72. Wan SY. *Da-huang*. In: Chang HM, But PPH, editors. *Pharmacology and applications of Chinese materia medica*. Philadelphia: World Scientific Publishing Co Pte Ltd 1986; 1: 72-83.
73. Jiangsu College of New Medicine. *Gan-cao*. In: *Zhong Yao Da Zi Dian* (Encyclopedia of Chinese materia medica). Shanghai: Shanghai Science and Technology Publishers 1977; 1: 567-73.
74. Chu Y. *Gancao*. In: Chang HM, But PPH, editors. *Pharmacology and applications of Chinese materia medica*. Philadelphia: World Scientific Publishing Co Pte Ltd 1986; 1: 304-17.
75. Kraus SD. Glycyrrhetic acid - a triterpene with anti-oestrogenic and anti-inflammatory activity. *J Pharm Pharmacol* 1960; 12: 300-6.
76. Kageyama Y, Suzuki H, Saruta T. Glycyrrhizin induces mineralocorticoid activity through alterations in cortisol metabolism in the human kidney. *J Endocrinol* 1992; 135: 147-52.
77. Stormer FC, Reistad R, Alexander J. Glycyrrhizic acid in liquorice - evaluation of health hazard. *Food Chem Toxicol* 1993; 31: 303-12.
78. Stewart PM, Whorwood CB, Walker BR. Steroid hormones and hypertension: the cortisol-cortisone shuttle. *Steroids* 1993; 58: 614-20.
79. Zhang YH, Isobe K, Nagase F, Lwin T, Kato M, Hamaguchi M, et al. Glycyrrhizin as a promoter of the late signal transduction for interleukin-2 production by splenic lymphocytes. *Immunol* 1993; 79: 528-34.
80. Numazaki K, Umetsu M, Chiba S. Effect of glycyrrhizin in children with liver dysfunction associated with cytomegalovirus infection. *Tohoku J Exp Med* 1994; 172: 147-53.
81. Sardana MK, Sassa S, Kappas A. Adrenalectomy enhances the induction of heme oxygenase and the degradation of cytochrome P-450 in liver. *J Biol Chem* 1980; 255: 113-20.
82. Sardana MK, Sassa S, Kappas A. Hormonal regulations of heme oxygenase induction in avian hepatocyte culture. *Biochem Pharmacol* 1985; 34: 29-37.
83. Rodgers PA, Stevenson DK. Developmental biology of heme oxygenase. *Clin Perinatol* 1990; 2: 275-91.
84. Institute of Chinese Medicine of Shanghai. Neonatal jaundice. In: *Chinese Pediatrics*. 5th edition. Hong Kong: the Commercial Press Ltd, 1988: 283-8. (In the Chinese language).
85. Huang DM. Causes and management of neonatal unconjugated hyperbilirubinemia. *Chinese Pediatric Journal* 1989; 27: 11-3. (In the Chinese language).
86. Fan SZ, editor. In: *The Chinese and Western treatment of children's diseases*. Shanghai: University of Chinese Medicine of Shanghai Press 1994: 25-8.
87. Wu TW, Li GS. A new bilirubin degrading enzyme from orange peels. *Biochem Cell Biol* 1988; 66: 1248-52.
88. De Smet PAGM. Is there any danger in using traditional remedies? *J Ethnopharmacol* 1991; 32: 43-50.