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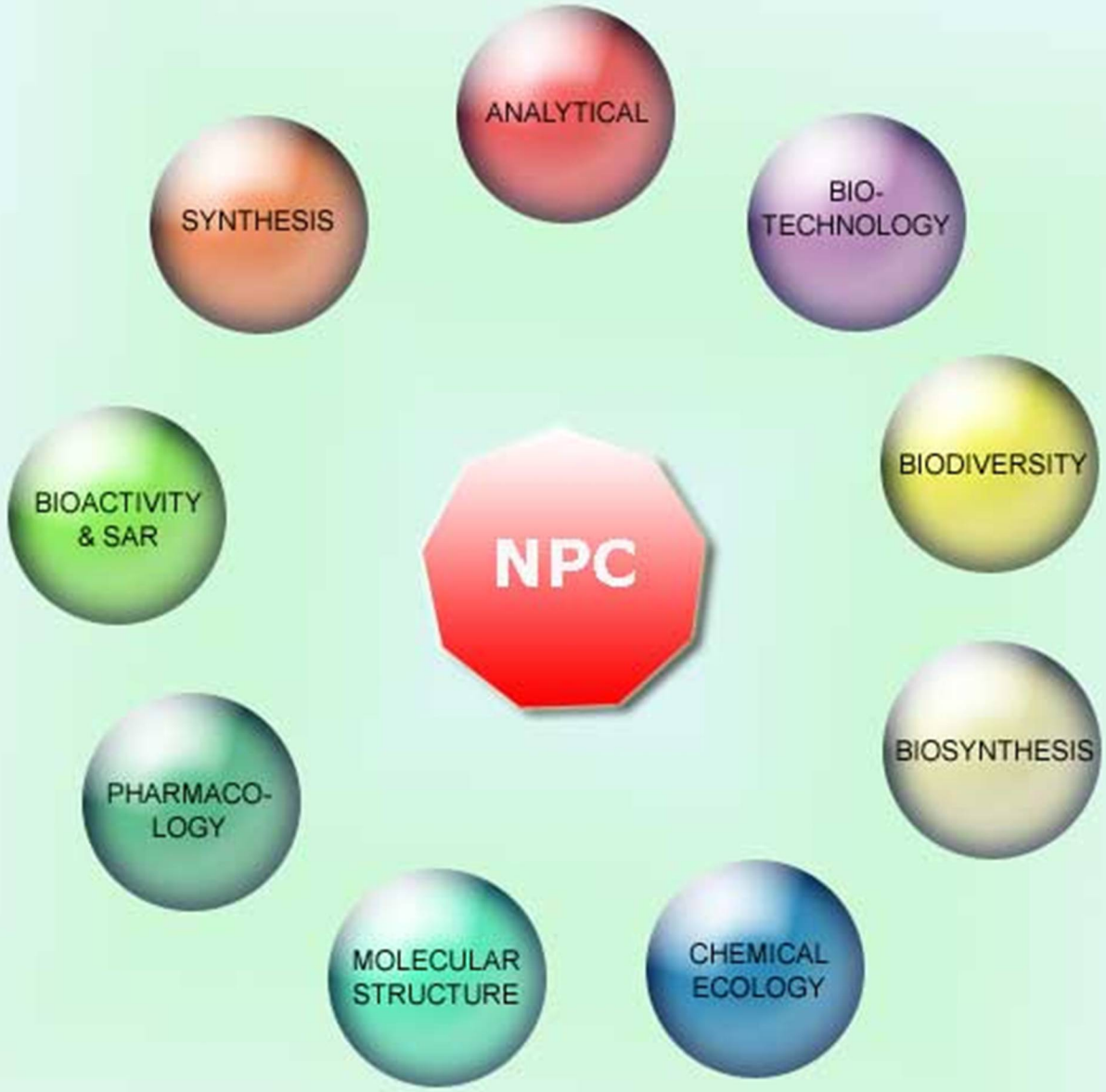

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Phenols, Alkaloids and Terpenes from Medicinal Plants with Antihypertensive and Vasorelaxant Activities. A Review of Natural Products as Leads to Potential Therapeutic Agents

Francesco Maione[a], Carla Cicala[a], Giulia Musciacco[a], Vincenzo De Feo[b], Anibal G. Amat[c,¶], Armando Ialenti[a] and Nicola Mascolo[a]*

[a]*Dipartimento di Farmacia, Università di Napoli Federico II, Via D. Montesano 49, 80131 Napoli, Italy*

[b]*Dipartimento di Scienze Farmaceutiche e Biomediche, Università degli Studi di Salerno, Via Ponte don Melillo, 84084, Fisciano (Salerno), Italy*

[c]*Facultad de Ciencias Exactas, Quimicas y Naturales, Universidad Nacional de Misiones, Felix de Azara 1552, 3300 Posadas, Misiones, Argentina*

nicola.mascolo@unina.it

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Numerous studies support the cardiovascular effects of medicinal plants. This review examines plants whose antihypertensive and vasorelaxant effects have been scientifically validated. Our study selected only chemically characterized plants whose mode of action had already been investigated. The aim of the paper is to provide a quick way to identify medicinal plants and their constituents with antihypertensive and vasorelaxant activities.

Keywords: Phenols, Alkaloids, Terpenes, Hypertension, Cardiovascular diseases, Drug discovery.

Hypertension is the most prevalent cardiovascular disease and is a leading cause of morbidity and mortality being, also, an important risk factor for the development of other cardiovascular disturbances [1]. The control of hypertension becomes imperative and conventional drug therapy demands, in most cases, the use of multiple drugs, often not devoid of side effects. It becomes, therefore, an urgent necessity to search for new drugs that possess the same therapeutic efficacy and which are contextually free of side effects. Medicinal plants are the major source of new compounds.

Despite the fact that many plants have been screened for their antihypertensive/vasorelaxant effect, only a small percentage has been chemically investigated and studied as potential therapeutic agents in the management of hypertension and its related complications.

Identification of plant active components and the understanding of their mode of action are crucial steps in the process of drug discovery [2].

The possibility of identifying new, potentially useful compounds from the plant kingdom is very high if the fact that only a small proportion (about 10%) of plants that has been biologically screened is also taken into consideration [3].

The aim of this review is to provide a concise discussion, by means of three summary Tables, that will help investigators to identify quickly medicinal plants with antihypertensive/vasorelaxant activities, their major constituents, and the mechanism underlying their effects.

Our review results (Tables 1-3) refer to a restricted number of medicinal plants whose antihypertensive/vasorelaxant effects have been scientifically validated. They belong to a broad spectrum of plant families used in folk medicine worldwide. Here we report 61 plants belonging to 57 genera in 36 families.

Compounds with different structures, but with the same antihypertensive activity, have been isolated from the above mentioned medicinal plants and studied, *in vivo* and *in vitro*, against experimentally induced hypertension and/or on isolated vessel tissues: 31 (50.8%) and 14 (22.9%) are studies reporting experiments conducted *in vitro* or *in vivo*, respectively and 16 (26.2%) are those undertaken both *in vitro* and *in vivo*.

Tables 1-3 also provide a chemical library of molecules of some interest. Phenols are pointed out as major constituents, followed by alkaloids and terpenes. All these active ingredients are the main compounds in medicinal plants with antihypertensive/vasorelaxtant action. Their antihypertensive effects have been attributed to the involvement of K^+ and Ca^{2+}-channels, adenilate cyclase, nitric oxide (NO) and adrenergic system (α- and β-receptor), angiotensin converting enzyme (ACE), serotonin (5HT), norepinephrine (NE), prostaglandins (PGs)- pathway, phosphodiesterase enzyme (PDE) and Na^+absorption. Among the compounds reported, terpenoids seem to be promising drug candidates or lead compounds for the development of novel therapeutic agents [45]. They include a wide range of di- tri-, sesqui- and tetraterpenoids, most of which have been investigated for their pharmacological activities.

Stevioside, from *Stevia rebaudiana* (Table 3), is an example of a diterpenoid glycoside, studied *in vivo* and *in vitro*, with a potential use in hypertension due to its capability to induce diuresis and a

[¶]Anibal G. Amat passed away and this paper is dedicated to his memory.

Table 1: Plants containing phenols as active constituents (All acronyms and abbreviations in tables 1-3 are reported in the text)

Plant/ botanical name	Family name	Chemical constituent(s)	Studies *in vitro/in vivo*	Mode of action	Reference
Acer nikoense (Miq.) Maxim.	Aceraceae	scopoletin cleomiscosin A aquillochin	*in vitro*	Ca^{2+}-channel antagonist	[4]
Achillea millefolium L.	Asteraceae	artemetin	*in vivo*	ACE-inhibitor	[5]
Agastache Mexicana (Kunth) Lint & Epling	Lamiaceae	tilianin	*in vitro*	NO release and K^+ channels modulator	[6]
Ailanthus excelsa Roxb.	Simaroubaceae	apigenin luteolin kaempferol quercetin	*in vivo*	ACE-inhibitor	[7-10]
Angelica keiskei Koidz.	Apiaceae	xanthoangelol hydroxyderricin	*in vitro/in vivo*	PDE-inhibitor	[11,12]
Calycotome villosa Link	Fabaceae	chrysin	*in vitro/in vivo*	NO release	[13]
Cnidium monnieri (L.) Cusson	Apiaceae	osthole	*in vitro*	Ca^{2+}-channel antagonist	[14]
Citrus sinensis Osbeck	Rutaceae	hesperetin	*in vitro*	PDE-inhibitor	[15]
Cistanche tubulosa Wight	Scrophulariaceae	kankanoside F kankanose echinacoside acteoside cistanoside F	*in vitro*	Ca^{2+}-channel antagonist	[16,17]
Clerodendron trichotomum Thunb.	Lamiaceae	acteoside leucosceptoside martynoside	*in vitro*	ACE-inhibitor	[18]
Cuscuta japonica Choisy	Cuscutaceae	caffeoylquinic acid	*in vivo*	ACE-inhibitor	[19,20]
Daucus carota L.	Apiaceae	coumarin glycosides	*in vitro /in vivo*	Ca^{2+}-channel antagonist	[21]
Dioclea grandiflora Mart. ex Benth.	Leguminosae	dioclein	*in vitro/in vivo*	Ca^{2+} antagonist and K^+ -channel modulator	[22,23]
Diospyros kaki Thunb.	Ebenaceae	astragalin isoquercitrin quercetin	*in vitro*	ACE-inhibitor	[24]
Erythroxylum gonocladum O.E. Schulz	Erythroxylaceae	astilbin	*in vitro*	ACE-inhibitor	[25]
Euphoria longana Lam.	Sapindaceae	corilagin	*in vivo*	reduced NE and NO release	[26]
Gentiana kochiana E.P.Perrier & Songeon	Gentianaceae	gentiacaulein gentiakochianin butein	*in vitro/in vivo*	ACE-inhibitor	[27,28]
Geum japonicum Thunb.	Rosaceae	penta-*O*-galloyl-β-glucoside, casuariin and 5-desgalloylstachyurin	*in vitro*	NO release	[29]
Guazuma ulmifolia Lam.	Sterculiaceae	procyanidin	*in vivo*	NO release	[30]
Hibiscus sabdariffa Rottler	Malvaceae	cyanidin/delphinidin-3-*O*-sambubioside	*In vitro*	ACE-inhibitor	[31]
Lepechinia caulescens (Ortega) Epling	Lamiaceae	ursolic acid	*in vitro*	NO release	[32]
Ligusticum wallichii Franch.	Apiaceae	tetramethylpyrazine	*in vitro*	Ca^{2+}-channel antagonist	[33]
Ligustrum purpurascens Yang	Oleaceae	acteoside leucosceptoside A martynoside	*in vitro*	Ca^{2+}-channel antagonist and ACE-inhibitor	[24]
Lindera megaphylla Hemsl.	Lauraceae	dicentrine	*in vivo*	α_1. antagonist	[34]
Paeonia moutan Sims	Paeoniaceae	tetragalloylglucose pentagalloylglucose	*in vitro*	NO release	[35]
Phyllanthus niruri L.	Euphorbiaceae	methyl brevifolincarboxylate	*in vitro*	Ca^{2+}-channel antagonist	[36]
Phyllanthus urinaria L.	Euphorbiaceae	geraniin	*in vitro/in vivo*	ACE inhibitor	[37]
Salvia miltiorrhiza Bunge	Lamiaceae	salvianolic acid B lithospermic acid	*in vitro/in vivo*	Ca^{2+}-channel antagonist and ACE- inhibitor	[38-40]
Sedum sarmentosum Bunge	Crassulaceae	quercetin	*in vitro*	ACE-inhibitor	[41]
Selaginella tamariscina L.	Selaginellaceae	amentoflavone	*In vitro*	Ca^{2+}-channel antagonist	[42]
Tropaeolum majus L.	Tropaeolaceae	isoquercitrin kaempferol	*in vivo*	ACE inhibitor	[43]
Zingiber officinale Roscoe	Zingiberaceae	gingerol shogaol zingerone paradol	*in vitro/in vivo*	Ca^{2+}-channel antagonist	[44]

strong decrease in arterial pressure and heart rate in a dose-dependant fashion by acting on multiple targets such as the Ca^{2+}-channel, prostaglandins pathway and Na^+ absorption. Stevioside tested in humans was shown to be safe and effective in lowering blood pressure [46].

Concluding remarks

Since ancient times, plants have been used as medicines. Today, about 25% of the effective drugs in use are of natural origin [84]. Currently, throughout the world the development of new drugs seems to be slowing down despite large investments in research and development. Novel drugs can and must be useful in therapy. It is, indeed, expected that for a given disease a new drug should lead to a substantial improvement in comparison with drugs already in use. For this reason, it is necessary to return to plants as an inexhaustible source of substances that are interesting in both the chemical and pharmacological fields. Natural products are great tools for identifying novel structures as therapeutic agents in a drug discovery process that begins and ends in humans. We hope that this review may inspire new developments in organic chemistry in order to create analogues of the original lead compounds with improved pharmacological and/or pharmaceutical properties.

Table 2: Plants containing alkaloids as active constituents.

Species	Family name	Chemical constituent(s)	Studies *in vitro/in vivo*	Mode of action	Reference
Annona cherimolia Mill.	Annonaceae	anonaine roemerine pukateine	*in vitro*	Ca^{2+}-channel antagonist	[47,48]
Cassytha filiformis L.	Lauraceae	ocoteine	*in vitro*	α_1- antagonist	[49]
Corydalis racemosa Pers.	Fumariaceae	tetrahydropalmatine	*in vivo*	dcreased 5-HT release in hypotalamus	[50,51]
Evodia rutaecarpa L.	Rutaceae	rutaecarpine	*in vitro*	Ca^{2+}-channel antagonist	[52,53]
Fritillaria usuriensis Maxim.	Liliaceae	peimisine verticine verticinone	*in vitro*	ACE-inhibitor	[54]
Illigera luzonensis Merr.	Hernandia-ceae	*n*-methyl-actinodaphnine	*in vitro*	α_1- antagonist	[55]
Ligusticum wallichii Franch.	Apiaceae	tetramethylpirazine	*in vivo*	K^+-channel modulator	[56]
Lindera megaphylla Hemsl.	Lauraceae	dicentrine	*in vivo*	α_1- antagonist	[57]
Magnolia fargesii (Finet & Gagnep.) W. C. Cheng	Magnoliaceae	denudatin B	*in vitro*	Ca^{2+}-channel antagonist	[58]
Mahonia aquifolium Nutt.	Berberidaceae	berbamine oxyacanthine	*in vitro*	α_1 and Ca^{2+}-channel antagonist	[59]
Platycapnos spicatus Bernh.	Papaveraceae	nantenine domesticine nantenine	*in vitro* *in vivo*	α_1- antagonist Ca^{2+}-channel antagonist	[24]
Stephania glabra Miers	Menisperma-ceae	cycleanine	*in vitro*	Ca^{2+}-channel antagonist	[24]
Stephania tetrandra S. Moore	Menisperma-ceae	tetrandrine	*in vivo*	Ca^{2+}-channel antagonist	[60,61]
Uncaria rhynchophylla Miq.	Rubiaceae	hirsutine rhynchophylline	*in vitro*	Ca^{2+}-channel antagonist	[62]
Verbesina caracasana B. L. Rob. & Greenm.	Asteraceae	leonurine caracasandiamide	*in vitro/in vivo*	Ca^{2+}-channel antagonist	[63,64]

Table 3: Plants containing terpenes as active constituents.

Species	Family name	Chemical constituent(s)	Studies *in vitro/in vivo*	Mode of action	Reference
Aegle marmelos Correa	Rutaceae	auraptene	*in vivo*	Ca^{2+}-channel antagonist	[65]
Alepidea amatymbica Eckl. & Zeyh.	Apiaceae	kaurenoids	*in vitro*	Ca^{2+}-channel antagonist	[66]
Andrographis paniculata Nees	Acanthaceae	14-deoxy-11,12-didehydroandrographolide	*in vivo*	Non selective β- antagonist and ACE-inhibitor	[67]
Coleus forskohlii Briq.	Lamiaceae	forskolin coleonol	*in vitro/in vivo*	Adenilate Cyclase Activator	[68]
Croton cajucara Benth.	Euphorbiaceae	*trans*-dehydrocrotonin	*in vitro/in vivo*	Ca^{2+}-channel antagonist and NO release	[5,69]
Marrubium vulgare L.	Lamiaceae	marrubenol	*in vitro*	Ca^{2+}-channel antagonist	[70]
Mentha villosa Huds.	Lamiaceae	rotundifolone	*in vitro*	Ca^{2+}-channel antagonist	[71]
Moldenhawera nutans L.P.Queiroz, G.P.Lewis & Allkin	Caesalpinia-ceae	labd-8 (17)-en-15-oic acid	*in vitro/in vivo*	Non selective β- antagonist	[72]
Ocimum gratissimum L.	Lamiaceae	eugenol	*in vitro/in vivo*	Non selective β-antagonist	[73-75]
Petasites formosanus Kitam.	Asteraceae	iIso-S-petasin	*in vitro*	Ca^{2+}-channel antagonist	[76]
Polyalthia longifolia (Sonn.) Hook. f. & Thomson	Annonaceae	kovalenic acid	*in vitro/in vivo*	NO release	[68]
Stevia rebaudiana Bertoni	Asteraceae	stevioside	*in vitro/in vivo*	Ca^{2+}-channel antagonist PG's pathway Na^+absorption	[46,77-80]
Viguiera arenaria Baker	Asteraceae	ent-pimara-8(14),15-dien-19-oic acid	*in vitro*	α_1/ Ca^{2+}-channel antagonist	[81,82]
Xylopia aethiopica A. Rich	Annonaceae	kaurenoids	*in vivo*	Ca^{2+}-channel antagonist	[83]

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