Chapter 3

Acupuncture in Modulation of Immunity

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Additional information is available at the end of the chapter

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1. Introduction

Acupuncture is one of the Traditional Chinese Medicine (TCM) and perhaps most important, by the way the world is widely used as a treatment effective, because it is more structured in terms of legislation, education and research. Until recently it was mostly known for its analgesic effects, and has an large number of research demonstrating the benefits in this area [1,2,3].Within the thinking of acupuncture, each individual should be treated as the disturbance of energy imbalance that presents itself at the time of the session, seeking the well-known syndromic diagnosis [4]. For the same pain can have many points in common from one patient to another, but there are known as energetic characteristics that complement the individualized treatment. Some acupuncture points, but they are consecrated by its clinical efficacy, repeated year after year as part of the arsenal of the specialist training in acupuncture and traditional literature of how these professionals, translated into different languages [4,5,6]. These acupuncture points and / or their combinations and how they are applied has ensured the continuity of its increasing use by the population for this ancient technique that has survived more than 2400 years of recorded history.

Currently, the scientific world investigating acupuncture in the search, especially to understand its mechanisms of action, the "whys" of their therapeutic efficacy, as is the energy system of energy meridians of the nature of acupoints and the brain impressions stimulated by acupuncture [7,8,9]. Another line of research aims to verify the possible use of acupuncture to cure difficult diseases such as: cancer and acquired immunodeficiency syndrome (AIDS) [10,11]. Complaints such as fatigue resulting from the stress are common in acupuncture clinics, and there is research demonstrating such benefits with acupuncture in treatment of fatigue in cancer patients [12]. Many of the gains and benefits referred to as energy acupuncture are based on the classic books, such as points capable of mobilizing the qi (energy) and

xue (blood) [4]. Assuming that acupuncture improves vitality, science wants to know what the neuro-endocrine mechanisms, underlying biochemical [11]. Another line investigates whether these potential benefits can be extended to groups specific so far little exploited in research as gerontes, children and athletes [13].From the perspective of public health efforts are priorities immunologically vulnerable individuals, those most likely to get sick in the face of epidemics such as: children, elderly, pregnant women, immunosuppressed and immunodeficient [14].When comparing those most vulnerable, with the demands of patients in the acupuncture clinics, as well as in the research, notes that there are large numbers of elderly (gerontes), but very little children, pregnant women, immunosuppressed and imunodeficient patients. We believe the demand is low due to cultural issues, such as children and pregnant women afraid of needles. In immunodeficient and immunosuppressed patients there is no guidance of the benefits that acupuncture could provide, and some cultural preconceptions that isolate this resource as the possibility of complementary medicine, especially in the Western.The structure of this chapter, a brief look behind the immunity from the perspective of Traditional Chinese Medicine (TCM), then moving on to a more detailed study the applicability of acupuncture in the modulation of immunity, through a literature review, whose main focus is described in the methodology.

2. The pathogenesis and immunity against the perspective of Traditional Chinese Medicine (TCM)

The Traditional Chinese Medicine (TCM) has its pillars to support in philosophical foundations of Taoism, in a period of human history where there was no technological capabilities of modern diagnostics and treatments to cure of diseases. A need for greater interaction with the nature in the preservation of life, caused the man to develop a greater capacity for observing the natural cycles of climate change, time for crops, for work and home, the search for food, and therefore the preservation of health. As a result of observation and interaction with nature, the man identified prime materials for the cure of diseases and health preservation. Sustained for historical reasons there arose a form of healing spread in a philosophical and symbolic language, which for many today who do not study acupuncture / TCM appears be something still considered "mystical" or alien to Western rational mind. To understand the issue of immunity from the standpoint of TCM, it is necessary to recall some concepts that we will describe.

For TCM, the concept of health is the harmony or balance between yin and yang, or a perfect movement of the energy flow inside the body. Yin and yang are in turn defined as part of complementary and contradictory phenomena of nature and relate to each other [5].

From this reference, was formulated ratings patterns as well as supporting the symptoms syndromic, for example to be classified as ***Yin***; night, cold, weak, pale, chronic pathologic processes, fatigue, and classified as ***Yang*** their opposites; days, heat, strong, hyperemic, sharp,vitality. From the perspective western modern, we can say that there is a possible equivalence of classified the Sympathetic Nervous System (SNS) as *yang* and the Parasympathetic (SNP) as *Yin*.Is

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independent if the language to be Taoist symbolic or modern scientific, the body this whole time looking for this balance.Its is a dynamic process, and continue to sustain life. For the TCM the relationship health *vs* disease or loss of balance between *Yin* and *Yang* is related to the factors of resistance and organic etiological factors. Every day we face the many forms of climate change exposure, emotional imbalance, microorganisms, mechanical trauma, pollution, food with big load of pesticides and / or preservatives, these factors are considered etiological factors.The resistance factors in turn, are called in TCM with defense energy (*wei qi)* and are represented by the skin, mucous membranes, hair, controlling the opening and closing the pores and the sphincters of the body. An example that can illustrate when the body is affected by climate change like the wind-chill, it makes the hair stand on end in a shiver of cold, forming a protective voluminous layer and sequentially the pores are closed. In this state of trial protection as cited in this example, the body would result in the closing of the pores to retain the internal heat, which continued for more time will become pathological. This inbalance is expressed by some physiologic indicators of syndromic diagnosis of TCM.

Another example are some cases of urinary incontinence in the elderly, where the deficiency of *Yang* energy, represented by the weakness pelvic floor muscles, predisposes to not control the sphincters.

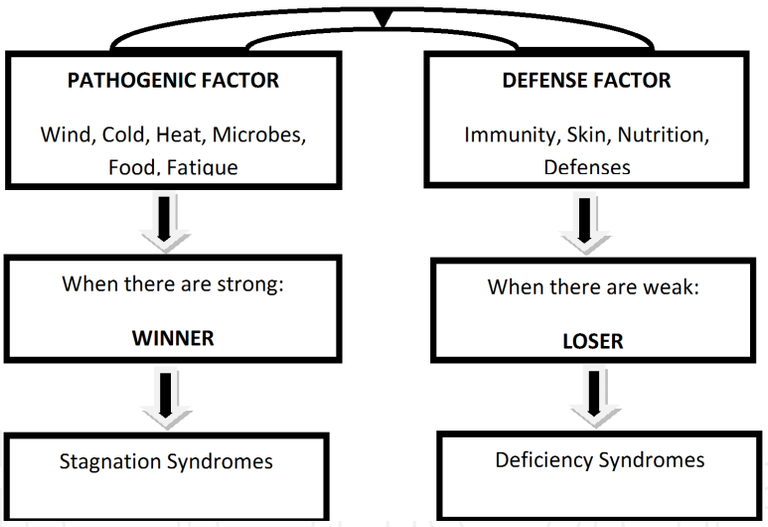

Figure 1. Pathogenic Factors *vs* Defense Factors

In this Figure 1 is showing two situations where the disease is established, because the defense factors are weak, or because the pathogenic factors are very strong, as occurs in viral epidemics where there is often an apparently healthy

Individual' immune profile might get sick. It is necessary to remember that when the TCM was formulated more than 2400 years ago, we had no knowledge of physiology, anatomy, biochemistry, and so little understanding of the immunology currently available for modern science. Is understandable within the context of the time theories were based on possibilities resources and understanding of man's relationship with the natural phenomena.

3. Applicability of acupuncture in the modulation of immunity: A literature review

3.1. Initial considerations and objectives

It is consistent the applicability of acupuncture in various phatological conditions.The modern science research resources to enhance health and quality of life. We understand that all possibilities to become viable are welcome. Although there are benefits of acupuncture modulation of immunity, there are gaps of knowledge,such as the best treatment techniques, which would be the best biochemical markers, which are the best acupoints.There is much information about research in this area, but they are highly dispersed, which causes difficulties in the conclusions, and thus clinical applicability.

The aim therefore of this review is to compile and discuss the scientific literature regarding the efficacy of acupuncture in modulation immunity.

3.2. Methodology

As from the selected article was organized some data that can help to support future work or point out gaps in knowledge,regarding the applicability of acupuncture in the modulation to immunity, choice of biochemical markers and immunomodulators acupuncture points.The use of systematic reviews as a means of research methodology, has increased,and has been shows to be of great contribuition and impacto internationally l [15]. To organize this chapter were considered scientific papers from journals, scientific repositories, MEDLINE, PUBMED, bibliography of articles on manual search, the Cochrane Library. The keywords "acupuncture and/or electroacupuncture in treatment of :"cancer", "immunossupressed"," immunodeficiency","allergic process","inflammation process","AIDS" and "modulation to immunity with acupuncture and/or electroacupuncture ".The reference lists of studies retrieved were examined to capture any other potentially relevant articles.

The inclusion criteria were:

a. Publication between january 2001 to december 2011.(The period was limited intentionally, because they understand that there was growing improvement in the methodology of scientific research, as well as growing interest in the field of acupuncture).

b. Clinical interventions and / or case studies, contain a description of immunological and biochemical markers, as well as the acupuncture points.

c. Experimental studies in human and / or animal,contain a description of immunological and biochemical markers, as well as the acupuncture points.

d. Reviews of clinical effectiveness of acupuncture, involving the key words.

e. Study of mechanisms of action of acupuncture modulation of immunity.

Studies were excluded if they:

a. Used mixed intervention whith other therapeutic techniques besides acupuncture and electroacupuncture, such as medication, surgery, physiotherapy.

b. Used mixed intervention whith other techniques of Traditional Chinese Medicine such as: moxibustion, herbal medicine,hot needles, auriculotherapy,bleeding and cupping.

From the variables studied aimed to answer the following questions:

a. Acupuncture is effective to strengthen the immunity?

b. What are the diseases or conditions are more studied?

c. What are the most appropriate markers to study the immunomodulatory effects of acupuncture?What are the most appropriate acupuncture points and designated for immunity?

d. What are the acupuncture techniques most frequently used in research on modulation of immunity ?

3.3. Results

The initial search identified 79 studies the databases. After reading these articles should were select and evaluated 67 relevant papers(Table 1 and 2). Table 1 shows the experimental and clinical studies with acupuncture,by humans and animals.In the Table 2 only the studies for style of a systematic review and / or models involving mechanisms of action of the immunity response to acupuncture. The summary of the data, were ordered by publication date, plus their respective authors, type of population, acupuncture technique, acupuncture points used and the main results or conclusions of the studies. From these structured to Figures 2 and 3 where only the most relevant results and those that are repeated in different papers, were considered. Tables 3 to 7 are summarized also derived from the contents carried compiled.

It can be seen by looking at Figure 2, the acupuncture point more tested in experimental studies in rats and humans was St 36 (Zusanli), together making a total of 39 articles (73.5%) of articles mentioning acupuncture points tested, and with animals, especially rats(14papers) and humans(25papers).As related to the point ST36 with the population profiles found in animals, 48% with inflammation [16,18,23,26,30,39,41,46,48,54,59], 26% of post-surgical, trauma or stress induced by cold [21,31,34,38,56,57]), 13% with cancer [48,50,58], 9% with allergic processes [42,52] and only 4% of healthy individuals [35].However in humans, there were no highlights for either disease as an object of study, and found the use of St 36 in inflammation [63], cancer [47], allergic rhinitis [17,27,29], elderdy [19,65] and athletes [24], healthy [40],depression [64] In humans, the equivalence point with ST36 (Zusanli) appears LI4 (Hegu), with 14 and 12 papers respectively, and in 8 of these items, the points LI 4, and St36 are used simultaneously. In animals there was only one papers used LI 4 acupuncture point, separately, being expressed clearly in Figure 2.

AUTHOR	YEAR	POPULATION	TECHNIQUE	POINTS	RESULTS/CONCLUSION
LI, YN.et al [16]	2001	rats inflammation	EA	ST36	↓ IL2, TNFα,IL6
PETTI, FB.et al [17]	2002	human allergic rhinitis	ACP	ST36 ,LI4	↓IL 10 ↑IL2 IL6 did not change
TIAN, L.et al [18]	2002	rats ulcerative colitis	EA	ST36	↓ TNFα
KARST, M.et al [19]	2002	human elderly	ACP	ST36,LI4,SP6	Neutrophil and respiratory burst did not change
MORI, H. et al [20]	2002	human healthy	EA	LI4, LU6	↓ Heart rate, stimulates SNP and suppresses SNS, modulates immunity, normalization of lymphocytes and granulocytes.
CHOI, GS. et al [21]	2002	rats hypothalamic lesion	EA	ST36	↑NK cells
KARST, M.et al [22]	2003	human healthy	ACP	LI11	↑ TNFα
TIAN, L. et al [23]	2003	rats ulcerative colitis	EA	ST36	↓ IL6,IL8, TNFα
AKIMOTO, T.et al [24]	2003	human athlets	ACP	ST36, LI4, ST6, LU6	↑ IgA salivary ↓ salivary cortisol
YU, P.et al [25]	2003	human Behcet's disease	ACP	No cites	↓ IgM, Zn, and recurrence rate
PARK, MB.et al [26]	2004	mice inflammation	EA	ST36	↓ IgE,IL4,IL13,inflammation INFg did not change
NG, DK .et al [27]	2004	human allergic rhinitis	ACP	ST36, yintang, shanyingxiang	IL6, eosinophils did not change. improvements in allergic symtoms
JOHANSEN, M.et al [28]	2004	human healthy	ACP	LI4	↑ IL2, IFNg
MAGNUSSON,AL.et al [29]	2004	human allergic rhinitis	ACP	LI4,LI20,ST36,L R3,LU7, yintang	↓ IgE Allergic symptoms did not change
SCOGNAMILLO-SZABO, MRV.et al [30]	2004	rats inflammation	ACP	ST36,DU1	↓ Peritoneal neutrophils and bacterias.
HAHM, ET .et al [31]	2004	rats hypothalamic lesion	EA	ST36	↑NK cells EA restores the suppression of NK cells in hypothalamic lesion
SCOGNAMILLO-SZABO, MRV.et al [32]	2005A	Rats peritoneal inflammation	ACP	DU20, yintang, KI7	↓ IL1b TNFα,IL10 did not change. Antiinflammatory effects of ACP does not involve steroids.
SCOGNAMILLO-SZABO, MRV.et al [33]	2005 B	rats peritoneal inflammation	ACP	K7, yintang DU20	↓ neutrophils, inflammation
WANG, J.et al [34]	2005	rats post-surgery	EA	ST36, lan wei	↓ Lymphocyte apoptosis by inhibiting FAS protein andimmune depletion after surgery
KIM, CK .et al [35]	2005	rats healthy	EA	ST36	↑ NKcells
KOU, W.et al [36]	2005	human healthy	ACP	ST36, LI11, SP10, DU14	↓ CD3 CD8 CD4 ↓ Leukocytes and lymphocytes.

AUTHOR	YEAR	POPULATION	TECHNIQUE	POINTS	RESULTS/CONCLUSION
					Did not change cortisol and norepinephrine
ZANG, RX.et al [37]	2005	rats inflammation	EA	GB30	↓ edema, inflammation↑ corticosterone
SHEN, GM.et al [38]	2006	rats cold stress	EA	ST36	↓ Gastric motility and nitric oxide.
HUANG, CL.et al [39]	2006	rats inflammation (lung)	ACP	ST36	↓ inflammatory injury ↓ nitric oxide and nitric oxide synthase
YAMAGUCHI, N.et al [40]	2007	human healthy	ACP	ST36, BL18, BL20, BL23	↑ CD2 CD4 CD8 CD11B CD16 CD19 e CD56 by exhaustion; activates macrophages
YIM, YK.et al [41]	2007	rats inflammation arthritis	EA	ST36	↓ IL6, TNF, INFy
LEE, Y.et al [42]	2007	allergic mice	EA	ST36	↓ IL4 anti CD3 and IgE block the allergic process
ARRANZ, L.et al [43]	2007	human anxious	ACP	LI4, ST36,SP6, GB34,GB43, LI11, PC6, SI3,RN3,RN4,RN6, RN15, HT5, HT3, SJ5	Modulates the immune system to anxiety. ↑ phagocytosis, NK cells, lymphocytes; ↓ Reactive oxygen species (ROS)↓ anxiety
LU, W . et al [44]	2007	human after chemotherapy	ACP	No cites	↑ leukocytes in leukopenic post chemotherapy (average of 1221 cells / ul)
LI , YM. et al [45]	2007	human allergic rhinitis	EA	LI20, yintang, shanyingxiang	↓VIP, substance P
HUANG, CL.et al [46]	2007	rats inflammation (kidney/liver)	ACP	ST36	-**ACP before treatment**: ↓ injury by inflammation (kidney) ↑ Nitric oxide renal and NO synthase,but did not occur in liver injury. - **ACP post injury**: the inflammatory process is not contained in liver and kidney.
YE, F .et al [47]	2007	human after chemotherapy	EA	ST36,SP6,PC6	↓ Depletion of chemotherapy did not change:IgG,IgM,IgA,CD3, CD4,CD8,NK cells, leukocytes
MAO, HJ.et al [48]	2008	rabbits leukopenia+ inflammation	EA	ST36, BL17 DU 14	↓ leukocyte inflammatory process ↑ leukocytes in leukopenia.
ZHANG, LJ.et al [49]	2008	human mammary hyperplasia	EA e ACP	BL23, DU4, DU16, KI24, KI22,LR14	↑CD4 ,CD8
LAI, M. et al [50]	2008	rats /cancer	EA	ST36,LR4,SP6	↑ IgA,IgG,IgM,CD4 ↓CD8
YAN, J.et al [51]	2009	rats	EA	ST37	↑IL4

AUTHOR	YEAR	POPULATION	TECHNIQUE	POINTS	RESULTS/CONCLUSION
		ulcerative colitis			↓IL1b
KIM, SK.et al [52]	2009	mice/allergy	EA	ST36	↓ IL4 e IgE Effects independent of frequency
GAO, H. et al [53]	2009	human allergy	ACP	DU11	↓ IgE, did not change symptoms
FERREIRA, AS.et al [54]	2009	rats inflammation (lung)	ACP	ST36	↓ Inflammatory process (neutrophils, lymphocytes, total leukocytes, monocytes). Acupuncture was prophylactic.
LU, W.et al [55]	2009	human after chemotherapy	EA	ST36,LI4, LI11, SP6, LR3, DU20, SP10,LU6,KI3	CSFg did not change ↑ leukocytes, softened effects chemotherapy
WANG, J .et al [56]	2009	rats surgical injury	EA	ST36	Inhibits inflammatory cytokines↓ inflammation
WANG, K.et al [57]	2009	rats surgical injury	EA	ST36 ,*lanwei*	↑IL2,INFα
LEE, HJ.et al [58]	2009	rats cancer	EA	ST36	↑ 51.46% more β endorphin in blood and 12.6% in the brain compared to the untreated group.↓ Substance P
SENA-FERNANDES, V.et al [59]	2010	rats inflammation	ACP	ST36,SP6	ST36 is better than anti-inflammatory SP6 for gastrointestinal disorders.
MATSUBARA, Y.et al [60]	2010	human sedentary	EA	ST36, LI4, LU6, ST6	Acupuncture attenuates the decrease in salivary IgA caused by physical exhaustion.
KARST,M.et al [61]	2010	human healthy	ACP	LI11	↑ IL8 TNFα,IL 10 and endorphin did not alter
HAN, YF. et al [62]	2010	human leukopenic	ACP	SJ6,IG4,IG11	↑ CSF_g , ↑ maturation of neutrophils
OUYANG, BS.et al [63]	2010	human rheumatoid arthritis	ACP, EA	ST36,LI11,SJ5G B20,RM4, DU20	↓ IL1, IL4, IL6,IL10,
SUN, H. et al [64]	2010	human depressive	EA	ST36,DU20	↓ IL1, IL6 TNFα not changed
PAVAO, TS.et al [65]	2010	human elderly	ACP	LI4,ST36,SP6	↑ lymphocytes T
SILVA, MD.et al [66]	2010	rats peritoneal inflammation	ACP	SP6	↑ IL10 and ↓ adrenal stimulation by inflammation; not changed TNF α e IL1b
YUAN, SY.et al [67]	2011	human prostatites	EA	RM3,ST29, SP9,SP6,RM4,ST 28,SP10, LR3	↓ IL10,IL8,TNFα

ACP= acupuncture

EA=electroacupuncture

Table 1. Experimental and clinical studies on acupuncture modulation of immunity

AUTHOR	YEAR	APPROACH	TECHNIQUE	POINTS	CONCLUSION
ZIJLSTRA, FJ.et al [68]	2003	immunophysiological (inflammation)	ACP	No cites	ACP has pro-inflammatory effects with ↓ TNF, and anti-inflammatory with ↑ IL10
CHEN, JX et al [69]	2006	neuroimmunological	ACP	Meridians and acupoints	In the acupuncture point and meridians is increased norepinephrine, and modulation of L-arginine-derived nitric oxide by the SNS (sympathetic nervous system)
CHO, ZH. et al [70]	2006	neurophysiological and neuroimaging	ACP/EA	No cites	Acupuncture acts in neurophysiology and molecular basis, and its effects can be evaluated mechanisms also by functional magnetic resonance (fRMI) and tomography
MA, XM.et al [71]	2007	immunohistochemical of the meridians and acupuncture points	ACP	Meridians: Pericardium and Bladder	The nitric oxide is at high levels in the skin surface in the acupoints and meridians and no nitrate is reduced by skin bacteria.
KAVOUSSI, B; ROSS, BE. [72]	2007	immunophysiological (inflammation)	ACP	E36 mechanisms of action	↓TNFα,IL6,IL18,IL1b,macrophages.
CABIOGLU, MT ; CETIN, BE [73]	2008	neurophysiological	EA e ACP	No cites	ACP EA and modulate the immune system, for local , neuronal and neurohumoral expression.
PENG, G [74]	2008	neurophysiological	ACP	No cites	ACP makes immunomodulation by complex mechanisms of the HPA axis and cholinergic anti inflammatory pathways.
ROBERTS, J et al [75]	2008	allergic rhinits/clinical efficacy	ACP	No cites	There is no sufficient evidence that the ACP is effective..
BRINKHAU, SB .et al [76]	2008	allergic rhinits/clinical efficacy	ACP	No cites	ACP has clinical efficacy
LEE, MS et al [77]	2009	allergic rhinits/clinical efficacy	ACP	No cites	ACP has clinical efficacyFuture studies require inclusion of groups shan, controls, and larger samples
TAKAHASHI,T.et al [78]	2009	immunophysiological	EA e ACP	No cites	- ACP modulation function and number of neutrophils; ↓ Apoptosis after injury and FAS protein; - EA ↓ norepinephrine corticosterone B endorphin and ACTH in stress

AUTHOR	YEAR	APPROACH	TECHNIQUE	POINTS	CONCLUSION
HE,TF et al [79]	2011	rheumatoid arthritis	EA	ST36,GB39,V23	↓ edema, ↑ VIP (vasoactive intestinal peptide)
JOHNSTON,MF.et al [11]	2011	human and rats cancer	ACP	Mecanisms of ACP in the prevention of cancer	It increases the cytotoxic activity of NK cells by cross effect between neurotransmitters and the immune system (nitric oxide, endorphins, cytokines).
MANNI, I .et al [80]	2011	neuroimmunological	EA	No cites	There is a biochemical synergism between EA and neurotrofina NGF, which explains immunologic improvement.

ACP= acupuncture

EA=electroacupuncture

Table 2. Papers with mechanism of action models of acupuncture in immunomodulation and reviews.

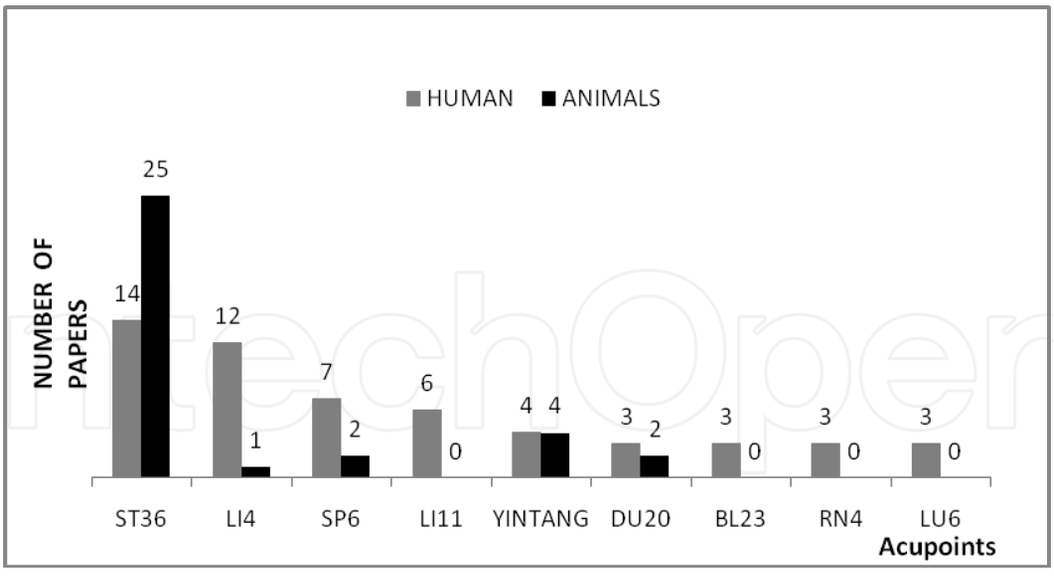

Figure 2. Main immunomodulators acupuncture points cited on the papers.

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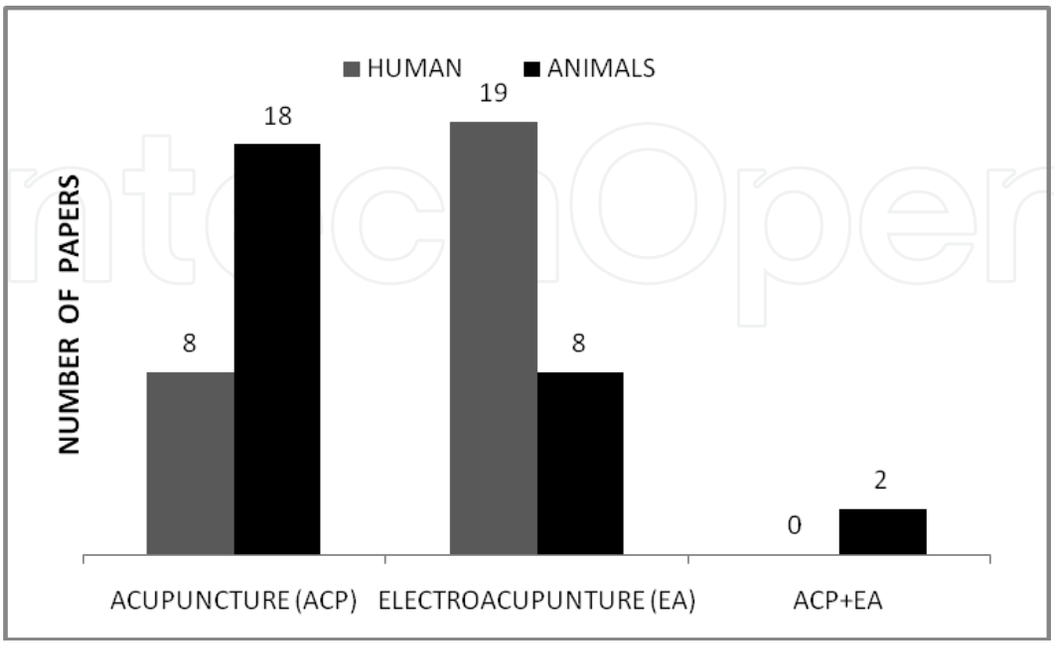

Figure 3. Number of papers *vs* techniques

In view of the purposes stated in the methodology of this review, prepared to Figure 3, which shows the distribution of numbers of papers regarding the use of the techniques of acupuncture (ACP) and electroacupuncture (EA) or both simultaneously (ACP + EA). Of the 56 papers that reported the technique used, 26 papers used ACP, 27 EA and 2 used both techniques (ACP + EA).

Elaborated the tables 3 to 7 on the basis of immunological and biochemical markers found in the papers of this study.

markers	IL1β	IL2	IL 4	IL 6	IL 8	IL 10	IL 18	Total
increase	---	3	1	---	3	2	---	9
decrease	5	1	4	5	1	3	1	20
no change	1	---	---	2	---	2	---	5

Table 3. Number of papers that used Interleukins (IL) *vs* effects of acupuncture or electroacupuncture.

Table 3 shows the number of papers mentioning the Interleukins (IL) and immunological markers in studies with acupuncture or electroacupuncture. If we add all papers, where after acupuncture decreased the Interleukins, make up 58% versus 27%, which increased and 15% that have not changed.

markers	CD 2	CD 3	CD 4	CD 8	CD11B	CD 16	CD 19	CD 56
increase	1	2	4	5	3	1	1	1
decrease	---	2	2	2	1	---	---	---
no change	---	---	---	---	---	---	---	---

Table 4. Number of papers that used markers CD vs effects of acupuncture or electroacupuncture.

Table 4 expressed a distribution of the papers mentioning the immunological markers of type CD. It is felt that there was a higher concentration in the selection of CD4 and CD8 markers. Important to note that the use of CD11b, CD16, CD19 and CD59, it is one and the same article [40]. There is a distribution of 72% of the papers where there were increases in CD, compared with 28% reduction and no article with "no change" after the intervention with acupuncture or electroacupuncture.

markers	Leukocytes	Eosinophils	Lymphocytes	Moncytes	Neutrophils
increase	3	---	2	---	2
decrease	3	---	2	1	2
no change	1	1	---	---	1

Table 5. Number of papers used for Blood cells *vs* effects of acupuncture or electroacupuncture.

In the Table 5 were grouped the blood cells, relating them to their results after the intervention of acupuncture or electroacupuncture. Were the most representative use of total leukocytes, primarily found in 38% of the papers, followed by, lymphocytes and neutrophils, with 26% each, and eosinophils, monocytes with 5% each.

markers	increase	decrease	no change
Ig A	3	---	1
Ig E	---	4	---
Ig M	---	1	---
IFNg/y	2	1	1
CSFg	---	2	---
TNFα	1	7	3
NK cells	5	--	---
endorphins	---	13	---

Table 6. Immune-biochemicals markers after the intervention; effects of acupuncture or electroacupuncture.

In the Table 6,are grouped the markers that were present in at least three or more papers. Were excluded from the markers that were cited in the minority (IgG, cortisol, CGFS, lymphocyte apoptosis, VIP (vasoactive intestinal peptide), substance P, reactive oxygen species (ROS), nitric oxide and macrophages).

characteristics	increase	decrease	no change
inflammation	-	8	1
symptoms	-	13	2

Table 7. Distribution of the presence of terms of service and Symptoms Inflammation X after the intervention effects with acupuncture and electroacupuncture.

To end the presentation of results was elaborated in Table 7 that grouped the papers about some terms that, although generic, were explicit in the results and / or completion of the articles studied. Since the terms chosen: **inflammation** and **clinical symptoms**. Of the articles that included in their conclusions applicability of techniques for ACP and EA the terms inflammation, in the 88% of the papers cited have demostrated decrease, and only 11,2% cited,no change in the inflamatory process.No papers cited the occurrence of increased inflamatory process.When refers to symptoms have been reported in articles 15, and these 86,6% it is stated that reduction of pathological symptoms studied, and there were no changes 13,3%. No papers mentioned that the pathological symptoms increased. Among the symptoms referred to in these papers are specific: present in respiratory allergy rhinitis, edema, depression, physical exhaustion, adverse effects of chemotherapy and anxiety.

3.4. Discussion

3.4.1. As for immunomodulation effects and clinical efficacy

The ACP and EA its shares in neurophysiology and molecular basis [70]·Its effects and mechanism of action can be evaluated by magnetic resonance imaging and computed tomography [70]. Ma [71] following another line of study, demonstrated the immunohistological nature of the meridians and acupoints, where he verified that there is high concentration of nitric oxide. The immunomodulatory effects of ACP and EA are confirmed by studies with diverse biochemical markers described in Table 1.

They are among the principal effects immunomodulatory:

a. Decrease of celular apoptopsis

b. Increase cytotoxic activity

c. Synergism biochemical between the EA and neurotrophyn(NGF)

d. Mobilization of corticosterone,endorphine and ACTH.

e. Pro-inflamatory and antinflamatory effects.

We observed that acupuncture has clinical efficacy in some situations, as in allergic processes, and in pain [1,2,3]. In other stages as inflammation can reduce or block the inflammatory process, but will depend on the stage he is and also the origin of this process. Recall for example in case of tendonitis, that acupuncture can reduce pain, edema, hyperemia, provide gain range of motion.However the origin of tendinitis is caused by repetitive strain, compression of nerve roots, weakness or muscle shortening, which in these cases need conventional physiotherapy intervention, exercise, manipulation, and / or resting muscle.Finally we have a group of pathogenic conditions where acupuncture may improve symptoms and quality of life, but the effect is still very poor immunological results and research in the area are being made, as in the case of degenerative processes, immunodeficient [10] and immunosuppressed patients [60]. In patients or cancer models, as well as elderly, where usually has low of immunity defenses, the acupuncture and electroacupuncture demonstrated in this study that increases the immunity, being a possibility of complementary therapeutic resource.In the acute or cronic inflammation and allergic processes ACP and/or EA demonstrated modulate the immune response, decreasing the hyperresponsiveness of the markers pro – inflammatory [48].

3.4.2. As for the immunologic markers

3.4.2.1. Interleukins (IL)

Interleukins (IL) constitute a class of cytokines, and soluble proteins that act as humoral regulators at nano or picomolar concentration by modulating the functional activities of cells and tissues through specific receptors of target cells [81]. In this study, we included studies of acupuncture in humans and animals, whereas several groups with different immune deficits, such as those with cancer, allergies, physical exhaustion, inflammation, and studies with healthy groups. In general there were more studies demonstrating that after acupuncture decreases interleukins, with 58% of research, compiled and summarized in Table 4. Were 27% that increased and 15% of the research there were no changes. It is understood that specificity is in the release of each group of interleukins. Some authors demonstrate that IL-6 [82] and IL10 [83] may increase after intense physical exhaustion, simulating an "inflammatory reaction" while IL8 increase but at a later continuous process of exhaustion [83]. In this review, it was shown that IL6 interleukin decreased after acupuncture in 5 of 7 of the articles has been markers, slowing a reduced immunological response. The interleukin appeared in two papers which show increase [66,68], where tree have decrease [17,63,67] and two no change [32,61], the results so far divided.Tian et al [18] in a research with EA says it is still unknown whether electroacupuncture can keep the balance between the anti-inflammatory and pro-inflamatory cytokines.He further states that the specific mechanisms of regulation of IL4, IL10 and IL13, when acupuncture have decreased these pro-inflammatory cytokines not been totally elucidated. Perhaps this explanation justifies the inconclusive results of the use of IL10 in our review.

3.4.2.2. Blood cells

a. Total leukocyte and interleukins acute stage

As for total leukocytes, as shown in Table 6, there was a decrease in 43% of research [36,48,54].Had increased by 43% [44,48,55] and in 14% of papers no change [47].Is remarkable to note that the papers that report that acupuncture increased the total leukocytes, are all with a population of leukopenic patients after chemotherapy, and in papers that report decreased after acupuncture are affected population inflammatory process. This data, demonstrate that acupuncture can both increase or decrease the inflammatory response, corroborating with Zijlstra [68], whose author claims that acupuncture has immunomodulatory effect. According to Silva [84],the leukocytes produce IL-1 and IL-6 among the main defense markers in acute inflammatory response. Looking at Table 4 the papers that were used as a marker of immune IL1, 86% after acupuncture had a decrease [32,51,63,64,72], and 14% no change [66]. The IL-1 has a similar function to the tumor necrosis factor (TNF), which is to mediate the innate immune response in especially inflammatory type.The main cellular source of IL-1 second as report by Abbas [85] are th'activated mononuclear phagocytes.

In the specific case of IL6, 75% of the papers that used this marker, decreased after acupuncture [23,41,63,64,72] against 25% no change [17,27]. It is noteworthy that all the items where IL1 and IL6 are decreased refer by population studies with inflammatory processes. This fact therefore confirms the literature and demonstrates that acupuncture can be an resource to inhibit the firing of immune responses to acute inflammatory origin. The mechanism for this increase suggests, is associated with the fact that IL-6 produced by fibroblasts and mononuclear phagocytes in response to IL-1 stimulates the hepatocytes to synthesize acute phase proteins, which act on the hypothalamus. Cooper [86] in his studies, concluded that the mechanism of action by which acupuncture makes its immunomodulatory effects are associated with stimulation of the hypothalamic-pituitary-adrenal axis, showing links between the endocrine,nervous and immune systems.

Enhancing the action of acupuncture and electroacupuncture in immunomodulation of the acute process was found 64% reduction in the articles that have been used as a marker of TNF [16,18,23,41,67,68,72],compared with 27% of the articles without change [61,64,66], and only 10% with an increase [22]. The studies in oncology are of unquestionable importance. Leukopenia is a constant in cancer patients submitted to chemotherapy.In the research compiled here, showed that the ACP and EA can modulate in a positive way by increasing leukocytes [44,48,55]. Lu, W.et al [44] came to the conclusion in a study involving humans with EA after chemotherapy there was an average increase of 1221 white cells / ul. These data are encouraging, especially if added to increase the cytotoxic activity of NK cells, as reported by other authors [11,21,31,35,43].

b. Lymphocyte

As for lymphocytes, no conclusive interpretation in the literature, for some authors, such as Lu et al [55] and Pavão et al [65], that acupuncture said increases lymphocytes, while others such as Kou et al [36] and Ferreira et al [54] found a decrease in their research.

This apparent contradiction of results must be interpreted in light of the the therapeutic objectives that acupuncture provides to different pathological conditions. Evaluating the articles can see that those among populations where there was an increase of lymphocytes, are patients with cancer and inflammatory processes. In these cases, therefore it is desirable that there is an increase in defenses

Furthermore, papers which show after acupuncture lymphocytes decreased were evaluated in a population with predominantly inflammatory process, therefore also a desirable result. It is concluded therefore that acupuncture has an immunomodulatory effect, can raise or lower the lymphocytes, depending on immuno-pathogenic requirements. In cellular immunity, T cells CD4+, activates macrophages to destroy phagocytosed microorganisms while CD8+ T lymphocyte,kill infected cells whiyh intracellular microbes [85]. The Complement System, consisting of serum glycoproteins and cell membrane, which along with the antibodies form the main mediators of the humoral immune response in the inflammatory process [85].The compiled studies show that acupuncture helps in stimulating this pathway of immune response, with 72% who used the results of immunochemical markers CD system, pointing to an increased presence of complement, after the intervention [40,49]. All research were performed in humans with cancer and also healthy, submitted to physical exhaustion, pointing to possibilities of acupuncture not only strengthen the immune process, but also be preventive. As for the markers of the complement system there was no consensus on what would be the most suitable. Of the five papers in the literature, the data were repeated if more CD4 + and CD8 + T cells.

The lymphocytes T, still produce CD3,IL2,IL4,IL5,IL6,IL8,IL10,IL13 and IFNy. With this comprehension is justifiable the increase demonstrated in the distribution illustrated in the Table 4. The papers, where CD3, CD4 and CD8 presented decrease after the acupuncture [36,54], were singularly at the same population profiles where there were lymphocytes decrease (stress,inflammation). Agrees, therefore desirable this decrease, like form of blocking the of the inflammatory process.

3.4.2.3. Immunoglobulins (Ig)

The immunoglobulins or antibodies represent a glycoproteins family related structurally, produced by the lymphocytes B, linked or secreted by cellular membrane [85].Among immunoglobulins, find IgA present in great quantity in mucosal. Akimoto [24]and Gleesen [87] show that IgA salivate decreases in exercises exhausting case, as well as the population of total lymphocytes predisposing especially athletes population the diseases of the respiratory treatment. The results expressed in the Table 6, they demonstrate that the acupuncture can increase IgA indices after exhaustion as in physical depletion cancer processes [24,50,60], signalling for acupuncture possible benefits in immunomodalation. Other immunoglobulin related in the papers was Ig E. According Abbas. [85], individuals with allergic process is found high levels of immunoglobulin IgE, in response to environment allergens, in the same way that IL4. In 100% of the papers that used IgE as markers, the results found after the acupuncture went of reduction in the serum levels [26,29,52,53].In the same way found a coherence in the citations of other authors, white respect to decrease to IL4 after the acupuncture

[26,42,52,63]. Such fact corroborates with a tendency for consensus that the acupuncture effect is immunomodulators in the allergic processes, being. Therefore IgE and IL4 are the best markers for researches and clinical support.

3.4.2.4. Markers of adaptive immune response

According to Abbas [85] the immunity immunity also known as it specifies is mediated by the lymphocytes and stimulated by infectious agents. It characterizes by the rare specificity of the distinct macromolecules and memory. They make her part the liberation of comprises the following cytokines: TNFα, IFNy or gamme (g) that then it stimulates the interleukin proliferation IL2.The production of interferon IFNy (in animals) and IFNg (in humans) is produced starting from NK cells activated and lymphocytes T(effectors). Is consistent data that demostrate the correlation among the increases of NK cells and IFNy/g. The studies that were used of interferon IFNy/g with marker, there were 50% of the papers with increase [28,57], 25% with reduction [41] and 25% no change [26]after the acupuncture or eletroacupuncture. As for IL2 also followed the same line of results, with increase serum levels predominance with 75% of the papers that were used of this marker relating increase [17,28,57] and 25% decrease [15].

Although NK cells are part of the innate immune response, and not the adaptive response, this class of lymphocytes trigger the release of the adaptive response through the production of interferon (IFN). In our studies was verified in the Table 7 that in 100% of these papers,were used of the NKcells as markers, there was increase after acupuncture and electroacupuncure [11,21,31,35,43]. There were no papers that are used as a marker of NK cells expressed reduction. Therefore the result obtained in studies of NK cells are consistent to those found with IFN, demonstrating that the ACP and EA immunomodulators.

3.5. As for the acupuncture points

The acupuncture point is specified location along the route known as meridians. Although known by physicians for thousands of years, acupuncture points or acupoints as they are known, attracted a few decades ago the condition of being surveyed with modern resouces. Chen et al [69] showed that the acupuncture points and meridians is increased norepinephrine, and modulation of arginine,derived nitric oxide by the sympathetic nervous system (SNS). Ma et al [71] also found high concentrations of nitric oxide, and these did not suffer reduced to nitrate by bacteria in skin. The acupoint ST 36 has its original name as *Zusanli*, in chinese *ZU* means foot, and three *SAN LI* distance, translated as the point that "tones the body to walk long distances" [6]. It is a point used in clinical routine as a useful point to treat fatigue and low immunity, and analgesics, which goes against the findings in the studied articles, where the results shows that the ST36 is the most researched, both in humans and in animals.and is its present in 73.5% of the papers. We believe that this effect occurs because of the ease and stability in the anatomical containment and retention in rats when compared with other points, and because there is an established animal model in this location [52].The LI 4 was the second most cited in humans, with 12 papers. This acupoint is easily located on the back of the hand between the first and second metacarpal, within the second half of the metacarpal bone, is very

suitable in the literature for improving immunity in particular inflammation, fever, and as a powerful analgesic [4,5]. However it is observed that no uniformity in relation to the use of this point in the human population under study, with respect to pathologies. It was used in work with proposed immunity in asthmatic subjects, anxious, healthy, sedentary and athletes. In animals, however there was only one article that used the LI 4.

We believe that is due to the high pain sensitivity, found in the distal portion of forepaws and little anatomical support, which would make the containment of animals and maintenance of the needles.Although escarces research, the use of aggregate LI 4 acupoint appears to others. Can not conclude therefore that the immunomodulatory effect shown is resulting from the isolated use of LI 4, as occurred with ST36.

3.6. The use of techniques of acupuncture (ACP) and electroacupuncture (EA)

The act of dry needling, known with acupuncture is the most technique standard of Traditional Chinese Medicine. Known millennially is widely used in clinical and research of acupuncture in humans and / or animals. In our study we noticed an homogenic distribution between the techniques, in the papers that used the ACP with 47% against 49% who used EA, and 4% with both techniques: ACP + EA. It was found as expressed in Figure 3 a greater number of papers with ACP in humans, animals and against EA was correspondingly higher. As the technique of acupuncture to more classic and old, it's understandable that it is more accepted in research with humans, both for its ease of operation, whether the receptivity of the volunteer. Recalling that there for fear of "get a shock," in EA justification is consistent with other authors [2].

Electroacupuncture compared with classical acupuncture with dry needling, is relatively more recent In approaching to research, and clinical applicability has much to be investigated, especially as regards the physical parameters that EA should follow to achieve their therapeutic effects [3], although their use is spreading might rate around the world. Cabioglu [73] dont differs in its conclusions, the ACP and EA, allocating both the fact that modulate the immune system for local, neuronal and neurohumoral expression.

The ways in which EA works in the body is well studied with regard to their analgesic effects [2], but very little about their imunomodulatory effects in order to differentiate it from ACP. In our studies we found only one papers [78] which conclude that differences in the various substances to be detected, demonstrated in Table 2. The way the immune mechanism of action of EA suggested by this author proposes that EA inhibits excessive ACTH in the processes of stress. Johnston et al [11] studying the mechanism of action of ACP on cancer prevention found that there is an increase of cytotoxic activity of NK cells by cross effect between neurotransmitters and immune system (nitric oxide, endorphins, and cytokines). Remember that EA in the case of the effect of electric current enhances the release of endorphins, a mechanism already well studied in analgesia [3].By crossing the use of EA to the research, it was not found relationship as the selection of immune-biochemical markers. However the majority of studies with EA,were carried with inflammation experimental models. It is believed that because of the ease induction of inflammation in animal models it has been a relevant factor and consequently represented by a large percentage (70%) of perpers with EA.

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4. Final remarks

The studies compiled in this chapter, shows that the ac and EA are effective in the modulation of immunity.In these final remarks aimed to answer the questions proposed in this study.

The best markers for acute inflammatory processes are: IL1, IL6 and TNF alpha, and it is desired decrease in majority cases with ACP and EA. The best markers for allergic processes are IgE and IL4.

With respect to count of eosinophil cell, was not conclusive for the scarce number of papers in whith they where present. There were no articles describing the C-reactive protein (CRP) as a biochemical marker. We recommend its use in future research. Is relevancy the number of papers that relate in their conclusions, the reference to the generic term of "inflammation" as well as of "clinical symptoms". As described in the methodology, were excluded studies which were based on exclusively on symptomatic evaluation, but in 15 papers appear in their conclusions with immunological and / or biochemical markers, the terminology such as inflammation and symptoms. We believe it is a way to supplement the data by adding a reference to qualitative and quantitative, which has its importance and merit. The ST36(Zusanli) acupoint, was the most studied regarding immunomodulation in humans and animals and to for demonstrating satisfactory effects. We recommends your use in the clinic and research. The LI 4(*Hegu*) acupoint was so as screened for the ST36. However all the research this point appears along with others. We suggest to research the LI 4 acupoint in modulation of immunity, in an isolated manner, because can not conclude that the immunomodulatory effect shown is resulting from the isolated use of LI 4, as occurred with ST36.We suggest comparative research between the ACP and use of EA modulation of immunity. It is necessary also to EA more research in humans, because we observed that most research made in this technique occurs in animals.The modern science advances to each moment, for wide steps, especially with regard to technological resources for evaluation. However the human suffering still persists, especially for the ones that do not have access to sources.As a researcher and expert in acupuncture more than two decades ago, we imagine there is still understandings that underlie the basic theories of TCM, acupuncture with respect to the future will be revealed comprehensible from the viewpoint of immunology.

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