Review Article

The new revolution of immunotherapy: is it time to pair it with the old one? —Yellow Leader as a candidate

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Abstract: With the advent of immunotherapy in cancer treatment, the natural history of this disease has changed. The immune checkpoint therapies have shown great promise in this setting, by potentiating the body's natural immune response against tumor cells. Checkpoint inhibitors (CPIs) have definitively consolidated the target of reversing the immunoevasion as one of the most universal strategies to change the natural evolution of advanced oncological diseases, and to maximize CPI treatment efficacy, synergies in immune system modulation must be seriously considered. In the field of Integrative Oncology, Chinese medicinal mushrooms have been increasingly promoted as excellent anticancer immunoenhancers. However, many plants of traditional Chinese medicine have been less visible, but—as scientific literature reveals—not less powerful as antitumor immunomodulators. Astragalus membranaceous root is a venerated plant as a tonic in traditional Chinese pharmacopoeia. This is known to be beneficial to relieve mild disorders and to help in more serious diseases, such as cancer. For this great restorative capacity was why it won the name of Huang Qi, "leader of all tonics", or Yellow Leader, because of its colour. Astragalus root contains a variety of immunoactive constituents. Its power as an antitumor root is not only due to its immunomodulatory activity; it is able to modulate several apoptotic and antiangiogenic signaling pathways and interact with specific transcription molecules. We propose a rational model of the combination of CPI with Astragalus root chosen as representative of traditional immunotherapy, to set a paradigmatic frame to develop novel target-specific combinations with natural immunomodulators. We are convinced that by combining these two strategies in immunotherapy—the new one and the old one—we can definitely overcome immune cell exhaustion, boost the response to immunocheckpoint treatment, and minimize side effects, to get better and more efficient results in cancer immunotherapy.

Keywords: Immunotherapy; checkpoint inhibitor (CPI); astragalus

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The revolution of immunotherapy in oncology: the anti PD-L1/PD-1

With the advent of immunotherapy in cancer treatment, the natural history of this disease has taken a 380-degree turn, both in survival and in the quality of life of the affected people. It has been only seven years since the first clinical trials were published with checkpoint inhibitors (CPI), to block the immunosuppressive signal dependent on the PD-1 and its PD-L1 ligand pathway, which have shown unprecedented results in a wide variety of tumors (1).

A key point in the mechanism of action of PD-1/PD-L1 pathway inhibitors is that they enhance the antitumor capacity of T cells, reversing the immunoevasion phenomenon (2-4). There are several CPIs which are already in clinical use: pembrolizumab, nivolumab, atezolizumab, durvalumab and avelumab. Lethal and devastating tumors such as lung cancer or melanoma have gone from months of survival—also with very poor tolerance to conventional cancer treatment (mainly chemotherapy)—to years of

quality living. Other cancers such as sarcoma, renal tumor, hepatocellular carcinoma, bladder tumor and breast cancer, have been added to the list of beneficiaries of immunotherapy (5-10). Thus, CPIs have definitively consolidated the target of reversing the immunoevasion as one of the most universal strategies to change the natural evolution of advanced oncological diseases.

The PD-1/PD-L1 pathway: between the immunocompetence and the immunotolerance

PD-1 is a protein that is normally expressed in the immune system cells, when they are activated: natural killer (NK) cells, myeloid cells, B and T lymphocytes. Two ligands have been identified for PD-1: PD-L1 and PD-L2. These two ligands are expressed by different cells in our body. In normal physiological conditions, The PD-L1/PD-1 interactions are key in the regulation of immunotolerance against autoantigens (11,12). When the immunocheckpoint pathway becomes dysfunctional, it contributes to the development and maintenance of pathologies such as chronic viral infections and autoimmune diseases, leading to the T cells depletion (13,14).

In cancer, it has been shown that practically all tumors overexpress the ligand PD-L1. The tumor cell PD-L1 binds to the lymphocyte PD-1 receptor, draining T cells by inhibiting their proliferation and activation; it dramatically enhances the immunoevasion phenomena in the tumor (15). Therefore, the PD-L1 overexpression in tumors is considered a worsening indicator and poor prognosis item, it is a dysfunctional antitumor immune barrier marker (16). Recent research shows that PD-L1 is able to send signals to the cancer cells directly to make them grow without needing the immune system as an intermediate step (17).

Immunoevasion in cancer: beyond the PD-1/PD-L1 pathway

Although PD-1/PD-L1 pathway is considered one of the essential points of immune checking modulating T cells response, it is not the only one. Although T cells are the main acquired immunity cells involved in tumor surveillance, other collaborators are needed for T cells to be efficient.

In order to recognize the antigenic peptides against which they will react, these peptides must be presented to T cells in advance; as do the antigen-presenting cells [dendritic cells (DCs) and macrophages]. The presented peptides must bind to the major histocompatibility complex molecules (MHC) of the cell surface to be duly recognized by T cell receptors and form the anchorage T cell receptor-peptide-MHC.

Moreover, T cells in order to be properly activated and proliferate they require a process called “co-stimulation”, a number of cascade immune cell activations where antigen presenting cells are also involved (18).

During cancer process, all of these immune agents are somewhat partners of the immunotolerance event carried out by the immunocheckpoint pathway; that is called “immunoedition”. Immunoedition is the ability of the immune system to maintain a dynamic equilibrium over time between malignant cells recognition and destruction, and tumor development. As cancer progresses, the immune system displays a bipolar behavior in their ability to promote or suppress tumor growth. As long as the number of cancer cell divisions are increasing, genetic instability and other aberrant events such as neoangiogenesis are taking place. This phenotype promotes a reduced tumor cell immunogenicity that allows them to escape from detection and elimination by the immune system (19).

It is important to highlight at least 3 events that take place during the immunoedition process. One of them is the suppression by the myeloid-derived suppressor cells (MDSCs). During the time of tumor growing, the innate and adaptative immunity that is supposed to destroy it, may be impeded by the suppressive action of MDSCs.

The MDSCs are a heterogeneous group of immune cells (immature macrophages, granulocytes, DCs) that come from the bone marrow in response to several tumor microenvironment stimuli. Once MDSCs reach the tumor bed, they are able to inhibit the function of local NK and T cells. The so called “tumor-associated macrophages” (TAMs) are also a type of macrophages belonging to MDSCs; they acquire a protumoral phenotype (M2) able to deactivate T cells and stimulate tumor growth, invasion and angiogenesis (20-24).

Another abnormality that may occur in this context is a failure in the antigens presentation system. MHC antigens I and II facilitate the recognition of tumor cells by cytotoxic T lymphocytes and NK cells through presentation of tumor antigens to such immune cells. Eventually, the tumor and immune cells conforming tumor microenvironment, instead of expressing the functional MHC can overexpress human leukocyte antigens (HLAs) and natural killer antigens (NKAs), which cause cytotoxic T cells and NK cells apoptosis and therefore immunosuppression (25).

A Yellow Leader to fight the immunoevasion: Astragalus root

Astragalus membranaceous grows in high areas of China. His Chinese name is Huang qi, which means Yellow Leader. It is popularly known as the "Root of Astragalus" because the part of the plant used is the dried root. Being a member of the Fabaceae family, there are many types of Astragalus. The most common genus is the Astragalus membranaceous variety Mongolicus, sometimes also called Astragalus propinquus (26).

Venerated plant as a tonic in traditional Chinese pharmacopoeia for more than 2,000 years ago, Astragalus radix is known beneficial to relieve multiple disorders: insomnia, anxiety, fatigue, impotence, infertility, allergies, eczema, diarrhea, herpes, colds, even more serious diseases such as diabetes, lupus, heart disease, cancer, etc. For this great restorative capacity was why it won the name of Huang Qi, "leader of all tonics" (27,28). Such ancestral properties have aroused great interest among the scientific community, and in recent decades Astragalus has been a subject of research, positioning it as a plant with promising active principles.

In the field of Integrative Oncology, Chinese medicinal mushrooms have been increasingly promoted as excellent anticancer immunoenhancers (29,30). For this reason, many plants of traditional Chinese medicine are less visible, but—as scientific literature reveals—not less powerful as antitumor immunomodulators (31). Examples such as ginseng root, capable of blocking the immunosuppressive action of MDSCs, or Scutellaria baicalensis, which can reprogram the protumoral (M2) phenotype of TAM macrophages to antitumor (M1) macrophages, are very representative (32-34).

It is not our purpose here to carry out an exhaustive review of the whole promising immunobotanical arsenal in cancer, but quite the opposite. The objective is to make a scope, and to propose a rational model of the combination of CPI with a single plant, in this case Astragalus root, chosen as representative of traditional immunotherapy. From here we suggest the reader to open their mind to consider other possible combinations from this paradigmatic frame, and encourage them to develop novel target-specific combinations with natural immunomodulators to enhance effective therapeutic results without major systemic side effects.

The immunomodulatory activity of Astragalus makes it an excellent plant—not only as an anti-infectious (35)—but as a basis for improving the pathophysiology of degenerative diseases such as diabetes, premature aging and cancer (36,37).

Astragalus root contains a variety of immunoactive constituents, the most studied ones, the polysaccharides. Recently, other Astragalus compounds have been tested such as isoflavonoids, coumarins and especially saponins (astragalosides), and they show good immunoregulatory activity (38-41). The best-known fraction of Astragalus—the polysaccharide one—contains mannose, D-glucose, D-galactose, xylose and L-arabinose. These macromolecules exhibit several pleiotropic effects on the immune system: clearance of the immunocomplexes to facilitate the immunological activity, increase in the number of bone marrow stem cells, stimulation of T lymphocytes transformation, macrophages, DCs, NK cells and B lymphocytes activation, inhibition of CD4 T cells negative immunoregulation, etc. (42-47). At high doses, the polysaccharide fraction seems to enhance the antigen presentation faculty, increasing the class II MHC antigens expression (48,49). Therefore, when Astragalus polysaccharide fraction is co-administered with vaccines it proves to be a potent immunogenic adjuvant (50-53).

Immunoregulatory action of Astragalus in cancer

The power of Astragalus as an antitumor root is not only due to its immunomodulatory activity; it is able to modulate several apoptotic and antiangiogenic signaling pathways and interact with specific transcription molecules (54-59). In clinical setting, a meta-analysis of randomized trials evaluating the benefits of Astragalus based Chinese treatment mixtures combined with chemotherapy for non-small cell lung cancer (NSCLC), showed benefit increasing effectiveness and reducing toxicity of chemotherapy (60).

The main actions of Astragalus antitumor immunomodulator can be summarized in the following (according to the available studies):

- Potentiating therapeutic efficacy of chemotherapy by reducing myelosuppression (36,61);
- Stimulating hematopoietic factors and interleukin (IL) production (62);
- Potentiating anti-tumor activity of recombinant lymphokine-activated killer (LAK) cells by means of tumor necrosis factor (TNF) and cytotoxic cells (with LAK-like activity) production (63,64);
- Enhancing immune defense (65);
- Increase in number of stem cells in bone marrow and

lymphatics (66);
- Stimulating NK cell activity (67);
- Activating proliferation and increase cytokine production of macrophages (68,69);
- Antagonizing the leukopenic effect of immunosuppressants (70);
- Increase in proliferation and antibody production from T and B lymphocytes (71);
- Stimulating DCs maturation by regulating toll-like receptor 4 (TLR4) (72);
- Inducing overexpression of MHC in tumor membranes (73).

Can the Astragalus root influence the expression of PD-1/PD-L1?

Recently, one study found that Astragalus polysaccharide could decrease the expression of both PD-L1 protein and PD-L1 mRNA in melanoma. By regulating PD-1/PD-L1 pathway, Astragalus is able to enhance the antitumor immune activity of T lymphocytes (74). Another study investigated the antitumor effect of a traditional Chinese medicine formula that contains astragalus [Bu-Fei Decoction (BFD)] on NSCLC. BFD interrupted the link between TAMs and cancer cells by inhibiting the expression of IL-10 and PD-L1 *in vitro* and *in vivo*. TAMs and IL-10 promoted the mRNA and protein expression of PD-L1 in NSCLC cells (75).

Three reasons to combine immunotherapy with Astragalus root

First and foremost, to be effective, immune checkpoint (ICP) immunotherapy requires the integrity of much of the rest of the stroma immune system. Different studies have verified that the ICP activity depends on the positive activity of CD8, together with a limited activation of regulatory T cells (TReg) (76,77). This fact seems crucial to predict good response to this treatment (78). As we have seen, some botanicals (79) and more specifically the root of Astragalus can modulate the immune microenvironment to align it in a synergistic action together with the IPC, for the sake of a longer and more lasting response to immunotherapy.

Secondly, cancer patients will need at some point in their illness corticosteroids to modulate any disease related problems such as: brain metastases, cancer pain, vomiting, etc., but above all to control ICP iatrogenic effects. As expected mechanistically, one of the most frequent and limiting side effects of the ICP therapy is the inflammation due to the reactivation of the immune fight in the tumor, and also in other parts of the body. This causes two problems: first, the difficulty in assessing the treatment response (80,81), thus appearing what are called "pseudoprogression" which confuse some when it comes to the decision on whether to continue the treatment or not, and can also cause clinical worsening (82,83); second: the onset of persistent arthritis (84,85) that can become limiting and end up forcing the use of corticosteroid therapy, even at low doses or at intervals. Logically, the use of corticosteroid therapy in these patients is contraindicated, since its immunosuppressive effect could interfere with the response (86,87), but also encourage the growth of the disease itself (88). As we have previously read, the polysaccharides and the other compounds of many of the immunomodulatory plants can offer an excellent balance between their immunoactivating capacity and their inflammation modulator action, becoming an ideal substitute for corticosteroids.

Finally, the use of botanicals as synergists in the conventional treatment of cancer has always been overshadowed by the risk of pharmacokinetic interactions, especially with regard to liver metabolism of both, drugs and plants. This is not the case of ICP molecules, as they suffer intracellular catabolism by lysosomal degradation (89).

Conclusions

The ICP therapies have shown great promise in the treatment of cancer by potentiating the body's natural immune response against tumor cells. For this reason, to maximize treatment efficacy, synergies in immune system modulation must be considered. Cytotoxic T cells, as well as other cell types in tumor microenvironment—such as suppressive Tregs and stimulatory T-helper cells—also affect the efficacy of ICP therapy. Additionally, the role that innate immune system plays in potentiating the anti-tumor immune response seems more important than previously realized.

In the view of these facts, and having seen the impressive effect of Astragalus by modulating the immune system in cancer, we are convinced that by combining these two strategies in immunotherapy—the new one and the old one—we can definitely overcome immune cell exhaustion, boost the response to immunocheckpoint treatment, and minimize side effects, to get better and more efficient results in cancer care.

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Footnote

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References

1. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455-65.
2. Hirano F, Kaneko K, Tamura H, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65:1089-96.
3. Karwacz K, Bricogne C, MacDonald D, et al. PD-L1 co-stimulation contributes to ligand-induced T cell receptor down-modulation on CD8(+) T cells. EMBO Mol Med 2011;3:581-92.
4. Blank C, Kuball J, Voelkl S, et al. Blockade of PD-L1 (B7-H1) augments human tumor-specific T cell responses in vitro. Int J Cancer 2006;119:317-27.
5. Chuk MK, Chang JT, Theoret MR, et al. FDA approval summary: accelerated approval of pembrolizumab for second-line treatment of metastatic melanoma. Clin Cancer Res 2017;23:5666-70.
6. Arasanz H, Lacalle A, Lecumberri MJ, et al. Immunotherapy in malignant melanoma: recent approaches and new perspectives. Melanoma Manag 2017;4:39-48.
7. Cho JH. Immunotherapy for Non-small-cell Lung Cancer: Current Status and Future Obstacles. Immune Netw 2017;17:378-91.
8. Powles T, Necchi A, Rosen G, et al. Anti-Programmed Cell Death 1/Ligand 1 (PD-1/PD-L1) Antibodies for the Treatment of Urothelial Carcinoma: State of the Art and Future Development. Clin Genitourin Cancer 2018;16:117-29.
9. Sathianathen NJ, Krishna S, Anderson JK, et al. The current status of immunobased therapies for metastatic renal-cell carcinoma. Immunotargets Ther 2017;6:83-93.
10. Qi X, Jia B, Zhao X, et al. Advances in T-cell checkpoint immunotherapy for head and neck squamous cell carcinoma. Onco Targets Ther 2017;10:5745-54.
11. Latchman YE, Liang SC, Wu Y, et al. PD-L1-deficient mice show that PD-L1 on T cells, antigen-presenting cells, and host tissues negatively regulates T cells. Proc Natl Acad Sci U S A 2004;101:10691-6.
12. Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.
13. Barber DL, Wherry EJ, Masopust D, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. Nature 2006;439:682-87.
14. Sharpe AH, Wherry EJ, Ahmed R, et al. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. Nat Immunol 2007;8:239-45.
15. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8:793-800.
16. Patel SP, Kurzrock R. PD-L1 Expression as a Predictive Biomarker in Cancer Immunotherapy. Mol Cancer Ther 2015;14:847-56.
17. Escors D, Gato-Cañas M, Zuazo M, et al. The intracellular signalosome of PD-L1 in cancer cells. Signal Transduct Target Ther 2018;3:26.
18. Mary Cavanagh, Science Museum London, UK. Updated by Emily Gwyer Findlay, University of Edinburgh, UK. Systems and Processes. T-cell activation. British Society for Immunology. Available online: https://www.immunology.org/public-information/bitesized-immunology/sistemas-y-procesos/t-cell-activation
19. Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol 2002;3:991-8.
20. Schiavoni G, Gabriele L, Mattei F. The tumor microenvironment: a pitch for multiple players. Front

Oncol 2013;3:90.
21. Talmadge JE, Gabrilovich DI. History of myeloid-derived suppressor cells. Nat Rev Cancer 2013;13:739-52.
22. Ruffell B, Affara NI, Coussens LM. Differential macrophage programming in the tumor microenvironment. Trends Immunol 2012;33:119-26.
23. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell 2010;141:39-51.
24. Solinas G, Germano G, Mantovani A, et al. Tumor-associated macrophages (TAM) as major players of the cancer-related in ammation. J Leukoc Biol 2009;86:1065-73.
25. Campoli M, Ferrone S. Tumor escape mechanisms: potential role of soluble HLA antigens and NK cells activating ligands. Tissue Antigens 2008;72:321-34.
26. Fu J, Wang Z, Huang L, et al. Review of the botanical characteristics, phytochemistry, and pharmacology of Astragalus membranaceus (Huangqi). Phytother Res 2014;28:1275-83.
27. Wagner HB, Xiao PG, Chen JM, et al. Radix Astragali (Huangqi): Chinese Drug Monographs and Analysis Germany. Wald: Verlag, 1997:1-17.
28. Hsu HY. Oriental Materia Medica: A Concise Guide. Long Beach: Oriental Healing Arts Institute, 1986.
29. Rossi P, Difrancia R, Quagliariello V, et al. B-glucans from Grifola frondosa and Ganoderma lucidum in breast cancer: an example of complementary and integrative medicine. Oncotarget 2018;9:24837-56.
30. Patel S, Goyal A. Recent developments in mushrooms as anti-cancer therapeutics: a review. 3 Biotech 2012;2:1-15.
31. Xu J, Song Z, Guo Q, et al. Synergistic Effect and Molecular Mechanisms of Traditional Chinese Medicine on Regulating Tumor Microenvironment and Cancer Cells. Biomed Res Int 2016;2016:1490738.
32. Wang R, Li Y, Wang W, et al. Compound K suppresses myeloid-derived suppressor cells in a mouse model bearing CT26 colorectal cancer xenograft. Nan Fang Yi Ke Da Xue Xue Bao 2015;35:748-52.
33. Tan HY, Wang N, Man K, et al. Autophagy-induced RelB/p52 activation mediates tumour-associated macrophage repolarisation and suppression of hepatocellular carcinoma by natural compound baicalin. Cell Death Dis 2015;6:e1942.
34. Gong SQ, Sun W, Wang M, et al. Role of TLR4 and TCR or BCR against baicalin-induced responses in T and B cells. Int Immunopharmacol 2011;11:2176-80.
35. Sun JL, Hu YL, Wang DY, et al. Immunologic enhancement of compound Chinese herbal medicinal ingredients and their efficacy comparison with compound Chinese herbal medicines. Vaccine 2006;24:2343-8.
36. Chu DT, Wong WL, Mavligit GM. Immunotherapy with Chinese medicinal herbs. II. Reversal of cyclophosphamide-induced immune suppression by administration of fractionated Astragalus membranaceus in vivo. J Clin Lab Immunol 1988;25:125-9.
37. Auyeung KK, Han QB, Ko JK. Astragalus membranaceus: A Review of its Protection Against Inflammation and Gastrointestinal Cancers. Am J Chin Med 2016;44:1-22.
38. Yang ZG, Sun HX, Fang WH. Haemolytic activities and adjuvant effect of Astragalus membranaceus saponins (AMS) on the immune responses to ovalbumin in mice. Vaccine 2005;23:5196-203.
39. Li Y, Hao N, Zou S, et al. Immune Regulation of RAW264.7 Cells In Vitro by Flavonoids from Astragalus complanatus via Activating the NF-κB Signalling Pathway. J Immunol Res 2018;2018:7948068.
40. Upton RSC. Astragalus root: Analytical, quality control, and therapeutic monograph. Scotts Valley: American Herbal Pharmacopoeia, 1999:1-25.
41. Jiao Y, Wen J, Yu X. Influence of flavonoid of Astragalus membranaceus's stem and leaves on the function of cell mediated immunity in mice. Zhongguo Zhong Xi Yi Jie He Za Zhi 1999;19:356-8.
42. Mao XF, Piao XS, Lai CH, et al. Effects of beta-glucan obtained from the Chinese herb Astragalus membranaceus and lipopolysaccharide challenge on performance, immunological, adrenal, and somatotropic responses of weanling pigs. J Anim Sci 2005;83:2775-82.
43. Jiang J, Wu C, Gao H, et al. Effects of astragalus polysaccharides on immunologic function of erythrocyte in chickens infected with infectious bursa disease virus. Vaccine 2010;28:5614-6.
44. Shao P, Zhao LH, Zhi-Chen, et al. Regulation on maturation and function of dendritic cells by Astragalus mongholicus polysaccharides. Int Immunopharmacol 2006;6:1161-6.
45. Liu QY, Yao YM, Yu Y, et al. Astragalus polysaccharides attenuate postburn sepsis via inhibiting negative immunoregulation of CD4+CD25high T cells. PLoS One 2011;6:e19811.
46. Denzler KL, Waters R, Jacobs BL, et al. Regulation of inflammatory gene expression in PBMCs by immunostimulatory botanicals. PLoS One 2010;5:e12561.
47. Qin Q, Niu J, Wang Z, et al. Astragalus embranaceus extract activates immune response in macrophages via heparanase. Molecules 2012;17:7232-40.

48. Kallon S, Li X, Ji J, et al. Astragalus polysaccharide enhances immunity and inhibits H9N2 avian influenza virus in vitro and in vivo. J Anim Sci Biotechnol 2013;4:22.
49. Zhang N, Li X, Cheng G, et al. Effects of astragalus polysaccharide on the immune response to foot-and-mouth disease vaccine in mice. Carbohyd Polym 2010;82:680-6.
50. Hong F, Xiao W, Ragupathi G, et al. The known immunologically active components of Astragalus account for only a small proportion of the immunological adjuvant activity when combined with conjugate vaccines. Planta Med 2011;77:817-24.
51. Ragupathi G, Yeung KS, Leung PC, et al. Evaluation of widely consumed botanicals as immunological adjuvants. Vaccine 2008;26:4860-5.
52. Chen Y, Wang D, Hu Y, et al. Astragalus polysaccharide and oxymatrine can synergistically improve the immune efficacy of Newcastle disease vaccine in chicken. Int J Biol Macromol 2010;46:425-8.
53. Li J, Zhong Y, Li H, et al. Enhancement of Astragalus Polysaccharide on the immune responses in Pigs innoculted with foot-and mouth disease virus vaccine. Int J Biol Macromol 2011;49:362-8.
54. Lin, J, Dong HF, Oppenheim JJ, et al. Effects of astragali radix on the growth of different cancer cell lines. World J Gastroenterol 2003;9:670-3.
55. Lau BH, Ruckle HC, Botolazzo T, et al. Chinese medicinal herbs inhibit growth of murine renal cell carcinoma. Cancer Biother 1994;9:153-61.
56. Cui R, He J, Wang B, et al. Suppressive effect of Astragalus membranaceus Bunge on chemical hepatocarcinogenesis in rats. Cancer Chemother Pharmacol 2003;51:75-80.
57. Auyeung KK, Woo PK, Law PC, et al. Astragalus saponins modulate cell invasiveness and angiogenesis in human gastric adenocarcinoma cells. J Ethnopharmacol 2012;141:635-41.
58. Tin MM, Cho CH, Chan K, et al. Astragalus saponins induce growth inhibition and apoptosis in human colon cancer cells and tumor xenograft. Carcinogenesis 2007;28:1347-55.
59. Wang Y, Auyeung KK, Zhang X, et al. Astragalus saponins modulates colon cancer development by regulating calpain-mediated glucose-regulated protein expression. BMC Complement Altern Med 2014;14:401.
60. Yue Ai, Guo YL, Wang GX, et al. Astragalus-based Chinese traditional medicine combined with chemotherapy for non-small-cell lung cancer treatment: meta-analysis of randomized trials. Int J Clin Exp Med 2016;9:20542-51. Int J Clin Exp Med 2016;9:20542-51.
61. Duan P, Wang ZM. Clinical study on effect of Astragalus in efficacy enhancing and toxicity reducing of chemotherapy in patients of malignant tumor (in Chinese). Chinese Journal of Integrated Traditional and Western Medicine 2002;22:515-7.
62. Yesilada E, Bedir E, Calis I, et al. Effects of triterpene saponins from Astragalus species on in vitro cytokine release. J Ethnopharmacol 2005;96:71-7.
63. Chu DT, Lin JR, Wong W. The in vitro potentiation of LAK cell cytotoxicity in cancer and AIDS patients induced by F3-a fractionated extract of astragalus membranaceus. Zhonghua Zhong Liu Za Zhi 1994;16:167-71.
64. Cho WC, Leung KN. In vitro and in vivo immunomodulating and immunorestorative effects of Astragalus membranaceus. J Ethnopharmacol 2007;113:132-41.
65. Chu DT, Wong WL, Mavligit GM. Immunotherapy with Chinese medicinal herbs. I. Immune restoration of local xenogeneic graft-versus-host reaction in cancer patients by fractionated Astragalus membranaceus in vitro. J Clin Lab Immunol 1988;25:119-23.
66. Sun Y, Hersh EM, Lee SL, et al. Preliminary observations on the effects of the Chinese medicinal herbs Astragalus membranaceus and Ligustrum lucidum on lymphocyte blastogenic responses. J Biol Response Mod 1983;2:227-37.
67. Block KI, Mead MN. Immune System Effects of Echinacea, Ginseng, and Astragalus: A Review. Integr Cancer Ther 2003;2:247-67.
68. McCulloch M, See C, Shu XJ, et al. Astragalus-based Chinese herbs and platinum- based chemotherapy for advanced non-small-cell lung cancer: Meta-analysis of randomized trials. J Clin Oncol 2006;24:419-30.
69. Zee-Cheng RK. Shi-quan-da-bu-tang (ten significant tonic decoction), SQT. A potent Chinese biological response modifier in cancer immunotherapy, potentiation and detoxification of anticancer drugs. Methods Find Exp Clin Pharmacol 1992;14:725-36.
70. Qiua H, Guilin Cheng G, Xu J, et al. Effects of Astragalus Polysaccharides on Associated Immune Cells and Cytokines in Immunosuppressive Dogs. Proc Vaccinol 2010;2:26-33.
71. Wang YP, Li XY, Song CQ, et al. Effect of astragaloside IV on T, B lymphocyte proliferation and peritoneal macrophage function in mice. Acta Pharmacol Sin 2002;23:263-6.
72. Tian Y, Li X, Li H, et al. Astragalus mongholicus regulate the Toll-like-receptor 4 meditated signal transduction of

dendritic cells to restrain stomach cancer cells. Afr J Tradit Complement Altern Med 2014;11:92-6.
73. Li YL, Sun BG, Xiang T, et al. Effect of invigorating spleen and detoxification decoction on MHC I/MHC II in spleen-deficiency liver cancer rats survival. Zhong Yao Cai 2014;37:454-60.
74. Wang JR, Wang JY, Zhang TT, et al. Regulatory Effect of Astragalus Polysacharin on Expression of PD-1/PD-Ls Molecules in Melanoma Mice. Acta Universitatis Traditionis Medicalis Sinensis Pharmacologiaeque Shanghai 2014;28:74-9.
75. Pang L, Han S, Jiao Y, et al. Bu Fei Decoction attenuates the tumor associated macrophage stimulated proliferation, migration, invasion and immunosuppression of non-small cell lung cancer, partially via IL-10 and PD-L1 regulation. Int J Oncol 2017;51:25-38.
76. Diem S, Hasan Ali O, Ackermann CJ, et al. Tumor infiltrating lymphocytes in lymph node metastases of stage III melanoma correspond to response and survival in nine patients treated with ipilimumab at the time of stage IV disease. Cancer Immunol Immunother 2018;67:39-45.
77. Tumeh PC, Harview CL, Yearley JH, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 2014;515:568-71.
78. Tang H, Wang Y, Chlewicki LK, et al. Facilitating T Cell Infiltration in Tumor Microenvironment Overcomes Resistance to PD-L1 Blockade. Cancer Cell 2016;29:285-96.
79. Guo Q, Li J, Lin H. Effect and Molecular Mechanisms of Traditional Chinese Medicine on Regulating Tumor Immunosuppressive Microenvironment. Biomed Res Int 2015;2015:261620.
80. Kataoka Y, Hirano K. Which criteria should we use to evaluate the efficacy of immune-checkpoint inhibitors? Ann Transl Med 2018;6:222.
81. Beer L, Hochmair M, Prosch H. Pitfalls in the radiological response assessment of immunotherapy. Memo 2018;11:138-43.
82. Winer A, Bodor JN, Borghaei H. Identifying and managing the adverse effects of immune checkpoint blockade. J Thorac Dis 2018;10:S480-9.
83. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical. Practice Guideline. J Clin Oncol 2018;36:1714-68.
84. Leipe J, Christ LA, Arnoldi AP, et al. Characteristics and treatment of new-onset arthritis after checkpoint inhibitor therapy. RMD Open 2018;4:e000714.
85. Pundole X, Abdel-Wahab, N, Suarez-Almazor ME. Arthritis risk with immune checkpoint inhibitor therapy for cancer. Curr Opin Rheumatol 2019;31:293-9.
86. Mattern J, Büchler MW, Herr I. Cell Cycle Arrest by Glucocorticoids May Protect Normal Tissue and Solid Tumors from Cancer Therapy. Cancer Biol Ther 2007;6:1345-54.
87. Della Corte CM, Morgillo F. Early use of steroids affects immune cells and impairs immunotherapy efficacy. ESMO Open 2019;4:e000477.
88. Obradović MMS, Hamelin B, Manevski N, et al. Glucocorticoids promote breast cancer metastasis. Nature 2019;567:540-4.
89. Centanni M, Moes DJAR, Trocóniz IF, et al. Clinical Pharmacokinetics and Pharmacodynamics of Immune Checkpoint Inhibitors. Clin Pharmacokinet 2019. [Epub ahead of print].

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