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Potential Phytotherapy use of Artemisia Plants: Insight for Anti-Hypertension

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ABSTRACT

Artemisia plants had been used to treat many diseases. While there many controversies concerning their effects on the cardiovascular system, Artemisia extracts could be envisaged as anti-hypertensive and to prevent cardiovascular damages. In raison of its bare toxicity, using the crude extracts will be of much importance in this field.

INTRODUCTION

Hypertension is a trait of multifactorial nature with both genetic and environmental influences; and usually associates with other diseases and pathological complications. Although the outstanding advances in medicine and related technologies and sciences, hypertension is still a worldwide major problem with a projected occurrence of 1,56 billion patients, in 2025 (Kim *et al*., 2010).

Many cardiovascular conventional drugs, even as efficient, did present adverse outside effects; and so much safe therapeutic substances are in need. The therapeutic approaches become more and more ambiguous, when the disorder is associated with other pathological conditions such as diabetes mellitus and obesity. Else more, there are several mechanisms leading to hypertension.

Mending one of them, whenever ameliorates the case, did not totally relief the illness (refce?1,2???). Recently, evidenced knowledge proved the utility and safety of various medicinal plants against many pathologic disorders (Mohanty *et al*., 2012). Artemisia, plants from the Asteracaea, had been used from the olden days against many diseases. Its therapeutic usefulness gained much popular and scientific approval; but this plant effects on the cardiovascular system remain unclear. So, this paper put forward new insight for the utilization of Artemisia plants to counteract cardiovascular diseases with special focus on hypertension.

Artemisia description

Artemisia genus (Asteraceae, Anthemideae, Artmisiianae) comprises hundreds (about 500) of different species, but its systematic classification remains discussed. In general five different subtaxa are considered (Torrell and Valles, 2001; Valles and McArthur; 2001).

This complexity arose from its genomic 'polymorphism', essentially the ploidy levels sought as the promoter mechanism for evolution and ecological adaptation (Badr *et al*., 2012; Torrell and Valles, 2001). Artemisia shrub occupies worldwide geographical areas; and attracted much attention for its highly economic values, in particular for its medicinal patterns. Rationally these plants were used from the olden days as, anti-venom, anthelminthic, antidepressant, antiseptic, diuretic, antispasmodic, hypoglycemic, anti-cancer etc., throughout the World; and were subjected to intensive scrutiny (Ashraf *et al*., 2010a,b; Gautam *et al*., 2003; Lai, 2009; Tardio *et al*., 2006).

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Amongst these customary phytotherapeutic uses, the artemisinin which is isolated from the Chinese *Artemisia annua* L showed important anti-malarial effects and owed great attention for treating such disease particularly in less developed countries (Wilcox *et al*., 2004; De Ridder *et al*., 2008; Muzemil, 2008; Tu, 2011; Ho, 1996; Germer and Sinar, 2010). As well, many other compounds have been characterized in this vegetal that act through disparate pathways in diseases' curing.

Additionally, Artemisia extracts showed no real toxicological patterns, an indispensible feature for pharmaceutical use (Mukina, 2005; Mansi and Lahham, 2008). Besides its genetic and ecological diversity, inter and intra-specific variability in Artemisia chemical composition was proved, and might explain the diversity of extracts' biological activities and ethno-pharmacy. Obviously, Artemisia extracts potently scavenge free radical compounds (Canadanovic-Brunet *et al*., 2005; Wang *et al*., 2007; Ayoughi *et al*., 2011; Wojcikowski *et al*., 2007) that are common traits of many diseases (Higdon *et al*., 2012; Dalle-Donne *et al*., 2006). However, there were controversial findings concerning Artemisia extracts on cardiovascular system regulation.

Chemical composition of Artemisia shrub

Artemisia shrub is a rich source of bioactive substances such as apigenin, hesperetin, kaempferol, luteolin, quercetin, 1,8-cineole; alpha- and beta- thujone, camphor, borneol) coumarin, acetylenes; and many other substances (table 1).

Nonetheless, important qualitative and quantitative variability in the chemical composition of the plant extracts, exist not only between different species, but also intra-specifically within the geographical localization and the ecological milieu (soil and climate) (Judzentiene and Buzelyte, 2006; Salido *et al*., 2004). For exemple, the total phenolic acids produced by in vitro cultured cells and extracted using 70% methanol, greatly differ between *A. frigida*, *A. campestris* and *A. vulgaris* plants (173,9, 75,2 and 69,5 µmol/g of dry weight; respectively) (Riedel *et al*., 2010). Further chemical changes could also be observed dependently on the biological cycle (Germination, Flowering, seedling and Fructification); and the used part of the vegetal (Judzentiene and Buzelyte, 2006).

Methods of extraction (aqueous, ethanol, etc.) and/or traditional application (drinking, ointment, inhalation, etc.) add much persuasive miscellany to its therapeutic potential (Salido *et al*., 2004; Vinatoru *et al*., 1997; Naczk and Shahidi, 2004). In addition, Artemisia organs are exceptionally enriched in Chloride, HCO_3, SO_4, fluoride , sodium, potassium, magnesium and many other minerals (Hussain *et al*., 2011; Ashraf *et al*., 2010). We will discuss some of these tremendously influencing factors, reliably to the sought cardiovascular effects of the plant.

Anti-hypertensive effects of Artemisia extracts

Using animal model, Esmaeili *et al*. (2009) proved that *A. Persia* extracts reversed the epinephrine induced- hypertension much more than enalapril, a conventional anti-hypertensive drug. However, the real mechanisms of these effects are still blurred (table 2). Such divergence could be attributed to the quantitative and qualitative chemical composition variability, as discussed above. In fact, many Artemisia derivatives might modulate the heart and vascular function either directly or indirectly through the control of endocrine and, or nervous cardiovascular regulations.

Neuronal modulation

Pharmacologically, the dosage and routes of administration are prominent influencing factors. The application of moxa, which is the inhalation of volatilized substances during the plant burning, may firstly affect the pulmonary tissues (Novak *et al*., 1993) and consequently exert pulmonary vasodilatation that probably help into pulmonary diseases healing such as asthma and bronchospasm (Chen

g *et al*., 2011). Interestingly, in this Chinese therapy, general body depression and heart rate decrease are common occurrences (Kim *et al*., 2010; Zhao *et al*., 2011). Many investigations brought substantial knowledge on such process. In sub-chronically or acutely exposed animals to *Artemisia* derivatives, a decrease in heart rate and systolic blood pressure was observed in association to aorta and heart lowered responsiveness to the contractile epinephrine and enhanced response to acetylcholine (Tigno *et al*., 2000; Esmaeili *et al*., 2009 and 2012; Mojarad *et al*, 2005).

The vascular smooth muscle relaxation was similarly induced in rabbit jejunum following *A. herba-alba* essential oils application (Aziz *et al*., 2012). To understand the mechanism of this relaxation, five falavonoids (jaceosidine, eupafolin, leuteolin, quercetin and apigenin) and three coumarins (aesculetin, aesculetin 7- methyl ether and scopoletin) have been extracted from the Korean mugwort (*A. vulgaris* L.) and assayed to determine their inhibitory capacities on the brain monoamine oxidase. This enzyme plays a key role in various neuromediators metabolism such as, epinephrine, nor-epinephrine, dopamine and serotonin (Lee *et al*., 2000).

The isolated *Artemisia* chemicals abolished this enzyme activity with IC_{50} ranging from 1 to 45 µmol. This might result in epinephrine production fail, and thereby counteract hypertension (Lee *et al*., 2000). Consequently, it is suggested that *Artemisia* compounds modulates the cardiovascular function at the neuro-vascular (expectedly neuro-cardiac, too) bed through the regulation of neurotransmitters and their appropriate receptors interactions. Accordingly, smelling essential oils of *A. dracunculus* and *A. vulgaris* stimulates the sympathetic activity that changes the low frequency amplitude of blood pressure, perhaps via adrenaline concentration shift (Haze *et al*., 2002, Zhao *et al*., 2011).

In an elegant fashion, Luedtke and collaborators (2003) examined the competitive potential of various plants derivatives binding to D1 and D2 dopaminergic receptors in modified Human cells; Amongst these studied compounds, the *A anomala* (estragon) unspecifically binds to both receptors with a preference to D1 (D1:D2= 2). Interestingly, the extract inhibited the adenylyl cyclase activity that mediated the signal transmission; but independently from binding to receptors (Leudtke *et al*., 2003).

In summary, the nervous mediated regulation of the cardiovascular function by *Artemisia* shrub extracts appears to be mediated by functional inhibition of enzymes controlling neurotransmitters release.

The competitive binding to adrenergic receptors is thought to be ineffective docking- interactivity, or following the compound interaction with an appropriate site in close proximity to adrenergic receptors that will interact with the compound in allosteric manner, like as how did hispidulin, a flavone found in many *Artemisia* species (Kavvadias *et al*., 2004). The direct (independent from receptor stimulation/ inhibition) abolishing of adenylyl cyclase and its mediated signal, constitutes another possible hypotensive mechanism for Artemisia extracts.

Endocrine regulation

Nitric oxide (NO) is prominent endogenous vasodilator acting through the activation of the soluble guanyly cyclase, and increases the cyclic guanosine-3':5'-monophosphate (cGMP) in smooth muscles (Bigaud *et al*., 1990). Whilst required at low concentration to maintain hemodynamic equilibrium, the NO excessive release contributes to circulatory shock and cell death through its potential to react with oxygen species (ROS). The ROS property of NO is engulfed into the endorsed oxidant/anti-oxidant system (Achike and Kwan, 2003).

In studies using knockout mice deficient to endothelial nitric oxide synthase (eNOS) and cyclooxygenases-1 (COX-1), Scotland and colleagues proved that NO, PGI_2 (prostaglandin I_2) and EDHF (endothelium-derived hyperpolarizing factor) acts synergistically in retrieving blood pressure increase.

They concluded for a gender dependant-divergence on this process: (i) the eNOS and COX-1 deficiency profoundly breakdown the NO and PGI_2 hypotensive effect in males; (ii) in contrary, the EDHF pathway dominates the process in females (Scotland *et al*., 2005). In accordance, Ryu and colleagues (1998) mentioned that yomogin (*A. verlotorum lamottee*) potently inhibited the inducible form of NOS, and thereby will abolish the vasodilator NO production, as like as did extracts from *A. absthinium* (quercetin) (Mahmoudi *et al*., 2009) and *A. herba alba* (Messaoudene *et al*., 2011). Irrespectively, Artemisia extracts mostly induced a blood pressure decrease, and it is attended to get NO overproduction at the time of treatment (Yamahara *et al*., 1989a, b; Calderone *et al*., 1999). Since the iNOS inhibition was localized into blood cells (Ryu *et al*., 1998), it is supposed to marginally affect the vessels tonus. Consequently, the observed NO increase will probably originate from eNOS activity or released from adjacent nervous terminations. Instead of inducing NO production, *Artemisia* extracts appeared to stimulate the cGMP-dependent signaling pathway of the nitric oxide which contributes to smooth muscles relaxation.

Furthermore, other mediators, such as histamine and substance P, could mandate this induced hypotension (Okazaki *et al*., 1990).

Blood rheology and cardiovascular protection

Many researches showed that *Artemisia* compounds improve the blood rheology, essentially through their anti-thrombosis activity which prevents blood clot formation, reduces the sheer stress and enhances blood circulation, especially in microvasculature (Harborne *et al*., 2000; Shahriyary and Yazdanparast, 2009). The modus operandi of anti-thrombosis might involve the peroxisome proliferator-activated receptors (PPARs) components st

imulation (O'Brien *et al*., 2006). So, the increased mRNA expression of PPARs by A. iwayomogi, in combination to *Morrus alba* and *Melissa officinalis* is envisaged to recover platelet aggregation and thrombosis (Lee *et al*., ????), Furthermore, cardiovascular dysfunction and tissular damages are roughly subsequent to ROS generation (Dalle-Donne *et al*., 2006). Reestablishing the oxidant / anti- oxidant system equilibrium constitutes a basic mechanism for cardiovascular diseases therapy. Thus, it is fair-minded to apply *Artemisia* treatments to prevent these disorders, because of its powerful ROS scavenging potential (Akrout *et al*., 2012; Wojcikowski *et al*., 2007, Wang *et al*., 2007; Ayoughi *et al*., 2011; Canadanovic-Brunet *et al*., 2005, Kadri *et al*., 2011).

Infective endocaditis is a pathogenic disease. It is characterized by lesions consisting of vegetations including platelets, fibrin, microorganisms and inflammatory cells; in association to vessel bed disruption (Thiene and Basso, 2006). For that reason, *Artemisia* extracts could be envisaged as therapeutic for infective endocarditis; not only for its antimicrobial potential (Khanahmadi *et al*., 2009), but for the above mentioned patterns (anti-thrombotic, anti-oxidant) and its anti-inflammatory effects (Messaoudene *et al*., 2011), too. The cardiovascular dysfunction is, also, a frequent occurrence in lipids and glucose metabolic disorders. By lowering serum triglycerides, cholesterol and glucose concentrations; and reestablishing insulin function (Watcho *et al*., 2010 and 2011; Weinohrl, 2010), Artemisia holding substances may recover the vascular resistance and blood circulation.

Else more, given that the cardiovascular and urinary functions are tightly dependent one on the other, attenuating kidneys dysfunction is thought to ameliorate the blood circulation. In this view of point, the combined use of cordyceps (fungi) powder and artemisinin (2-4:0,6 w/w) efficiently protects the kidney function into patients with lupus nephritis unresponsive to corticosterone and cyclophosamide(reviewed by Wojcikowski *et al*., 2004).

The 20- hydroxeicosatetraeinoic acid inhibition by the sesame (a lignan isolated from Atemisia) will improve sodium reabsorption in the renal proximal tubule and consequently modulates natriuresis pressure (Miyata and Roman, 2005; Wu *et al*. 2009). Eventually, the richness of Artemisia plant in various minerals (Hussain *et al*., 2011; Ashraf *et al*., 2010) will improve the blood rheology and homeostasis.

Table. 1: list of the first 10th dominant compounds characterized in hydro-distillated essential oils of various Artemisia species.

A. hahssknechtir		***A. abrotanum***		***A. dracunculus***		***A. herba-alba***	
Camphor	12,4	Piperitone	17,5	(Z)-Anethole	51,7	β-Thujone	68,4
α-Tepineol	9,9	Dawanone	16,7	Elemicin	48,7	Camphor	68,2
Davanana ether	6,2	1,8 Cineole	12,5	Sabinene	18,8	α-Thujone	57
Borneol	4,9	Artedouglasia oxide B	6,7	(E)-Asarone	13,3	Davanone	51,2
Ipsdienol	4,5	Silphiperfol-5-en-3-ol A	6,2	(Z)-β- Ocimene	8,3	Chrysanthenene	36,4
Borneol acetate	3,7	Germacrene D	5,8	Methyl-eugenol	8,0	Cis-Chrysanthenol	27,8
1,8 Cineole	3,7	Artedouglasia oxide D	4,7	Limonene	4,9	1,8 Cineole	25,8
Yomogi alcohol	3,5	Siphiperfol-5-en-3-one A	2,5	Linalool	4,4	p-Cymene	20,6
p_Cimene	3,2	Ocymene	2,3	α-Terpinene	3,8	Cis-Chrysantenyl acetate	18,4
Neryl acetate	3,2	Artedouglasia oxide C	1,8	Allo-Ocimene	3,2	α-Pinene	17,2

A. vulgaris		***A. sieberi***		***A. khorasanica***	
Camphor	47,7	β-Thujone	19,8	Davanone	36,4
Isobronyl isobutyrate	38,0	Camphor	19,5	p-Cymene	16,5
Caryophyllene oxide	31,1	α-Thujone	10,6	(Z)-Citral	8
β-Pinene	30,1	Verbenol	9,7	β- Ascaridol	5,9
β-Thujone	20,8	p-mentha-1,5-dien-8-ol	6,4	(Z)- Jasmone	3,8
α-Phellandrene	17,3	Davanone	5,8	Thymol	3,7
Luratol	15,1	1,8- Cineol	5,7	Linalool	2,5
Trans- isoelemicin	15,1	Camphene	3,6	1,8-Cineol	2
α-Pinene	15	α-Pinene	2,5	Zingiberene	1,8
1,8 -Cineol	11,7	p- Cymene	1,2	α-Pinene	1,7

Values represent the maximal abundance (%) of compounds, as quantified using Gas-Chromatography, checked across the reported literature: Ayoughi, *et al.*, 2011; BenJilali and Richad, 1980; Ghorbani-Ghouzdi *et al*., 2008; Judzentiene *et al.*, 2006; KhanAhmadi *et al*., 2009; Kowaliski *et al*., 2007 and 2011; Tajadod *et al*., 2012; and Salido *et al*., 2004.

Table. 2: divervent effects of some Artemisia extracts or derivatives on the cardiovascular function.

Plant	**Extract / compound**	**Effect**	**Refce**
A. capillaris (flos)	Scoparone	Increase heart rate and coronary flow. No influence on cadiac output and LV performance Inhibition of the ST wave (antianginal action)	Yamahara *et al*., 1989a, b
A. annua	Artesunate (derived artemisinin)	Inhibit angiogensis	Dell'Eva *et al*., 2004
A. verlotorum	Water extract	Transient hypotension in mesentery	Calderone *et al*., 1999
A. vulgaris		No effect on heart and mean arterial pressure Hypotension in mesenteric arteries	Tigno *et al*., 2000
A. persia	Methanol and water	Reduces heart rate and systolic blood pressure	Esmaeili *et al*., 2012
A. vulgaris	Moxa	Reduces heart rate	Zhao *et al*., 2011
A. annua		enhances the acetylcholine induced endothelial-dependent relaxation of aorta	Mojarad *et al*., 2005

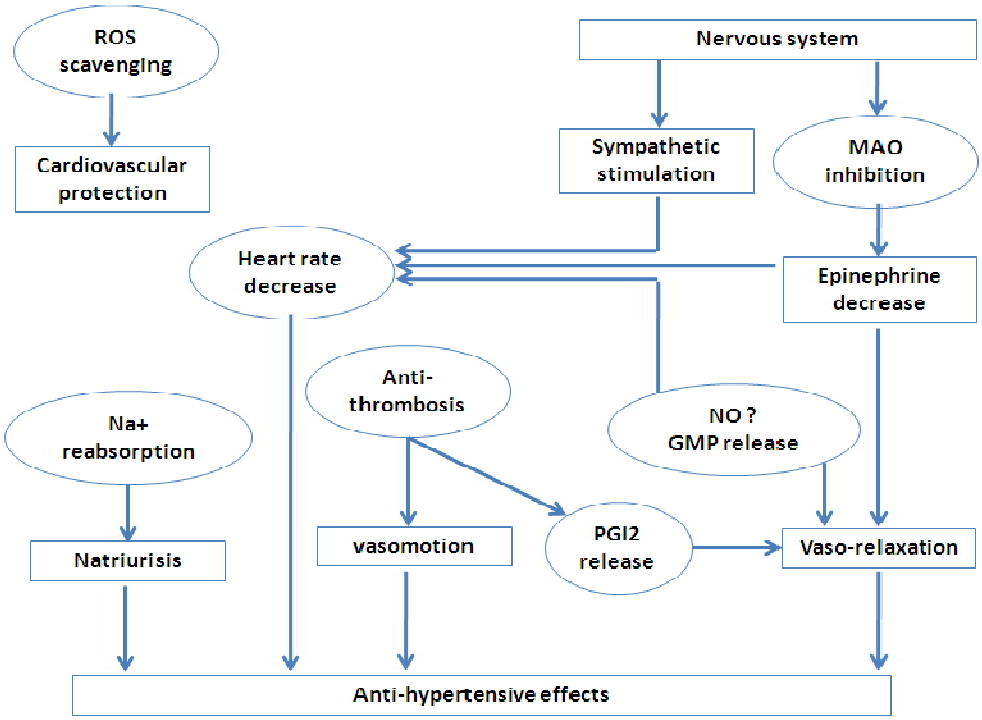

Fig.1: overall schematic representation for the anti-hypertensive effect of Artemisia extracts. The circled sequences stand for experimentally or clinically evidenced actions of Artemisia extracts. Abbreviations: GMP: guanisodine monophosphate, MAO: monamine oxidase, NO: nitric ooxide, PGI2: prostagalandin I2; and ROS: eactive oxygen species.

Concluding remarks

Much scientific researches pointed toward the anti-hypertensive utility of *Artemisia* plants. However, there was no succinct experimental or clinical works delineating its real mechanisms and the involved contained compounds. Nevertheless, using whole extracts of Artemisia could better improve the cardiovascular disorder, since they combined many biological activities that are effective in concurrently healing many disorders (Figure 1). Likely, the effects of these plants extracts on blood pressure are thought to originate, essentially, from the inhibitions of the adenylyl cyclase and stimulation of cGMP enzymes. In such manner, there will be dampened energetic machinery which is needed for vascular constriction. Perspective systemic works are required to outline the importance of whole Artemisia extracts against cardiovascular disorders. A pharmacological model putting into a head objective the anti-hypertensive and cardiovascular protector effects of Artemisia extracts will inevitably improve our understanding of such effects and delineate the utility of these plants in this field.

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