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Review Article

Search for Potential Calcium Channel Blockers from Medicinal Plants

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Abstract

Hypertension is a global disease whose prevalence is estimated to be about one billion, projected to increase to 1.54-1.58 billion by 2025. It is estimated that_hypertensive patients accounted for about 31.1 % of the global adult population in 2010. Current treatment options include angiotensin-converting enzyme inhibitors (ACEIs) such as Captopril and Enalapril, which are first-line drugs for hypertensive patients that are under 55 years old, angiotensin receptor antagonists (ARA) such as candesartan and telmisartan that are used in patients who are intolerant to ACEIs, β-blockers (metoprolol, esmolol, and atenolol) are not prescribed as first-line antihypertensives unless there are additional reasons, such as after a heart attack or atrial fibrillation, calcium channel blockers, like verapamil, are the first-line therapy for primary hypertension in adults over 55 and black people of African or Caribbean ancestry, and aliskiren which is the only direct renin inhibitor prescribed to patients who are intolerant to other antihypertensives. However, despite a multitude of treatment options available, many patients are still unable to control hypertension. Adverse effects also preclude the use of existing antihypertensives in a significant fraction of the patient population. In the last few decades, there has been a revival in the interest in using medicinal plants as a treatment for hypertension. In this manuscript, we explored medicinal plants possessing promising calcium channel-blocking activities. Several medicinal plants and phytocompounds are identified in this review that could be a good starting point for an effective and safe calcium channel blocker that may ultimately land in clinics.

Keywords: Hypertension, medicinal plants, traditional use, calcium channel blocker, antihypertensive medication.

Introduction

According to WHO, hypertension (HTN), also known as high blood pressure (HBP), is a medical disorder that is characterized by persistently elevated blood pressure in arteries. American Heart Association categorizes blood pressure into normal (systolic less than 120 mmHg and diastolic less than 80 mm Hg), elevated, (systolic 120-129 mmHg and diastolic 80-89 mm Hg) stage 1 (systolic 130-139 mmHg and diastolic less than 80 mm Hg) stage 2, (systolic 140 or higher mmHg and diastolic 90 or higher mm Hg) and hypertensive crisis (systolic higher than180 mmHg and diastolic higher than 120 mm Hg) (Harvard Health Publishing 2019). Long-term elevated blood pressure is associated with heart failure, coronary artery disease, atrial fibrillation, chronic kidney disease, peripheral arterial disease, vision loss, stroke, and dementia (Lackland and Weber 2015; Mendis et al. 2011; Hernandorena et al. 2017). HTN, being a major risk factor for heart diseases (Melo et al. 2016), is responsible for 8.5 million deaths from ischemic heart disease, stroke, vascular diseases, and renal disease (Olsen et al. 2016; Zhou et al. 2021).

HTN is classified into primary and secondary HTN depending on its etiology. About 90 to 95% of cases are of primary HTN that is due to genetic factors and non-specific lifestyle, while 5 to 10% of cases are categorized as secondary HTN, i.e., having an identifiable cause such as kidney disorder, endocrine disease, or

narrowing of kidney arteries (Poulter, Prabhakaran, and Caulfield 2015). Chest pain, dyspnea, and headache are the most common symptoms in HTN patients. Organ damage that may occur in HTN patients includes hypertensive encephalopathy, acute pulmonary edema, and cerebral infarction (Zampaglione et al. 1996). Common presenting symptoms of HTN are headache and chest pain, as shown by a study in which 73,063 emergency room visits from 2005 to 2010 were analyzed (Almas et al. 2014). Several antihypertensive agents are available for treating HTN, such as thiazide diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors), and angiotensin receptor blockers (ARBs).

Epidemiology of Hypertension

HTN is a global disease, and its prevalence was estimated to be about one billion, which is projected to increase to 1.54-1.58 billion by 2025 (Kearney et al. 2005). Katherine and her colleagues estimated the number of hypertensive patients to be about 31.1 % of adults or around 1.39 billion in 2010 (Mills, Stefanescu, and He 2020). Tables 1, 2, 3, and 4 show the top 10 countries with the highest and lowest prevalence of HTN among men and women in 2019 ((WHO) 2021).

Table 1: Top 10 countries with the lowest hypertension prevalence among women in 2019.

Ranking	Country	Prevalence as % Population
1.	Switzerland	17 %
2.	Peru	18 %
3.	Canada	20 %
4.	Taiwan	21 %
5.	Spain	21 %
6.	Republic of Korea	21 %
7.	Japan	22 %
8.	United Kingdom	23 %
9.	China	24 %
10.	Iceland	24 %

Pathophysiology of Hypertension

The pathogenesis of HTN is complicated and still unclear. However, there are mechanisms that play a role in the pathogenesis of HTN (figure 1). The autoregulation system plays a crucial role in the pathophysiology of HTN. The ability of the organs (brain, heart, and kidneys) to retain blood flow despite changes in perfusion pressure is known as autoregulation. If the autoregulation fails, the perfusion pressure lowers, resulting in reduced blood flow and increased vascular resistance. There is a lack of autoregulation in the vascular bed and blood flow during the hypertensive crisis; a rapid rise in blood pressure and systemic vascular resistance may occur, leading to mechanical stress and endothelial damage (Taylor 2015). Another mechanism that is involved in the pathophysiology of HTN is the renin-angiotensin system (RAS). Activation of this system results in more vasoconstrictions which may also lead to ischemia (Papadopoulos et al. 2010). Genetic changes also play a role in the pathophysiology of HTN. Some gene mutations may cause the Medallion form of hypertension (Lifton, Gharavi, and Geller 2001). These mutations impact blood pressure by altering how kidneys handle salt absorption(Corvol et al. 1999). Endothelium dysfunctions also have a role in the pathogenesis of HTN. In hypertensive patients, endothelium damage leads to alteration in vascular tone, coagulation, and fibrinolytic pathways.

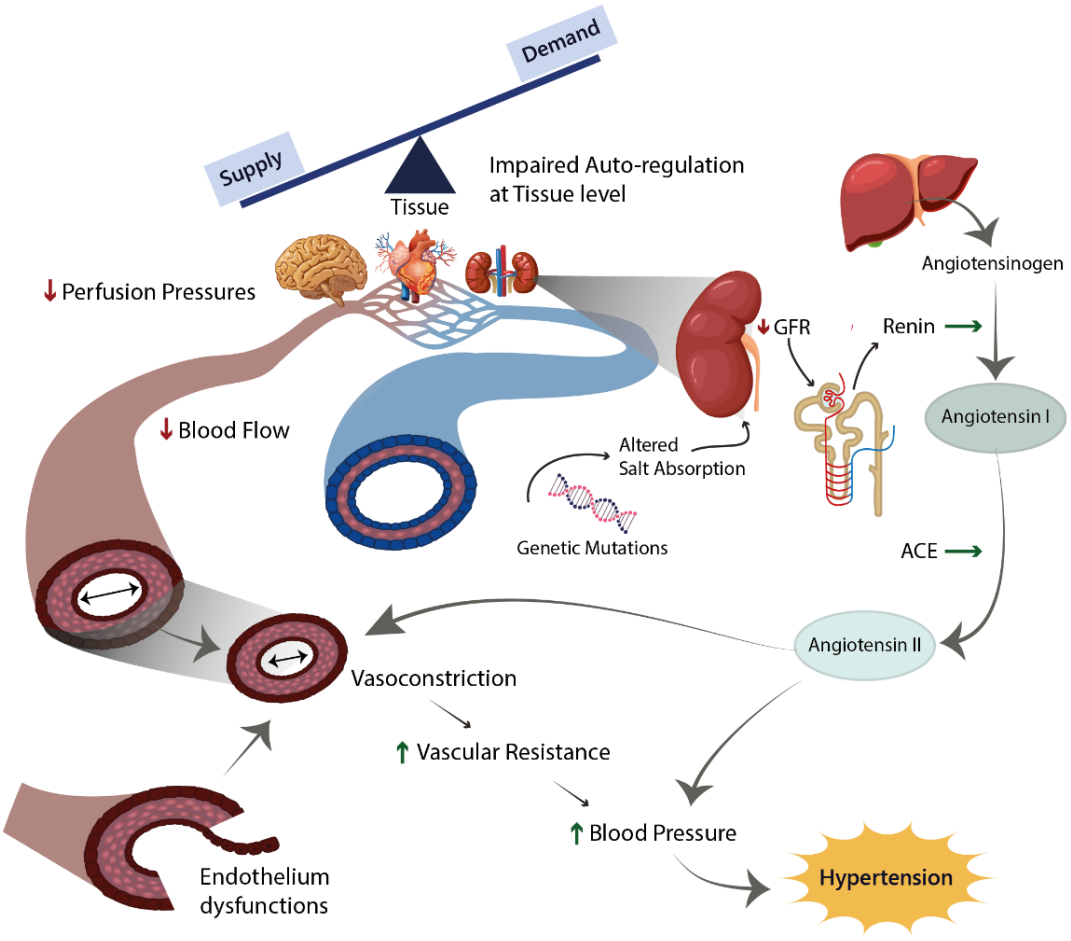

Figure 1 Pathogenesis of hypertension

Treatment Options

Several options are available to treat HTN. Angiotensin-converting enzyme inhibitors (ACEIs) such as Captopril and Enalapril are first-line drugs for hypertensive patients that are under 55 years old ("NICE Guideline 127. Hypertension: Clinical Management of Hypertension in Adults. Manchester: National Institute for Health and Clinical Excellence, 2011"). ACE is a metallopeptidase enzyme that is present mainly within the pulmonary vasculature. This enzyme converts angiotensin I to angiotensin II as well as reduces the metabolism of peptide bradykinin. The reduction of angiotensin II is responsible for most of the therapeutic effects of ACEIs (Clinic 2021). Angiotensin receptor antagonists (ARA) such as candesartan and telmisartan are used in patients who are intolerant to ACEIs (Smith and Jackson 2010). β Blockers (Metoprolol, esmolol, and atenolol) are not prescribed as first-line antihypertensives unless there are additional reasons, such as after a heart attack or atrial fibrillation (Jackson and Bellamy 2015). Calcium channel blockers, like verapamil are the first-line therapy for primary hypertension in adults over 55 and black people of African or Caribbean ancestry (figure 2) (Smith and Jackson 2010). Aliskiren is the only direct renin inhibitor prescribed to patients who are intolerant to other antihypertensives. Aliskiren inhibits the enzyme renin, which is secreted by the juxtaglomerular apparatus' granular cells.(Brown 2008).

Table 2: Top 10 countries with the lowest hypertension prevalence among men in 2019.

Ranking	Country	Prevalence as % Population
1.	Eritrea	22 %
2.	Peru	23 %
3.	Bangladesh	24 %
4.	Canada	24 %
5.	Ethiopia	25 %
6.	Solomon Islands	25 %
7.	Papua New Guinea	25 %
8.	Lao PDR	26 %
9.	Cambodia	26 %
10.	Switzerland	26 %

Promising Medicinal Plants

Androsace foliosa (Af)

In Pakistan's Kashmir, Hazara, and Murree hills, Af grows abundantly. In English, this plant is known as the common rock jasmine, while in Urdu, it is known as Andros. This plant's common name is Thandi booti, and it is a member of the Primulaceae family. The possible action of AF n-hexane fraction was examined in isolated rabbit aorta. Phenylephrine (agonist) was used to steady the tissue, while to observe the CCB effect, tissue was treated with Af n-hexane fraction and indicated that Af n-hexane fraction inhibits calcium channels in a similar manner to verapamil. Af 5mg/ml showed 70±5% blockage of the calcium channel (Zaheer et al. 2019).

Morinda citrifolia (Mc)

Mc, also known as Noni or Indian mulberry, is a member of the Rubiaceae family. It is found in India, Southeast Asia, and Australia (Potterat and Hamburger 2007). It's an edible plant that's been utilized in herbal treatments for treating a variety of ailments and maintaining overall health (Wang et al. 2002). Antiinflammatory, analgesic (Basar et al. 2010), and antioxidant (Zin, Abdul-Hamid, and Osman 2002) effects of Mc are reported. In a study, isolated tissue rabbit jejunum, rat and rabbit aorta, and guinea pig atria were used to assess the effect of ethanolic extract of Mc. Results suggested that Mc inhibits atrial force and rate of spontaneous contractions in guinea-pig right atria, it also inhibits contraction in rat thoracic aortic induced by phenylephrine. As verapamil cause right ward shift in the concentration response curves of Ca++ Mc also showed same effect. In Guinea pig isolated atria force and rate of contraction suppress with effective concentration (Ec_{50}) values of 2.52mg/ml and 2.68mg/ml. In isolated rabbit jejunum preparation Mc inhibited the spontaneous contractions in a concentration-dependent manner with EC50 0.30 mg/ml. It is suggested that Mc can be a promising plant to treat hypertension by blocking calcium channels. (Anwarul Hassan Gilani et al. 2010).

Viola odorata (Vo)

Vo, generally known as sweet violet in English, is a member of the Violaceae family. In Indo-Pakistan, it is known as Banafsha (Siddiqi et al. 2012). In a study, Vo inhibits the rate of spontaneous atrial contractions and force in isolated guinea-pig atria. In the isolated guinea-pig atrium, Vo decreased force and rate of spontaneous contracting atria EC50 values of 0.39 and 0.40 mg/ml. Vo causes vasorelaxation in phenylephrine-induced vasoconstriction and causes ca^{++} rightward shift and suggested that Vo extract can be a promising plant for the treatment of hypertension via calcium channel blocking (Siddiqi et al. 2012).

Table 3: Top 10 countries with the highest hypertension prevalence among women in 2019.

Ranking	Country	Prevalence as % Population
1.	Paraguay	51 %
2.	Tuvalu	51 %
3.	Dominica	50 %
4.	Dominican Republic	49 %
5.	Sao Tome and Principe	48 %
6.	Jamaica	48 %
7.	Haiti	48 %
8.	Iraq	48 %
9.	Eswatini	47 %
10.	Botswana	47 %

Hibiscus sabdariffa (Hs)

Hs is a member of the Malvaceae family, and it is also known as Roselle, Rozelle, Indian sorrel, Sour tea, and Karkade. It has been used as an antihypertensive for a long time (Oliver 1960). Due to flavonoids and vitamins, it has an antioxidant effect (Hirunpanich et al. 2005). In a study, the aorta was isolated from hypertensive rats and access effect of methanolic extract of Hs. Contractions induced by high K+- and phenylephrine decrease with Ec50 values of 3.37mg/ml and 3.83mg/ml. Results demonstrated that via calcium channel blockage, Hs reduced hypertension (Ajay et al. 2007).

Petroselinum crispum (Pc)

Pc is a medicinal plant commonly known as parsley and a member of the Apiaceae family. It is also reported that parsley is used as an antidiabetic, antifever, and also used in skin infection in Morroco (Eddouks, Ajebli, and Hebi 2017). In a study effect of Pc was determined in the rat-isolated thoracic aorta. The result demonstrated 160mg/kg aqueous extract of Pc decrease diastolic, systolic, and arterial pressure in hypertensive rats through the inhibition of calcium channel (Ajebli and Eddouks 2019).

Olea europea (OE)

OE is commonly known as zaitoon and is found in southern Europe and Asia. OE belongs to Oleaceae family (K. Nadkarni and Nadkarni 1976). It is reported that OE decreases the incidence of coronary heart disease (Ziyyat et al. 1997). In a study, OE methanolic extract decreased phenylephrine-induced vasocontraction and suggested that OE can be promising against hypertension via the blockage of calcium channels. However, OE produces a dose-dependent fall in arterial blood pressure with 30-100mg/kg of the extract, and 100mg/kg produces a high hypotensive effect (Hassan Gilani et al. 2005).

Table 4: Top 10 countries with the highest hypertension prevalence among men in 2019

Ranking	Country	Prevalence as % Population
1.	Paraguay	62 %
2.	Hungary	56 %
3.	Poland	55 %
4.	Argentina	54 %
5.	Lithuania	54 %
6.	Romania	53 %
7.	Belarus	52 %
8.	Croatia	51 %
9.	Tajikistan	51 %
10.	Serbia	50 %

Acorus calamus (AC)

AC has been known for more than 2000 years; Ibn Sina called it "waj" and Dioskurides "akopov" (Wiart C. Medicinal Plants of South East Asia. Malaysia: Prentice Hall and 2002:328–329). It belongs to the Araceae family and is found commonly in North America, Europe, and Asia, particularly in the northern areas of Pakistan ("Chiej R. Encyclopaedia of Medicinal Plants. Virginia, MacDonald; 1984"). In a study, isolated rats and rabbit aorta were used to determine the antihypertensive effect of AC extract. AC crude extract shifted Ca+2 concentration–response curves to the right and suppressed phenylephrine-induced peak formation, with an EC50 value of 0.05mg/kg, inhibiting maximum contraction induced by phenylephrine (A.J. Shah and Gilani 2009).

Artemisia scoparia (As)

As (also known as kit) is a perennial herb found throughout Pakistan and a member of Compositae (Baquar 1989). As is known for its antispasmodic, diuretic and febrifuge effect (Chin, Pharmaceutical Institute of the Academy of Medicine, and Peking.). It is already reported that As methanolic extract tends to protect against acetaminophen-induced hepatotoxicity in rats (A.-u.H. Gilani and Janbaz 1993). In a study, the methanolic extract of As suppressed the movement of rabbit jejunum in a concentration-dependent manner. K^+ induced contraction inhibit by As extract in a manner as like inhibited by verapamil. As decreased blood pressure with dose-dependent effect with 3-30mg/kg , with 30 mg/kg dose As show maximum hypotensive effect (Anwar H Gilani et al. 1994).

Andropogon muricatus (Am)

Am is commonly known as khus (A. Gilani et al. 2000) and found in Burma, India, Malaya, Philippine (Jayaweera 1981), and in different regions of Pakistan (Baquar 1989). It is reported that Am has antifungal (Chaumont and Bardey 1989), antibacterial (Gangrade et al. 1990), and antioxidant properties (Kim et al. 2005). Methanolic crude extract of Am was used in a study to investigate its cardiovascular effect. Results suggested that this extract inhibits contraction induced by K^+, possibly mediated through the inhibition of calcium channels. CCB activity of Am was confirmed when it shifted Ca^+ dose response curve to right as like showed response by verapamil. Am extract showed dose dependant effect with 50mg/kg decrease maximum mean arterial (Anwar H Gilani et al. 2007).

Elettaria cardamomum (Ec)

Ec, commonly known as elaichi, belongs to the family Scitaminacea, a perennial herb found in India, Sri Lanka, Burma, and Pakistan (K.M. Nadkarni, 1976. Indian Materia Medica, third ed. Popular Prakashan, and Bombay). Crude extract of Ec is used to determine the hypotensive effect in a study. Am inhibits spontaneous contraction induced by K^+ and shifts Ca + curves to the right, just like the effect of verapamil. Ec extract relax contraction caused by phenylephrine with EC50 value of 2.94mg/kg (Anwarul Hassan Gilani et al. 2008).

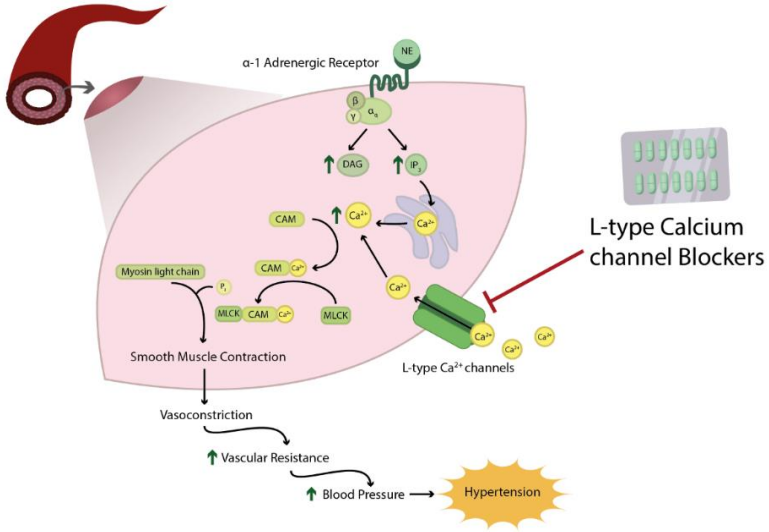

Figure 2 Mechanism of action of calcium channel blockers.

Zingiber officinale (Zo)

Zo is also known as ginger and is a member of the Zingiberaceae family. It is widely used and considered an essential component of the home kitchen. Zo mostly grows in Indo-Pak subcontinent and is exported around the world (Fischer 1976). Ginger has been reported to have an effect on the treatment of constipation, diarrhea, anorexia, colic, dyspepsia, nausea, vomiting, and in motion sickness (K. Nadkarni and Nadkarni 1976; M. Ghayur and Gilani 2004). A study reported that a crude extract of Zo decreases blood pressure with Ec50 value of .9mg/ml in anesthetized rats. In Guinea pig's atria, Zo crude extract decreases spontaneous force and beating rate of atrial contractions with Ec50 value of 0.57mg/ml (M.N. Ghayur and Gilani 2005). CCB effect was confirmed when Zo crude extract shifted the Ca2+dose–response curves to the right, similar to the effect of verapamil.

Orchis mascula (Om)

Om is also locally known as salab misri and is a member of Orchidaceae. Major source countries of Om are Iran and Afghanistan. For medicinal purposes, its root is used along with other herbs for nervous and muscular, as well as sexual dysfunction and cardiovascular diseases (Aziz et al. 2009). Om extract showed a dose-dependent (10-30mg) effect and decreased blood pressure. Maximum blood pressure decreases with 30mg/kg dose. Om extracts decrease contraction caused by Phenylephrine and High K^+ with an Ec50 value of 2.6 mg/100ml and 1.08 mg/ml (Aziz et al. 2009).

Acacia nilotica (An)

An is widely grown in Pakistan and commonly known as Babul or Kikar and is a member of the family Mimosaceae (Baquar 1989). It is reported that An has an antibacterial (Abd El Nabi et al. 1992), antiinflammatory (Dafallah and Al-Mustafa 1996), and antiplatelet effect (B.H. Shah et al. 1997). In a study methanolic extract of An 30mg/kg decreased maximum blood pressure in anesthetized rats, while in Guinea pigs' atria, An extract inhibited force and rate of atrial contraction in Guinea pigs atria with 3mg/kg.

Buddleja crispa (Bc)

Bc is a widely growing plant in Pakistan, Afghanistan, and North India and belongs to Buddlejaceae (Abdullah 1974). In a study, CCB inhibitory activity was determined in which it was shown that a 30mg/kg dose of crude extract of Bc decreased blood pressure. Furthermore, Bc extract inhibits contraction caused by K^+ with Ec50 value of 0.20mg/ml (Anwarul H Gilani et al. 2009).

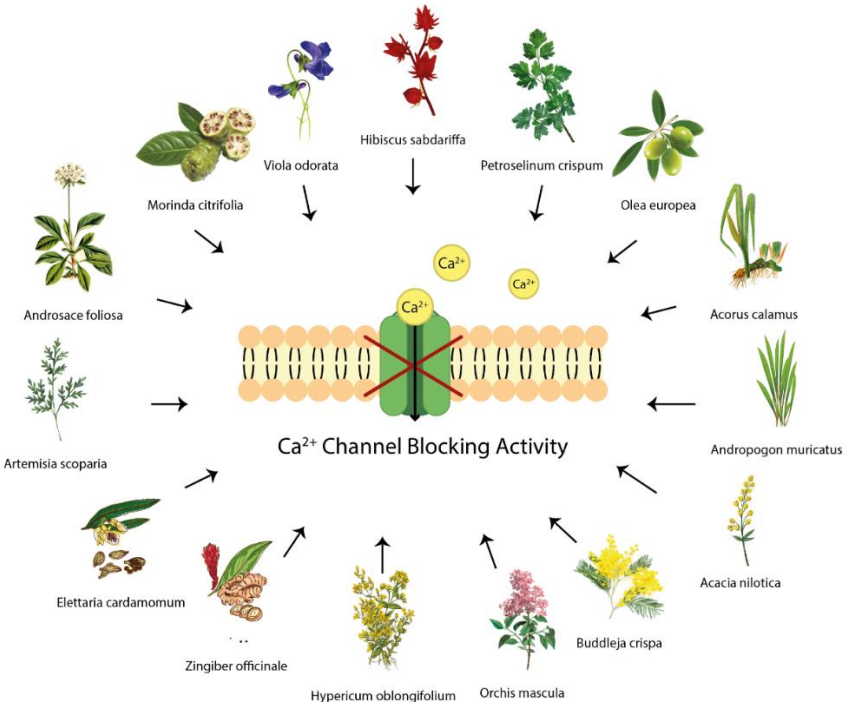

Figure 3 Medicinal plants with calcium channel blocking activities.

Hypericum oblongifolium (Ho)

Ho is a member of Hypericaceae and commonly grows on Khasia Hill in china and the Himalayas (Chopra, Chopra, and Varma 1974). In Pakistan, it grows in Hazara, Kashmir, and Murree Hills (Jafri, Nasir, and Ali 1973).It's used in traditional medicine to treat hepatitis, bacterial infections, and nasal bleeding, and it's also seen to help with dog bites and bee stings (Ferheen et al. 2006). In a study, Ho crude extract with Ec50 value 0.08 mg/ml caused relaxation in Guinea pig trachea while when on rabbit aorta, Ho extract effect determined with Ec50 value 0.74 and 0.55mg/ml inhibit contraction induced by phenylephrine and K^+. Ho crude extract 100mg/kg dose decreases maximum blood pressure in anesthetized rats.

Conclusions

With regard to the growing elderly population, a considerable amount of attention is being given to developing new calcium channel blockers with the aim of improving their quality of life as best as possible. Conventional therapies for treating hypertension, as mentioned in this review, have mostly been targeted toward symptomatic control, and while these drugs do achieve that goal to some extent, they do so with a plethora of side effects that are especially debilitating for the elderly. Phytocompounds have been used in the treatment of neurological diseases for centuries. Even today, these compounds have proven to be very resourceful, especially in discovering novel lead compounds that target various disorders. Extensive experimental research on these plants has led to the discovery of a number of phytocompounds whose effects have been shown to go well beyond just attenuating and treating hypertension.

After a thorough literature search, we have concluded that several phytocompounds and plant extracts have shown promising results in the calcium channels. Phytocompounds belonging to the flavonoids and xanthone glycoside groups have shown remarkably high potency against calcium channels. This review provides insight into some of the most potent phytocompounds that have shown promising antihypertensive activity. It is also likely that after structure-activity relationship experimentations, several of these compounds may prove to be safer and more potent than the existing standard care for hypertension. Therefore, future studies should be directed at the discovery of novel lead compounds with higher efficacy and a wider therapeutic window.

Conflict of Interest

The authors declare that they have no competing interests.

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Consent Forms

Not applicable

Authors Contribution

AU Conceptualized the study, AU and HMI wrote the initial manuscript, HMI helped in the analysis and writing the first draft, did the literature analysis, and AU supervised the whole project and wrote the final manuscript.

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