CHINESE HERB GARDEN
UNIVERSITY OF BRISTOL BOTANIC GARDEN

This article was written by Tony Harrison (RCHM) and reprinted from the Register of Chinese Herbal Medicine Journal 2022

THE ETHNOPHARMACOLOGY DISPLAY

The focus of this article is to provide background information to complement the information presented on the public interpretation sign in the new ethnopharmacology display bed within the Chinese Herb Garden. In particular it is designed to provide some scientific evidence for statements made on the sign and to present the baseline for additional articles to be posted on the RCHM outreach website.

WHAT IS ETHNOPHARMACOLOGY?
There are several definitions depending on your area of work (1). The one I use is:
The integrated study of traditional herbal medicine with modern scientific analysis
It is a deceptively simple definition which amalgamates a range of disciplines including botany, pharmacology, anthropology, and cultural medical systems of health and disease.
As a recent branch of ethnobotany, it also incorporates the botanical identity, quality and sustainability of wild herb plants through conservation and cultivation.
Unlike modern drugs which are standardised to a single chemical ingredient, the quality of a herb is variable as it depends on many factors such as how it is grown and processed.

The aim that lies behind this project is to draw together research from traditional herbal medicine and modern science but to give equal emphasis to both. In this way we can understand the strengths and weakness of each. There is then potential to enter a real dialogue between European and Traditional Chinese Medicine (TCM). The integration of these two systems is currently a major part of the modernisation of TCM within China.


Outside display with Isatis tinctorum (da qing ye) in flower

THE LIVING PHARMACY COLLECTION
The ethnopharmacology collection has been given a particular emphasis.

One of the most pressing medical needs currently is to counteract antibiotic drug resistance. We have decided with this collection to gather plants which have both a long-term traditional use, and also modern history of scientific research in this area of medicine. Although many are used in Chinese herbal medicine, the list includes plants from other herbal traditions.
Some of the most important and hardy herbs are grouped together in a dedicated outside display bed and others are in other areas of the botanic garden. More tender herbs will be kept in the relevant zone of the greenhouse complex.

LIST OF PLANTS

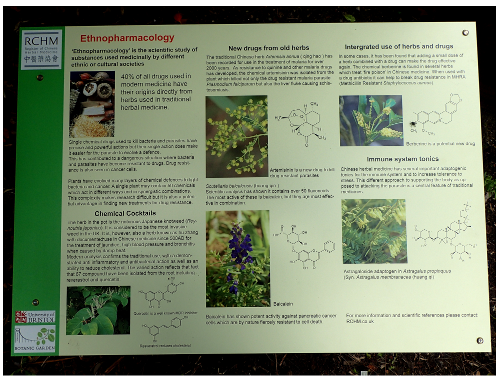
Anti bacterial/parasitic/cancer herbs

Polygonum cuspidatum (hu zhang)
Phellodendron japonica (huang bai)
Mahonia fortunei (gong lao mu)
Berberis vulgaris (berberis)
Rheum palmatum (da huang)
Salvia officinalis (sage)
Rosmarinus officinalis (rosemary)
Thymus vulgaris (thyme)
Malaleuca alternifolia (tea tree)
Tanecetum vulgare (feverfew)
Glycyrrhiza glabra (gan cao)
Artemisia annua (qing hao)
Isatis tinctorium (da qing ye/ ban lan gen)
Nigella sativa (nigella seed)
Scuttelaria baicalensis (huang qin)
Dryopteris crassiorhizoma (guang zhong)
Polygonum multiflorum (he shou wu)
Morus alba (sang)
Zingziber officinalis (sheng jiang)
Cinnamomum zeylandica (cinnamon)
Curcuma longa (jiang huang)
Geranium strictipes
Arctostaphylos uva ursi (bearberry)
Andrographis paniculata
Perlagonium sisoides
Coptis chinensis (huang lian)

Immune tonics (adaptogens)

Astragaulus propquinqus (syn membranacea) (huang qi)
Schisandra chinensis (wu wei zi)
Panax quinqufolius (xi yang shen)

THE DISPLAY BOARD



Ethnopharmacology Interpretation board

Interpretation of such a complex subject is a much bigger challenge than simply explaining Chinese medicine as in the case of the 'use class' display. It has to be easily explained by the garden tour guides but also needs to satisfy the requirements for a leading university for accurate statements based on scientific validation. I have decided that the best approach is to isolate a few fundamental principles with examples. The background can then be enlarged through articles on the website which can be kept up to date with research papers when needed.

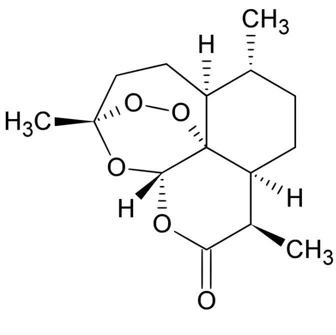
PRINCIPLE 1: NEW DRUGS FROM OLD HERBS

Around 40% of approved drugs during the last 30 years are derived from plants (4)
Some studies have also indicated that of 122 plant derived drugs, 80% of their use in modern medicine were related to the same medical application used in the original traditional medicine (5)
Herb plants from China and the far east are one of the richest regions for drug prospectors today (2,7). China has over 30000 species of plant of which 3000 have been claimed to have specific traditional medicinal use. The process of finding and testing the chemicals is a long and expensive process and funding has reduced considerably in developing new drugs from natural materials (1), but there are several which show potential to assist with drug resistance (1,3).


Artemisia annua is source of qing hao herb.

In 1967 the Vietnamese army asked China to assist with persistent malaria in the troops. Herbs were sourced from traditional herbal medical texts. These texts are know as the 'ben cao' and are a major resource as documented records of herbal use for over 2000 years (6,8). They represent a long-term human clinical trial but without the control required by scientific RCT (random controlled trials). Traditional herbs which have been used for malaria symptoms were screened. The most effective was the herb *Artemisia annua* (qing hao) which first appeared in the Shen Nong Ben Cao written around 150AD. This lead to the discovery of the drug artemisinin, as the main active anti malarial component.

The sesquiterpene lactone (9,10,12) drug artemisinin has a unique and highly unstable structure due to the double bond trioxane group shown at the bottom of the molecule .


Artemisinin molecule with unstable double bond oxygen group

The effect of the trioxane bond is to oxidise iron to form toxic free radicals. The malaria parasite *Plasmodium vivax* survives by digesting the host haemoglobin. It is more sensitive to the free radicals than the human host cells and hence the parasite is killed and the malaria halted. The drug also attacks in a second way at the same time to disrupt the DNA of the parasite.
Artemisinin has also been found to kill the liver fluke parasite responsible for schistosomiasis which is second only to malaria as a parasitic killer in the tropics (16,17).
The effect on cancer cells is also interesting. Some cancer cells are also high in iron and are also damaged by the iron oxidising effects of artemisinin
Because artemisinin is so unstable, it proved very difficult and expensive to synthesise as a drug. New strains of *Artemisia annua* were cultivated with 20 times the content of artemisinin. Genetically modified yeast has also been developed which manufacture the drug , making it less dependent on the plant source

(13). It is often forgotten that chemical synthesis of drugs is an important factor in the conservation of the original wild herb plants which would otherwise be over exploited.

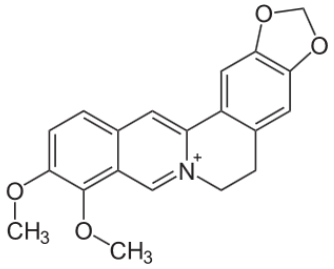
As this was a new method of attack compared to the quinine drug, artemisinin was able to provide an effective treatment for the problem of drug resistance which had developed with quinine drugs, and had fewer side effects compared to piperiquin alone. Initially the mortality rate was 30% lower compared to treatment with quinine (14,15).
Artemisinin is very fast acting drug with a half life of 1 hour, hence it is best used with a slow release drug to combat the parasite and prevent resistance. WHO guidelines now state that it should not be used on its own for this reason (18). Despite its initial dramatic effect, drug resistance to artemisinin is becoming apparent (20). Adaptation is occurring.
There is no doubt that concentrated artemisinin as a drug is a more powerful antimicrobial than the herb. Artemisinin as a drug however, is not exactly the same as *Artemisia annua* the herb.
Artemisia annua also contains many other chemicals including the anti-inflammatory scopoletin, which could explain its ability to reduce fever. One of these other chemicals is a methylated flavenoid which increases the action of the artemisinin although it does not actually kill the parasite itself. Could these play a part in its action in preventing drug resistance to artemisinin?

PRINCIPLE 2: CHEMICAL COCKTAILS

A single herb plant has manufactured many chemicals which have evolved to enable growth and reproduction and to protect themselves from environmental stress. Plants have an immune system which can react within seconds to a predator to protect them from being eaten or resist disease pathogens such as virus or bacteria. As these pathogens have evolved new methods of attack, so the plant has manufactured new chemicals. But they also retain the old chemical defences creating an historical armoury and ability to act in several ways at the same time.
Bacteria and other pathogens that attack humans are not that different in structure than those that attack plants. They have similar cell walls and use similar methods to attack. Hence it is not surprising that they can also work for human pathogens.

One drug that has attracted research is the alkaloid berberine. This is a chemical found in many herbs used in most traditional medicine systems for treating infection and also the underlying inflammation. Examples include *Phellodendron amurnesis, Coptis chinensis, Mahonia species, Berberis species.*

Yellow berberine drug seen in Phellodendron amurense bark (huang bo)



Structure of berberine alkaloid molecule

Isolated berberine alkaloids in pure form do have antimicrobial activity.
When there are only a few bacteria they secrete a chemical which attracts other bacteria but when the bacterial colony reaches a certain size they produce a different chemical which causes them to secrete a slimy biofilm over the entire bacterial colony. This alteration in response to bacterial population numbers is known as quorum sensing. Berberine is thought to destroying the biofilm protection defences by the bacteria. Berberine can also weaken the bacterial cell wall and enter the bacteria causing more damage. The bacteria have evolved a mechanism known as an 'efflux pump' which literally pumps the berberine back out. As a counter strategy the plant produces another chemical (5 methoxyhydnocarpin) which inhibits the action of the efflux pump.

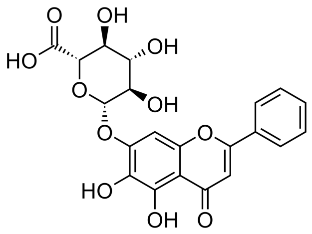
One of the reasons that penicillin was so effective for so long was that it contains two lines of attack on the pathogen.
When we subject a pathogen to a single attack, it is relatively easy for it to evolve a response. A simple attack promotes a simple evolutionary defence and drug resistance can develop more quickly.
This may explain why plants have often developed chemicals which can attack in more than one way, or a group of chemicals which can launch a complex attack or increase the action of each other.

PRINCIPLE 3 : SYNERGY – MORE THAN THE SUM OF THE PARTS

The ability for a mixture of chemicals to have a greater effect than ether on its own is termed synergy. We can see this in all the examples given but I would suggest that synergy is central to the action of all herbs and it what distinguishes the action of a drug from that of a herb.

Synergy has been observed where a herb or extracted chemical from a herb is given at the same time as an antibiotic drug which has ceased to become effective as in drug resistance. The combination can be more powerful than either the herb alone or the antibiotic (38-47).

Scuttelaria baicalensis (huang qin)



Structure of baicalein flavenoid molecule

The root of *Scutellaria baicalensis* (huang qin) is traditional Chinese herb has been used for at least 200 years as a herb in the damp heat class (6,7,8). From a western perspective it has been employed for reducing fever, treating hepatitis and for infection in the lungs/bowel and bladder.
The main active component has been isolated as the polyphenolic flavenoid drug baicalein. Phenolic compounds are often used as antimicrobial compounds (3).

Recently attention has been turned on the ability of baicalein to kill cancer cells. Drugs used in the treatment of cancer are also becoming less effective due to drug resistance by cancer cells (4-52). Baicalein as a drug has shown potent activity against pancreatic cancer cells which are by nature fiercely resistant to cell death (21-24). It also has few side effects which is a bonus when treating this disease. The mechanism of action on cancer cells is multi layered. In this case 3 mechanisms have been found. It appears to decrease the ability of the cancer cells to produce a protein which enables the cancer cell to evade cell death. It also induces the cell mitochondria to programme cell death. Finally, baicalein, inhibits the fat metabolism pathway that enables proliferation of the cancer cells. In other words this appears to be a highly sophisticated multi action weapon developed by the plant.
Plants also suffer from cancer disaeases.

Baicalein is also only 1 of 50 flavenoids in the plant which act more effectively if used together as opposed to a single drug extract (25-27). A whole extract of *Scutellaria baicalensis* has been demonstrated to re-sensitise drug resistant MRSA bacteria to become susceptible again to conventional antibiotics (26-31).
The use of complex whole herb extracts at the same time as a lower dose of strong antibiotic drugs is a novel approach to antibiotic resistance.
Synergy research has become a new development in the pharmaceutical industry so we may see a new approach developing in the future (38,39,40).

PRINCIPLE 4 ; REGULATE THE IMMUNE SYSTEM

All the above examples are focussed on killing parasites. This is a natural way of approaching the problem. The battle between pathogens and host is as old as cellular life evolved and drug resistance is not a new event.
The creation of concentrated antibiotics drugs has been a true life saver and the search for new antibiotic drugs with new strategies of attack will continue as it has done in plants.

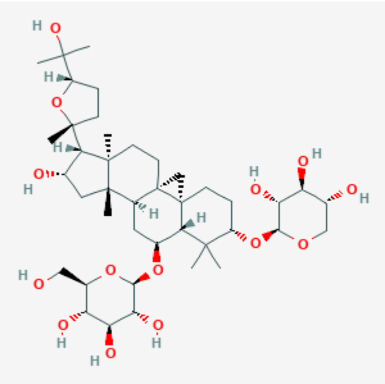
However if a person is weak then it is just as important to regulate the host immune system.
Herbal medicine does not have the same power to deal with acute infection, but it does have a potential role in long-term balancing of the immune system.
Within the Chinese materia medica there are herbs which are traditionally used to strengthen the immune system.

One key herb is *Astragalus membranaceus* (Huang Qi).


Astragalus membranaceus is a member of the pea family (Fabaceae)

Over 100 chemicals have been isolated from this herb including polysaccharides, flavenoids and saponins (7). Most attention with respect to immunity has centred on the effects of the saponins which are steroidal in form.

Unbalanced immunity can be deficient leading to a lack of response. However it can also be excessive causing allergy, autoimmune diseases or chronic inflammation. The pharmacology of *Astragalus* has yet to be studied in any real detail but there is some evidence that in vitro these saponins promote B cell proliferation and antibody production (58) .Whilst it may appear that *Astragalus* does have some components in the form of steroidal saponins, which have effects similar to or are synergistic with the drug inteferon (7) which triggers immune responses, as a whole herb it has demonstrated an ability to control chronic bowel inflammation from an overactive immune response (54,55).


Astragaloside steroidal saponin

Astragalus membranaceus belongs to a class of herbs which are considered to be adaptogenic. This means they have the ability to help the body adapt to stress, which includes attack by a pathogen. The action of adaptogens is complex but thought to work in general through the hormone mechanism by regulation of cortisone and adrenal function (53).

Plants also have a well developed hormonal system, and the structure of hormones across plants, insects and man is similar. It is interesting to note that the chemistry of these steroidal compounds in *Astragalus* , which is in the plant family of Fabaceae , are similar to other key adaptogenic herbs in an unrelated family. *Panax ginseng* (ren shen) and *Eutherococcus gracilistylus* (wu jia pi) in Araliaceae also contain steroidal based glycosides.


Panax ginseng(ren shen)root has adaptogenic properties

Panax ginseng (ren shen) has been studied in more depth and it appears that there are 2 main groups of steroidal glycosides at work .The first are the triol gingenosides (Rg1) which stimulate the body and the other are the diol gingenosides (Rb1) which are sedating and calming. The action of these on the body is considered to be via the hypothalamus and adrenal gland (56). Contradictory actions within a single herb are not uncommon and this may be how they can regulate. This is also seen in sugar regulation where the whole extract of *Panax* will reduce blood sugar levels in hyperglycaemia but raise it in hypoglycaemia (57). They are more homeostatic in action than simply synergistic.

What can we gain from this type of analysis?
With the combined knowledge of traditional herbal experience and modern scientific precision we can learn from plants which have been working on the problem of drug resistance for millions of years longer than humans.

REFERENCES

General References

1: Ethnopharmacology ; Michael Heinrich:Anna Jager 2015
Pub: John Wiley ISBN 9781118930748

2: Medicinal Plants of the Asia Pacific- Drugs for the future
Christopher Wiart World Scientific Publishing 2006
ISBN 981-256-341-5

3: Marjorie Murphy Cowan: Plant Products as Antimicrobial Agents
Clin Micobiol Rev 1999 Oct; 12(4): 564-582

4: Veeresharam C. : Natural products derived from plants as a source of drugs
J Adv Pharm Technol Res: 2012: 3(4); 200-1

5: Fabricant DS, Farnsworth NR: The values of plants used in traditional medicine for drug discovery
Environ Health Perspect 2001: 109(1); 69-75

6: Chinese Medical Herbology and Pharmacology
J.Chen, T.Chen Art of Medicine Press 2001 ISBN 0-9740635-0-9

7: Chinese Materia Medica.; Chemistry, Pharmacology and Applications
You Ping Zhu Harwood Academic Publishers 1998 ISBN 90-5702-285-0

8: Chinese Herbal Materia Medica:
D.Benski, S.Clavey, E.Stoger Eastland Press 2004 ISBN 0-939616-4-24

9: The Constituents of Medicinal Plants
A.Pengelly: 2004: CABI ; ISBN 0 85199 807 0

10: Simon Mills, Kerry Bone: Principles and Practice of Phytotherapy – Modern Herbal Medicine
Churchill Livingstone 2007 ISBN: 978 0 443 060168

11: Zuo GY, Zhang ZY, et al: Evaluation of traditional Chinese medicinal plants for anti MRSA activity with reference to the treatment record for infectious diseases.
Molecules 2012: 17: 2955-67

Artemisia annua

12: Rodriguez,E et al.1976, Biological activities of sesquiterpene lactones,
Phytochemistry 15 :1573-1580

13: Ro DK, Paradise EM, et al: Production of anti malarial drug precursor artemisininic acid in engineered yeast:
Nature 2006 ; 440: 940-3

14: Dondorp AM, Fanello CI,Hendrikson IC: Artensuate versus quinine in the treatment of severe falciparum malaria in African children.
Lancet (2010) 376(9753):1647-57)

15: Douglas NM, Anstey NM et al : Artemisinin combination therapy for vivax malaria
Lancet Inffect Dis 10 (6) 405-16

16: Utzinger J, et al: Oral artemether for prevention of Schistosomer infection.
Lancet 355 (2000) (9212):1320-5

17: Li YS, Chen HG et al: double blind field trial on effects of artemether on Schistosoma japonica infection in southern China
Acta trop (2005) 96(23): 184-90

18: WHO Press Release 19th Jan 2006 calls for immediate halt to provision of single drug artemisinin pill

19: Wright CW., Linley,PA.,Brun et al. Ancient Chinese methods of artemisinin rich extracts of qing hao with potent antimalarial activity.
Molecules (15) 804-812

20: Ashley, Elizabeth A et al: Spread of resistance of Artemisinin resistance in Plasmodium falciparum malaria
The New England Journal of Medicine 2014 : 371(5): 411-23

Scuttelaria baicalensis

21: Bonham M, Posakony J. et al: Characteristics of chemical constituents in Scuttelaria baicalensis with anti androgenic and growth inhibitory activities towards prostate carcinoma.
Clin Cancer research 2005: 11(3905-14)

22: Ma Z, Otsuyama K et al: Baicalein leads to suppression of proliferation and induction of apoptosis in human myeloma cells.
Blood 2005: 105 (527)

23: Graham Donald, Kathleen Herzer, Giulo Elbl
Baicalein-An intriguing therapeutic phytochemical in pancreatic cancer
HSS Public Access PMC3678518

24: Chiu YW, Lin TH et al : Baicalein mediates inhibition of migration and invasiveness of skin carcinomas in A431 cells.
Toxicol Appl Pharmacol. 2011: 11 (527)

25: Hui KM, Wang XH et al: Interaction of flavones from Scutellaria baicalensis with benzodiazepine site
Planta Med 2000 66: 1 (91-3)

26: Chan BC et al: Synergistic effects of baicalein with ribavirin against influenza
Antiviral research 2011 ; 91; 3 (314-20)

27: Chan BC, Ip M et al: Synergistic effects of baicalein with ciproflaxin against NorA MRSA
J Ethnopharmacology 2001: 137(1): 767-73

28: Fu Z, Lu H, et al; Combination of baicalein with beta lactam antibiotics against methycillin resistant Staphylococcus aureus.

Biol Pharma Bull: 2011 : 34(2) : 214-8

29: Chang PC, li HY et al: In virtro synergy of baicalein and gentomycin against vancomycin resistant enterococcus :
Microbiol Immunol Infect 2007 : 40(1) : 56-61

30: Sato Y, Suzaki S, et al: Phytochemical flavones isolated from Scutellaria barbata and antibacterial activity against MRSA
J Ethnopharmacology 2000; 72(3); 483-8

31: Fujita M, Shiota S et al: Synergies between baicalein and tetracycline and beta lactams against MRSA.
Microbiol Immunol 2005: 49(4); 391-6

32: Luo JY, Yan D et al: Study of MRSA activity of Rhizoma coptidis by chemical fingerprinting and broth microdilution
Chin J Nat Med 2014 ;12(5) 393-400

Berberine

33: Zuo GY, LiY et al: Antibacterial and synergy of berberines with antibacteriological agents against multi drug resistant isolates of MRSA.
Moleculaes 17(9): 10322-30

34: Zhang S, Zhang B et al: Inhibitory effect of Coptis chinensis and berberine on Microcystis aeruginosa
Water Science and technology: 61(3); 763-9

35: Stermitz FR, Lorenze P et al: Synergy in a medicinal plant: antimicrobial action of berberine potentiated by 5 methoxyhydnocarpin – a multi pump inhibitor
Proc Natr Acad Sci USA 2000 97(4); 1433-7

36: Stermitz FR, Beeson TD, et al: Staphylococcus aureus MDR efflux pump inhibitors from Berberis and Mahonia species
Biochem Syst Ecol. 2001 29(8); 793-98

37: Wojtyczka RD, Dziedzic et al: Berberine enhances antibacterial activity of selected antibiotics against Stapyhloccus in vitro
Molecules: 2014 19(5) ; 6583-96

Synergy

38: Wagner H, Ulrich Merzenich G: Synergy research: approach to a new generation of phytopharmacueticals
Phytomedicine 2009: 16(2-3); 97-110

39: Hemaiswarya S, Kruthiventi AK et al: Synergism between natural products and antibiotics against infectious diseases.
Phytomedicine 2008 15(8); 693-52

40: Gertsch J, Botanical drugs, synergy and network pharmacology
Planta Med 2011 77(11); 1086-98

41: Yang ZC, Wang BC et al: The synergistic activity of antibiotics combined with eight traditional Chinese medicines against two different strains of Stapylococcus aureus.
Colloids Surf Biointerfaces 2005; 41(2-3):79-81

42: Yang Y, Zhang Z et al: Synergy effects of herb extracts: pharmokinetics and pharmacodynamic basis. Fitoterapia Jan 2014 ;92(133-47)

43: Liu Q, Niu H et al: Synergy between thymol, eugenol, berberine, cinnemaldehyde and streptomycin against planktonic and biofilm associated food borne pathogens
Lett Appl Microbiol 2015 Feb 7th

44: Lee YS, Kang OH, Choi JG et al: Synergistic effect of emodin in combination with ampecillin or oxacillin against MRSA
Pharm Biol 2010 ; 48(11); 1285-90

45: Joung DK eta al: Synergistic effect of rhein in combination with ampecillin or oxacillin against MRSA
Exp Ther Med: 2012 3(4); 608-12

46: Kang HK, Kim HY et al: Synergistic effects between silibin and NN diclohexycarbonimide in MRSA
Biotchnol J. 2011; 6(11); 1397-408

47: Hemaiswarya S, Dobie M et al: Synergistic interaction of eugenol with antibiotics against gram negative bacteria.
Phytomedicine 2009: 16(11); 997-1005

Cancer

48: Pharmacological strategies for overcoming multidrug resistance (MDR)
Nobillii S et al Curr Drug Targets 2006(7): 861-79

49: Inhibition of multidrug resistance in cancer cells by natural diterpenes,triterpenes and carotendoids
Molnar et al Curr Pharm Des 2006 12(3) 287-311

50: Mechanism of cancer drug resistance
Gottesman Annu Rev Med 2002(53) : 615-27

51: Emerging significance of flavenoids as P-glycoprotein inhibitors in cancer chemotherapy
Bansol.T et al. J Pharm pharm Sci 2009 12(1) : 46-78

52: Overcoming tumor multidrug resistance using drugs to evade P-glycoprotein.
Nobilii. S et al Med Res Rev 2012 32(6) : 1220-62

Immune regulation -adaptogenic

53: Plant adaptogens –review- Earlier and more recent aspects and concepts on their mode of action
A. Panossian, G.Wikman, H.Wagner Phytomedicine 1999 Vol.6(4) 287-300

54: Auyeung K, Han.QB, Ko JK Astragalus membranaceus – Review of protection against inflammatory and gastrointestinal cancers
Am J Chin Med 2016. 44(1): 1-22

55: Qi Y, Gao F, Hou L , Wan C Anti inflammatory and imunostimulatory action of astragalosides
Am J Chin Med 2017, 45(6) : 1157-67

56: Chang HM, But PP : Pharmacology and applications of Chinese Materia Medica 1986
Vol 1: World Scientific Singapore

57: Chen X: Abst Chin Med 3(91 (1989)

58: Singh, VK et al :Planta Medica 50, 462 (1984)

59: Shibata S, et al Chemistry and pharmacology of Panax
Farnsworth: Economic and Medicinal Plant Research Vol 1 1985