Send Orders for Reprints to reprints@benthamscience.net

Recent Patents on Inflammation & Allergy Drug Discovery **2014**, *9*, 000-000

Arsenic Immunotoxicity and Immunomodulation by Phytochemicals: Potential Relations to Develop Chemopreventive Approaches

Sabina I. Ramos Elizagaray[a,b] and Elio A. Soria[a]*

[a]*Instituto de Investigaciones en Ciencias de la Salud, Universidad Nacional de Córdoba - CONICET, n/n Enrique Barros, Córdoba, Argentina;* [b]*Consejo Interuniversitario Nacional, Pacheco de Melo 2084, Ciudad Autónoma de Buenos Aires, Argentina*

Received: March 7, 2014; Accepted: June 17, 2014; Revised: June 18, 2014

Abstract: Arsenic (As) contaminates drinking water worldwide, and As exposure, hypersensitivity and deficiency are involved in the immunopathogenesis of various health problems. Its chemoprevention thus has a high health impact. Given its oxidative potential, antioxidant compounds are good candidates to counteract arsenic's deleterious effects on humans. Phytochemicals (e.g., phenolics, carotenoids, etc.) act through free radical chelation activity and regulation of cellular targets. Consequently, they are appropriate for developing anti-As strategies derived from plants, and Argentinean flora is rich in useful species. Several molecular pathways involved in immune regulation are at the same time targets of exogenous agents, and oxidative stress itself is a modulating phenomenon of immunity. Since xenohormesis has been described as the organic enhancement of resistance to stress conditions (e.g., oxidation, pollution, etc.) by consuming xenobiotics, immunoxenohormesis implies also defense improvement. This review focuses on recent patents on the development of vegetable redox-related immunomodulating agents, which might be applied in As-induced dysfunctions, with their scientific basis being reviewed.

Keywords: Antioxidant, arsenicosis, chemoprevention, cytoprotection, immunomodulation, medicinal plant, phytomedicine, polyphenol.

INTRODUCTION

1. Hydroarsenicism

a. Concept

Hydroarsenicism is chronic poisoning by arsenic (As) through the consumption of contaminated water, known in Argentina by the Spanish acronym HACRE (i.e. regional-endemic chronic hydroarsenicism) and internationally as arsenicosis. This disease has a strong health and socioeconomic impact, affecting densely populated agricultural areas in the Americas and Asia [1]. About 60 to 100 million people worldwide are exposed to excessive levels of As (>10 µg/L) [2], with roughly 14 million in Latin America, including 5 million in Argentina [3]. The considerable evidence of the toxic effects of As has led international and national organizations to establish threshold limit values of total (organic and inorganic) As in human drinking water. This threshold is at 50µg/L for Argentina [4], and economic and political efforts would be required for this level to approach 10µg/L, the maximum set by the World Health Organization [5].

*Address correspondence to this author at the Instituto de Investigaciones en Ciencias de la Salud, Universidad Nacional de Córdoba - CONICET, n/n Enrique Barros, Córdoba (5014), Argentina; Tel:/Fax: 0543514334020; E-mail: easoria@fcm.unc.edu.ar

b. Environmental Exposure

Arsenic is ubiquitous across the earth's surface, forming part of numerous inorganic and organic compounds. Its lack of odor, taste and color led to it being studied by toxicology, due its use in homicides and suicides, which caused fear until the development of the Marsh test for detecting As in 1836 [6]. Throughout history, arsenic has been used in medicine (Fowler solution for malaria, syphilis, psoriasis, etc.; chemotherapy; oriental herbal therapy), agriculture (pesticides, herbicides), industry (copper smelting, wood preservatives, pigments, cosmetics, wall paper, electronic components) and mining [7]. These activities have caused environmental pollution of air, land and water, which has spread to the flora and fauna of the affected ecosystem. Except for these anthropogenic sources, the main source of arsenic in water is natural, geologically determined by magmatic and hydrothermal fluids, volcanic ash emitted into the atmosphere or weathering [8]. Elevated levels of arsenic in drinking water are a significant health problem in China, India, Bangladesh, and most of the countries of Central and South America [9]. In Argentina, arsenic has been found in the Chaco-Pampean Plain, an area of about 1 million km^2 extending northwest to southeast, related to volcanic and hydrothermal activity in the Andes during the Tertiary and Quaternary, with secondary scattering through surface water swept out to the Pacific

1872-213X/14 $100.00+.00

coast (Chile) and the Atlantic (Argentina) [10]. This geological sequence met an area of low relief (plain) that allowed concentrations to accumulate, which currently exceed 1000 μg/L in the Argentine provinces of Tucumán [11], Cordoba [12], Chaco [13] and La Pampa [14]. These high values correlate with the incidence of HACRE in the inhabitants.

Besides humans, numerous animal and plant species are exposed to arsenic contamination and metabolize it, so that it is found in foods such as fish, beef, leafy green vegetables, legumes, milk, vegetables, etc. [15, 16]. In these natural compounds, As can be found as organic (combined with carbon and hydrogen) or inorganic (combined with oxygen, chlorine and sulfur), given its ability to form substances in different valence states by oxidation: AS^0: Arsenic, As^{III}: arsenite, As^V: arsenate, As^{-III}: arsine and arsenide [17]. In water environments, arsenite, arsenate, methyl or dimethyl derivatives and bioorganic compounds have been identified in fishes, shellfish and aquatic flora (arsenobetaine, arsenocholine, arsenolipids and arsenosugars) [18]. There are variations in concentrations of the different arsenic compounds according to their origins in seawater, fresh water or ground water [19]. However, the inorganic forms As^{III} and As^V are predominant, and the soluble concentration depends on microbiological [20] and physicochemical water factors (pH, redox potential, ions, organic matter content) and solid-liquid interface processes (such as dissolution, precipitation, adsorption, desorption, ion exchange, etc.) [21]. Thus, in the oxidizing conditions commonly found in surface water, arsenic is found mainly as arsenate and its concentration is affected by rains and droughts. Groundwater, however, usually has reduced pH so the most toxic and abundant species is arsenite, which also occurs in hot springs [8].

c. Metabolism of Arsenic

Ingesting contaminated food and water is the main mechanism of entry into the human body, although it can also enter through inhalation or transdermally. In the intestinal lumen, trivalent arsenic is absorbed mostly by simple diffusion through aquaporins (AQP10, AQP3) or using glucose transporters (GLUT5, GLUT2) and organic anion transporter polypeptides (OATPB), while pentavalent As uses an energy-dependent phosphate transporter (Na/P) [22]. After absorption, AS^V is reduced by glutathione (GSH) to As^{III}, for which it is previously converted into arsenilated products by the action of phosphorolytic enzymes (ATP synthetase and glutathione synthetase), which are unable to structurally differentiate inorganic phosphates from arsenates [23]. Arsenite is an uncharged species at physiological pH, and so it diffuses freely across cell membranes to be methylated by the enzyme arsenite methyltransferase (As3MT) using s-adenosylmethionine as cosubstrate. This generates methylarsonic acid (MMA^V), which is reduced to methylarsinic acid (MMA^{III}) using electrons from thioredoxin, an antioxidant protein recently proposed as a serological marker of chronic arsenic exposure [24]. MMA^{III} is also an As3MT enzyme substrate, forming dimethylarsonic acid (DMA^V), a significantly less toxic compound than any of its precursors. These methylations occur mainly in the liver, though many organs may perform this: kidney, lung, bladder, heart, brain and adrenal glands [25]. The major route of arsenic excretion is in urine, 60-70% as DMA^V and the rest as intermediates, with a small amount in inorganic form. These values are quite variable, with a proportional decrease in dimethylated metabolites with increasing dose and tissue accumulation [26]. Other possible routes of elimination are integuments, bile and stools. However, tissue accumulation is common, occurring in quantitatively decreasing order in kidney> lung> bladder> skin> blood> liver [27].

As toxicity depends largely on its genetic methylation pattern, which in turn determines the phenotype of arsenical distribution and retention [28]. This is also related to the dose-dependent saturation of methylation reactions [29]. Nevertheless, although inorganic As methylation is considered a detoxification mechanism, this concept is being challenged by the finding of trivalent urinary metabolites (MMA^{III}, DMA^{III}) that are more reactive and cytotoxic than their precursors and even than As^{III} [30].

d. Mechanism of Action

The harmful effects of arsenic depend on its speciation, entry route into the body and dose, exposure time, and the age and sex of the individual. Part of As^V's toxicity is due to its being reduced to As^{III}. Moreover, it effectively emulates inorganic phosphates, and replaces them by its greater affinity for membrane transporters and enzymatic pathways of oxidative phosphorylation. In the presence of As^V, the cell synthesizes unstable ADP-arsenate adducts (instead of ATP), which auto-hydrolyze and uncouple energy capacity and cell metabolism [31].

Trivalent species have a special affinity for sulfhydryl groups (thiols) present in the cysteine of different proteins and cofactors. They bind to and alter metabolic and enzymatic processes, and so are considered more toxic than pentavalent forms. The following are the main targets of As^{III}:

- *Redox-dependent enzymes:* Modifies the expression of heme oxygenase type 1 and VEGF (vascular endothelial growth factor): cytoprotective inflammatory response, with stimulation of endothelial proliferation, angiogenesis and heme metabolism, among others. The site of action has been identified in cysteine residues of a transcriptional repressor (Bach-1) [32]. In addition, enzyme depletion/induction (glutathione and thioredoxin reductase, glutathione peroxidase and transferase, catalase, superoxide dismutase, etc.) may have cytoprotective or cytotoxic consequences, depending on the organ, dose, exposure time, etc. [33].
- *Other enzymes:* Inhibition of pyruvate dehydrogenase (PDH), in which As^{III} binding to dihydrolipoamide (a dithiol) alters acetyl-CoA production and consequently the citric acid cycle, the respiratory chain and ATP production [34]. Inhibition of p450, soluble epoxide hydrolase, and arachidonic acid metabolism [35].
- *Carbohydrate metabolism:* Partly by depletion of precursors for gluconeogenesis, causing inhibition of α-

ketoglutarate PDH or dehydrogenase. Diabetes type 2 is strongly linked with the generation of reactive oxygen species (ROS), which seems to intervene in the insulin receptor-dependent cascade of intracellular phosphorylation (PKB/AKT), generating resistance to insulin and reduced expression of GLUT4 [36].

- *Genetic material and cell cycle:* DNA damage and chromosomal abnormalities are strongly related to the occurrence of tumors. These gene injuries are caused by inhibition of enzymes that repair or methylate DNA (e.g., DNA polymerase), either by direct action of As or mediated by oxidative stress that results from this. Arsenic is also able to bind to tubulin and disrupt the mitotic spindle, leading to aneuploidy, polyploidy or mitotic arrest [37]. Apoptosis is also induced by As through modulation of protein (caspase 3 and 9, p53, Bax, Bak, Mcl-1) and intracellular signaling pathways (PBK/AKT inhibition, MAPK activation, JNK kinases) [38, 39].

Alterations in the redox state are the common point of most mechanisms of arsenic-induced cell injury. Among the free radicals that accumulate, ROS are the most abundant and include superoxide anion ($O^{\bullet 2-}$) and its derivatives: hydroxyl radicals ($^{\bullet}OH$) and peroxyl radicals. Their production is dose-time dependent and occurs mainly in mitochondria of cells exposed to MMA^{III} or As^{I}, while exposure to DMA^{III} has the endoplasmic reticulum as its target organelle [40]. Increased ROS activate nuclear transcription factors that modulate gene expression of pro/antiapoptotic and antioxidant proteins (NF-κβ and Nrf2, respectively), leading the cell to an early oxidative imbalance [41]. The activity of these factors is constitutively repressed by intracellular molecules that induce permanent degradation in the proteasome, and its modulation offers a new therapeutic arsenal for chronic pathologies [42]. Lipid peroxidation, glutathione depletion, alterations in intracellular signaling cascades and cytokine expression, are related mechanisms often involved in the immunosuppressive effects of As [43].

b. Clinical Implications

Human disease linked to arsenic is mainly acquired by accident, attempted suicide or murder, food or professionally, mainly due to excessive As consumption. However, pathologies arising from its deficiency have also been documented in animal models, probably due to its physiological role in methionine metabolism [44].

i *Acute toxicity* presents clinically, depending on the dose ingested, from mild gastrointestinal disorder (dose < 5mg) to death within 24 to 96 hours by bloody profuse watery diarrhea, severe dehydration and hypovolemic shock (lethal dose: 0.6mg/kg/day). The most common clinical manifestations are gastrointestinal (nausea, vomiting, acute abdominal pain, cholera-like diarrhea and sialorrhea), hematological (bone marrow depression with severe pancytopenia and normochromic normocytic anemia, disseminated intravascular coagulation), neurological (seizures, rapidly evolving peripheral neuropathy, encephalopathy), respiratory (acute pulmonary edema, respiratory failure), metabolic (acidosis, hypoglycemia, hypocalcaemia), diffuse erythema and toxic cardiomyopathy. The best method of diagnosis of recent intake is the concentration of As in urine [45].

ii *Chronic toxicity* is caused by exposure to sublethal doses of arsenic for long periods of time. When it is present as a pollutant in drinking water in concentrations > 0.01 μg/L, a pathological condition (HACRE) appears after 1-20 years of continuous intake depending on the dose [5]. The first cases of this disease in Latin America were described by Goyenechea in 1913, who analyzed skin lesions in residents of Cordoba (Argentina) [46]. In fact, skin lesions are the first clinical expression: hyperkeratosis, hyperpigmentation, transverse white lines on nails and Bowen's disease, with earlier onset and greater severity in individuals with low weight and nutritional deficiencies [47]. Other important disorders are Cardiovascular: atherosclerosis, ischemic heart disease, hypertension, arrhythmias, peripheral vascular disease (black foot disease); Neurological: peripheral neuropathy, sensory and motor disorders, cerebrovascular disease, headaches, disturbances of sleep, memory and concentration; Hematological: anemia, leucopenia and thrombocytopenia; gastrointestinal: diffuse abdominal pain, dyspepsia, hepatomegaly with hepatic fibrosis and portal hypertension (very common). Other systems, respiratory, renal, reproductive and endocrine, are variously affected [48]. Arsenic has been epidemiologically linked with higher incidence of cancer (lung, bladder, kidney, skin, liver, colon and prostate), which is why the International Agency for Research on Cancer classifies this metalloid as a Group 1 carcinogen [49]. Risk factors considered in this pathological process that modify the toxicokinetics and dynamics include gender, age at first exposure, genetic polymorphism, smoking and nutritional deficiencies, some of which are modifiable from the preventive point of view [50]. In this context, one of the main targets is the immune system, which is suppressed by As, impacting the whole organism and promoting neoplasia and other chronic diseases [51].

2. Environmental Immunotoxicity

a. Introduction to the Immune System

The immune system is a complex set of biological resources designed to maintain the homeostasis of the individual against a potentially hostile environment. It has three key properties: a wide repertoire of molecular receptors to recognize multiple agents, cellular and humoral responsiveness, and tolerance to avoid tissue damage to it. This defense system is organized into two large, closely interrelated subsystems: the innate immune system and the adaptive system [52].

i Innate immunity: Cells (macrophages, dendritic cells, NK cells, leukocytes, mast cells and epithelial cells) use recognition proteins (lectins, leucine-rich proteins, pentraxins, macrophage scavenger receptors, lipid trans-

ferases, integrins, etc.) [53]. They eliminate microorganisms by engulfing microorganisms and producing inflammatory cytokines (interleukins, interferon, TNF) and antimicrobial peptides (defensins, cathelin, granulysin, hystatin, etc.) [54]. Depending on the simultaneity and order of appearance of these molecules, cells can proliferate, differentiate, become unresponsive (anergy) or start their apoptosis [55].

ii *Adaptive immunity*: Lymphocytes (Li) T and B use surface receptors for each microorganism, and thus the host response gains specificity, specialization and immune memory, through the coordination of cellular and humoral immunity, respectively. T cells recognize antigens, expand clonally, differentiate, migrate to the inflammation site and lyse foreign cells or own infected cells: virgin Li, helper T Li (CD4+) and cytotoxic T Li (CD8+), and all their differentiated subclasses, each with its own functions [56]. B cell activation turns them into plasma cells secreting specific antibodies, and into memory B Li, which persistently and recurrently safeguard the immune potential, with tight reciprocal regulation [57].

b. Immunomodulation

Loss of immune functions from developmental or genetic disorders is called primary immunodeficiency, while that derived from the action of external agents or disease is called secondary. The agents responsible for immune injury can be classified according to their nature as physical (radiation), biological (antibodies, microorganisms) or chemical (drugs, As), and many of these are present in the diet [58]. Many immunosuppressants are xenobiotic substances whose molecular target is immunocytes [59] and their potential is used in clinical practice as therapy in autoimmune diseases, immune tolerance of transplants and malignancies (leukemia, lymphoma) [60]. However, immunosuppression makes the host susceptible to common infectious, autoimmune (thyroiditis, hemolytic anemia, leukopenia, etc.) and tumor diseases [61]. Some signs such as premature loss of teeth or recurrent gingivitis, disruption or delay in wound healing, recurrence of skin warts, unexplained bronchiectasis, intestinal malabsorption, growth alterations, etc., are correlated with antibodies and nutrient deficiencies and failures in phagocytic function or cellular immunity [62]. Moreover, it is clinically important to recognize the signs of protein-energy malnutrition, which affects large parts of the population, primarily pediatric, leading to thymic atrophy and lymphoid dysfunction of cell-mediated immunity (lower CD4/CD8 ratio) and phagocytosis (opsonization deficit and cytokine production) [63].

Agents capable of modifying regulatory balance and the final integrated response of immune response are called immunomodulators. Those providing a real benefit to the host are called immunostimulants. Among the latter, biological response modifiers such as interferons, interleukins, monoclonal antibodies, anti-angiogenic and hematopoietic agents, etc., currently represent a therapeutic strategy for chronic diseases occurring with immunosuppression [64].

c. Secondary/Acquired Immunodeficiency

A wide variety of external agents condition the clinical immunodeficiency described above. Some rapidly deteriorate the immune response, such as extreme temperatures, high altitudes (including space flight), exposure to UV rays and surgical or trauma stress. Others act more insidiously; frequent among these are severe protein-calorie or elemental nutritional deficits, accompanying hunger and unsatisfied basic needs of large sectors of the population. These are responsible for most of the secondary immunodeficiencies in the world, since they directly alter the immune response and thus predispose to infectious diseases [65]. Obesity is also associated with this disorder, often as part of the accompanying metabolic syndrome [66]. Other chronic diseases also alter the immune response by mixed mechanisms of nutritional and metabolic imbalance. These include renal and hepatic insufficiencies, diabetes, nephrotic syndrome, protein-losing enteropathy, extensive burns, etc. Although with lower incidence, genetic diseases such as cystic fibrosis, Down and Turner syndromes also occur with immunocompromise [67]. In the case of oncological diseases, tumor pathogenesis largely explains the damage to immune function, but this is intensified by the chemotherapy and ionizing radiotherapy received by these patients. Immune system compromise is a factor that contributes significantly to the process of carcinogenesis, given its specific potential to destroy tumor cells [68]. Moreover, in addition to those mentioned, anergy from infectious causes is usually transient, reversible and of viral etiology, with the exception of HIV, which is able to develop a potentially fatal syndrome of sustained immunosuppression, epidemic in character [69]. Immunosuppression is also common in patients with autoimmune diseases, allergy, transplant or graft-versus-host disease, derived both from the pathology itself and from medical treatment with immunomodulating, anti-inflammatory and immunosuppressive drugs, such as calcineurin inhibitors, cytotoxic agents, glucocorticoids, antilymphocyte globulin, etc. Other drugs such as antiepileptics, NSAIDs and some antibiotics can also cause immunosuppression as an adverse drug or idiosyncratic reaction [70].

Finally, it should be noted that psychological elements can also affect the immune system, and so psychiatric symptoms such as depression may present with immunocompromise. In recent years, psycho-neuroimmuno-endocrinology (PNIE) has provided a comprehensive and integrated view of all the factors involved [71]. Of particular interest is the study of endocrine-disrupting chemicals, present in many products of human consumption with demonstrated immunotoxicity [72]. It is useful in clinical assessment of patients with immune deficiency to assess the epidemiological importance of each of the aforementioned predisposing factors to which they are exposed, and consider the frequent coexistence and simultaneous interaction of several of these.

Table 1. Immunotoxic Effects of Arsenic*.

T lymphocytes: depresses proliferation in a dose-dependent way, correlated with a decreased secretion of cytokines by Th Li (TNF-α, IFN-γ, IL2, IL5, IL4, IL-13, IL-10)	[73]
Also increases the expression of redox-sensitive genes in these cells, probably because their destruction is associated with oxidative and nitrosative stress caused by arsenic, depletion of glutathione and the overproduction of hydrogen peroxide	[74]
Inflammatory mediators: modulates the expression of TNF, VEGF and CYP3A transcription (drug-metabolizing enzyme), while also decreasing the proteasome-regulated RXR process	[75]
Langerhans cells: alters their migration, reduces their presence in peripheral tissues and increases lymph node proliferation, correlating with increased Th1 response and expression of homeostatic chemokines	[76]
Splenocytes: inhibits their proliferation and cytokine production (IL-2, IFN-γ, IL-4 or IL-10), an effect influenced by aging	[77]
Also alters the CD4/CD8 ratio, increases phosphorylation of kinases associated with TCR (T cell receptor) and increases apoptosis	[78]
Mastocytes: interferes with degranulation of IgE-mediated stimulation by environmental antigen	[79]
Macrophages: alters adhesion and phagocytic capacity (decreases the expression of adhesion molecules such as CD54 and F-actin), and NO production, possibly by the involvement of Rho A-ROCK pathway	[80]
Monocytes: reduces their macrophage differentiation and marker expression. Antioxidants and thioreducers are being studied that might counteract this effect	[81]

* The numbers in the second column indicate the corresponding references

d. Arsenic Immunotoxicity

Although As-induced oxidative imbalance is able per se to alter immune response, As has specific mechanisms of immune injury. Major developments in the study of the immunotoxic effects of arsenic are shown below [73-81] (Table **1**).

3. Immunomodulation by Phytochemicals

a. Plant Bioactive Compounds

The search for pharmaconutrients in *Plantae* dates back to ancient times, and is currently encouraged by the possibility of finding compounds with therapeutic bioactivity in traditional herbal knowledge [82]. Among the known bioactive plant compounds, fatty acids (mainly polyunsaturated) and phenols (especially polyphenols), stand out as including a large number of redox-active substances, and being potentially chemopreventive and immunoprotective when are present in the diet [83].

- *Polyphenols:* Phenolic compounds are essential physiological constituents of all plants. They are involved in plant morphology, growth and propagation, through their pigmenting, antifungal, antioxidant and UV protective properties, and as modulators of nitrogen fixation, herbivorism, and auxin hormone, among others. These plant secondary metabolites are known to have great structural diversity, and they can be found as aglycones or glycosides, as monomers or constituting highly polymerized structures, associated with other phenols, amines, lipids, carbohydrates or carboxylic acids [84]. Those compounds with more than one phenol group in their molecule are called polyphenols, most of which are biosynthesized from p-coumaryl-SCoA. This is produced by the action of CoA ligase on p-coumarin, which in turn derives from the hydroxylation of cinnamic acid, which arises from phenylalanine after the action of phenylalanine ammonialyase [85]. The shikimic acid pathway is the main supplier of phenylalanine, and therefore of polyphenols in higher plants, although the polyketide pathway (malonic acid) also participates to a lesser extent in this process [86]. Once the phenolic skeleton is synthesized, it is glycosylated at different positions, enabling them to be classified according to their chemical structure (Table **2**) [87].

  The presence of these compounds is highly variable between species, and they are even responsive to quali-quantitative changes induced by genetic factors or environmental stressors (temperature, humidity, germination, flowering, contaminants, etc.) [88]. Moreover, their distribution in the plant is not uniform and their stability varies significantly, so that the extraction and isolation of these substances requires an optimized and individualized procedure [89].

  Among the bioactive polyphenols, flavonoids comprise the largest and most extensive group, being present in over 60% of plant species, in flower and fruit pigments, with antioxidant and free radical chelating properties. This means that they have functions of growth modulation, cell differentiation and development in the plant [90].

Table 2. Classification of Plant Polyphenols .*

Group	Subgroup	Examples	Plants Containing Them	Skeleton Bases
Phenols and phenolic acids	Simple phenols	Hydroquinone, vanillin, salicyl alcohol		C6
	Phenolic acids	Benzoic acid (p-hydroxybenzoic acid, gallic, syringic, vanillic)	Blueberries, raspberries, plums	C6-c1
		Cinnamic acids: p-coumaric acid, caffeic, ferulic, eugenol, tyrosine, chlorogenic	Fruits, grains and seeds (husk, bran)	C6-c3
Phenylpropanoids, coumarins and chromones	Simple coumarins	Aesculetin	Umbellíferas, rue, curry tree, Apiaceae (giant parsley, splint)	
	c-Prednilada	Suberosin		
	Dicumarols	Dicumarol		
Quinones and anthracenosides	Benzoquinones	Plastoquinone, ubiquinone (Q coenzyme)	Widely distributed in Rubiaceae, Rhamnaceae and Polygonaceae	C6
	Naphthoquinones	Plumbagone, juglone, K vitamin		C6-C4
	Oxanthrones, anthrones	Aloin, chrysaloin		C6-C1-C6
	Anthraquinones	Emodin, modin, carminic acid, chrysophanol, alizarin, rein	Aloe, legumes, sacred bark, buckthorn, rhubarb	C6-C2-C6
	Anthracyclinone	Tetracyclines		
Stilbenes	Resveratrol		Grapes, red wine	
Flavonoids	Isoflavonoid	Formononetin, genistein, daidzein, glicitein	Leguminous plants	C6-C3-C6
	Neoflavonoids	Dalbergin	Guttíferaceae, favaceae y rubiaceae	
	Chalcones	Chalconaringenin, butein	Apples, hops for beer	
	Flavones	Nobiletin, tangeritin, apigenin, luteolin	Yellow flowers, chamomile, grapes, hawthorn	
	Flavonols	Quercetin, kaempferol, myricetin	Fagaceae leaves and flowers, grapes	
	Flavanones	Hesperitin, naringenin, naringin, naritulin	Citrus fruits, grapes, licorice, sarsaparrille	
	Flavanololes	Taxifolin, dihydroquercetin, dihydrokaempferol		
	Flavanols	Catechin, epicatechin, gallocatechin	Skin of grapes, apples and blueberries	
	Anthocyanidins	Cyanidin, delphinidin, peonidin, pelargonidin, petunidin, malvidin	Pigment red, blue and violet of flowers, fruits, vegetables and grains	
	Polyphenolic amides	Capsaicinoids, avenanthramides	Chili (spicy), oat	
Tannins	Hydrolysable tannins	Polymers of several phenolic acids: gallotannins, ellagitannins	Woody dicotyledons, hazelnut, pomegranate, rhubarb, hamamelis, maple	
	Condensed tannins (proanthocyanidins or catechinics)	Anthocyanidins polymers: leucocyanidin, leucodelphinidin	Nuts, sorghum, grapes, peanuts, berries or fruits of the forest	(C6-C3-C6)n
Lignans	Simple	Podophyllotoxin, peltatin	Flax, sesame and other grains, milk thistle, Sapindaceae	(C6-c3)2
	Flavanolignans	Silybinin, silydianin, silycristin (silymarin)		
	Lignins	Polymers of various acids and alcohols	Woody plants	(C6-C3)n

* Data were grouped according to Marcano *et al.* [87].

- *Polyunsaturated fatty acids*: Fatty acids (FA) structure lipids. Their chemical constitution is based on pairs of C atom chains (2 to 36), headed by a carboxyl group at one end and a methyl group at the other. FA that have single bonds are called Saturated (myristic, palmitic, stearic acids, etc.), while those with one double bond are Monounsaturated (oleic acid), all being biosynthesized in the animal cell, with malonyl-CoA as a substrate and process controller [91]. When they have two or more double bonds, they are called Polyunsaturated, and most of these are considered essential FA (EFA), as their sources are marine animals and plants, and mammals have to acquire them through diet [92]. There are two major groups of EFA:
    - *ω6 acids. Linoleic acid and derivatives:* γ-linolenic acid, arachidonic acid (AA), present in corn oil, sunflower, avocado, nuts, sesame, acacia cyanophylla, among others.
    - *ω3 acids. α-linolenic acid and derivatives:* stearidonic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid, dihomo-γ-linolenic acid, present in chia seeds, flax, olive oil and fish oils, among others [93, 94].

The bioactivity of these compounds is quite variable. Pro- or anti-inflammatory effects appear to be caused by eicosanoid synthesis, increasing the bioavailability of its precursors (AA and EPA) [95], while cytoprotective results are caused in part by the ability of PUFA to modulate cell membrane properties and signaling cascades [96]. Moreover, nutrigenomics emphasizes the role of nuclear receptors in modulating effects of PUFAs, since their binding to these receptors enables them to regulate the gene expression of signaling molecules, enzymes involved in their metabolism (desaturases), and others [97].

The beneficial effects of the consumption of these compounds have not yet been fully elucidated, although it is postulated that they may depend on a greater intake of ω3 and ω9 FA, followed by ω6 and a low intake of saturated EFA [98]. This would be the appropriate dietary profile to prevent the development of chronic inflammatory diseases [99, 100].

Table 2

b. Immunomodulatory Potential of Plant Xenobiotics

The immune system is a real crossroads in the origin, development and progression of oxidative/inflammatory-based disease patterns and so its modulation by phytonutrients would be an invaluable resource [101]. Oxidative stress is central to this process, and its concept recognizes the need for a balance between oxidant (ROS, RNS, and RSS) and antioxidant species (cytochromes, GSH, glucuronate) to achieve cellular homeostasis, because they play important physiological roles in metabolic and signaling pathways [102]. The dietary intake of antioxidant phytonutrients enables the result of this process to be modulated and the immunotoxicity caused by oxidative stress chemoprevented [103]. This antioxidant potential depends on many factors and is found primarily in traditional medicinal plants of *Lamiaceae* (rosemary, sage, oregano, marjoram, basil, thyme, mint, lemon balm), *Apiaceae* (cumin, fennel, caraway) and *Zingiberaceae* (turmeric, ginger) [104]. Some of the plant-derived compounds scientifically shown to be phytotherapeutic were identified in these: *N*-acetylcysteine, α-lipoic acid, vitamins E, C and D, quercetin, curcumin, propolis, flavonoids, triterpene saponins, essential oils, naphthoquinones (thyme, licorice, ginseng, lapacho tree), among others [105]. Among these, polyphenols are generally accepted as beneficial to the immune system, although this varies with each particular compound, as some have prooxidant and cytotoxic properties [106]. Specifically, dietary polyphenols have shown inhibition of T-2 helper lymphocyte activation in allergic diseases [107]. This mechanism is shared by ω3 FA, which inhibits lymphocyte proliferation and production of gamma-interferon (IFN), interleukin-6 (IL) and tumor necrosis factor (TNF) [108]. Besides their antioxidant effects, other polyphenols and ω3 FA have shown modulation of the inflammatory cascade dependent on the synthesis of eicosanoids and other arachidonic acid derivatives [109, 110].

In assessing the incorporation of phytopharmaceuticals into a complex biological system, the metabolic and pharmacokinetic aspects that affect phytochemical bioavailability must not be disregarded, and for this, the development of updated databases will be useful [111]. Some other problems to be solved in the development of these compounds are the chemical modifications suffered in the lumen, and their interactions with tissue, food, drugs or the intestinal microbiome, considering the toxic potential that can derive from this [112].

c. Immunomodulation by Phytopharmaceuticals

The use of plant extracts for the prevention or treatment of immune pathologies associated with arsenic is a promising area of research, given its relatively inexpensive and environmentally-sustainable potential. Three classes of peptides (glutathione, metallothioneins and phytochelatins) have been shown to contribute to arsenic resistance in plants. This underlies both phytoremediation for ecological approaches and phytomedicine for human health in contaminated environments [113]. Biotechnology provides a strategy for these purposes, generating genetically-modified organisms that tend to biosynthesize an extensive variety of bioactive anti-As molecules [114]. These developments are encouraged by the almost total lack of plant derivatives used to treat arsenic immunotoxicity, although there are some phytochemicals that are potentially beneficial because they act in the sites which may be targets of As in the immune system [115-122] (Table **3**).

d. Potential of Lantana spp.

Within the great *Verbenaceae* family, the genus *Lantana* of shrubs contains several bioactive species. Among these, the most studied is *Lantana camara* Linn (Spanish flag), a ubiquitous weed known in folk herbalist tradition to be hepa-

Table 3. Immunomodulating Phytochemicals*.

Title	Immune effects	Ref.
Morinda citrifolia based formulations for regulating T cell immunomodulation in neonatal stock animals	Enhance the development of immune systems, lymphocyte proliferation and CD25 expression on $CD4^+$, $CD8^+$ and γδ T cells	[115]
Extracts of the *Acanthospermum hispidum* plant	Induces the proliferation of B-lymphocytes and IgM synthesis, the proliferation of adult bone marrow macrophages and interferon formation. Induces the proliferation of peripheral human lymphocytes	[116]
Immune enhancement by seed oil and/or seed flour	Boost the immune system by encouraging the population growth of CD 8(+) lymphocytes and NK cells	[117]
Dioscorea extracts for enhancing immune system	Increases the activities of a NF-κB-inducible ELAM-1 composite promoter and a GM-CSF promoter, who stimulates stem cells to produce granulocytes and monocytes. It can be used as an adjuvant agent or adjuvant in combination with other compound, such as cytokines (TNF-α, IL-8, IL-12, IL-2 and IL-6), to enhance the proliferation of the cells	[118]
Garcinia mangostana L. and iridoid based formulations	Inhibits COX-1/COX-2, histamine release and the complement pathway, regulates TNF-γ, NO, 5-LOX and elastase enzyme activity, increase IFN-γ secretion. Inhibits DNA repair systems, cancer cell growth and act as a cytotoxic agent against cancer cells. Provides DPPH scavenging effects	[119]
Methods and compositions associated with administration of an extract of *Ganoderma lucidum*	Modulates protein kinase pathways associated with inflammatory cytokine IL-1 and differentiation of a mononuclear cell, enhances cytotoxicity of an NK cell against an NK-sensitive tumor cell, activates the expression of cytokines, induces Blimp-1 expression in splenic B cells, mature splenocytes or dendritic cells, inhibits LPS induced nitric oxide production in macrophages, activates spleen cells proliferation, and modify the proteome of a spleen cell	[120]
Phytochemical combinations that regulate pathological immunity	Spices combination: turmeric and ginger, turmeric (curcumin) and *capsicum*, and paprika and nutmeg inhibits LPS-stimulated expression of the IL-8 inflammatory biomarker	[121]
Herbal compositions, methods of stimulating immunomodulation and enhancement of immunomodulating agents using the herbal compositions	Herbal mixture of Shiitake mushroom, *Aloe vera* leaf, Brewer's yeast, Coriolus mushroom and AHCC (Active Hexose Correlate Compound). Direct activation of NK cells and induction of CD69	[122]

* The numbers in the second column indicate the corresponding references.

totoxic and cholestatic [123]. This plant has shown a wealth of polyphenolic and lantadene compounds (pentacyclic triterpenoids), and its cytotoxic and even antitumor properties are attributed to these [124]. However, recent studies contradict this, showing considerable antioxidant and free radical chelating activity *in vitro* by lantadenes, which would mean a potential cytoprotective effect [125]. Other species under study are *Lantana montevidensis* Briq (potential antibacterial) [126], *Lantana cramera* (insecticidal activity) [127], *Lantana macrophylla* Schauer (placental and trophoblast toxicity) [128], among others.

In contrast to these, *Lantana grisebachii* Seckt var *grisebachii* (lantana) is used in folk medicine as an antipyretic and emetic, although scientific evidence for these properties is limited. Potential acetylcholinesterase inhibitory activity for ethanolic extract is thus not very encouraging [129], and the essential oils obtained by steam distillation possess effective and selective inactivating activity *in vitro* against herpes simplex virus type 1 (HSV-1) and dengue virus type 2 (DENV-2) [130]. The aqueous extract of this plant has also demonstrated a potent *in vitro* antioxidant effect, protecting cells from oxidative stress induced by arsenic [131]. This is important because, if similar effects are found *in vivo*, a management strategy through infusion would be easily applicable in the population at risk.

CURRENT & FUTURE DEVELOPMENTS

Several molecular pathways involved in immune regulation are at the same time targets of exogenous agents (e.g. oxidative contaminants, xenobiotics). Oxidative stress itself also modulates immunity. Vegetable redox-active compounds, which are thought to be protective, can simultaneously improve the immune response. This is very important because allergic and inflammatory pathologies can be induced by environmental stress conditions, with the immune system being critically affected. The immunotoxic effect of this metalloid triggers both hypersensitivity and anergy [132]. However, there has been scant development of immunoprotective phytodrugs to prevent or counteract arsenic-related health disorders. For example, garlic-derived

biomembrane permeable organ sulfur compounds, which can participate in cellular cycles in response to redox disturbances, act as arsenic-detoxifying and antiinflammatory agents [133]. These approaches need to consider different aspects for phytodrug development, such as shared mechanisms of action in immunocytes and changes in their cellular biology in order to modify their resistance to stress. Since xenohormesis has been described as the organic enhancement of resistance to stress conditions by consuming xenobiotics, we propose the term immunoxenohormesis when this involves improvement of immune defenses. Thus, chemopreventive plant derivatives, such as proanthocyanidin-containing extracts, modulate inflammation and improve immunological resistance to infections. They can therefore be useful in subjects at risk of developing arsenic-induced diseases [134]. Among Argentinean plants, *Lantana grisebachii* is a strong candidate, given its immunoxenohormetic activity against arsenic [135], which has shown beneficial potential as a source of chemopreventive phytochemicals.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest, and would like to clarify that the patents cited were selected using descriptive criteria depending on their thematic relevance and current validity, without prejudice to those not included, or implying recommendation of those mentioned.

This work was supported by the National University of Cordoba [Grant Number 162/12].

ACKNOWLEDGEMENTS

The authors would like to thank Joss Heywood, a native English speaker, who critically revised the manuscript.

The first author was a fellow of the National Inter-University Council.

LIST OF ABBREVIATIONS

AA	=	Arachidonic Acid
ADP	=	Adenosine diphosphate
Ag	=	Antigen
AQP10, AQP3	=	Aquaporins
As	=	Arsenic
As3MT	=	Arsenite Methyltransferase
ATP	=	Adenosine Triphosphate
DENV-2	=	Dengue Virus type 2
DMA^V	=	Dimethylarsonic Acid
DNA	=	Deoxyribonucleic Acid
EFA	=	Essential Fatty Acid
FA	=	Fatty Acid
GLUT5, GLUT2	=	Glucose Transporters
GSH	=	Glutathione
HACRE	=	Endemic Regional Chronic Hydroarsenicism (from Spanish: *Hidroarsenicismo Crónico Regional Endémico*)
HIV	=	Human Immunodeficiency Virus
HSV-1	=	Herpes Simplex Virus type 1
IL	=	Interleukin
INF	=	Interferon
Li	=	Lymphocyte
MMA^{III}	=	Methylarsinic Acid III
MMA^V	=	Methylarsonic Acid V
NSAIDs	=	Non Steroidal Anti-inflammatory Drugs
OATPB	=	Organic Anion Transporter Polypeptides
PDH	=	Pyruvate Dehydrogenase
PNIE	=	Psycho-Neuro-Immuno-Endocrinology
PUFA	=	Polyunsaturated Fatty Acid
Ref	=	References
RNS	=	Reactive Nitrogen Species
ROS	=	Reactive Oxygen Species
RSS	=	Reactive Species of Sulfur
TNF	=	Tumoral Necrosis Factor
UV	=	Ultraviolet light
VEGF	=	Vascular Endothelial Growth Factor

REFERENCES

[1] Sigrist M, Beldoménnco H, MR R. Evaluation of the influence of arsenic levels in cow's raw milk from Argentinean dairy farms. Food Chem 2010; 121(2): 487-91.

[2] Ng JC. Environmental contamination of arsenic and its toxicological impact on humans. Environ Chem 2005; 2(3):146-60.

[3] Blanco MC, Paoloni JD, Morrás HJ, Fiorentino CE, Sequeira M. Content and distribution of arsenic in soils, sediments and groundwater environments of the southern Pampa region, Argentina. Envirol Toxicol 2006; 21(6): 561-74.

[4] ANMAT, Ministerio de Salud de la Nación. Bebidas hídricas, aguas y aguas gasificadas agua potable. In: Código Alimentario Argentino. Buenos Aires: ANMAT 1994; 1-42.

[5] World Health Organization. Guidelines for drinking-water quality. 4th ed. WHO: Malta 2011.

[6] Marsh J. Separation of arsenic. Am J Pharm 1837; 2: 307-14.

[7] Hughes MF, Beck BD, Chen Y. Arsenic exposure and toxicology: A historical perspective. Toxicol Sci 2011; 123(2): 305-32.

[8] López DL, Bundschuh J, Birkle P, Armienta MA, Cumbal L, Sracek O, *et al.* Arsenic in volcanic geothermal fluids of Latin America. Sci Total Environ 2012; 429: 57-75.

[9] Tseng CH. A review on environmental factors regulating arsenic methylation in humans. Toxicol Appl Pharmacol 2009; 235(3): 338-50.

[10] Bundschuh J, Litter MI, Parvez F, Román-Ross G, Nicolli HB, Jean JS, *et al.* One century of arsenic exposure in Latin America: A review of history and occurrence from 14 countries. Sci Total Environ 2011; 429: 2-35.

[11] Nicolli HB, García JW, Falcón CM, Smedley PL. Mobilization of arsenic and other trace elements of health concern in groundwater from the Salí River Basin, Tucumán Province, Argentina. Environ Geochem Health 2012; 34(2): 251-62.

[12] Francisca FM, Carro-Perez ME. Assessment of natural arsenic in groundwater in Cordoba province, Argentina. Environ Geochem Health 2009; 31(6): 673-82.

[13] Blanes PS, Buchhamer EE, Giménez MC. Natural contamination with arsenic and other trace elements in groundwater of the Central-West region of Chaco, Argentina. J Environ Sci Health A Tox Hazard Subst Environ Eng 2011; 46(11): 1197-206.

[14] O'Reilly J, Watts MJ, Shaw RA, Marcilla AL, Ward NI. Arsenic contamination of natural waters in San Juan and La Pampa, Argentina. Environ Geochem Health 2010; 32(6): 491-515.

[15] Perez-Carrera A, Perea-Gardiner ML, Fernandez-Cirelli A. Presencia de arsénico en tejidos de origen bovino en el sudeste de la provincia de Córdoba, Argentina. InVet 2010; 12(2): 59-67.

[16] Lozna K, Biernat J. The occurrence of arsenic in the environment and food. Rocz Panstw Zakl Hig 2007; 59(1): 19-31.

[17] Orloff K, Mistry K, Metcalf S. Biomonitoring for environmental exposures to arsenic. J Toxicol Environ Health B Crit Rev 2009; 12(7): 509-24.

[18] Sharma VK, Sohn M. Aquatic arsenic: Toxicity, speciation, transformations, and remediation. Environ Int 2009; 35(4): 743-59.

[19] Schaeffer R, Fodor P, Soeroes C. Development of a liquid chromatography/electrospray selected reaction monitoring method for the determination of organoarsenic species in marine and freshwater samples. Rapid Commun Mass Spectrom 2006; 20(19): 2979-89.

[20] Lièvremont D, Bertin PN, Lett MC. Arsenic in contaminated waters: Biogeochemical cycle, microbial metabolism and biotreatment processes. Biochimie 2009; 91(10): 1229-37.

[21] Nicolli HB, Jochen-Bundschuh J, Garcia JW, Falcón CM, Jean JS. Sources and controls for the mobility of arsenic in oxidizing groundwaters from loess-type sediments in arid/semi-arid dry climates evidence from the Chaco Pampean plain (Argentina). Water Res 2010; 44(19): 5589-604.

[22] Calatayud M, Barrios JA, Vélez D, Devesa V. *In vitro* study of transporters involved in intestinal absorption of inorganic arsenic. Chem Res Toxicol 2012; 25(2): 446-53.

[23] Németi B, Anderson ME, Gregus Z. Glutathione synthetase promotes the reduction of arsenate via arsenolysis of glutathione. Biochimie 2012; 94(6): 1327-33.

[24] Li Y, Gao Y, Zhao L, Wei Y, Feng H, Wang C, *et al*. Changes in serum thioredoxin among individuals chronically exposed to arsenic in drinking water. Toxicol Appl Pharmacol 2012; 259(1): 124-32.

[25] Thomas DJ, Li J, Waters SB. Arsenic (+3 oxidation state) methyltransferase and the methylation of arsenicals. Exp Biol Med (Maywood) 2007; 232(1): 3-13.

[26] Wu H, Krishnamohan M, Lam PK, Ng JC. Urinary arsenic speciation profiles in mice subchronically exposed to low concentrations of sodium arsenate in drinking water. Kaohsiung J Med Sci 2011; 27(9): 417-23.

[27] Kenyon EM, Hughes MF, Adair BM, Highfill JH, Crecelius EA, Clewell HJ, *et al*. Tissue distribution and urinary excretion of inorganic arsenic and its methylated metabolites in C57BL6 mice following subchronic exposure to arsenate in drinking water. Toxicol Appl Pharmacol 2008; 232(3): 448-55.

[28] Chen B, Arnold LL, Cohen SM, Thomas DJ, Le XC. Mouse arsenic (+3 oxidation state) methyltransferase genotype affects metabolism and tissue dosimetry of arsenicals after arsenite administration in drinking water. Toxicol Sci 2011; 124(2): 320-6.

[29] García-Montalvo EA, Valenzuela OL, Sánchez-Peña LC, Albores A, Del-Razo LM. Dose-dependent urinary phenotype of inorganic arsenic methylation in mice with a focus on trivalent methylated metabolites. Toxicol Mech Methods 2011; 21(9): 649-55.

[30] Naranmandura H, Carew MW, Xu S, Lee J, Leslie EM, Weinfeld M, *et al*. Comparative toxicity of arsenic metabolites in human bladder cancer EJ-1 cells. Chem Res Toxicol 2011; 24(9):1586-96.

[31] Jomova K, Jenisova Z, Feszterova M, Baros S, Liska J, Hudecova D, *et al*. Arsenic: Toxicity, oxidative stress and human disease. J Appl Toxicol 2011; 31(2): 95-107.

[32] Meng D, Wang X, Chang Q, Hitron A, Zhang Z, Xu M, *et al*. Arsenic promotes angiogenesis *in vitro* via a heme oxygenase-1-dependent mechanism. Toxicol Appl Pharmacol 2010; 244(3): 291-9.

[33] Rana T, Bera AK, Das S, Bhattacharya D, Pan D, Das SK. Metabolic adaptations to arsenic-induced oxidative stress in male wistar rats. J Biochem Mol Toxicol 2012; 26(3): 109-16.

[34] Bergquist ER, Fischer RJ, Sugden KD, Martin BD. Inhibition by methylated organo-arsenicals of the respiratory 2-oxo-acid dehydrogenases. J Organomet Chem 2009; 694(6): 973-80.

[35] Anwar-Mohamed A, El-Sherbeni AA, Kim SH, Althurwi HN, Zordoky BN, *et al*. Acute arsenic toxicity alters cytochrome P450 and soluble epoxide hydrolase and their associated arachidonic acid metabolism in C57Bl/6 mouse heart. Xenobiotica 2012; 42(12): 1235-47.

[36] Xue P, Hou Y, Zhang Q, Woods CG, Yarborough K, *et al*. Prolonged inorganic arsenite exposure suppresses insulin-stimulated AKT S473 phosphorylation and glucose uptake in 3T3-L1 adipocytes: Involvement of the adaptive antioxidant response. Biochem Biophys Res Commun 2011; 407(2): 360-5.

[37] Kitchin KT, Wallace K. The role of protein binding of trivalent arsenicals in arsenic carcinogenesis and toxicity. J Inorg Biochem 2008; 102(3): 532-9.

[38] Ruiz-Ramos R, Lopez-Carrillo L, Rios-Perez AD, De Vizcaya-Ruíz A, Cebrian ME. Sodium arsenite induces ROS generation, DNA oxidative damage, HO-1 and c-Myc proteins, NF-kappaB activation and cell proliferation in human breast cancer MCF-7 cells. Mutat Res 2009; 674(1-2):109-15.

[39] Yen YP, Tsai KS, Chen YW, Huang CF, Yang RS, Liu SH. Arsenic induces apoptosis in myoblasts through a reactive oxygen species-induced endoplasmic reticulum stress and mitochondrial dysfunction pathway. Arch Toxicol 2012; 86(6): 923-33.

[40] Naranmandura H, Xu S, Koike S, Pan LQ, Chen B, Wang YW, *et al*. The endoplasmic reticulum is a target organelle for trivalent dimethylarsinic acid (DMAIII)-induced cytotoxicity. Toxicol Appl Pharmacol 2012; 260(3): 241-9.

[41] Li B, Li X, Zhu B, Zhang X, Wang Y, Xu Y, *et al*. Sodium arsenite induced reactive oxygen species generation, nuclear factor (erythroid-2 related) factor 2 activation, heme oxygenase-1 expression, and glutathione elevation in Chang human hepatocytes. Environ Toxicol 2013; 28(7): 401-10.

[42] Chitra S, Nalini G, Rajasekhar G. The ubiquitin proteasome system and efficacy of proteasome inhibitors in diseases. Int J Rheum Dis 2012; 15(3): 249-60.

[43] Das S, Pan D, Bera AK, Rana T, Bhattacharya D, Bandyapadyay S, *et al*. Sodium arsenite mediated immuno-disruption through alteration of transcription profile of cytokines in chicken splenocytes under *in vitro* system. Mol Biol Rep 2011; 38(1): 171-6.

[44] González-Muñoz MJ, Meseguer-Soler I, Mateos-Vega CJ. Elementos ultratrazas nutrientes o tóxicos Rev Toxicol 2009; 26(2-3): 93-103.

[45] Tournel G, Houssaye C, Humbert L, Dhorne C, Gnemmi V, Bécart-Robert A, *et al*. Acute arsenic poisoning: Clinical, toxicological, histopathological, and forensic features. J Forensic Sci 2011; 56(1): S275-9.

[46] Goyenechea M. Sobre la nueva enfermedad descubierta en Bell-Ville. Rev Med Rosario 1917; 7: 485.

[47] Valenzuela OL, Drobná Z, Hernández-Castellanos E, Sánchez-Peña LC, García-Vargas GG, Borja-Aburto VH, *et al*. Association of AS3MT polymorphisms and the risk of premalignant arsenic skin lesions. Toxicol Appl Pharmacol 2009; 239(2): 200-20.

[48] Mazumder DG, Dasgupta UB. Chronic arsenic toxicity: Studies in West Bengal, India. Kaohsiung J Med Sci 2011; 27(9): 360-70.

[49] Marshall G, Ferreccio C, Yuan Y, Bates MN, Steinmaus C, Selvin S, *et al*. Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. J Natl Cancer Inst 2007; 99(12): 920-8.

[50] Singh N, Kumar D, Sahu AP. Arsenic in the environment: Effects on human health and possible prevention. J Environ Biol 2007; 28(2): 359-65.

[51] Acharya S, Chaudhuri S, Chatterjee S, Kumar P, Begum Z, Dasgupta S, *et al*. Immunological profile of arsenic toxicity: A hint to-

wards arsenic-induced carcinogenesis. Asian Pacific J Cancer 2010; 11(2): 479-90.

[52] Fauci AS, Braunwald E, Kasper DL, Hauster SL, Longo DL, Jameson JL, *et al*. Principios de medicina interna. 17th ed. McGraw-Hill Interamericana Editores: México DF 2009.

[53] Kabelitz D. Toll-like receptors: Recognition receptors of the innate immune system and target structures for therapeutical intervention. Med Monatsschr Pharm 2012; 35(7): 238-44.

[54] Yanai H, Ban T, Taniguchi T. High-mobility group box family of proteins: Ligand and sensor for innate immunity. Trends Immunol 2012; 33(12): 633-40.

[55] Wang L, Zhao Y, Shi S. Interplay between mesenchymal stem cells and lymphocytes: Implications for immunotherapy and tissue regeneration. J Dent Res 2012; 91(11): 1003-10.

[56] Samson M, Lakomy D, Audia S, Bonnotte B. T(H)17 lymphocytes: Induction, phenotype, functions, and implications in human disease and therapy. Rev Med Interne 2011; 32(5): 292-301.

[57] Yoshizaki A, Miyagaki T, Dilillo DJ, Matsushita T, Horikawa M, Kountikov EI, *et al*. Regulatory B cells control T-cell autoimmunity through IL-21-dependent cognate interactions. Nature 2012; 491(7423): 264-8.

[58] Elgert KD. Immunology: understanding the immune system. 2nd ed. Wiley-Blackwell Publishers: Hoboken 2009.

[59] Grinyó JM, Cruzado JM, Bestard O, Vidal-Castiñeira JR, Torras J. Immunosuppression in the era of biological agents. Adv Exp Med Biol 2012; 741: 60-72.

[60] Baek JH, Moon CH, Cha SJ, Lee HS, Noh EK, Kim H, *et al*. Arsenic trioxide induces depolymerization of microtubules in an acute promyelocytic leukemia cell line. Korean J Hematol 2012; 47(2): 105-12.

[61] Azar AE, Ballas ZK. Evaluation of the adult with suspected immunodeficiency. Am J Med 2007; 120(9): 764-8.

[62] Trushina EN, Mustafina OK, Nikitiuk DB, Kuznetsov VD. Immune dysfunction in highly skilled athletes and nutritional rehabilitation. Vopr Pitan 2012; 81(2): 73-80.

[63] Savino W, Dardenne M. Nutritional imbalances and infections affect the thymus: Consequences on T-cell-mediated immune responses. Proc Nutr Soc 2010; 69(4): 636-43.

[64] Bisht M, Bist SS, Dhasmana DC. Biological response modifiers: Current use and future prospects in cancer therapy. Indian J Cancer 2010; 47(4): 443-51.

[65] Porteus MH, Fischer A. Engineering the immune system to cure genetic diseases, HIV, and cancer. Curr Opin Immunol 2012; 24(5): 576-9.

[66] Finn OJ. Immuno-oncology: Understanding the function and dysfunction of the immune system in cancer. Ann Oncol 2012; 23(8): 6-9.

[67] Hyland ME. Network origins of anxiety and depression. Behav Brain Sci 2010; 33(2-3): 161-2.

[68] Pőcze B, Németh P, Langer R. Recent options in drug therapy after solid organ transplantation. Orv Hetil 2012; 153(33): 1294-301.

[69] Chinen J, Shearer WT. Secondary immunodeficiencies, including HIV infection. J Allergy Clin Immunol 2010; 125(2): 195-203.

[70] De-Heredia FP, Gómez-Martínez S, Marcos A. Obesity, inflammation and the immune system. Proc Nutr Soc 2012; 71(2): 332-8.

[71] Kuo CH, Yang SN, Kuo PL, Hung CH. Immunomodulatory effects of environmental endocrine disrupting chemicals. Kaohsiung J Med Sci 2012; 28(7): S37-42.

[72] Taylor AK, Cao W, Vora KP, De-La-Cruz J, Shieh WJ, Zaki SR, *et al*. Protein energy malnutrition decreases immunity and increases susceptibility to influenza infection in mice. J Infect Dis 2013; 207(3): 501-10.

[73] Morzadec C, Bouezzedine F, Macoch M, Fardel O, Vernhet L. Inorganic arsenic impairs proliferation and cytokine expression in human primary T lymphocytes. Toxicology 2012; 300(1-2): 46-56.

[74] Thomas-Schoemann A, Batteux F, Mongaret C, Nicco C, Chéreau C, Annereau M, *et al*. Arsenic trioxide exerts antitumor activity through regulatory T cell depletion mediated by oxidative stress in a murine model of colon cancer. J Immunol 2012; 189(11): 5171-7.

[75] Noreault-Conti TL, Fellows A, Jacobs JM, Trask HW, Strom SC, Evans RM, *et al*. Arsenic decreases RXRα-dependent transcription of CYP3A and suppresses immune regulators in hepatocytes. Int Immunopharmacol 2012; 12(4): 651-6.

[76] Lee CH, Hong CH, Yu CL, Wang LF, Clausen BE, Liao WT, *et al*. Arsenic mobilizes Langerhans cell migration and induces Th1 response in epicutaneous protein sensitization via CCL21: A plausible cause of decreased Langerhans cells in arsenic-induced intraepithelial carcinoma. Biochem Pharmacol 2012; 83(9): 1290-9.

[77] Cho Y, Ahn KH, Back MJ, Choi JM, Ji JE, Won JH, *et al*. Age-related effects of sodium arsenite on splenocyte proliferation and Th1/Th2 cytokine production. Arch Pharm Res 2012; 35(2): 375-82.

[78] Soto-Peña GA, Vega L. Arsenic interferes with the signaling transduction pathway of T cell receptor activation by increasing basal and induced phosphorylation of Lck and Fyn in spleen cells. Toxicol Appl Pharmacol 2008; 230(2): 216-26.

[79] Hutchinson LM, Trinh BM, Palmer RK, Preziosi CA, Pelletier JH, Nelson HM, *et al*. Inorganic arsenite inhibits IgE receptor-mediated degranulation of mast cells. J Appl Toxicol 2011; 31(3): 231-41.

[80] Banerjee N, Banerjee S, Sen R, Bandyopadhyay A, Sarma N, Majumder P, *et al*. Chronic arsenic exposure impairs macrophage functions in the exposed individuals. J Clin Immunol 2009; 29(5): 582-94.

[81] Wang L, Weng CY, Wang YJ, Wu MJ. Lipoic acid ameliorates arsenic trioxide-induced HO-1 expression and oxidative stress in THP-1 monocytes and macrophages. Chem Biol Interact 2011; 190(2-3): 129-38.

[82] Yeşilada E. An overview of turkish folk medicine; past and present. Curr Drug Deliv 2013; 10(1): 92-5.

[83] Ortega RM. Importance of functional foods in the Mediterranean diet. Public Health Nutr 2006; 9(8A): 1136-40.

[84] Quideau S, Deffieux D, Douat-Casassus C, Pouységu L. Plant polyphenols: Chemical properties, biological activities, and synthesis. Angew Chem Int Ed Engl 2011; 50(3): 586-621.

[85] Ferrer JL, Austin MB, Stewart C Jr, Noel JP. Structure and function of enzymes involved in the biosynthesis of phenylpropanoids. Plant Physiol Biochem 2008; 46(3): 356-70.

[86] Tsao R. Chemistry and biochemistry of dietary polyphenols. Nutrients 2010; 2(12):1231-46.

[87] Marcano D, Hasegawa M. Consejo de Desarrollo Científico y Humanistico. In: Fitoquimica orgánica. 2nd ed. Torino: Caracas 2002; 117-234.

[88] Francisco M, Cartea ME, Butrón AM, Sotelo T, Velasco P. Environmental and genetic effects on yield and secondary metabolite production in *Brassica rapa* crops. J Agric Food Chem 2012; 60(22): 5507-14.

[89] Santos-Buelga C, Gonzalez-Manzano S, Dueñas M, Gonzalez-Paramas AM. Extraction and isolation of phenolic compounds. Methods Mol Biol 2012; 864: 427-64.

[90] Agati G, Azzarello E, Pollastri S, Tattini M. Flavonoids as antioxidants in plants: Location and functional significance. Plant Sci 2012; 196: 67-76.

[91] Foster DW. Malonyl-CoA: The regulator of fatty acid synthesis and oxidation. J Clin Invest 2012; 122(6): 1958-9.

[92] Tvrzicka E, Kremmyda LS, Stankova B, Zak A. Fatty acids as biocompounds: Their role in human metabolism, health and disease a review. Part 1: Classification, dietary sources and biological functions. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2011; 155(2): 117-30.

[93] Kuhnt K, Degen C, Jaudszus A, Jahreis G. Searching for health beneficial n-3 and n-6 fatty acids in plant seeds. Eur J Lipid Sci Technol 2012; 114(2): 153-60.

[94] Russo GL. Dietary n-6 and n-3 polyunsaturated fatty acids: From biochemistry to clinical implications in cardiovascular prevention. Biochem Pharmacol 2009; 77(6): 937-46.

[95] Deckelbaum RJ, Torrejon C. The omega-3 fatty acid nutritional landscape: Health benefits and sources. J Nutr 2012; 142(3): 587S-91S.

[96] Willis LM, Shukitt-Hale B, Joseph JA. Modulation of cognition and behavior in aged animals: Role for antioxidant- and essential fatty acid-rich plant foods. Am J Clin Nutr 2009; 89(5): 1602S-6S.

[97] Vanden-Heuvel JP. Nutrigenomics and nutrigenetics of ω3 polyunsaturated fatty acids. Prog Mol Biol Transl Sci 2012; 108: 75-112.

[98] Lorgeril M, Salen P. New insights into the health effects of dietary saturated and omega-6 and omega-3 polyunsaturated fatty acids. BMC Med 2012; 10(1): 50.

[99] Lands B, Lamoreaux E. Using 3-6 differences in essential fatty acids rather than 3/6 ratios gives useful food balance scores. Nutr Metab (Lond) 2012; 9(1): 46.

[100] Asif M. Health effects of omega-3, 6, 9 fatty acids: *Perilla frutescens* is a good example of plant oils. Orient Pharm Exp Med 2011; 11(1): 51-9.

[101] Mastaloudis A, Wood SM. Age-related changes in cellular protection, purification, and inflammation-related gene expression: Role of dietary phytonutrients. Ann N Y Acad Sci 2012; 1259: 112-20.

[102] Labunskyy VM, Gladyshev VN. Role of reactive oxygen species-mediated signaling in aging. Antioxid Redox Signal 2013; 19(12): 1362-72.

[103] Ströhle A, Hahn A. Importance of micronutrients for immunity preventive and therapeutic aspects. MMW Fortschr Med 2009; 151(3): 133-41.

[104] Skrovánková S, Mišurcová L, Machů L. Antioxidant activity and protecting health effects of common medicinal plants. Adv Food Nutr Res 2012; 67: 75-139.

[105] Chirumbolo S. Plant phytochemicals as new potential drugs for immune disorders and cancer therapy: Really a promising path? J Sci Food Agric 2012; 92(8): 1573-7.

[106] Paszkiewicz M, Budzyńska A, Różalska B, Sadowska B. The immunomodulatory role of plant polyphenols. Postepy Hig Med Dosw 2012; 66: 637-46.

[107] Magrone T, Jirillo E. Influence of polyphenols on allergic immune reactions: Mechanisms of action. Proc Nutr Soc 2012; 71(2): 316-21.

[108] Johansson S, Lönnqvist A, Ostman S, Sandberg AS, Wold AE. Long-chain polyunsaturated fatty acids are consumed during allergic inflammation and affect T helper type 1 (Th1)- and Th2-mediated hypersensitivity differently. Clin Exp Immunol 2010; 160(3): 411-9.

[109] Mitjavila MT, Moreno JJ. The effects of polyphenols on oxidative stress and the arachidonic acid cascade. Implications for the prevention/treatment of high prevalence diseases. Biochem Pharmacol 2012; 84(9): 1113-22.

[110] Miles EA, Calder PC. Influence of marine n-3 polyunsaturated fatty acids on immune function and a systematic review of their effects on clinical outcomes in rheumatoid arthritis. Br J Nutr 2012; 107(2): S171-84.

[111] Rothwell JA, Urpi-Sarda M, Boto-Ordoñez M, Knox C, Llorach R, Eisner R, *et al*. Phenol-Explorer 2.0: A major update of the Phenol-Explorer database integrating data on polyphenol metabolism and pharmacokinetics in humans and experimental animals. Database (Oxford) 2012; 2012: bas031.

[112] Fimognari C, Ferruzzi L, Turrini E, Carulli G, Lenzi M, Hrelia P, *et al*. Metabolic and toxicological considerations of botanicals in anticancer therapy. Expert Opin Drug Metab Toxicol 2012; 8(7): 819-32.

[113] Alcantar, N.A., Fox, D.I. Cactus mucilage and ferric ions for the removal of arsenate. WO2013040389 (**2013**).

[114] Meagher, R.B., Yujing, L., Dhankher, O.P. Metal resistant plants and phytoremediation of environmental contamination. US7700827 (**2010**).

[115] Darien, B.J., Godbee, R.G. *Morinda citrifolia* based formulations for regulating T cell immunomodulation in neonatal stock animals. US20090068204 (**2009**).

[116] Eichmann, K., Modolell, M. Extracts of the *Acanthospermum hispidum* plant. EP0436690 (**1994**).

[117] Saltzman, D.A., Leonard, A.S., Mueller, M.J. Immune enhancement by seed oil and/or seed flour. US20090324759 (**2009**).

[118] Yang, N., Wang, J. Wei, W. Dioscorea extracts for enhancing immune system. US7972645 (**2011**).

[119] West, B.J., Jensen, C.J., Palu, A.K., Deng, S., Wasden, J.A. *Garcinia mangostana* L. and iridoid based formulations. US20120021079 (**2012**).

[120] Wong, C., Hsu, H., Hua, K., Lin, C., Hsu, J., Chen, S., Lin, K., Yang, W., Yu, J., Yu, A. Methods and compositions associated with administration of an extract of *Ganoderma lucidum*. WO2006044616 (**2006**).

[121] Cowan, F.M. Phytochemical combinations that regulate pathological immunity. US20110305779 (**2011**).

[122] Holt, S. Herbal compositions, methods of stimulating immunomodulation and enhancement of immunomodulating agents using the herbal compositions. US20070196381 (**2007**).

[123] Sharma OP, Sharma S, Pattabhi V, Mahato SB, Sharma PD. A review of the hepatotoxic plant *Lantana camara*. Crit Rev Toxicol 2007; 37(4): 313-52.

[124] Sharma M, Rakhi A, Dalal N, Sharma N. Design, synthesis and evaluation of lantadene A congener with hydroxyl functionality in ring A as an antitumour agent. Nat Prod Res 2011; 25(4): 387-96.

[125] Grace-Lynn C, Darah I, Chen Y, Latha LY, Jothy SL, Sasidharan S. *In vitro* antioxidant activity potential of lantadene A, a pentacyclic triterpenoid of Lantana plants. Molecules 2012; 17(9): 11185-98.

[126] Sousa EO, Rodrigues FF, Campos AR, Lima SG, da-Costa JG. Chemical composition and synergistic interaction between aminoglycosides antibiotics and essential oil of *Lantana montevidensis* Briq. Nat Prod Res 2013; 27(10): 942-5.

[127] Tripathy A, Samanta L, Das S, Parida SK, Marai N, Hazra RK, *et al*. The mosquitocidal activity of methanolic extracts of *Lantana cramera* root and *Anacardium occidentale* leaf: Role of glutathione S-transferase in insecticide resistance. J Med Entomol 2011; 48(2): 291-5.

[128] Da-Conceição AO, De-Oliveira FF, De-Oliveira RA, De-J-da-S Junior A, Takser L, Reyes-Moreno C, *et al*. *Lantana macrophylla* Schauer (Verbenaceae) ethanolic extract induces activation of ERK1/2 and p38 MAPKs pathway and Ca^{2+} imbalance in human trophoblasts derived cell lines. Food Chem Toxicol 2012; 50(3-4): 1001-12.

[129] Carpinella MC, Andrione DG, Ruiz G, Palacios SM. Screening for acetylcholinesterase inhibitory activity in plant extracts from Argentina. Phytother Res 2010; 24(2): 259-63.

[130] García CC, Acosta EG, Carro AC, Fernández-Belmonte MC, Bomben R, Duschatzky CB, *et al*. Virucidal activity and chemical composition of essential oils from aromatic plants of central west Argentina. Nat Prod Commun 2010; 5(8): 1307-10.

[131] Soria EA, Goleniowski ME, Cantero JJ, Bongiovanni GA. Antioxidant activity of different extracts of Argentinian medicinal plants against arsenic-induced toxicity in renal cells. Hum Exp Toxicol 2008; 27(4):341-6.

[132] Volger, O.L., Shao, J., Cornelis Maria Peijnenburg, A.A. *In vitro* method for determining immunotoxicity of a compound. US20140080734 (**2014**).

[133] Ott, D.M. Personal care and medicinal products incorporating bound organosulfur groups. US20140050677 (**2014**).

[134] Khoo, C., Liska, D., Percival, S.S. Inflammation and immunity treatments. US20140134206 (**2014**).

[135] Soria EA, Quiroga PL, Albrecht C, Ramos Elizagaray SI, Cantero JJ, Bongiovanni GA. Development of an antioxidant phytoextract of *Lantana grisebachii* with lymphoprotective activity against *in vitro* arsenic toxicity. Adv Pharmacol Sci 2014; 2014: 416761.