Design and Evaluation of a Complex Phytoceutical Formulation for Circulatory Diseases

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1. Introduction

Although herbal/natural remedies have been, and are still being used, in the treatment of chronic degenerative diseases, little is known about basic principles -or theory- to combine these components and attain synergistic, gene modulating, as well as clinical health improving effects. This chapter is divided into six sections. Section 2 reviews the background which gives origin and establishes the Systemic Theory and Systemic Medicine. The section also provides the general precepts to structure Circulat -a complex herbal formulation- for the treatment of circulatory chronic degenerative diseases. Section 3 is an outline of an investigation into the aforementioned formulation's role and capability to modulate various gene expression levels -in cultured human fibroblasts- including those associated with diabetes. On the other hand, Section 4 presents a review of Circulat's clinical properties through a Diabetic Foot management Study. An abbreviated limited Phase 2 GSPECT evaluated Chronic Ischemic Disease -another circulatory chronic disease- study is presented in Section 5. Finally, Section 6 provides some conclusions concerning the use of a complex herbal formulation as well as some reflections on the future design of such compositions.

2. The origin of Systemic theory and Systemic medicine: Relevance to complementary and alternative medicine

Past and Present Phytomedicine and natural practitioners: Tomorrow's Systemics? Recent past -and even present- successful phytomedicine practitioners and naturalists share a long and honorable tradition of knowledge and pride in the cure of illnesses, which goes back to written history and beyond. These qualities have been substantiated by the successes of the Chinese (Chen *et al.*, 2004; Wago & Deng, 2004), Kampo (Terasawa, 2004; Yamada, 2004), Ayurvedic (Naik *et al.*, 2003), Chumash (Adams and Garcia, 2005) or Mayan (Peña, 2002) traditional medicines among many others. These traditional medicines 'demonstrated that every culture is capable of understanding and "inventing" the meaning of disease and its cure, even when it is different from our modern medical views' (Peña, 2002). The variability and extent of cultures to provide answers -or traditional medicines- to pathologies are embedded in the curiosity and observational

capabilities of the human race. There are also collective factors such as 'a background of extensive family in traditional medicine' (Vandenbroek *et al.*, 2004) which play an important role in the communication and survival of medicinal plant knowledge among ethnic groups. A potential issue, though, is the possible curtailment of the wisdom -and therapies- of traditional medicines within geographical and ethnic boundaries. In any case, the amount of plants, potential formulations or properties are a massive concern for any given individual caregiver or group to understand, store and transmit. Some exceptional individuals seem to have come by this ability. One of these gifted health care practitioners was Maurice Messegue, whom Mistinguet and Konrad Adenaur -among his famous patients- swore that only he could treat their illnesses. More recently, both, Dr. Rusudan Lomidze, using the Georgian Kohlkian traditional medicine, and Lonrig Dangar, a Tibetan physician who applied the rich Tibetan traditional medicine have also obtained significant success. These gifted individuals have shown that traditional medicine is a successful medicine. But a question still hangs in the air. Might a theory be devised by which regular practitioners, health care specialists devoid of the naturalists' extensive background, formulate natural organic therapeutic protocols? Furthermore, is it possible to set up a system -or periodic table- where plants and other natural remedies could, according to superior therapeutic properties, be arranged to produce specific formulae that provide well-being for a given pathology? The treatment of circulatory pathologies with substances which act only on function and structure might be an incomplete approach. Whether the investigations in circulatory chronic disease studies -and their results- can be generalized in confirmation of a systemic approach is something that should be pursued as this may pave the way for a new integral vision of therapeutics in general and/or in circulatory chronic diseases such as Diabetes in particular.

2.1 Prior developments of a natural therapeutic protocol: Systemic Theory

Aggressors or stressors were identified by Professor Hans Selye, and described and classified in over 1500 articles and 32 books. He formulated the General Adaptation Syndrome (Selye, 1976), which classified effects on animals and humans affected by threats (exhaustion, disease, fear, extreme cold ...) as: alarm (body's recognition of danger and its preparation to deal with threats); resistance (or adaptation, in which the body adapts to resist stress); and exhaustion (condition in which the body's energy supply is depleted). The next step was taken by Soviet scientists led by Lazarev and Brekhman, who investigated properties of substances, with the ability to increase adaptability and resistance to stress. They named these 'adaptogens'. By 1960 more than 1000 studies had been published by Soviet scientists concerning the use of adaptogens. In 1962, *Eleutherococcus senticosus*, *Rhaponticum carthamoides* and *Rhodiola rosea*, all adaptogens, were included in the Soviet Union's Pharmacopoeia. Since then many other plants and sources have been found to have similar properties (Brekman and Ivanov, 1969; Khasina *et al.*, 1983; Bhattacharya and Muruganandam, 2003; Dhuley, 2000) and increasing resistance to stressors as depicted by Selye, enhancing energy, and regulating immune, neuroendocrine and cellular function. Although the adaptogen definition in science is questioned by some researchers, most concur on their health enhancing properties (Davydov and Krikorian, 2000). Figure 1 (Olalde, 2005a) is an interpretation of Energy drop (E↓) in relation to Selye's description of biochemical collapse (I↓) and organic dysfunction (O↓). This paved the way to the E, I and O triangle.

Fig. 1. Functional energy reserve ladder. Energy drop affects the human organism, going from a state of well being with high Energy reserves and low entropy - low disorder- through various stages and finally to that of death, or state of zero energy and maximum disorder

2.1.1 Life and negentropy: Rationalization for the use of phytomedicines

The second law of thermodynamics states that a system logically tends to go from a state of higher energy and order to one of lower energy and disorder. This is more so in living systems where internal entropy tends to increase in its journey through life, going from health, energy and physiological order towards sickness, asthenia (the loss or lack of bodily strength; weakness) and physiological disorder. Illness, however, can be countered based on quantum physicist's Erwin Schrödinger's notion that the general change of entropy in an open system, such as a living (biological) system, consists of (i) internal entropy variations and (ii) entropy exchange of the system with the environment; i.e. $\Delta S = \Delta S_{\text{internal}} + \Delta S_{\text{exchange}}$. Internal entropy in a biological organism, by definition, tends to be greater than zero due to inner irreversible processes. Therefore, the increase in entropy of an open biological system, and thus illness, may be reduced (von Stockar and Liu, 1999) by providing negative entropy -or negentropy- from the environment. This is pivotal as nature provides a source of negative entropy. '... The decrease of entropy in living systems is provided by free energy, released when nutrients consumed from the outside dissociate, i.e. at the expense of the sun's energy. Thus, the flow of negative entropy is essential to compensate for inner destructive processes as well as for the decrease of available free energy dissipated by spontaneous metabolic reactions. This last, is the key point, circulation and transformation of free energy, which drives the functions of living systems ...' (Korotkov *et al.*, 2004).

2.2 ↑ Health ↔ entropy ↓

How does life defy entropy? In physics, entropy is defined as the measure of disorder in a system. Disorder, in turn, can be mathematically expressed by the probability of random occurrence. All pathologies, by definition, result from a higher than normal organic entropy; thus, to induce health, entropy must first be reduced; this is bi-conditional. Contemporary thermodynamics defines entropy (or chaos) in an intelligent system as a deficiency in energy

and/or information. Therefore, entropy is inversely related to information and energy availability. According to Shannon -father of the Information Theory- and Weaver 'information is always a measure of the decrease of uncertainty at a receiver or molecular machine' (Shanon and Weaver, 1999). Thus was born the concept of informational entropy, which they concluded was equivalent to a shortage of information content in a message. About the same time, Weiner (Weiner, 1954) established the possibility of interpreting information carried by a message as '... essentially the negative entropy, and the negative logarithm of its probability' since 'the relationship between information (J) and thermodynamic entropy (S) is constant ($S + J = \text{const}$)' (Korotkov, 1988). Thus, the work of such eminent minds as: Boltzmann (Lindley, 2001), Gibbs (Deltete, 1995), Szilard (Leff & Rex, 1990), Von Neumann (Heims *et al.*, 1980), Schrödinger (1992), Prigogine (1984), Shannon and Weaver (1999) and Weiner (Heims *et al.*, 1980; Weiner, 1954), brought about the dawn of new emergent fields, including: informational thermodynamics, information theory, biological information theory and cybernetics all dealing with energy, information and entropy in mechanical and living systems. A basic common premise in the new thinking proposes that information and energy had an inverse, i.e. opposite, correlation with entropy. In other words, evidence suggests that no suitable organization can be attained in living systems that possess reduced levels of information or energy. Disease, therefore, may be defined as a state of disorganization, i.e. higher organic entropy, corresponding with a low energo-informational status of the system. In consequence, if a reduction in illness is to be achieved, entropy must be reduced. A comprehensive way of accomplishing this, is administering negative entropy, or order, through matter which stimulates the production of energy and provides survival information to the immune, neuroendocrine and cellular systems. To recap, the tendency to reach order depends on the energy and information available within the system, which determines the possible level of stable organization possible. The quantity of true information (conceptual data, not noise) transferred to the system's modulating intelligence allows for chaos and/or confusion management and, enhances the system's ability to attain a higher organization level. Moreover by definition, only an intelligent system can process information and energy to reduce entropy. This unequivocal fact demonstrates the existence of a regulating biological intelligence within the human body. Intelligence is the way in which life affronts entropy.

2.2.1 The E, I and O health triangle

All living systems are functional units that seek maximum survival. The cell is the simplest form of a living system that functions as a basic building block of the living universe, just as an atom does in matter. Conversely, a virus is the simplest living unit, which in some situations acts as destroyer of living systems. **I** (or Intelligence) is the backbone of every living system in equilibrium. **I** controls, regulates, adapts and develops the living system. Chaos occurs in its absence. The proof of this is that no living system can exist without intelligence. The intelligence of the system, **I**, creates and utilizes **E** (or Energy) with the primary role of achieving **O** (Organization) and evolving into a higher system (Owens and Van de Castle, 2004). **I** also creates/builds **O** with the primary end of producing **E**. There can be a corollary: as a consequence, **I** cannot act optimally when subjected to a severe deficiency of **E**. Finally, **I** is the most important side of the health triangle since it concurrently generates both energy (**E**) and organization (**O**). One phytochemical that can increase all sides is *Panax ginseng* (Figure 2).

Fig. 2. (a) Example of a living system's health triangle. (b) Evolution from a given health situation and initial E, I, O triangle (left) to an improved E, I, O triangle (right). All sides are boosted due to negative entropy provided by *Panax ginseng*.

2.2.2 Example of I, E and O increase by providing *Panax ginseng*

Panax ginseng active principles are bonded to beta-adrenoceptors in the cellular membrane, triggering a secondary transmitting message system (cyclic AMP) which travels through a transducer pathway to the mitochondria to increase MDH, SDH and CTS activity, enzymes of the glycolysis or tricarboxylic acid cycle. ATP generation is thus increased, raising energy levels using glucose as fuel (Figure 3a). Thus, either the ATP/ADP ratio increase or the binding of ginsenosides to cell membrane receptors results in the KATP channel closure and insulin secretion (Rotsheyn & Zito, 2004) (Figure 3b). Thus with the increase of energy a larger health triangle is obtained and the system's intelligence has acquired more capacity to organize. *Panax ginseng* provides an example of a remarkable phytomedicine which is capable of enhancing I, E and O simultaneously in the living system.

2.3 Significance of the intelligence (I) within the systemic triangle. What is intelligence?

The importance (and significance) of a system's intelligence is pivotal. How can this controversial and subjective concept be defined accurately? Olalde (2005a) confronted this dilemma by examining its definition in different fields. Table 1 lists different concepts of the term intelligence.

Fig. 3. a: (top) *Panax* intracellular action mechanism results in ATP synthesis stimulation, whose hydrolysis produces energy; b: (bottom) shows the Sodium-potassium ATP pump, illustrating ATP generation by administering ginsenosides in *Panax ginseng* to the Living System.

Domain	Reference	Definition of intelligence
Cybernetics	Wiener, 1954	That whose core concepts are communication, control and learning, by means of feedback mechanisms.
Physics		Refers to regulation processes.
Biophysics		Living system's endogenous regulation processes effectively constitute intelligence.
Encyclopedic Neufeldt V, Guralnik D (Eds)	Webster's New World Dictionary(1988)	(a) Ability to learn or understand from experience. (b) Ability to acquire and retain knowledge. (c) Ability to respond quickly and successfully to a new situation. (d) Use of the faculty of reason in resolving problems, directing conduct, etc. effectively. (e) An intelligent spirit or being. (f) Having knowledge, understanding or awareness.
Multivarious	World Wide Web	a) Ability of a system to process general information to react appropriately to specific events; b)The product of communication, resulting from the collection, processing, integration, analysis, evaluation and interpretation of available information; c)Ability to acquire, store, retrieve, process and generate information; d) Ability to learn or understand or to deal with new or challenging situations; e) Accumulation of experiences together with the understanding of how these experiences are connected; f)Capacity to act purposefully, to think rationally, to communicate and to deal effectively with his or her environment. (g) Entity. (h) Emergent.

Table 1. Definitions of Intelligence

2.3.1 Intelligence = Informational entity

By analyzing common traits within the definitions given in Table 1, intelligence may be defined as that emergent informational entity, capable of learning, exerting control, emitting and receiving communication, handling energy flows, establishing feedback mechanisms and creating organization for survival. Emergent implies a higher level of intelligence of the whole, stemming from the intelligence of its parts. According to Laszlo, living systems are special third-stage systems, self-creating and self-replicating, that engender order out of chaos (Lazlo, 1987). However, Wiener states 'It is my thesis that the physical functioning of the living individual and the operation of some of the newer communications machines are precisely parallel in their analogous attempts to control entropy through feedback' (Wiener, 1954). The notion of intelligence that Olalde (2005) adopts is that of an informational entity, i.e. one which is emergent, can generate, process and exchange informational flows in order to control entropy. The concept of intelligence becomes more objective, and functional, when treated as an informational entity, one dependent on information exchange, which as we know has a thermodynamic interpretation. A change of entropy (ΔS) will produce a change or variation in information availability, and therefore a change in intelligence and

order in the biological system. Any entity that can exchange informational flows can also generate changes of entropy. Thus, informational flow $\leftrightarrow$ change in entropy $\leftrightarrow$ change in intelligence. According to Stonier's proposed theory 'Pure energy can perform no 'useful' work (entropy reducing) without a concomitant input of information (Stonier, 1996). Conversely, all expenditures of energy lead to a reorganization of the universe, hence a change in its information status. Energy and information are inter-convertible'. This theory could provide additional support for the indispensable existence of an intelligent entity to handle information, since information without intelligence is without value. A possible corollary is: intelligence is that entity which can causatively alter entropy; and vice versa, entropy changes will also affect intelligence. Figure 4 shows an intelligent cell, an example of an informational entity capable of modifying entropy.

Fig. 4. A living system possesses intelligence and is capable, as human cells demonstrate, of an informational flow and exchange with other cells, organs and living systems. This communicational flow may have various 'vehicles' and 'avenues'.

2.4 Synergy and informational systems

Synergy is a quality of informational systems. It may be understood as emergent, i.e. the informational participation of each fractal member of the system in order to achieve a higher plateau of self-organization and survival (Haken, 2005). It can also be understood as the resulting effect that is greater than the algebraic sum of the parts. Synergy is an important characteristic of third-stage systems. The increase of energy availability within a third-stage, living, system also decreases its entropy, potentially generating an endogenous tendency for informational flow and a heightened intelligence; this in turn generates organization. By analogy, an increase of information will, on its own, raise intelligence which will positively influence energy and organization. In synergic terms, each of the three elements shown above has the capacity to affect (increase or decrease) the other two. Thus we derive the following synergic bi-conditionals, inherent to any third-stage system: survival potential = health = $\uparrow I \leftrightarrow \uparrow E \leftrightarrow \uparrow O \leftrightarrow S \downarrow$ and also demise = sickness = $\downarrow I \leftrightarrow \downarrow E \leftrightarrow \downarrow O \leftrightarrow S \uparrow$.

2.4.1 Informational substantiation of biological intelligence

If there is communication, intelligence exists. Communication is a manifestation of intelligence. The existence of biochemical and bio-photonic communication in cells has been corroborated: biochemical communication, for example, between the neurological and

immune systems, has been examined, among others, by Blalock (1989), Cavagnaro and Lewis (1989) and more recently Takeda and Okomura (2004) and Cooper (2004). The biophotonic communication concept was discovered by Alexander Gurwitsch in 1923, as an 'ultraweak' photon emission from living systems (Gurwitsch, 1991). About the same time, Frolich, father of the 'coherent' notion of living systems, discovered that nucleated cells are capable of picking up, storing and broadcasting information about the environment. The term biophotons '...denotes a permanent spontaneous photon emission from all living systems...' and explains '... biological phenomena like intracellular and intercellular communication, cell growth and differentiation, interactions among biological systems and microbial infections...' (Popp, 2003). Different scientific groups have confirmed the existence of (and suggested some uses for) this subtle photon emission in: Australia (Tilbary & Quickenden, 1988; Trushin 2003), Japan (Kobayashi *et al.*, 1996; Takeda *et al.*, 1998), Poland (Slawinska & Slawinski, 1987) and Germany (Popp, 2003). Other prominent scientists in the study of biophotons are Professor Voikov (Voikov, 2003) and Dr. Albrecht-Buehler. This last sustains the thesis that cells are intelligent: 'capable of deriving abstract data and emitting near infrared signals' (Albrecht-Buehler, 1998, 1985).

2.4.2 Biological Intelligence (BI)

Intelligence is best measured by its manifestations. In structural terms, the BI is 'omnipresent' in the organism due to the intelligent nature of all cells (Gurwitsch, 1991); however, in functional terms, the BI's common denominator is comprised of the immune intelligence (II), cellular intelligence (CI) and biochemical (or neuroendocrine) intelligence (BI) (Blalock, 1989; Cavagnaro and Lewis, 1989; Cooper, 2004; Takeda and Okomura, 2004). The BI functions as an emergent informational entity, oriented towards survival, capable of auto-regulation, bidirectional communication, generating, processing and manipulating energy flows within the body. It is in charge of establishing, maintaining and restituting the organization. Figure 5 shows the interaction between neuroendocrine, immune and cellular intelligence. CI is the most important of BI's constituents since it regulates genetics and metabolism of each and every organic cell and gives birth to the autonomous II and BI. These three elements also constitute a synergistic trio, since none of them can exist in the absence of another, due to essential feedback and information exchange amongst them (Blalock, 1989; Cavagnaro and Lewis, 1989; Cooper, 2004; Takeda and Okomura, 2004). BI could also be represented schematically as a triangle, since alterations to one side of a triangle always affect the other two. Its healing potential may be defined as the mathematical product of its immune, cellular and neuroendocrine state, i.e. BI (Healing Potential) = $II \times CI \times BI$. In consequence, it is possible to enhance BI by increasing any of its three essential components, for example with immune modulators (Bocharova *et al.*, 2003; Geng *et al.*, 2005; Kidd, 2000; Kohguchi *et al.*, 2004; Kormosh *et al.*, 2004). The opposite also holds true, a collapse of any component will affect the other two.

2.5 From Systemic theory to Systemic medicine

At the beginning of this section a question was posed. Was it possible to set up a system -or periodic table- where plants and other natural remedies could, according to their superior medicinal properties, be arranged to produce specific formulae that provide well-being for a given pathology? The Systemic Theory was set forth to provide an answer to this crucial question. Systemic Theory postulates that Health (H) is directly proportional to the integrity

of a living system's Energy (E), Bio-Intelligence (I) and Organization (O). Systemic Theory also established a common denominator to all sickness and ascertains the cause of all diseases to be an entropy increase: 'disorder augmenting within the biologically open system, stemming from energo-informational and organizational impacts, either of external or internal nature' (Olalde, 2005c). Systemic Therapeutics -or Medicine- should then include a negentropy supply to enhance the system's: energy-work capacity or E (i.e. physiological mechanisms associated with ATP synthesis, such as oxidative phosphorylation, Krebs cycle, β -oxidation etc.), its informational potential intelligence or I (i.e. the entity responsible for regulating neuroendocrine, biochemical, immune and cellular processes) and finally structure and functional organization or O. Systemic Medicine's (SM) treatment strategy is based on identifying and prescribing superior herbs—tonic or adaptogenic—or any nutraceuticals or medicine with potential to strengthen E, I, O by providing energo, informational and organizational aid to the overall network of intelligent cells and cell systems that constitute the body. The main premise proposes that when all three factors are brought back to ideal levels patients' conditions begin recovery to normal health. Table 2 provides a list of some E, I and O ceuticals -or superior medicines- whose capacity to enhance E, I and O have been studied and referenced.

Fig. 5. An example of known cross-talk communication, bidirectional and bi-conditional, between the I^I (immune intelligence), C^I (cellular intelligence) and B^I (biochemical or neuroendocrine intelligence) in a human living system.

E-Energoceuticals that enhance mitochondrial ATP synthesis and resynthesis		I- Infoceuticals that enhance biointelligence on cellular, neuroendocrine and immune levels		O-Organoceuticals that specifically enhance organ function and structure	
Names	References	Names	References	Names	References
<i>Acantopanax senticosus</i>	Wu <i>et al.</i>	<i>Uncaria tomentosa</i>	Sheng <i>et al.</i> ; Akesson <i>et al.</i>	<i>Glycyrrhiza glabra</i>	Acharya <i>et al.</i>
<i>Cornu Cervi pantotrichum</i>	Kim KS <i>et al.</i> Zhang <i>et al.</i>	<i>Aloe vera</i>	Kim HS <i>et al.</i>	<i>Curcuma Longa</i>	Chainani-Wu
<i>Ilex paraguariensis</i>	Gorgen <i>et al.</i>	<i>Andrographis paniculata</i>	Matsuda <i>et al.</i> ; Puri <i>et al.</i>	<i>Ulmus fulva</i>	Brown <i>et al.</i>
<i>Lepidium meyenii</i>	Lopez-Fando <i>et al.</i>	<i>Astragalus membranaceus</i>	Wang <i>et al.</i> ; Shao <i>et al.</i>	<i>Angelica sinensis</i>	Mei <i>et al.</i> ; Yin
<i>Ocimum sanctum</i>	Agrawal <i>et al.</i>	<i>Croton lechleri</i>	Risco <i>et al.</i>	<i>Chondroitin/ glucosamine</i>	Houpt <i>et al.</i>
<i>Panax ginseng</i>	Yang <i>et al.</i>	<i>Echinacea purpurea</i> and <i>E. angustifolia</i>	Randolph <i>et al.</i> , Cundell Kohguchi <i>et al.</i> ; Jiang <i>et al.</i>	<i>Chitin fiber</i>	Jing <i>et al.</i>
<i>Panax quinquefolius</i>	Wang <i>et al.</i>	<i>Ganoderma lucidum</i>		<i>Crataegus oxyacantha</i>	Rigelsky and Sweet ; Lacaille-Dubois <i>et al.</i>
<i>Pfaffia paniculata</i>	Kotsiuruba <i>et al.</i> ; Tashmukhamedova <i>et al.</i>	<i>Grifola frondosa</i>	Odama <i>et al.</i> ; Lin <i>et al.</i>	<i>Dioscorea villosa</i>	Shealy; Ladriere <i>et al.</i>
<i>Ptychopetalum olacoides</i>	Siqueira <i>et al.</i>	<i>Hydrastis canadensis</i>	Rehman <i>et al.</i>	<i>Plants enzymes</i>	Popiela <i>et al.</i>
<i>Rhaponticum carthamoides</i>	Kutuzova <i>et al.</i>	<i>Morinda citrifolia</i>	Su <i>et al.</i>	<i>Equisetum arvense</i>	Blumenthal <i>et al.</i> ; Fleming
<i>Rhodiola rosea</i>	Maslova <i>et al.</i> ; Spasov <i>et al.</i>	<i>Petiveria alliacea</i>	Ruffa <i>et al.</i> ; Malpezzi <i>et al.</i>	<i>Ginkgo biloba</i>	Kubota <i>et al.</i> ; Pepe <i>et al.</i>
<i>Schizandra chinensis</i>	Antoshechkin	<i>Sutherlandia frutescens</i>	Bence and Crooks; Jang <i>et al.</i> Planchon <i>et al.</i> ; Li <i>et al.</i>	<i>Gotu kola</i>	Incandela <i>et al.</i>
<i>L-arginine</i>	Gupta <i>et al.</i>	<i>Tabebuia avellana</i>		<i>Sargassum fusiforme</i>	Ji <i>et al.</i>
<i>Ubiquinone (Coenzyme Q10)</i>	Baggio <i>et al.</i>	<i>Valeriana officinalis</i>	Dietz <i>et al.</i>	<i>Harpagophytum procumbens</i>	Chrubasik <i>et al.</i>
		<i>Vitex agnus castus</i>	Kobayakawa and Sato-Nishimori; Ohyama <i>et al.</i>	<i>Vitamins</i>	Carrero <i>et al.</i>
		<i>Lentinus edodes</i>	Borchers <i>et al.</i> ; Wasser and Weis	<i>Minerals</i>	Hercberg <i>et al.</i>
		<i>Coriolus versicolor</i>	Sun and Zhu, Sun <i>et al.</i>	<i>Ptycopetalum olacoides</i>	Bucci; Siqueira <i>et al.</i>

E-Energoceuticals that enhance mitochondrial ATP synthesis and resynthesis	I- Infoceuticals that enhance biointelligence on cellular, neuroendocrine and immune levels	O-Organoceuticals that specifically enhance organ function and structure
	<i>Cordyceps sinensis</i> Leu <i>et al.</i>	<i>Pygeum africanum</i> Freeman and Solomon, Santa Maria Margalef <i>et al.</i> <i>Rhamnus purshiana</i> Ma <i>et al.</i> <i>Ruscus aculeatus</i> Redman, Bouaziz <i>et al.</i> <i>Salix alba</i> Chrubasik <i>et al.</i> <i>Sena alejandrina</i> Franz <i>Serenoa repens</i> Goldmann <i>et al.</i> ; Iguchi <i>Silibum marianum</i> Halim <i>et al.</i> ; Chrungoo <i>et al.</i> <i>Smilax china</i> Lee <i>et al.</i> <i>Tribulus terrestris</i> Hong <i>et al.</i> <i>Vaccinium myrthillus</i> Zaragoza <i>et al.</i> ; Savickiene <i>et al.</i> <i>Viburnum spp.</i> Calle <i>et al.</i> <i>Zingiber officinalis</i> Young <i>et al.</i>

Table 2. Examples of ceuticals -or superior medicines- whose capacity to enhance E, I and O has been studied and referenced

2.5.1 The case for a systemic complex herbal formulation: Circulat

Thus a composition was formulated taking into account the precepts established in both the Systemic Theory and Medicine. Circulat is a systemic standardized HPLC fingerprinted plant extract combination which consists of: 1) Energy plants (E) associated with ATP synthesis (such as tricarboxylic acid cycle, oxidative phosphorylation, etc) which boost the system's energy-work capacity: *Eleutherococcus senticosus*, *Leuzea carthamoides*, *Panax ginseng*, *Panax quinquefolius*, *Pfaffia paniculata*, and *Rhodiola rosea*; 2) Bio-Intelligence plants (I) which modulate the neuroendocrine and immunological systems and cellular processes enhancing the system's informational potential intelligence (specifically in this formulation they increase insulin production, insulin receptor sensitivity, improve intracellular glucose uptake, contribute anti-microbial properties, improve inflammation as well as humoral and unspecific cellular immunity): *Echinacea angustifolia*, *Echinacea purpurea*, *Ganoderma lucidum*, *Grifola frondosa*, *Hydrastis canadensis*, *Petiveria alliacea*, *Sutherlandia frutescens*, and *Uncaria tomentosa*; and finally 3) Organizational plants (O) which enhance the structure and functional organization of specific organs supporting overall health (in Circulat's case, among others, promoting vasodilatation, tissular perfusion improvement, regeneration and skin scarring): *Angelica sinensis*, *Crataegus oxyacantha*, *Croton lechleri*, *Ginkgo biloba*, *Hydrocotyle asiatica*, *Ruscus aculeatus*, *Vaccinium myrthillus*, and *Tabebuia avellanedae*. Although some of these plants act predominantly over one of the factors that influence individual's overall health (E, I, and O), some act over more than one factor (i.e. *Panax* and *Ganoderma*). Please, see Table 3.

Energy plants	
<i>Panax ginseng</i> and <i>Panax quinquefolius</i>	Increases ATP synthesis by stimulating activities of enzymes related to tricarboxylic acid cycle and oxidative-phosphorylation, such as succinate dehydrogenase, malate dehydrogenase, citrate synthetase, cytochrome oxidase, and phosphorylase (Wang <i>et al.</i> , 2003).
<i>Eleutherococcus senticosus</i>	Increases ATP synthesis by stimulating activities of enzymes related to tricarboxylic acid cycle, such as succinate dehydrogenase and malate dehydrogenase (Sugimura <i>et al.</i> , 1989).
<i>Leuzea carthamoides</i> and <i>Pfaffia paniculata</i>	Increase ATP synthesis, stimulates activities of enzymes related to tricarboxylic acid cycle, such as succinate dehydrogenase. Also, normalize NADH dehydrogenase activity, enzyme related to the oxidative phosphorylation processes, contributing to buildup the electrochemical potential used to produce ATP (Tashmukhamedova <i>et al.</i> , 1986).
<i>Rhodiola rosea</i>	Activates ATP synthesis/resynthesis in mitochondria, stimulates reparative energy processes (Abidov <i>et al.</i> , 2003).
Anti-inflammatory-Immunostimulant plants (Immune Intelligence)	
<i>Tabebuia avellanadea</i>	Inhibits NO, iNOS, COX-2 and PGE(2) release. Attenuates expression of mRNA and pro-inflammatory cytokines proteins, such as interleukin (IL)-1beta, IL-6 and tumor necrosis factor (TNF)-alpha. Suppresses NF-kappaB activation by blocking IkappaBalpha degradation and downregulating ERK, p38 mitogen-activated protein kinase (MAPK) and Akt pathway (Moon <i>et al.</i> , 2007).
<i>Echinacea angustifolia</i> and <i>Echinacea purpurea</i>	Due to: a) reduction of IL-2 production (Sasagawa <i>et al.</i> , 2006); and b) down-regulation of COX-2 expression (Groom <i>et al.</i> , 2007). Immune-stimulant due to: a) macrophage phagocytosis stimulation (Raso <i>et al.</i> , 2002); b) cellular immunity and neutrophils' phagocytosis stimulation. Increases number of leucocytes and lymphocytes, especially T lymphocytes (Jurkstiene <i>et al.</i> , 2004); c) Significant enhancement of IgM specific antibody forming cell response (Freier <i>et al.</i> , 2003); d) complement properdin increases (Kim <i>et al.</i> , 2002).
<i>Ganoderma lucidum</i>	Promotes phagocytosis and cytotoxicity of macrophages (Zhu <i>et al.</i> , 2007).
<i>Grifola frondosa</i>	Antiinflammatory: because it inhibits cyclooxygenase (COX) enzyme (Zhang <i>et al.</i> , 2002). Immunoestimulant because it: Increases IL-10, NO and IFN-gamma. Enhances both the innate and adaptive arms of the immune response (Kodama <i>et al.</i> , 2004).
<i>Hydrastis canadensis</i>	Antiinflammatory due to a prostaglandin E2 production reduction as a result of AP-1 binding inhibition (Kuo <i>et al.</i> , 2004).
<i>Sutherlandia frutescens</i>	Antiinflammatory, inhibits COX-2 and through activation of activator protein-1 (AP-1) (Kundu <i>et al.</i> , 2005).
<i>Uncaria tomentosa</i>	Antiinflammatory achieved by a TNFalpha and PGE2 production inhibition (Piscoya <i>et al.</i> , 2001). Immunostimulant because it stimulates macrophage phagocytosis (Groom <i>et al.</i> , 2007).
<i>Panax ginseng</i> and <i>Panax quinquefolius</i>	Antiinflammatory: It inhibit iNOS and COX-2 protein expression, and activates the transcription factor, NF-kappaB (Park <i>et al.</i> , 2004). Immunomodulator: Increases neutrophiles and macrophages phagocytosis, stimulates humoral and cell immune factors and induces important regulating cytokins – interferone gamma and tumor necrosis factor (Smolina <i>et al.</i> , 2001).

<i>Eleutherococcus senticosus</i>	Immunoestimulant: Activates B cells and macrophages (Han <i>et al.</i> , 2003).
<i>Pfaffia paniculata</i>	Increases macrophage activity (Pinello <i>et al.</i> , 2006)
<i>Angelica sinensis</i>	Immunomodulatory activity by regulating expression of Th1 and Th2 related cytokines (Yang <i>et al.</i> , 2006).
Hypoglycemic plants (Biochemical Intelligence)	
<i>Panax ginseng</i>	Reduces blood glucose levels (Reay <i>et al.</i> , 2005). Inhibits glycated hemoglobin formation (Bae and Lee, 2004).
<i>Panax quinquefolius</i>	Decreases postprandial glycemia (Vuksan <i>et al.</i> , 2000)
<i>Eleutherococcus senticosus</i>	Lowers circulating glucose and lipids, and enhances insulin action (Park <i>et al.</i> , 2006). Improves insulin sensitivity (Liu <i>et al.</i> , 2005).
<i>Ganoderma lucidum</i>	Stimulates glucose uptake, stimulating the activity of phosphatidylinositol 3-kinase, Protein kinase B, AMP-activated protein kinase which are regulatory molecules in the glucose uptake pathway (Jung <i>et al.</i> , 2006). Lowers glucose levels through insulin-releasing activity due to facilitation of Ca ²⁺ inflow to pancreatic beta cells (Zhang and Lin, 2004).
<i>Grifola frondosa</i>	Decreases fasting plasma glucose levels and increases insulin sensitivity (Hong <i>et al.</i> , 2007).
<i>Hydrastis canadensis</i>	Stimulates glucose uptake via: increasing GLUT1 activity and adenosine monophosphate-activated protein kinase and acetyl-coenzyme A carboxylase phosphorylation (Zhou <i>et al.</i> , 2007); and through AMP-AMPK-p38 MAPK pathway (Cheng <i>et al.</i> , 2006). Inhibitor of aldose reductase (Feng <i>et al.</i> , 2005).
<i>Petiveria alliacea</i>	Decreases: a) blood glucose levels (Lores and Cires Puyol, 1990); and b) fasting glucose, post-prandial glucose levels, and hemoglobin A1c in type 2 diabetic patients, by acting downstream in the insulin signaling pathway (Kim <i>et al.</i> , 2007).
<i>Sutherlandia frutescens</i>	Normalizes insulin levels and increases glucose uptake (Chadwick <i>et al.</i> , 2007). Decreases fasting glucose, post-prandial glucose levels, and hemoglobin A1c in type 2 diabetic patients, by acting downstream in the insulin signaling pathway (Kim <i>et al.</i> , 2007).
Antimicrobial and Skin Scarring plants (Organization)	
<i>Tabeuia avellanadae</i>	Antibacterial activity against methicillin-resistant <i>S. aureus</i> , <i>S. epidermidis</i> and <i>S. haemolyticus</i> strains, being the two last ones hetero-resistant to vancomycin (Pereira <i>et al.</i> , 2006).
<i>Petiveria alliacea</i>	Broad spectrum of antimicrobial activity (Kim <i>et al.</i> , 2006).
<i>Hydrastis canadensis</i>	Broad spectrum of antimicrobial activity (Scazzocchio <i>et al.</i> , 2001).
<i>Sutherlandia frutescens</i>	Antibacterial against <i>S. aureus</i> , <i>E. faecalis</i> and <i>E. coli</i> (Katerere and Elfo, 2005).
<i>Uncaria tomentosa</i>	Antimicrobial activity on Enterobacteriaceae, <i>S. mutans</i> and <i>Staphylococcus</i> spp. (Ccahuana-Vasquez <i>et al.</i> , 2007).
<i>Croton lechleri</i>	Potent anti-bacterial activity (Chen <i>et al.</i> , 1994). Cicatrizant effect because it increases the migration of skin fibroblasts (Vaisberg <i>et al.</i> , 1989).
<i>Hydrocotyle asiatica</i>	Promotes fibroblast proliferation and extracellular matrix synthesis in wound healing because it upregulates 54 genes with known functions for cell proliferation, cell-cycle progression and synthesis of the extracellular matrix (Lu <i>et al.</i> , 2004).

Table 3. Circulat's E, I and O -referenced- components and action mechanisms.

3. Assessment of Circulat's capability to modulate diabetes related gene expression levels in cultured human fibroblasts

Circulat had provided an auspicious early clinical proof of its effectiveness (Olalde *et al.*, 2005) in the treatment of Diabetic Foot –a circulatory disease. However, a pending assignment was to confirm its molecular activity. One way to test this characteristic was to identify the modulating and/or synergistic roles that such formulation could have in diseases such as Diabetes Mellitus (I and II). The study called 'Analysis of the Effects of the Herbal preparation Circulat on Gene Expression Levels in Cultured Human Fibroblasts' was carried out in cooperation with the Pennsylvania State University, Department of Genetics (Antoshechkin *et al.*, 2007).

3.1 Materials and methods

Circulat whole composition -a lyophilized ethanol/water extract of 22 known medical plants in different ratios- and its three E, I and O fractions (or components 1, 2 and 3) identical and in the same proportion as in the formula were tested using microarray analysis using the Affymetrix GeneChip Human Genome U133 Plus 2.0 arrays that provide full genomic coverage and contain probes for more than 47 000 unique transcripts corresponding to more than 38 500 human genes. This allowed monitoring simultaneously the expression levels of practically all annotated genes of the human genome in an unbiased manner. Following hybridization and scanning, raw data in the form of image files were converted to gene expression files using the Affimatrix GeneChip Operating Software (GCOS) which utilizes MAS 5.0 algorithm for data normalization, background subtraction, and the estimation of nonspecific binding, calculation of detection p-values and generation of presence calls. Two-tailed Taylor Student's t-test assuming unequal sample variance was used to identify genes that displayed significant changes in the mean expression levels between control and each of the treated samples with the t-test-p value less than 0.05 and the mean fold change of at least 2. By comparing up and down regulated genes in each individual fraction and whole Circulat, additional genes were identified that were regulated between 1.5 and 2 fold in the whole preparation and followed the same trend as in individual fractions, where they were up -or down-regulated by at least 2 fold.

3.1.1 Results

The Affymetrix GeneChip represents state of the art in microarray design and features both perfectly matched and off-by-one probes that together with sophisticated processing algorithm allow distinguishing precisely between specific and non-specific hybridization signals. It has been proven to produce highly reliable data, which in combination with the high quality of starting RNA and sufficient number of replicates virtually eliminates false-positives. Significant changes in the mean expression levels between control and treated samples resulted in a list of 87, 96, 24 and 187 genes (probes) that were significantly up - or down- regulated upon treatment with components 1, 2, 3 and whole Circulat, respectively. The genes regulated by the individual components and the whole Circulat formula showed a significant overlap, as expected. More than 80% of the genes affected by the individual fractions were also affected by the whole preparation. Analysis of the data for each of the three components also identifies a sizable number of genes (23) that

did not show up in the whole Circulat analysis. On the other hand, 55 genes the expression of which changed significantly after Circulat treatment were not observed in any of the three fractions. The regulation of these 32 genes by Circulat is more likely due to the interaction between active ingredients of the three components that produce a synergistic effect on gene regulation. Taken together the data demonstrates that: 1) Treatment of human fibroblast cells with either Circulat or its components result in marked changes in gene expression patterns; 2) Significant interactions between the active ingredients of Circulat exist resulting in a more complex pattern of gene expression in the complete preparation when compared with those of the isolated components which can be understood to be synergistic. Figure 6.

The formulation modulates 32 additional genes than the sum of formulas' individual fractions

Fig. 6. Circulat -as a whole- modulates 187 genes, 32 genes more than the sum of the E, I and O fractions that make it up.

3.1.2 Analysis of processes and pathway affected by circulat

Examination of the biological process subset of Gene Ontology (GO) terms (Ashburner *et al.*, 2000) associated with each gene and their distribution revealed that genes affected by Circulat are involved in a variety of cellular processes including protein, nucleic acid, lipid and carbohydrate metabolism, regulation of transcription, response to endogenous and external stimuli and stress, signal transduction and cell communication, cell growth and proliferation, development, protein modification and biosynthesis, generation of precursor metabolites and energy, etc. The broad spectrum of processes potentially regulated by Circulat (Figure 7) is consistent with the established ability of Circulat to prevent the development of severe manifestations of type 2 diabetes, which is a complex syndrome

involving many intracellular signaling cascades and pathways as well as cell-cell interactions.

Fig. 7. Number of genes involved in a particular process that were affected by treatment is indicated. Numbers correspond to the number of probes that are annotated within a particular process.

Many of those pathways are involved in energy generation and are regulated on both transcriptional and post-transcriptional levels in response to endogenous or exogenous stimuli. A high proportion of genes identified in the experiments are implicated in the regulation of transcription (e.g. ATF3, Kruppel-like factor 4 Zinc finger protein 117, SATB2), energy production and glucose metabolism (thioredoxin domain containing 11, ATP5F1, PGK1) and signal transduction corroborating the hypothesis that Circulat is capable of normalizing molecular processes perturbed in the course of type 2 diabetes. Specially, Circulat proves to be effective in the treatment of diabetic gangrene, which is often resistant to common treatments. Previous studies have suggested that impaired fibroblast function such as proliferation, cell migration, growth factor production and collagen synthesis may be part of the mechanism of diabetic necrotic damage. Fibroblasts are central to the processes of extracellular matrix deposition and remodeling that take place during tissue repair process. It functions both as a synthetic cell, depositing a collagen-rich matrix, and a signaling cell, secreting the growth factors important for cell-cell communication during the tissue repair process. Many Circulat-regulated genes play roles in signal transduction and cell communication (ADAM32, TRIO, RAB7), response to endogenous and exogenous stimuli, an essential component in wound healing (FANCB, SLC19A2, C4A), growth factor-mediated signaling and cell motility (IL6, CXCL2, VIM), cell proliferation and biosynthesis (PBEF1, ABP1, PTGS2) corroborating Circulat's effectiveness in tissue repair. Furthermore, tissue remodeling involves both the generation of new cell types as well as regulated cell death, and several genes important for cell differentiation and apoptosis were identified in the experiment (KLF4, RTN1,

PDCD5). It was also observed that significantly down-regulated genes are enriched for members of signaling cascades known to regulate transcription and progression through the mitotic cycle such as FOSB, SNF1-like kinase and PRKAR1A (cAMP-dependent protein kinase regulatory subunit), cyclin L2. Up-regulated genes also contain a high number of genes involved in progression through the cell cycle as well as in DNA damage response, including cyclin M, GTSE1, FANCB and BRIP1 (BRCA1 interacting protein C-terminal helicase 1), cyclin-dependent kinase inhibitor C2 (CDKN2C). A number of transcription factors and members of protein degradation machinery (ubiquitin-conjugating enzyme E2E 3, Ring finger and WD repeat domain 2) are also present among those genes. Data suggest that one of the reasons for Circulat's therapeutic effects is derived from its ability to stimulate cellular activities that respond to internal and external stress by slowing or arresting the cell cycle to allow repair of cellular components that could be damaged in the course of the disease, such as DNA and proteins, to be carried out by repair enzymes.

3.2 Discussion

It was shown that four genes, IL6, HMGA1, SLC19A2 and C4A that are known to be involved in the development and progression of diabetes are strongly regulated by Circulat. This not only validated the experimental approach, but also allowed for the first time to suggest an explanation for the clinical effectiveness of Circulat at the molecular level. The role of interleukin-6 (IL6) in diabetes type 1 and 2 is thoroughly documented (for a review see Kristiansen and Mandrup-Poulsen, 2005). Low-grade inflammation has been proposed to be involved in the pathogenic processes causing type 2 diabetes and inflammatory mechanisms are known to play a key role in the pathogenesis of type 1 diabetes. As a mediator of inflammation, IL6 is thought to be involved in events causing both types of the disease when present at elevated levels. In addition, IL6 can also regulate glucose homeostasis and metabolism directly and indirectly by both increasing the destruction of insulin producing β -cells by promoting apoptosis and playing a role in mounting insulin resistance in skeletal muscle, adipocytes and other tissues. Since elevated levels of IL6 are the known predisposition factors for development of diabetes, reduction of IL6 concentration should have the opposite therapeutic effect. The results demonstrate that Circulat treatment reduces IL6 expression more than two fold. (0.42, $p = 0.002$) providing a solid link between the molecular events and the clinical manifestations taking place upon Circulat treatment. HMGA1 expression levels were elevated by more than two fold (2.07, $p = 0.02$) in samples treated with Circulat. Mutations in this small nuclear protein that acts as an architectural transcription factor have been detected in individuals suffering from type 2 diabetes (Foti *et al.*, 2005). This correlated with the insulin receptor's expression reduction and consequent development of insulin resistance. Deletion of HMGA1 gene in mice resulted in almost a complete loss of insulin receptor expression, development of insulin resistance and type 2 diabetes-like symptoms. HMGA1 thus plays a crucial role in glucose homeostasis and its increased expression promoted by Circulat may counteract deleterious effects caused by the loss of insulin receptor observed in type 2 diabetic patients. Two other genes, SLC19A2 and C4A, that are affected by Circulat (0.43, $p = 0.03$ and 0.48, $p = 0.02$, respectively) have also been unequivocally linked to diabetes. SLC19A2 encodes a thiamine transporter protein and causes thiamine-responsive megaloblastic anemia (TRMA) also known as Rogers

syndrome, when mutated (Labay *et al.*, 1999). Diabetes (both type 1 and 2) is the primary disease that defines the syndrome. C4A encodes the acidic form of complement factor 4, part of the classical activation pathway. Deficiency of this protein is associated with systemic lupus erythematosus and type 1 diabetes mellitus (Palsdottir *et al.*, 1983). While no direct link between C4A and diabetes type 2 has been found thus far, it has been suggested that the two types of the disease share many of the underlying processes thus making C4A involvement in type 2 diabetes a real possibility. Precise molecular mechanisms of SLC19A2 and C4A involvement in the disease development are not established as well as for IL6 and HMGA1. Nevertheless, their link to diabetes is indisputable and the ability of Circulat to influence their expression suggests additional possible Circulat action mechanisms. Analysis of genes affected by Circulat also reveals that 26 of them have been implicated in many human diseases other than diabetes. It is possible that some of those diseases and syndromes could be caused by misregulation of the same (or similar) genetic pathways that are perturbed in type 2 diabetes, which could be one of the explanations for this observation. On the other hand, it raises an exciting possibility that Circulat could be effective for treatment of conditions other than type 2 diabetes. Finally, analysis of genes regulated by the total Circulat and its individual components demonstrated the existence of significant interactions between the active ingredients of Circulat suggesting that the full therapeutic effects can only be achieved by administration of the complete preparation.

3.3 Significance of gene expression analyses

The application of full-genome expression analyses to phytopharmacology opens new horizons for carrying out scientific studies of herbal remedies and integration of herbal-based treatments into mainstream medicine. Using this approach, the physiologically active fractions of effective herbal extracts can be isolated and their specific activities can be determined. Such separation of different activities of a particular extract may enable researchers to selectively regulate the expression of specific genes (or gene groups) by varying the composition of the herbal preparation. It is likely therefore, that expression-profiling-based approaches to studies of herbal medicines will become standard in phytopharmacology in the near future. This section, explained Circulat's molecular modulating capabilities. Section 4 will examine its clinical effectiveness through a diabetic foot study synthesis.

4. Circulat's therapeutic properties in diabetic foot: Synthesis

The World Health Organization estimated that more than 220 million people worldwide have diabetes (WHO, 2011). This number was likely to more than double by 2030. Diabetic foot ulcers are one of the most frequent complications of this disease. The prevalence of diabetic foot ulcers has been estimated, at the time of the study, between 2.2 and 15%. Differences being attributed to risk factor diversity: ethnicity, age, sex, education level, health service quality, and others (Table 4). Diabetic foot ulcers represent a large emotional and economic burden on patients and caregivers, as well (Gulam-Abbas *et al.*, 2002). Foot complications are caused by diabetic neuropathy or peripheral ischemic vessel disease or a combination of both (Ratzmann *et al.*, 1994) and are the most frequent reason for hospitalization in patients with diabetes.

Diabetic foot ulcers prevalence	Country	References
2.2 %	UK	Abbott <i>et al</i> , 2002
3-8%	Sweden	Apelqvist and Larsson, 2000
4.6%	Kenya	Nyamu <i>et al</i> , 2003
5.3-5.6%	Finland	Lehto <i>et al</i> , 1996
5.4 - 7.3%	USA	Moss <i>et al</i> , 1996
10.2%	Sri Lanka	Fernando, 1996
15%	Tanzania	Gulam-Abbas <i>et al</i> , 2002

Table 4. Examples of diabetic foot ulcer prevalence by country and references

Diabetic foot complications are the most common cause of non-traumatic lower extremity amputations in the industrialized world. The risk of lower extremity amputation is 15 to 46 times higher in diabetics than in persons who do not have diabetes mellitus (Armstrong, 1997). Approximately 40-60% of all lower extremity amputations are performed in patients with diabetes. More than 85% of these amputations are precipitated by a foot ulcer deteriorating to deep infection or gangrene (Apelqvist and Larsson, 2000). In people with healed diabetic foot ulcers, the 5 year cumulative rate of ulcer recurrence is 66% and of amputation is 12% (Apelqvist *et al.*, 1993). The high amputation incidence and healing failure after lower extremity amputation for the treatment of diabetic foot ulcer (Malay *et al.*, 2006) is a distinct signal that the efficiency of conventional medical treatments used is less than optimal. This substantiates the need to search for effective therapeutic alternatives and diminish the suffering and high economic and social costs caused by this common diabetic patient complication. Various medicinal plants have been used traditionally for the treatment of circulatory obstructive diseases. In the last couple of decades many of their active principles and action mechanisms have been discovered. Also, traditional healing know-how has been proven to be effective in many cases. This raised the possibility of using herbal therapeutic protocols to complement conventional treatments for complications in diabetes. Specially, since there was mounting evidence which demonstrated that medicinal plants contained synergistic and/or side-effect neutralizing combinations (Thyagarajan *et al.*, 2007; Gilani and Rahman, 2005). In contrast to synthetic pharmaceuticals based upon single chemicals, phytomedicines exert their beneficial effects through the additive or synergistic action of their multitude of constituents acting at single or multiple target sites (Dalby-Brown *et al.*, 2005); because of their primary and secondary metabolite roles (Greenspan *et al.*, 1994) and the adjuvant substances which enhance the activity of components actually responsible for the effect (Gilbert *et al.*, 2003). In order to take the maximum advantage of the therapeutic properties as well as benefits of the synergistic action of the active principles in medicinal plants, it is necessary to use herbal combinations. Herbal formulations have been used for hundreds of years, however, little was known about the methodology to combine plants and obtain effective compositions. The Systemic Theory provided fundamentals which allowed the formulation of an effective herbal composition for treating diabetic foot (Olalde, 2005; Olalde *et al.*, 2005). The previous section revealed that Circulat's active principles exerted therapeutic effects through a synergistic action, as well as its potential for genetic normalization in diabetic patients (Antoshechkin *et al.*, 2007).

4.1 Objective, research design and methods

The aim was to appraise the clinical efficacy of Circulat in healing diabetic foot, measure the amputation rate and determine patient's tolerance to the treatment. Thus, a retrospective, cohort, study of patients with type 2 diabetes and foot ulcerations from 50 medical centers, from 2004 to 2007. Patients were classified in accordance with The University of Texas Health Science Center Diabetic Wound Classification System (Lavery *et al.*, 1997). Patients were being administered ten Circulat 800 mg capsules twice per day, on an outpatient basis, during a period of two to four months. Each case was followed-up during a period of six months, after the end of the treatment. A patient was considered to attain clinical improvement if the lesion visibly decreased in size and depth, or closure or scarring of the wound was attained. All patients received conventional treatment for metabolism correction, local topic cures and systemic antibiotics. The Inclusion criteria of the study were: Patients of any age and gender diagnosed with Diabetes mellitus type 2, grades D1, D2 and D3 (University of Texas Diabetic Wound classification).

4.1.1 Results and discussion

The total number of patients which completed the treatment in accordance with the study's inclusion criteria was 174. The mean was 61.3 years of age. The gender classification was: 101 male (58.1%) and 73 female (41.9%). Clinical results are reflected in Table 5. Amputations were prevented in 88.55% ($p < 0.00001$, 99.9999%) of all 174 patients in the D1-D3 categorization. The treatment was well tolerated; only 4 patients (2.3%) had minor gastrointestinal unrest which did not warrant treatment suspension. Conventional diabetic foot treatments, based on: risk factors control, affected area's functional relaxation, metabolism correction, topical cures, antibiotics, rheology improving agents, prostanoid vasoactive therapy, platelet aggregation inhibitors, thrombolytic agents, tricyclic antidepressants or benzodiazepines for neuropathies and invasive treatments, such as endovascular, endarterectomy, by-pass or sympathectomy surgeries, do not manage to prevent small and large amputations which occur in 1.86 to 5.9 per every 1.000 diabetics per year (Bilenko *et al.*, 2006; Winell *et al.*, 2006; Rayman *et al.*, 2004; Lavery *et al.*, 2003; Trautner *et al.*, 2001). Circulat- in combination with conventional therapy- prevented more amputations than various conventional treatments reported (Figure 8).

University of Texas Diabetic Wound classification Grade	N	Total scarring	Improvement	Total scarring + Improvement	Amputation
D1: Infected ischemic superficial wounds, no tendon, capsule, or bone.	88	52 (59.09%)	36 (40.9%)	88/88 (100%)	-
D2: Infected ischemic wounds, penetrating to tendon or capsule.	80	32 (40%)	30 (37.5%)	62/80 (77.5%)	18/80 (22.5%)
D3: Infected ischemic wounds, penetrating to bone or joint.	6	4 (66.6%)	-	4/6 (66.6%)	2/6 (33.3%)
Total	174	88 (50.57%)	66 (37.9%)	154/174 (88.5%)	20/174 (11.5%)

Table 5. Results of Circulat treatment in Diabetic foot

Fig. 8. Examples of Diabetic Foot Amputation rates (%) in various countries

5. Formulation's potential in chronic ischemic heart disease treatment

Context: The previous clinical study (Olalde *et al.*, 2008) demonstrated a significant improvement in 174 diabetic foot patients. These encouraging outcomes and further evidence that other complex herbal formulations could help reduce atherosclerotic endothelium intima thickness (Tripathi *et al.*, 2005) prompted us to evaluate the formulation by measuring the arterial intima-media thickness, a structural marker of early atherosclerosis that relates to the severity and extent of artery disease (Järvisalo *et al.*, 2001), using high-resolution ultrasound (Celermajer *et al.*, 1992). The study (unpublished) showed that treatment with this herbal combination significantly reduced the arterial intima-media thickness. These results further encouraged the formulation of a new hypothesis: could similar results be obtained in the treatment of IHD? If so, is there a potential for CAM complex herbal formulations' intervention in the treatment of Ischemic Heart Disease? **Objective:** Assess the hypothesis that myocardial perfusion, in chronic ischemic heart disease patients, might safely improve with Circulat. This was evaluated with Gated Single Photon Emission Computerized Tomography (GSPECT) imaging.

5.1 Introduction

Ischemic heart disease (IHD) is the leading cause of death -in both genders- worldwide and a major public health problem in the world. WHO (2009) has estimated this to be 7.2 million deaths per year. IHD is the generic designation for a group of pathophysiologically related syndromes resulting from myocardial ischemia (an imbalance between supply -perfusion- and demand for oxygenated blood by the heart). IHD is caused by the atherosclerotic narrowing of one or more coronary arteries and endothelial dysfunction (Thadani, 2004, 2003, 1999). IHD brings oxygen insufficiency and reduces the availability of nutrients as well as the removal of metabolites. For this reason, IHD is generally less well tolerated by the heart than pure hypoxia, such as may be seen in severe anemia, cyanotic heart disease or advanced lung disease. Today much attention is being paid to Chronic Ischemic Heart Disease. This last is increasingly recognized as a dynamic condition. In addition to over acute myocardial infarction, which can precipitate at any time in patients with stable angina pectoris, clinical and sub-clinical ischemic

events may accumulate and in the long term generate diverse states of chronic cardiac dysfunction. Repetitive episodes of ischemia, whether stress induced or spontaneous, symptomatic or silent, may progressively impair myocardial contractile performance through myocardial stunning or hibernation, and eventually lead to left ventricular remodeling and heart failure. Evidence is accumulating that genetic variability and altered gene and protein expressions contribute to clinical outcomes in ischemic heart disease. Severe ischemic heart disease remains a clinical challenge; many patients have undergone myocardial revascularization procedures due to the extension and diffuseness of the disease. Also, viable options are becoming available for the 'no option' patients with chronic IHD. Instead of revascularization of the highly diseased epicardial coronary arteries, scientists and clinicians are looking –among other- at providing symptomatic relief in these patients via a biological bypass such as a 'master' cardiac stem cell for intra-coronary and intra-myocardial injections (Bu *et al.*, 2009). Current treatments include pharmacological agents such as nitrates, aspirin, beta-adrenoceptor antagonists and calcium channel blockers as well as invasive therapies aimed at restoring blood flow, e.g. coronary artery bypass graft (CABG) and improved percutaneous coronary intervention – PCI (Tin-Hay *et al.*, 2010). On the other hand, various medicinal plants are being used – and researched- for the treatment of coronary heart disease and angina pectoris in China and East Asia, and are referenced in *Chinese Materia Medica* (Tam *et al.*, 2009; Ling *et al.*, 2008; Duan *et al.*, 2008; Zhao *et al.*, 2007). This last does not preclude quite the contrary it demands, additional pharmacotherapy analysis and herbal medicines drug interaction research (Izzo *et al.*, 2005). Nevertheless, the study and development for synthetic (Yamaguchi *et al.*, 2009; Hirata *et al.*, 2009) and medicinal plant in cardiac treatments continues (Chen *et al.*, 2010; Luo *et al.*, 2009).

5.1.1 Study materials and methods

Inclusion Criteria: Patients diagnosed with Chronic Ischemic Cardiopathy. **Exclusion Criteria:** Acute Coronary Syndrome, severe aortic valve stenosis, arrhythmia with hemodynamic repercussion, acute pericarditis, acute myocarditis, decompensated cardiac insufficiency, acute aortic syndrome, severe anemia, pulmonary embolism, severe arterial hypertension, severe pulmonary arterial hypertension, chronic debilitating diseases, second or third degree atrioventricular block, hypertrophic obstructive cardiomyopathy and valvular cardiomyopathy with hemodynamic compromise. **Patients:** 20 patients diagnosed with Chronic Ischemic Heart Disease were evaluated. Prior to treatment, tests had determined that 4 of these patients had cardiac ischemia, assessed with cardiac angiography and non invasive methods, and the other 9 patients tested positive for cardiac ischemia with the exercise treadmill testing protocol (Bruce). Initial cardiac ischemia diagnosis was also corroborated by GSPECT control imaging prior to treatment. Patients were receiving treatment with aspirin, β -blockers, statins, nitrates, clopidogrel and anti-hypertensive medication (diuretics, ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers). Patients were given a complete physical examination at screening, each month and at the end of the treatment (sixth month). The patients' baseline factors, relevant cardiac conditions and ongoing treatments were established in Table 6. The most pervasive baseline condition risk, evidenced from patients' clinical history (Table 6) was Hypercholesterolemia (14/20; 70%). On the other hand, the most common treatment was aspirin (17/20; 85%).

Description	Patient Number																			
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Gender	M	F	M	M	M	M	M	F	M	F	F	F	M	M	F	M	F	M	M	M
Age	68	78	69	64	67	41	61	57	59	73	75	53	58	48	66	80	67	57	59	68
Myocardial infarction	N	Y	N	Y	N	N	N	N	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y
CABG	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
PCI	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N
Diabetes	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	Y	N	N	N	Y
Former smoker ≥ 30d	N	N	N	N	N	N	N	N	Y	N	N	N	Y	N	Y	N	N	N	Y	Y
Hypertension	N	Y	Y	Y	N	N	Y	N	Y	Y	N	N	N	N	Y	Y	Y	N	N	Y
Hypercholesterolemia	Y	Y	N	N	Y	Y	N	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
BAA	N	N	N	N	Y	Y	N	Y	Y	N	Y	N	N	N	Y	N	Y	N	N	Y
Statins	N	N	Y	Y	N	N	Y	N	N	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y
Aspirin	Y	N	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Oral Anti-diabetics	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	Y	N	N	N	Y
ACEI or ARB	N	N	Y	N	N	Y	N	N	Y	N	Y	N	N	N	Y	Y	Y	N	N	Y
Ca ²⁺ -channel antagonist	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Diuretics	N	N	N	N	N	Y	N	N	Y	N	Y	N	N	N	Y	Y	Y	N	N	Y
Legends. ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin -type I- Receptor Blocker; BAA: Beta Adrenoceptor Antagonists; CABG: Coronary Artery Bypass Graft; d: days, Female: F; Male: M; N: No; PCI: Percutaneous Coronary Intervention. Y: Yes. All data determined from patients' clinical histories.																				

Table 6. Patients' Baseline Characteristics

Patients were instructed to receive ten 800 mg capsules b.i.d., of the herbal composition. Assessment of cardiac functions: The Bruce test, named after Dr. Robert A. Bruce, involves walking on a slanted treadmill while patient's time resistance is measured and the heart is monitored by an electrocardiograph. Patients' Pre -and Post- treatment, treadmill resistance time (Functional Capacity Time or FCT) were determined and reflected in Figure 9.

Note: Patients 2, 13, 15, 16 and 20 were unable to carry out the test due to physical limitations.

Fig. 9. Pre and Post (After) Treatment Functional Capacity Time per patient

5.2 Assessment of regional myocardial perfusion defect

Patient's -before and after Circulat treatment- post-effort -left ventricle- myocardial perfusion defect percentages were assessed by GSPECT imaging with technetium 99m-tetrofosmin injection. This technique uses imaging procedures for detection with the help of gamma rays. In the procedure, the radioisotope is used on the patient and the gamma ray emitted by the technetium 99 that is in the radioisotope is captured on a special gamma camera. The total scanning time for the heart of a patient takes around twenty minutes which is enough time given the half life span of technetium 99. This isotope has a short half life -about six hours- and this small longevity is very useful for medical purposes. Recollection of data [imaging] is quick and the amount of radiation which a patient undergoes through is very low in intensity. GSPECT myocardial perfusion imaging is a widely used nuclear imaging procedure for diagnosis and management of coronary artery disease -which is the most common cause of heart failure. It is extensively available with superb standardization and reproducibility (Chen *et al.*, 2008). For this study, the Phillips Forte (2007 model) AZ Spect Dual Headed Camera with an AUTOQUANT -quantitative algorithm- program for image processing was used. A 20 segment analysis was performed. Results of Perfusion Defect evolution are reflected in Figure 10.

5.2.1 Results

Clinical: Patients' Pre and Post Treatment Functional Capacity Time (treadmill evaluation) comparison (Figure 9) revealed that all patients who were physically capable to carry test out -except patient 17- improved their timed resistance [Female Improvement Median = 42.2 sec; Male Improvement Median = 64.8 sec]. Finally, patients' Post-Effort Left Ventricle Perfusion Defect imaging percentage values (Figure 10) were compared before and after six months treatment. Of the study group, 15 patients [75%] improved their perfusion defect. Statistics: The significance of the results was determined with the Wilcoxon Matched-Pairs Signed-Ranks Test ($p \leq 6.104 \times 10^{-5}$; $\% = 99.9999$). All statistical data was determined using

SPSS 17.0 for Windows. Adverse events: No patients suffered any adverse events during the treatment.

Fig. 10. Patient Cardiac Perfusion Defect Evolution (Ranked by age and gender)

5.3 Discussion on ischemic heart treatment

The results answered the formulated [raised] hypothesis. Indeed, CAM -and Circulat- can have a role in the treatment of Ischemic Chronic Heart Disease. This is supported by the number of patients (15 out of 20) which quantitatively improved their left ventricular perfusion capacity. Effects of this treatment are thought to be caused, among others, by vascular endothelium structure and function improvement, angiogenesis and tissue perfusion enhancement. Also to be noticed is patients' disease evolution according to initial perfusion defect -reflected in Figure 10. There seems to be a correlation suggesting that initial stages of ischemia development -corresponding to lower Pre-Treatment perfusion defect- are more precociously responsive to a short (6 month) treatment, thus advocating use of the formulation as a preventive remedy against chronic ischemic heart disease. **However, to measure the treatment's potential effectiveness, in patients with acute perfusion defect, a longer lasting treatment -of at least one year is necessary. Just as pathologies -with critical conditions- warrant longer management periods.**

6. Conclusions on chapter

A theory is as good as the praxis that backs it up. On one hand the gene expression study (Antoscheckin *et al*, 2007) established that a complex herbal formulation, designed in accordance with Systemic Theory precepts, had synergistic properties as well as the capacity to modulate genes implicated in diabetes development, energy metabolism, protein synthesis, glucose metabolism and signaling pathways. It also demonstrated that four genes (IL6, HMG1A1, SLC19A2 and C4A) involved in the development and progression of diabetes are strongly regulated by Circulat. These bio-molecular results were confirmed with the further evaluation of diabetic foot management (Olalde *et al.*, 2008) which provided clinical substantiation that a complex herbal formulation could be successful in providing therapeutic response to such a circulatory chronic disease. However, the result obtained in the reduction of perfusion defect in Chronic Ischemic patients was unexpected. It also

requires further validation. The authors are prolonging the length of the treatment –and the study- to one year. From this distance a better image of its potential therapeutic use can be assessed. However, there is room for cautious optimism. Evidence is accumulating that genetic variability and altered gene and protein expressions contribute to clinical outcomes in ischemic heart disease. It is likely therefore, that expression-profiling-based approaches to chronic degenerative diseases such as diabetes and ischemic heart disease with herbal medicines will become standard in phytopharmacology in the very near future. Resuming: a) The confirmation of Circulat's synergistic synergistic gene modulating capabilities (in 32 genes, among which are four significant genes related to diabetes; b) The clinical outcomes of diabetic foot management which prevented the amputation of 88.5% of the study's total population ; and c) The good response to therapy in 75% of the patients ($p \leq 6.104e-05$; % = 99.9999) by the composition in a GSPECT evaluated limited Phase II Chronic Ischemic Heart Disease suggest that treatment of circulatory pathologies with substances which act only on function and structure might be an incomplete approach. Whether the findings in circulatory chronic disease studies –and their results- can be generalized in confirming the systemic approach (E, I and O) is something that should be continued in medicinal science. Since this may pave the way for a new integral vision of therapeutics in general having started to prove its validity in circulatory chronic diseases in particular.

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Obesity and type 2 diabetes are increasing worldwide problems. In this book we reviewed insulin secretion in both healthy individuals and in patients with type 2 diabetes. Because of the risk associated with progression from insulin resistance to diabetes and cardiovascular complications increases along a continuum, we included several chapters on the damage of endothelial cells in type 2 diabetes and genetic influences on endothelial cell dysfunction. Cardiovascular complications occur at a much lower glucose levels, thus a review on the oral glucose tolerance test compared to other methods was included. The medical conditions associated with type 2 diabetes such as pancreatic cancer, sarcopenia and sleep disordered breathing with diabetes were also discussed. The book concludes with several chapters on the treatments for this disease offering us hope in prevention and successful alleviation of the co-morbidities associated with obesity and type 2 diabetes.

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