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International Journal of Pharmacognosy and Chinese Medicine
ISSN: 2576-4772

Role of Phyto-Constituents in the Management of Hypertension

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Mini Review

Volume 3 Issue 2

Received Date: April 08, 2019

Published Date: May 03, 2019

DOI: 10.23880/ipcm-16000159

Abstract

Hypertension is one of the commonly prevailing ailments around the globe. It is evident that more than 7 million people are suffering from this disease every year. There is a wide variety of allopathic medicines available for the treatment of hypertension, but they are associated with drug dependence and fewer to larger number of adverse effects. Plants has been utilized as significant resources as therapeutic agents in the management of hypertension from the ancient time. There are so many categories of active constituents derived from plants which have excellent hypotensive properties. In this mini review, authors have summarized various phyto-constituents according to their classes which possess significant blood pressure lowering potential. The classes included are alkaloids, flavonoids, glycosides, coumarins and terpenoids.

Keywords: Dicentrine; Laurotetanine; Reserpine; Rhynchophylline; Tetrandrine; Puqienine

Introduction

Hypertension is a highly prevalent cardiovascular ailment throughout the globe due to prevailing longevity and increases in a number of its contributing factors [1]. The prevalence rate of hypertension is more in developing countries particularly in urban societies as compared to the developed countries [2]. Hypertension leads to 7.5 million annual deaths and contributes 4.5% to the global disease burden [3]. Although there are several kinds of treatments already available for the management of hypertension still it is inadequately managed [4]. Most of the drug candidates which are being employed in the treatment of hypertension suffer from a lack of therapeutic efficacy in single drug therapy and a wide range of side effects. Therefore, the need of the hour is to develop multi-target therapeutic agents to treat this ailment [5].

Natural products have been continuously explored for discovery and development of new drugs intended to use in the treatment of a wide variety of diseases [6]. Natural resources especially plants serve as largest contributors towards this purpose. The antihypertensive properties of plant-derived products and extracts have been already

well established. Alkaloids are one of the most potent active constituents of the plant and it is evident that these have a significant role in reducing the elevated blood pressure by different mechanisms. Various other phytochemical classes possessing hypotensive properties are flavonoids, glycosides, coumarins and terpenoids (Table 1). Some of the potent active constituents of these classes have been described here in the following sections.

Table 1: Some potent phyto-constituents as anti-hypertensive agents.

S. No.	Name of Moiety	Biological Source	Phytochemical Nature	Therapeutic Uses	References
1	Dicentrine	*Lindera megaphylla* and *Actinodaphne sesquipedalis*	Alkaloid	Reduces the elevated blood pressure	[7,8]
2	Laurotetanine	*Luureliu sempervirens*	Alkaloid	Hypotensive action	[9]
3	Reserpine	*Rauwolfia serpentine*	Alkaloid	Blocks the vesicular monoamine receptors	[10]
4	Lobeline	*Lobelia siphilitica*	Alkaloid	Useful in management of hypertension and atherosclerosis	[11]
5	Rhynchophylline	*Uncaria rhynchophylla*	Alkaloid	Reduces the blood pressure	[12]
6	Nantenine	*Nandina domestic*	Alkaloid	Treatment of asthma, uterine disorders and antihypertensive action	[13]
7	Tetrandrine	*Stephania tetranda*	Alkaloid	Suppresses the production of aldosterone	[14]
8	Isoliensinine	*Nelumbo nuciferagaertn*	Alkaloid	Reduce the diastolic and systolic blood pressures	[15]
9	PuqienineA, PuqienineB, and PuqienineE	*Fritillaria poiesis*	Alkaloid	ACE inhibitor and has hypotensive effect	[16]
10	Quercetin	*Quercus tinctoria*	Flavanoids	Reduces the systolic and diastolic blood pressure and has antioxidant property	[17]
11	Luteolin	*Aloe barbadensis*	Flavanoids	Reduces the systolic and diastolic blood pressure	[18]
12	Chrysin	*Oroxylum indicum*	Flavanoids	Lowers the blood pressure	[19]
13	Catechin	*Elaeis guineensis*	Flavanoids	Anti-hypertensive action, regulates vascular tone and cardiac electric activity	[20]
14	Hesperidin	*Citrus sinensis*	Glycosides	Reduces blood pressure in dose-dependent manner	[21]
15	Rutin	-	Glycosides	Inhibit ACE activity	[22]
16	Acteoside	*Syringa vulgaris*	Glycosides	Reduces sytolic, diastolic and mean arterial blood pressure	[23]
17	Dihydromammea	*Mammea africana*	Coumarins	Lowers the systolic blood pressure	[24]
18	Scopoletin	*Tetrapleura tetraptera*	Coumarins	Reduces systemic blood pressure and has smooth muscle relaxant activity	[25]
19	Visnadine	*Ammi visnaga*	Coumarins	Peripheral and coronary vasodilator activity	[26]
20	Auraptene	*Citrus aurantium* and *Aegle*	Coumarins	Hypotensive effect	[27]

		marmelos			
21	Marrubenol	*Marrubium vulgare*	Terpenoids	Reduces the systolic blood pressure	[28]
22	Trachylobane& Pimarane	*Croton zambesicus*	Terpenoids	Vascular relaxation activity	[29]
23	14-deoxy-11,12-didehydroandrographolide (DDA)	*Andrographis paniculata*	Terpenoids	Reduces mean arterial blood pressure and heart rate	[30]
24	Stevioside	*Stevia rebaudiana*	Terpenoids	Produce diuresis and natriuresis and cause lowering of blood pressure	[31]

Alkaloids

(+)-Dicentrine: (+)-Dicentrine (Compound1, Figure 1) is obtained from the plant species *Lindera megaphylla* and *Actinodaphne sesquipedalis.* It reduces the elevated blood pressure with a declining rate of 36.7% at a dose of 10mg/kg body weight in rats [7]. The extent of adverse effects on cardiacoutput, heartrate, and stroke volume are also negligible. The mechanistic studies revealed that it is α_1-adreno receptor antagonist [8].

Laurotetanine: Laurotetanine (Compound2, Figure 1) is isolated from the leaves of *Luureliu sempervirens*. It produces a significant hypotensive response in rats at a dose of 1mg/kg body weight within 2 minutes. It has proven to be very less toxic even at a high dose level [9].

Reserpine: Reserpine (Compound 3, Figure 1) is isolated from the roots of Indian Snake *Rauwolfia serpentine*. Reserpine exhibits its action by irreversibly blocking the vesicular monoamine receptors (VMAT) and depletes the catecholamines [10].

(-)-Lobeline: Lobeline is an alkaloidal constituent which is majority obtained from *Lobelia siphilitica*. Lobeline (Compound4, Figure 1) has been identified as a potent antagonist for the proliferation of human umbilical arterial vascular smooth muscle cells induced by endothelin-1. Hence it can be a suitable therapeutic agent for the management of hypertension and atherosclerosis [11].

Rhynchophylline: Rhynchophylline (Compound 5, Figure 1) is obtained from a Chinese plant *Uncaria rhynchophylla.* It reduces the blood pressure in anesthetized rats with a lowering rate of 32%. The reported mode of action is through the modulation of calcium ion channels [12].

(+)-Nantenine: (+)-Nantenine (Compound 6, Figure 1) is isolated from *Nandina domestic*. Extract of this plant is being used in the treatment of asthma and uterine disorders in Japan. The latest report revealed that it has a potential to totally relax the contractions produced by nor-adrenaline in rat aortic rings. Therefore, it can be a lead molecule for the further development of newer antihypertensive agents [13].

Tetrandrine: Tetrandrine (Compound 7, Figure 1) is an alkaloidal constituent obtained from *Stephania tetranda* plant. It is a calcium channel blocker and has equivalent potency to verapamil. It blocks T and L calcium channels and suppresses the production of aldosterone. It can produce a significant effect at a dose of 15mg/Kg body weight in rats. In higher doses, it can produce hepatotoxicity [14].

Isoliensinine: It is active constituent isolated from *Nelumbo nucifera gaertn* plant. Literature revealed that it has a tendency to reduce the diastolic and systolic blood pressures by 37% and 29% respectively at a dose of 2mg/Kg body weight in pithed rats. Isolinsenine (Compound 8, Figure 1) exhibits anti-hypertensive action by blocking calcium influx and α_1-adreno receptors [15].

Puqienine A, Puqienine B, and Puqienine E: It is evident that some of plant-derived steroidal alkaloids possess significant antihypertensive activity. Puqienine A (Compound 9, Figure 1), Puqienine B (Compound 10, Figure 1) and Puqienine E (Compound 11, Figure 1) are steroidal alkaloids derived from the plant *Fritillaria poiesis*. They inhibit angiotensin-converting enzyme (ACE) and produce significant hypotensive effect [16]. It is crystal clear that the plant-derived alkaloids possess antihypertensive activity by interacting with various targets and other mechanisms. These alkaloids can serve as new leads for the development of new therapeutic candidates by selective modification in their structure.

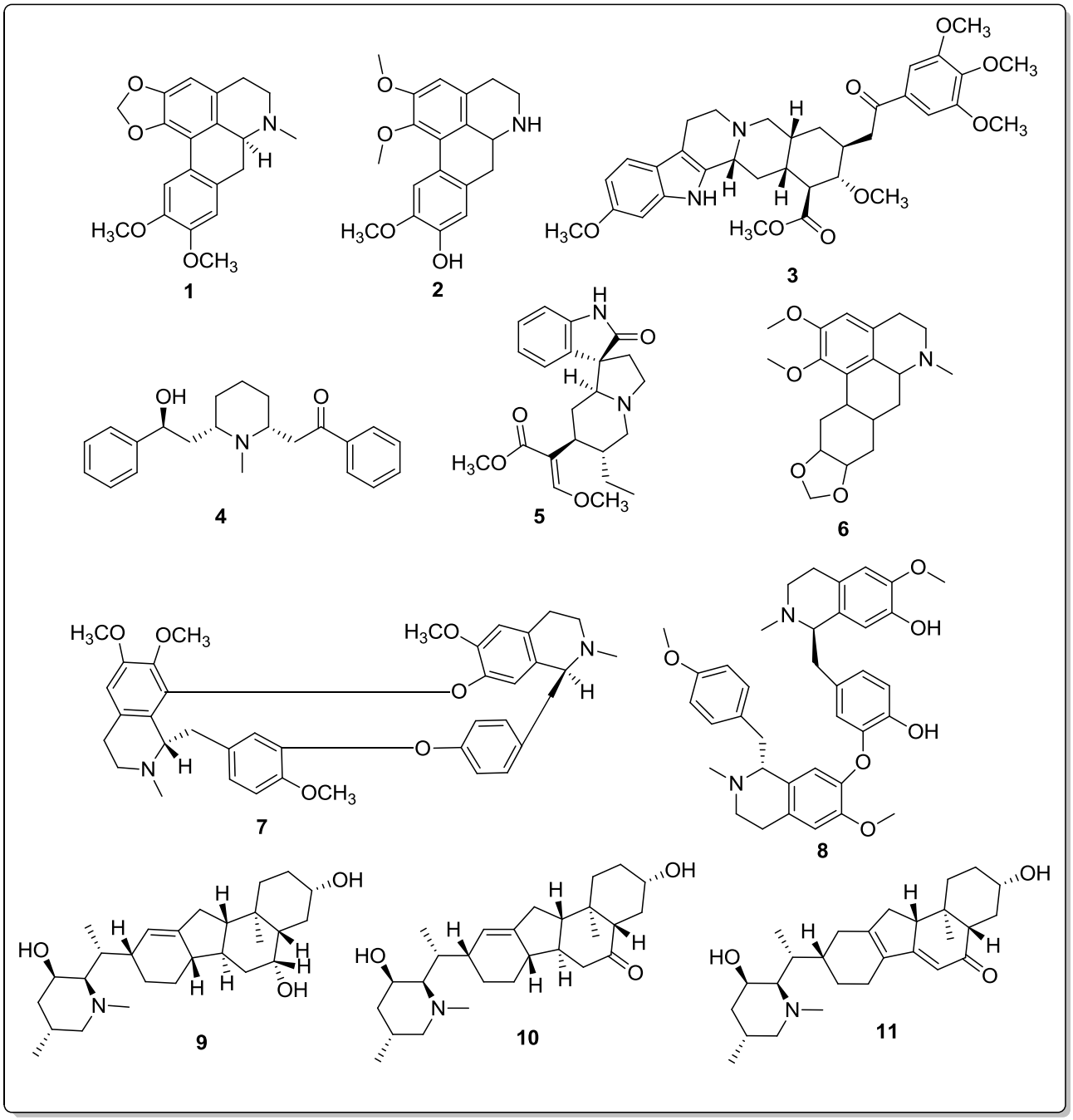

Figure 1: Natural alkaloids as antihypertensive agents.

Flavanoids

Quercetin: Quercetin (Compound 1, Figure 2) is obtained from the bark of *Quercus tinctoria.* It reduces the systolic and diastolic blood pressure at the rate of 18% and 23% respectively at the dose of 10mg/kg. This action is due to the reduced oxidant level because of the antioxidant property of drug [17].

Luteolin: Luteolin (Compound 2, Figure 2) is the main constituent obtained from the plants of aloe vera. It is

effective at the dose of 60mg/kg and reduces the systolic and diastolic blood pressure by 4.04% and 5.24% respectively and shows the synergistic effect when given with buddleoside. The mechanistic action of luteolin is through RAAS and endothelial system [18].

Chrysin: Chrysin (Compound 3, Figure 2) is isolated from the plant*, Oroxylum indicum*. It lowers the blood pressure in Nω-nitro-l-arginine methyl ester (l-NAME) induced hypertensive rats at the dose of 25mg/kg [19].

Catechin: Catechin (Compound 4, Figure 2) is obtained from the leaf extract of *Elaeis guineensis.* The compound was found to be effective as antihypertensive agent at the dose of 500mg/kg in the Nω -nitro-l-arginine methyl ester (l-NAME)-induced NO-deficient hypertensive rats. They act by mainly targeting the molecular structures that includes cardiovascular ion channels, important in vascular tone regulation and cardiac electric activity [20].

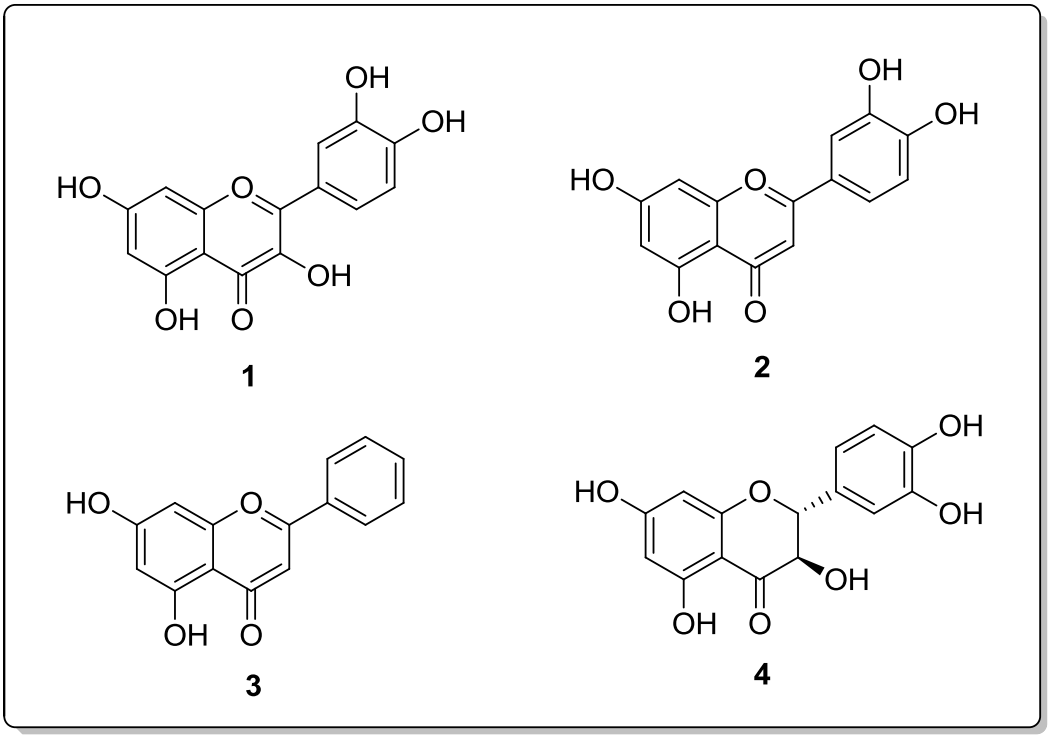

Figure 2: Natural flavanoids as antihypertensive agents.

Glycosides

Hesperidin: Hesperidin (Compound 1, Figure 3) is obtained from the fruits of *Citrus sinensis.* It reduces the blood pressure in a dose-dependent manner. The effect of hesperidin is exhibited through enhanced NO-mediated vasodilation [21].

Rutin: Rutin (Compound 2, Figure 3) is abundantly present in plants such as in buckwheat seed, fruits, and fruit rinds, especially citrus fruits. It is reported that rutin acts through NO/guanylate cyclase pathway and inhibition of ACE. 64μM concentration of rutin can inhibit ACE activity by 50% [22].

Acteoside: Acteoside (Compound 3, Figure 3) was isolated from the violet flowers of *Syringa vulgaris.* It was effective at the dose level of 10mg/kg and elicited a dose dependent reduction in sytolic, diastolic and mean arterial blood pressure in normotensive pentothal anaesthetized rats [23].

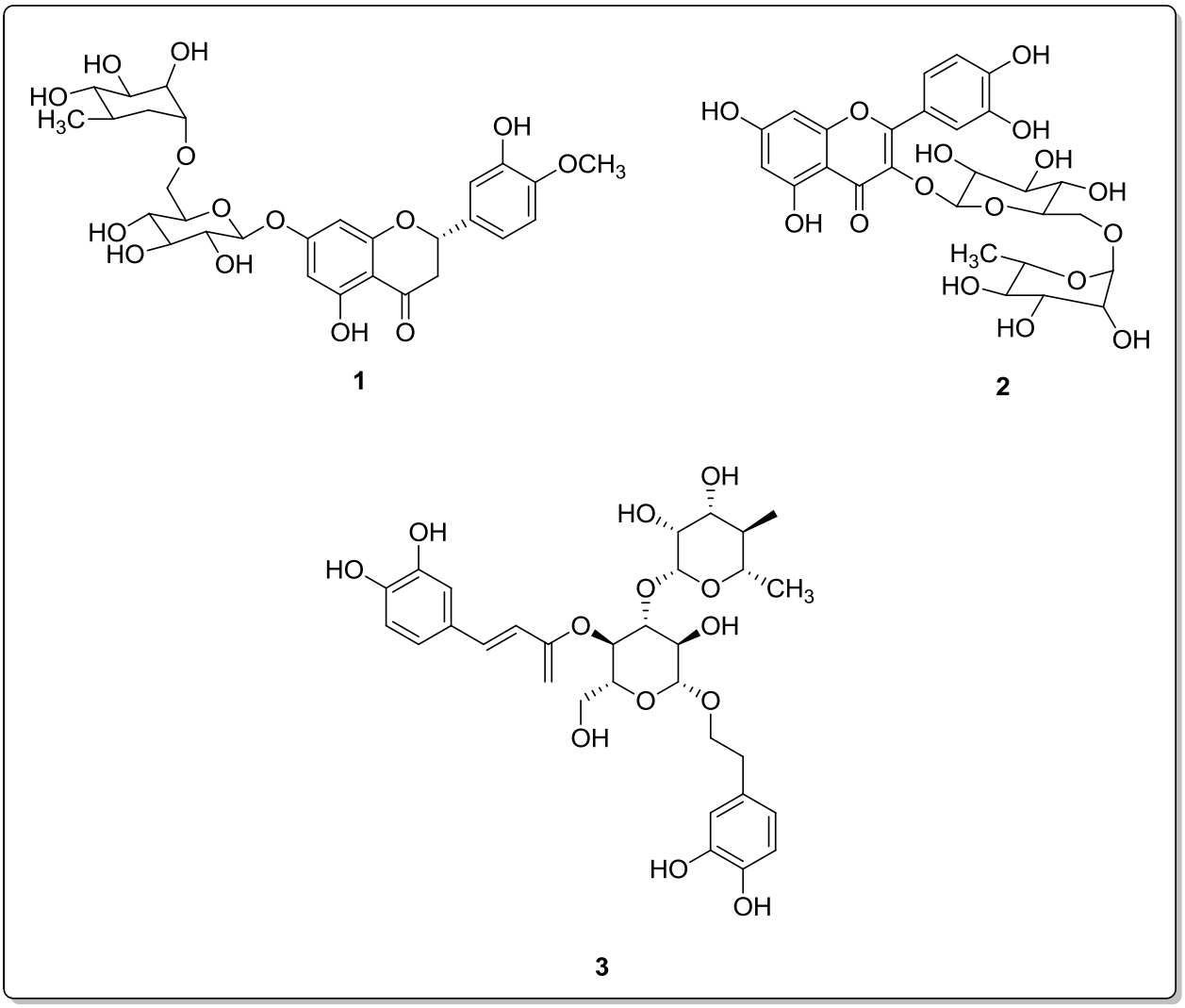

Figure 3: Natural glycosides as antihypertensive agents.

Coumarins

Dihydromammea: Dihydromammea (Compound 1, Figure 4) is obtained from the seeds of the West African tree *Mammea africana.* The methanol and dichlomethane extracts of stem bark from *M. africana* significantly lowers the systolic blood pressure in l-NAME induced hypertensive rats [24].

Scopoletin: Scopoletin (Compound 2, Figure 4) is obtained from the fruits of *Tetrapleura tetraptera*. It cause concentration-dependent reduction in systemic blood pressure in anaesthetized cats. Its hypotensive action is due to its smooth muscle relaxant activity [25].

Visnadine: Visnadine (Compound 3, Figure 4) is an active ingredient isolated from the fruit of *Ammi visnaga*. At lower concentration, it selectively inhibited the Ca^{2+} induced contractions and also depicts peripheral and coronary vasodilator activity [26].

Auraptene: Auraptene (Compound 4, Figure 4) is obtained from *Citrus aurantium* and *Aegle marmelos.* It exhibits dose-dependent hypotensive effect, more significant at 250 and 500 µg/kg. It acts through its smooth muscle relaxant activity [27].

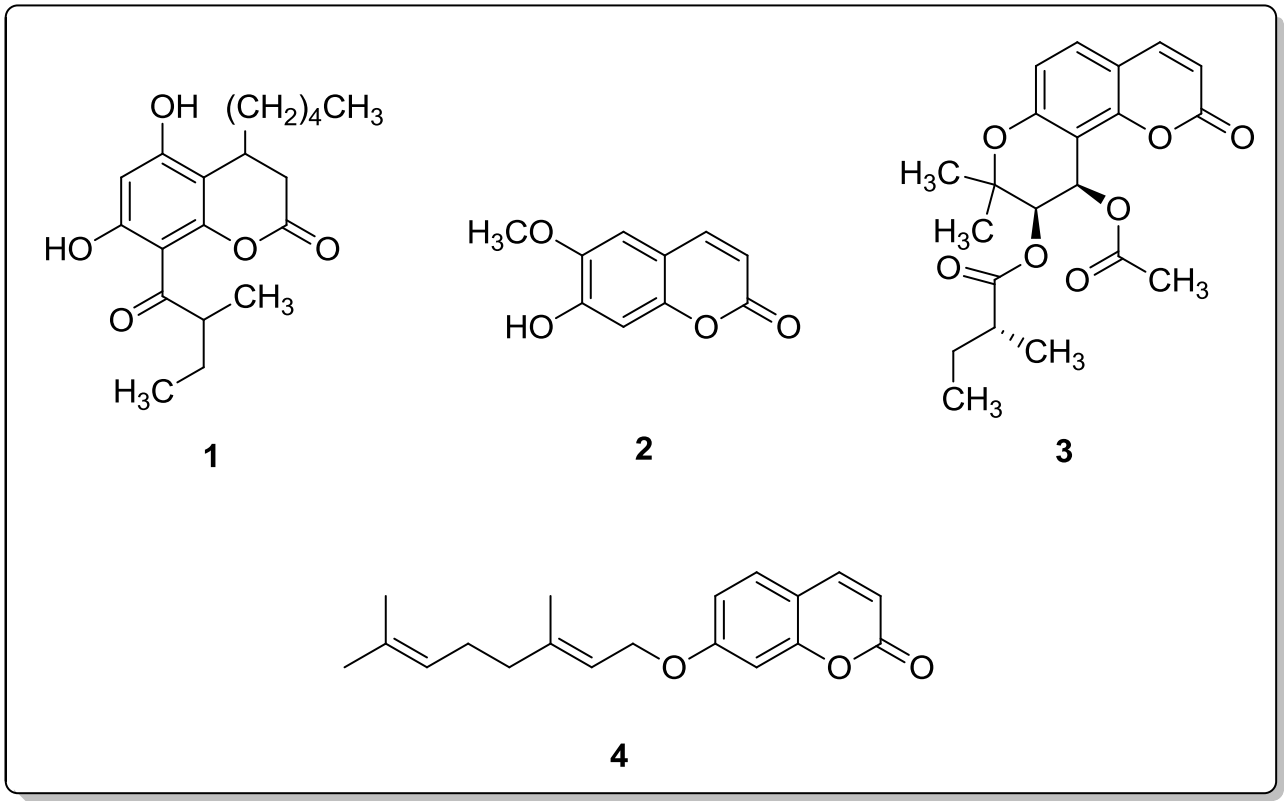

Figure 4: Natural coumarins as antihypertensive agents.

Terpenoids

Marrubenol: Marrubenol (Compound 1, Figure 5) is a diterpenoid isolated from *Marrubium vulgare.* It reduces the systolic blood pressure in spontaneously hypertensive rats and acts by inhibiting the smooth muscle contraction by blocking L-type Ca^{2+} channel [28].

Trachylobane & Pimarane: Trachylobane (Compound 2, Figure 5) & Pimarane (Compound 3, Figure 5) are the two diterpenes that are obtained from *Croton zambesicus*. The mixture of both compounds showed the higher activity than their purified forms. They exhibit vascular relaxation by blocking of extracellular Ca^{2+} influx [29].

14-deoxy-11,12-didehydroandrographolide (DDA): DDA (Compound 4, Figure 5) is a diterpenoid isolated from *Andrographis paniculata.* DDA significantly reduces mean arterial blood pressure and heart rate in a dose-dependent manner in anaesthetised Sprague-Dawley (SD) rats. The mechanistic action of DDA is through β-adrenoceptors, autonomic ganglion receptor and ACE inhibitory activity [30].

Stevioside: Stevioside (Compound 5, Figure 5) is a sweet diterpenoid glycoside obtained from *Stevia rebaudiana.* It inhibits the Ca^{2+} influx and the release of prostaglandins. It also produce diuresis and natriuresis which cause reduction of fluid volume and both these factors contribute to lowering of blood pressure. Even at higher dose (15g/kg), it causes no acute toxicity in rodents [31].

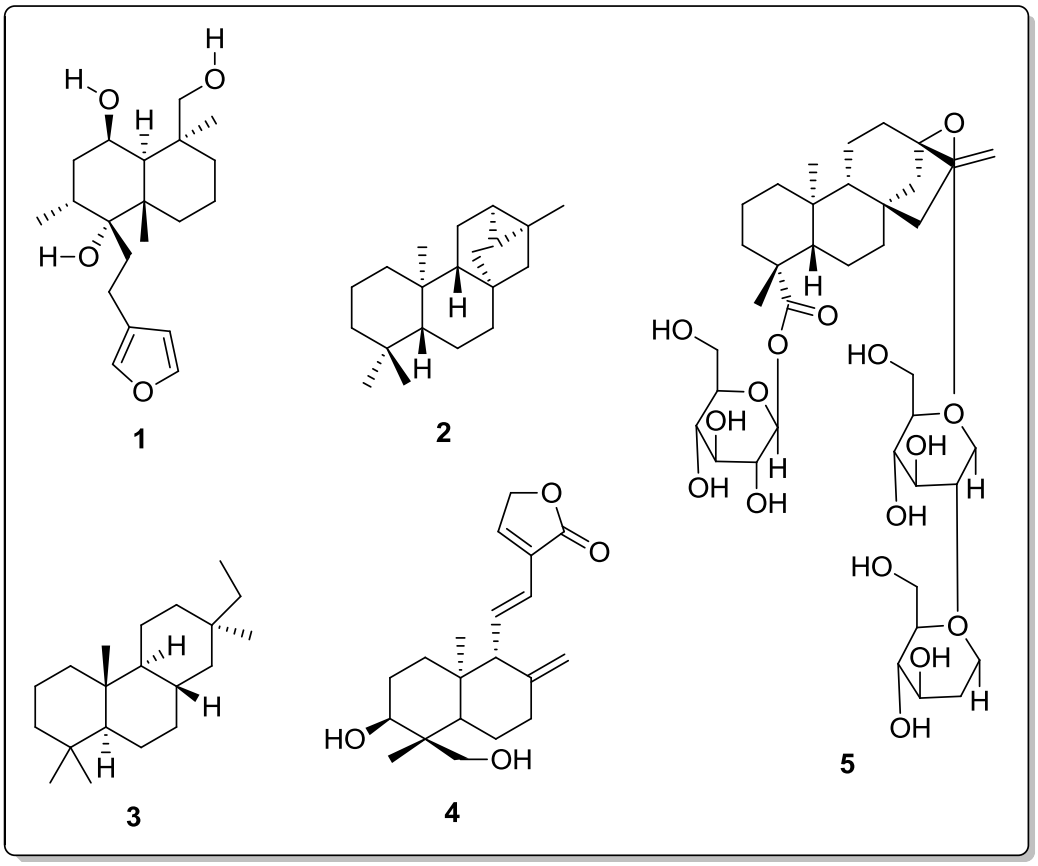

Figure 5: Natural terpenoids as antihypertensive agents.

Conclusion

The growing interest of researchers have brought a big revolution in utilization of plant resources to develop potent therapeutic candidates. The presented compilation was based on the investigation of anti-hypertensive potentials of some important chemical classes derived from plants. It is evident from the literature that various plant derived compounds have promising activities against hypertension. These constituents are distributed to various chemical classes like alkaloids, flavonoids, glycosides, terpenoids, coumarins and many others. Although many phyto-constituents have been identified, still very few are available in market as significant therapeutic agent. This is due to lack of pre-clinical and clinical studies on herbal medicines. The researchers should explore more and more plant resources to identify newer phyto-constituents in order to develop newer therapeutic agents.

References

1. Singh SB, Suh IL, Singh VP, Chaithiraphan S, Laothavorm P, et al. (2000) Hypertension and stroke in Asia: Prevalence, control and strategies in developing countries for prevention. Hum Hypertens 14(10,11): 749-763.

2. Yusuf S, Reddy S, Ounpuu S, Anand S (2001) Global burden of cardiovascular diseases. Part 1: General considerations, the epidemiologic transition, risk factors and impact of urbanization. Circulation 104(22): 2746-2753.

3. WHO (2002) The world health report 2002: Risk to health 2002. World Health Organization, Geneva.

4. Whitworth JA (2003) 2003 World Health Organization (WHO)/ International Society of Hypertension (ISH) statement on management of hypertension. J Hypertens 21(11): 1983-1992.

5. Bai RR, Wei Z, Liu J, Weijia X, Hequan Y, et.al. (2012) Synthesis and biological evaluation of 4'-

[(benzimidazole-1-yl) methyl] biphenyl-2 sulfonamide derivatives as dual angiotensin II/endothelin A receptor antagonist. Bioorg med chemlett 20(15): 4461-4667.

6. Newman DJ, Cragg GM (2012) Natural products as sources of new drugs over the thirty years from 1981 to 2010. J Nat Prod 75(3): 311-335.

7. Yu SM, Kang YF, Chen CC, Teng CM (1993) Effect of dicentrine on haemodynamic, plasma lipid, lipoprotein level and vascular reactivity in hyperlipidemic rats. Brit J Pharmacol 108(4): 1055-1061.

8. Mustafa MR, Achike FI (2000) Dicentrine is preferentially antagonistic to rat aortic than splenic α-1 adrenoceptor stimulation. Actapharmacol sin 21(12): 1165-1168.

9. Schmeda HG, Loyola JI, Rodriguez J (1994) Hypotensive effect of *Laureliasempervirens* on normotensive rats. Phytother Res 8(1): 49-51.

10. Varchi G, Battaglia A, Samori C, Baldelli E, Danieli B, et al. (2005) Synthesis of deserpidine from reserpine. J Nat Prod 8(11): 1629-1631.

11. Wang JJ, Liu SM, Chen R, Li L, Guo XS, et al. (2007) A novel effect of lobeline on vascular smooth muscle cell: inhibition of proliferation induced by endothelin-1. Pharmazie 62(8): 620-624.

12. Song CQ, Fan Y, Huang WH, Dazhenget Wu, Zhibi Hu (2000) Different hypotensive effects of various active constituents isolated from Uncariarhynchophylla. Chin Tradit Herb Drugs 31(10): 762-764.

13. Orallo F, Alzuta A (2001) Preliminary study of vasorelaxant effect of (+)-nantenine, an alkaloid isolated from Platycapnosspicata in rat aorta. Planta Med 67(9): 800-805.

14. Iturriaga Vasquez P, Miquel R, Ivorra MD, D'Ocon MP, Cassels BK (2003) Simplified tetrandrine congeners as possible antihypertensive agents with a dual mechanism of action. J Nat Prod 66(7): 954-957.

15. Shang J, Pang Y (2010) Advances in chemical and pharmacological research of isoliensinine. J Nanjing U Tradit Chi Med 26(3): 238-240.

16. An JJ, Zhou JL, Li HJ, Jiang Y, Li P (2010) Puqienine E: An angiotensin converting enzyme inhibitory steroidal alkaloid from Fritillariapuqiensis. Fitoterapia 81(3): 149-152.

17. Duarte J, Palencia RP, Vargas F, Ocete MA, Pérez-Vizcaino F, et al. (2001) Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats. Brit J Pharmacol 133(1): 117-124.

18. Lv GY, Zhang YP, Gao JL, Yu JJ, Lei J, et al. (2013) Combined antihypertensive effect of luteolin and buddleoside enriched extracts in spontaneously hypertensive rats. J Eth Pharmacol 150(2): 507-513.

19. Ramanathan V, Thekkumalai M (2014) Role of chrysin on hepatic and renal activities of N^{ω}-nitro-l-arginine-methylester induced hypertensive rats. Interl J Nut Pharmacol Neuro Dis 4(1): 58-63.

20. Jaffri JM, Mohamed S, Rohimi N, Ahmad IN, Noordin MM, et al. (2011) Antihypertensive and cardiovascular effects of catechin-rich oil palm (Elaeis guineensis) leaf extract in nitric oxide-deficient rats. J Med Food 14(7,8): 775-783.

21. Yamamoto M, Suzuki A, Hase T (2008) Short-term effects of glucosyl hesperidin and hesperetin on blood pressure and vascular endothelial function in spontaneously hypertensive rats. J Nut Sci and Vitaminol 54(1): 95-98.

22. Sharma S, Ali A, Ali J, Sahni JK, Baboota S (2013) Rutin: therapeutic potential and recent advances in drug delivery. Expert opinion on investigational drugs 22(8): 1063-1079.

23. Ahmad M, Rizwani GH, Aftab K, Ahmad UV, Gilani AH, et al. (1995) Acteoside: a new antihypertensive drug. Phytother Res 9(7): 525-527.

24. Venugopala KN, Rashmi V, Odhav B (2013) Review on natural coumarin lead compounds for their pharmacological activity. BioMed Res International.

25. Ojewole JA, Adesina SK (1983) Mechanism of the hypotensive effect of scopoletin isolated from the fruit of Tetrapleura tetraptera. Planta Med 49(1): 46-50.

26. Duarte J, Vallejo I, Vizcaino FP, Jiménez R, Zarzuelo A, et al. (1997) Effects of visnadine on rat isolated vascular smooth muscles. Planta Medica 63(3): 233-236.

27. Imenshahidi M, Eghbal M, Sahebkar A, Iranshahi M (2013) Hypotensive activity of auraptene, a monoterpene coumarin from Citrus spp. Pharmaceutical Biology 51(5): 545-549.

28. Bardai SE, Wibo M, Hamaide MC, Lyoussi B, Quetin Leclercq J, et al. (2003) Characterisation of marrubenol, a diterpene extracted from Marrubium vulgare, as an L-type calcium channel blocker. Br J Pharmacol 140(7): 1211-1216.

29. Baccelli C, Block S, Holle BV, Schanck A, Chapon D, et al. (2005) Diterpenes isolated from Croton zambesicus inhibit KCl-induced contraction. Planta Med 71(11): 1036-1039.

30. Zhang C, Kuroyangi M, Tan BK (1998) Cardiovascular activity of 14-deoxy-11,12-didehydroandrographolide in the anaesthetized rat and isolated right atria. Pharmacol Res 38(6): 413-417.

31. Tirapelli CR, Ambrosio SR, Oliveira AM, Tostes RC (2010) Hypotensive action of naturally occurring diterpenes: a therapeutic promise for the treatment of hypertension. Fitoterapia 81(7): 690-702.