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# Inhibition of Voltage-Gated Calcium Channels by Natural Alkaloids: Pharmacological and Therapeutic Effects

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**Abstract:** ***Medicinal plants are the oldest and the most common form of medication against health issues. Several studies have demonstrated that plant extracts and their secondary metabolites represent an interesting source for drug discovery. Alkaloids, a major group of naturally occurring organic nitrogen-containing bases, have been shown to be implicated in many physiological processes through the modulation of ion channels, in particular, voltage-gated calcium channels. Calcium channels are the key molecules responsible for the regulation of major intracellular processes through the mediation of calcium entry into cells in response to membrane depolarization. They are divided into two broad categories: The high (L-, N-, P-, Q- and R-types calcium channels) and the low (T-type calcium channels) threshold-activated calcium channels. However, calcium channels dysfunction can be responsible for a multitude of disorders including diabetes, several forms of cancer and epilepsy. The present article point out the scientific evidence of the effectiveness of natural alkaloids extracted from common medicinal plants including Peganum harmalaon the modulation of voltage-gated calcium channels as well as their pharmacological and therapeutic outcomes.***

**Keywords:** Voltage-gated calcium channels, medicinal plants, alkaloids, *Peganum harmala,* β-carbolines, bisbenzylisoquinolines, isoquinolines.

## 1. Introduction

Traditional medicinal plants have been used since ancient time as a rescue against many health ailments. All over the globe, especially in North African countries, the use of medicinal plants has significantly supported primary health care(Jamila *et al.*, 2014). They can provide valuable therapeutic effects against various metabolic diseases such as diabetes, cardiovascular complications and neurological disorders(Petrovska, 2012). They are readily available, affordable and have less side effects than pharmaceutical and industrial medications. Thanks to their ability to synthesize a multitude of secondary metabolites against threatening conditions and for their normal growth and development, medicinal plants represent an interesting source for drug discovery in pharmaceutical industry. Previous studies have demonstrated that plant extracts and their secondary metabolites exert their therapeutical effets through the modulation of ion channels, in particular, voltage-gated calcium channels (VGCC) (Karaki *et al.*, 1986; Gilani *et al.*, 1994).

Calcium is a major signaling molecule that enters excitable cells in response to action potentials and depolarizing signals. It serves as the second messenger for the initiation of a multitude of physiological events in different cell types; it can trigger a vast array of physiological roles likemuscle contraction, gene transcription and cell proliferation, (Berridge *et al.*, 2000; Berridge *et al.*, 2003; Clapham, 2007). VGCCare the key molecules that allow calcium entry into the cells (Clapham, 2007). VGCC are divided into two major categories based on their structural and biophysical properties: High-voltage activated channels (HVA); activated by large membrane depolarizations, and Low-voltage activated channels (LVA) that open in response to small depolarizations close to resting membrane potentials (Armstrong *et al.*, 1985). Both VGCC families share a common Cavα1 subunit that consists of four homologous domains (I-IV), with each domain containing six transmembrane segments (S1-S6) and an intracellular loop that allows the selective passage of $Ca^{2+}$ ions. The voltage variations are detected by positively charged aminoacid residues present in the segment 4 (S4) of each domain and mediate channels gating. The transmembrane domains are connected by large cytoplasmic loops and N and C termini at the cytoplasmic parts (Catterall *et al.*, 2005a). These regions are important sites for channels regulation by endogenous factors like second messengers, G proteins and protein kinases (Zamponi *et al.*, 1997; Chemin *et al.*, 2007). Beside the Cavα1 subunit, HVA channels comprise the intracellularβ and the transmembrane α2-δ subunits which makes of them multimeric transmembrane proteins. In contrast, LVA are monomers because they lack these functional subunits (Fig. 1) (Curtis *et al.*, 1984; Catterall *et al.*, 2005b). According to pharmacological and biophysical studies, VGCC involve three subtype families with different members: Cav1, Cav2 and Cav3 (Fig. 1)(Catterall *et al.*, 2005b).The genetic distribution and the pharmacological properties of the three VGCC subfamilies are quite distinct which allow them to control a variety of physiological and pathological processes in the central and the peripheral systems.

Inhibition of calcium channel currents with specific organic compounds has been intensively under investigation as an interesting tool for defining the physiological, the biophysical and biochemical properties of calcium channels as well as for the treatment of pathological conditions such

as diabetes and epilepsy. Our aim through this present paper is to point out the effect of natural alkaloids on the modulation of VGCC as well as their pharmacological and therapeutical virtues.

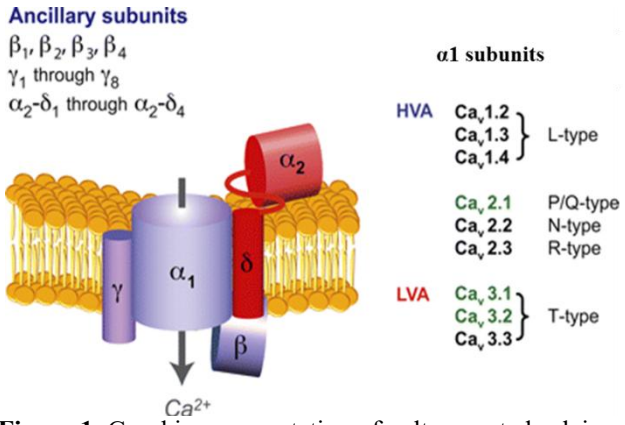



**Figure 1**: Graphic representation of voltage-gated calcium channels. Representation of the high voltage-activated calcium channel complex consisting of the main pore forming α1-subunit and ancillary, β-, γ-, and α2-δ-subunits. Low voltage-activated calcium channels may be formed of only the α1-subunit. Different α1-subunits correspond to different calcium channel isoforms Cav1, Cav2 (HVA) and Cav3 (LVA). [Adapted from (Khosravani et al., 2006)].

Alkaloids are a group of naturally occurring organic nitrogen-containing bases. They are found in a large variety of flowering plants and have been shown to be implicated in many physiological processes. In 1804, the first individual alkaloid, Morphine, was isolated from the opium poppy (*Papaver somniferum*) and has been used as a powerful analgesic against pain, pointing out the potential role of alkaloids in therapy. Morphine interacts with opioid receptors and produce analgesia by hyperpolarization of interneurons, leading to a release of transmitters associated with pain transmission (Lipp, 1991). Studies in the same context have shown that Morphine-induced-analgesia is more important the presence of VGCC blockers (Kumar *et al.*, 2010).

## 2. β-carboline Alkaloids: Harmala alkaloids *Harmaline, Harmane*

The β-carbolinesHarmaline and Harmane are the active principles present in the seeds of *Peganum harmala* as well as in other medicinal plants such as *Banisteriopsis caapi*(Fig. 2) (Handforth, 2012). A growing body of reports have shown the endogenous distribution of these harmala alkaloids in different mammalian tissues where they have been suggested to exert various pharmacological actions (Parker *et al.*, 2004; Miralles *et al.*, 2005; Herraiz *et al.*, 2006b; Herraiz *et al.*, 2006a).

Harmala alkaloids have been implicated in neurodegenerative disorders but also in neuroprotective processes because of their interaction with a large array of neurotransmitter receptors and ion exchangers. They have been shown to bind $GABA_A$ receptors (Rommelspacher *et al.*, 1980), activate $5HT_2A$ et $5HT_2C$ receptors (McCormick *et al.*, 1998), induce the impairment of $Na^+$ proton exchange and mitochondrial monoamine oxidase enzymes (Glennon *et al.*, 2000; Anderson *et al.*, 2003; Grella *et al.*, 2003; Herraiz *et al.*, 2010). Furthermore, studies have demostrated their ability to modulate ion channels ($I_{Na,}$ $I_K$), in particular VGCC. Haraki et al. have reported that the efficiency of *Peganum harmala* in treatment of colic is due to its antispasmodic effect resulting from the inhibition of intestinal calcium channels by the harmala alkaloids especially harmaline (Karaki *et al.*, 1986). Recent electrophysiological studies showed that harmala alkaloidsinhibitHVA ($I_{Ca,L}$ $I_{Ca,N}$) and LVA ($I_{Ca,T)}$ currents expressed in rat dorsal root ganglion (Fig. 2)(Splettstoesser *et al.*, 2005) and olivary neurons (Park *et al.*, 2010; Zhan *et al.*, 2012)over a wide range of voltage potentials and in a dose-dependant manner, indicating their potential implication in neuroprotective processes.

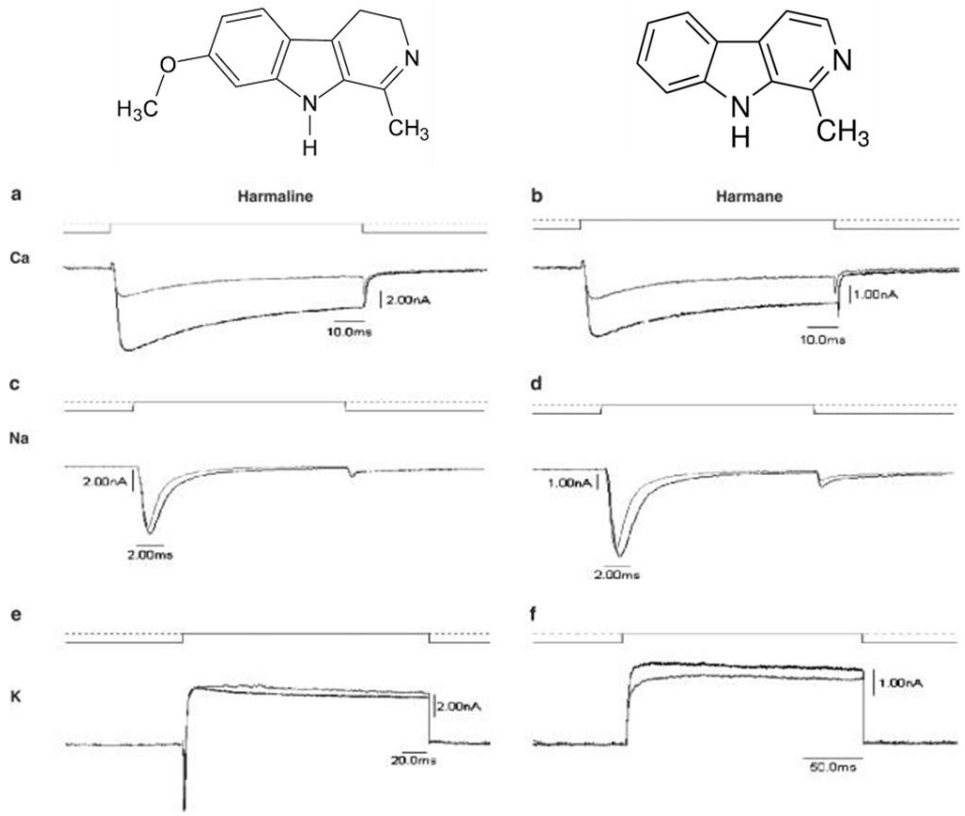



**Figure 2:** Schematic representation of the structure of harmala alkaloids; harmaline and harmane and raw traces of voltage-activated calcium channels (a-b), sodium channels (c-d) and potassium channels (e-f) after depolarisation from holding potential of −80 to 0 mV (upper trace). Currents under control conditions (black; lower traces) and after blockade of the channel currents (grey) by 100 $\mu$M harmaline (A) or 100 $\mu$M harmane (B) are superimposed. [Adapted from (Splettstoesser et al., 2005)].

**Isoquinoline alkaloids**

## 3. Berberine

Berberine is a pharmacologically active alkaloid that belongs to the group of isoquinoline alkaloids (Fig. 3). It is found in a large variety of medicinal plants including *Coptis chinensis*and *Coptis japonica* and has been used for digestive and cardiovascular disorders. Berberine triggers AMP-activated protein kinase by increasing its activity which explains its diverse benefitial effects (Lee et al., 2006). Electrophysiological studies have revealed that berberine attenated L- and T-type currents in guinea pig ventricular myocytes (Xu et al., 1997). Recently, the alkaloid berberine was reported to inhibit P/Q-type calcium currents leading to the attenuation of glutamate release from rat cortical synaptosomes (Lin et al., 2013), a mechanism that could underlie the anticonvulsant properties of berberine (Bhutada *et al.*, 2010).

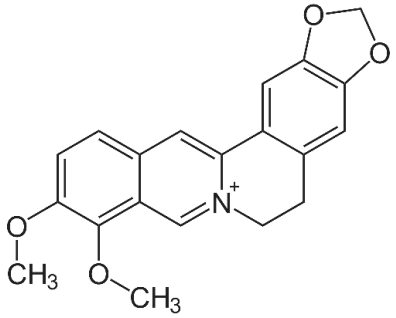


**Figure 3:** Chemical structure of berberine alkaloid

**Bisbenzylisoquinoline alkaloids**

Bisbenzylisoquinoline alkaloids (BBA) are a group of natural products distributed in a large variety of plants including Menispermaceae, Berberidaceae and Lauraceae families (Schiff, 1991).

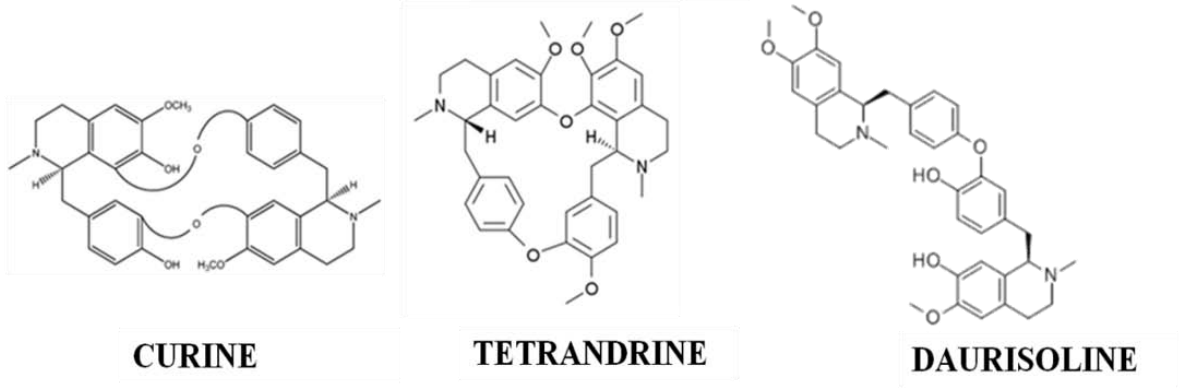
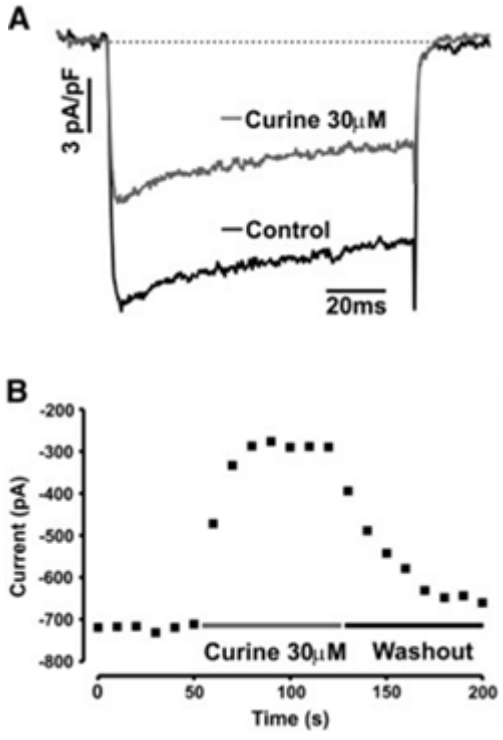



**Figure 4:** *Chemical structures of Bisbenzylisoquinoline alkaloids modulating voltage-gated calcium channels.*

## 4. Curine

Curine is the major BBA that is isolated from the root barks of *Chondrondendron platyphyllum*, a medicinal plant that naturally occurs in Brazil (Fig. 4). Curine has been suggested to induce vasodilatation in rat small mesenteric arteries through the inhibition of calcium channels (Dias *et al.*, 2002). In order to confirm the molecular mechanisms underlaying this effect, Medeiros et al. have shown, using whole-cell patch clamp technique, that curine inhibits L-type calcium channel (LTCC) currents in A7r5 vascular smooth muscle cells in a concentration-dependent manner. Curine affected the biophysical properties of LTCC by shifting the steady-state inactivation curve towards more negative membrane potentals which decreases global intracellular $Ca^{2+}$ concentrations and leads to vasorelaxation in rat aorta (Fig. 5)(Medeiros *et al.*, 2011). However, Further studies on the effect of Curine on the Cav2 and Cav3 calcium channels remain to be conducted.



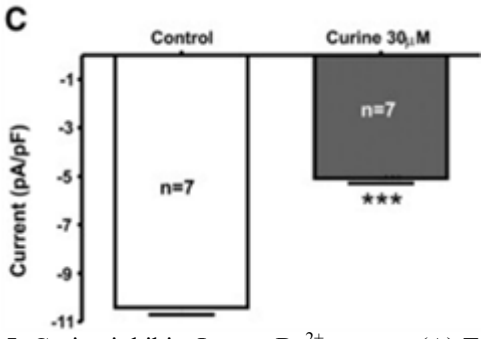




**Figure 5**: Curine inhibits L-type $Ba^{2+}$ current. (A) Typical $I_{Ba}$ traces before and after the application of 30 μM curine. Currents were elicited by stepping from -80 mV to + 10 mV for 100 ms. (B) Time course for curine effect. (C) Composite data showing current density before (control, open bar) and after the application of 30 μM curine (gray bar). [Adapted from (Medeiros *et al.*, 2011)].

## 5. Daurisoline

Daurisoline is another interesting BBA isolated from the rhizomes of the chinese medicinal herb *Menispermum dauricum* (Fig. 4). It has been traditionnally used in the treatment of asthma, hypertension and epilepsy (Waldmeier *et al.*, 1995). Daurisoline blocks neuronal NTCC by attenuating the depolarization-induced influx of calcium in presynaptic nerve terminals (Lu *et al.*, 1990). Further electrophysiology studies have shown the blockade P/Q-type calcium channels by daurisoline (Lu *et al.*, 1994). the mechanism by which calcium channel blockers like daurisoline inhibits glutamate release may explain in part its neuroprotective/anticonvulsant properties.

## 6. Tetrandrine

Tetrandrine is a BBA derived from the Chinese medicinal plant *Stephania tetrandra* (Fig. 4) (Zhang *et al.*, 2009). Tetrandine has been used as a remedy for various health problems including cardiac arrythmia and hypertension (Liu *et al.*, 1995; Wang *et al.*, 1995). A growing body of reports have shown that the antihypertensive, antiarythmic and antimyocardial ischemia propeties of tetrandrine are linked to its direct inhibition of calcium channels in neuroblastoma cells, neurohypophyseoal nerve terminals, mesenteric artery and cardiac cells (Liu *et al.*, 1995; Wang *et al.*, 1995). King et al. demonstrated that tetrandrine blocks LTCC activity in

$GH_3$ anterioir pituitary cells by interacting with the benzodiazepine receptor of the calcium bloker receptor complex (King *et al.*, 1988). Bickmeyer et al. showed that tetrandrine blocks voltage-operated calcium channels and increases intracellular calcium by blocking endoplasmic and other calcium pumps (Bickmeyer *et al.*, 1998). Further studies revealed that tetrandrine also inhibits neuronal N-type calcium channels(Wiegand *et al.*, 1990) and T-type caclium channels(Liu *et al.*, 1992; Rossier *et al.*, 1993) in different cell types with $IC_{50}$ values estimated to be within 4-20 µM, indicating a large non-selective spectrum of calcium inhibition by tetrandrine alkaloid (Kwan *et al.*, 2002).

## 7. Conclusions

The results of the studies of the modulation of voltage-gated calcium channels clearly showed that the alkaloids isolated from medicinal plants including *Peganum harmala*inhibit calcium channels subunits that are expressed in different tissus; a mechanism underlaying a multitude of therapeutical effects including vasodilating, neuroprotective and anticonvulsant properties.

## 8. Abbreviations

VGCC, Voltage-gated calcium channels; LTCC, L-type calcium channels; BBA, Bisbenzylisoquinoline alkaloids.

## 9. Conflict of Interest

The authors declare no conflict of interest.

## References

[1] Anderson NJ, Robinson ES, Husbands SM, Delagrange P, Nutt DJ, Hudson AL (2003). Characterization of [(3)H]harmane binding to rat whole brain membranes. *Annals of the New York Academy of Sciences***1009:** 175-179.
[2] Armstrong CM, Matteson DR (1985). Two distinct populations of calcium channels in a clonal line of pituitary cells. *Science***227**(4682)**:** 65-67.
[3] Berridge MJ, Bootman MD, Roderick HL (2003). Calcium signalling: dynamics, homeostasis and remodelling. *Nature reviews. Molecular cell biology***4**(7)**:** 517-529.
[4] Berridge MJ, Lipp P, Bootman MD (2000). The versatility and universality of calcium signalling. *Nature reviews. Molecular cell biology***1**(1)**:** 11-21.
[5] Bhutada P, Mundhada Y, Bansod K, Dixit P, Umathe S, Mundhada D (2010). Anticonvulsant activity of berberine, an isoquinoline alkaloid in mice. *Epilepsy & behavior : E&B***18**(3)**:** 207-210.
[6] Bickmeyer U, Weinsberg F, Muller E, Wiegand H (1998). Blockade of voltage-operated calcium channels, increase in spontaneous catecholamine release and elevation of intracellular calcium levels in bovine chromaffin cells by the plant alkaloid tetrandrine. *Naunyn-Schmiedeberg's archives of pharmacology***357**(4)**:** 441-445.
[7] Catterall WA, Goldin AL, Waxman SG (2005a). International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. *Pharmacological reviews***57**(4)**:** 397-409.
[8] Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J (2005b). International Union of Pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. *Pharmacological reviews***57**(4)**:** 411-425.
[9] Chemin J, Mezghrani A, Bidaud I, Dupasquier S, Marger F, Barrere C, *et al.* (2007). Temperature-dependent modulation of CaV3 T-type calcium channels by protein kinases C and A in mammalian cells. *The Journal of biological chemistry***282**(45)**:** 32710-32718.
[10] Clapham DE (2007). Calcium signaling. *Cell***131**(6)**:** 1047-1058.
[11] Curtis BM, Catterall WA (1984). Purification of the calcium antagonist receptor of the voltage-sensitive calcium channel from skeletal muscle transverse tubules. *Biochemistry***23**(10)**:** 2113-2118.
[12] Dias CS, Barbosa-Filho JM, Lemos VS, Cortes SF (2002). Mechanisms involved in the vasodilator effect of curine in rat resistance arteries. *Planta medica***68**(11)**:** 1049-1051.
[13] Gilani AH, Janbaz KH, Zaman M, Lateef A, Suria A, Ahmed HR (1994). Possible presence of calcium channel blocker(s) in Rubia cordifolia: an indigenous medicinal plant. *JPMA. The Journal of the Pakistan Medical Association***44**(4)**:** 82-85.
[14] Glennon RA, Dukat M, Grella B, Hong S, Costantino L, Teitler M, *et al.* (2000). Binding of beta-carbolines and related agents at serotonin (5-HT(2) and 5-HT(1A)), dopamine (D(2)) and benzodiazepine receptors. *Drug and alcohol dependence***60**(2)**:** 121-132.
[15] Grella B, Teitler M, Smith C, Herrick-Davis K, Glennon RA (2003). Binding of beta-carbolines at 5-HT(2) serotonin receptors. *Bioorganic & medicinal chemistry letters***13**(24)**:** 4421-4425.
[16] Handforth A (2012). Harmaline tremor: underlying mechanisms in a potential animal model of essential tremor. *Tremor and other hyperkinetic movements***2**.
[17] Herraiz T, Chaparro C (2006a). Analysis of monoamine oxidase enzymatic activity by reversed-phase high performance liquid chromatography and inhibition by beta-carboline alkaloids occurring in foods and plants. *Journal of chromatography. A***1120**(1-2)**:** 237-243.
[18] Herraiz T, Chaparro C (2006b). Human monoamine oxidase enzyme inhibition by coffee and beta-carbolines norharman and harman isolated from coffee. *Life sciences***78**(8)**:** 795-802.
[19] Herraiz T, Gonzalez D, Ancin-Azpilicueta C, Aran VJ, Guillen H (2010). beta-Carboline alkaloids in Peganum harmala and inhibition of human monoamine oxidase (MAO). *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association***48**(3)**:** 839-845.
[20] Jamila F, Mostafa E (2014). Ethnobotanical survey of medicinal plants used by people in Oriental Morocco to manage various ailments. *Journal of ethnopharmacology***154**(1)**:** 76-87.
[21] Karaki H, Kishimoto T, Ozaki H, Sakata K, Umeno H, Urakawa N (1986). Inhibition of calcium channels by harmaline and other harmala alkaloids in vascular and

intestinal smooth muscles. *British journal of pharmacology***89**(2)**:** 367-375.

[22] Khosravani H, Zamponi GW (2006). Voltage-gated calcium channels and idiopathic generalized epilepsies. *Physiological reviews***86**(3)**:** 941-966.

[23] King VF, Garcia ML, Himmel D, Reuben JP, Lam YK, Pan JX*, et al.* (1988). Interaction of tetrandrine with slowly inactivating calcium channels. Characterization of calcium channel modulation by an alkaloid of Chinese medicinal herb origin. *The Journal of biological chemistry***263**(5)**:** 2238-2244.

[24] Kumar R, Mehra R, Ray SB (2010). L-type calcium channel blockers, morphine and pain: Newer insights. *Indian journal of anaesthesia***54**(2)**:** 127-131.

[25] Kwan CY, Achike FI (2002). Tetrandrine and related bis-benzylisoquinoline alkaloids from medicinal herbs: cardiovascular effects and mechanisms of action. *Acta pharmacologica Sinica***23**(12)**:** 1057-1068.

[26] Lee YS, Kim WS, Kim KH, Yoon MJ, Cho HJ, Shen Y*, et al.* (2006). Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. *Diabetes***55**(8)**:** 2256-2264.

[27] Lin TY, Lin YW, Lu CW, Huang SK, Wang SJ (2013). Berberine Inhibits the Release of Glutamate in Nerve Terminals from Rat Cerebral Cortex. *PloS one***8**(6)**:** e67215.

[28] Lipp J (1991). Possible mechanisms of morphine analgesia. *Clinical neuropharmacology***14**(2)**:** 131-147.

[29] Liu QY, Karpinski E, Pang PK (1992). Tetrandrine inhibits both T and L calcium channel currents in ventricular cells. *Journal of cardiovascular pharmacology***20**(4)**:** 513-519.

[30] Liu QY, Li B, Gang JM, Karpinski E, Pang PK (1995). Tetrandrine, a Ca++ antagonist: effects and mechanisms of action in vascular smooth muscle cells. *The Journal of pharmacology and experimental therapeutics***273**(1)**:** 32-39.

[31] Lu YM, Frostl W, Dreessen J, Knopfel T (1994). P-type calcium channels are blocked by the alkaloid daurisoline. *Neuroreport***5**(12)**:** 1489-1492.

[32] Lu YM, Liu GQ (1990). The effects of (-)-daurisoline on Ca2+ influx in presynaptic nerve terminals. *British journal of pharmacology***101**(1)**:** 45-48.

[33] McCormick SJ, Tunnicliff G (1998). Inhibitors of synaptosomal gamma-hydroxybutyrate transport. *Pharmacology***57**(3)**:** 124-131.

[34] Medeiros MA, Pinho JF, De-Lira DP, Barbosa-Filho JM, Araujo DA, Cortes SF*, et al.*(2011). Curine, a bisbenzylisoquinoline alkaloid, blocks L-type Ca(2)(+) channels and decreases intracellular Ca(2)(+) transients in A7r5 cells. *European journal of pharmacology***669**(1-3)**:** 100-107.

[35] Miralles A, Esteban S, Sastre-Coll A, Moranta D, Asensio VJ, Garcia-Sevilla JA (2005). High-affinity binding of beta-carbolines to imidazoline I2B receptors and MAO-A in rat tissues: norharman blocks the effect of morphine withdrawal on DOPA/noradrenaline synthesis in the brain. *European journal of pharmacology***518**(2-3)**:** 234-242.

[36] Park YG, Park HY, Lee CJ, Choi S, Jo S, Choi H*, et al.* (2010). Ca(V)3.1 is a tremor rhythm pacemaker in the inferior olive. *Proceedings of the National Academy of Sciences of the United States of America***107**(23)**:** 10731-10736.

[37] Parker CA, Anderson NJ, Robinson ES, Price R, Tyacke RJ, Husbands SM*, et al.* (2004). Harmane and harmalan are bioactive components of classical clonidine-displacing substance. *Biochemistry***43**(51)**:** 16385-16392.

[38] Petrovska BB (2012). Historical review of medicinal plants' usage. *Pharmacognosy reviews***6**(11)**:** 1-5.

[39] Rommelspacher H, Nanz C, Borbe HO, Fehske KJ, Muller WE, Wollert U (1980). 1-Methyl-beta-carboline (harmane), a potent endogenous inhibitor of benzodiazepine receptor binding. *Naunyn-Schmiedeberg's archives of pharmacology***314**(1)**:** 97-100.

[40] Rossier MF, Python CP, Capponi AM, Schlegel W, Kwan CY, Vallotton MB (1993). Blocking T-type calcium channels with tetrandrine inhibits steroidogenesis in bovine adrenal glomerulosa cells. *Endocrinology***132**(3)**:** 1035-1043.

[41] Schiff PL, Jr. (1991). Bisbenzylisoquinoline alkaloids. *Journal of natural products***54**(3)**:** 645-749.

[42] Splettstoesser F, Bonnet U, Wiemann M, Bingmann D, Busselberg D (2005). Modulation of voltage-gated channel currents by harmaline and harmane. *British journal of pharmacology***144**(1)**:** 52-58.

[43] Waldmeier PC, Wicki P, Frostl W, Bittiger H, Feldtrauer JJ, Baumann PA (1995). Effects of the putative P-type calcium channel blocker, R,R-(-)-daurisoline on neurotransmitter release. *Naunyn-Schmiedeberg's archives of pharmacology***352**(6)**:** 670-678.

[44] Wang G, Lemos JR (1995). Tetrandrine: a new ligand to block voltage-dependent Ca2+ and Ca(+)-activated K+ channels. *Life sciences***56**(5)**:** 295-306.

[45] Wiegand H, Meis S, Gotzsch U (1990). Inhibition by tetrandrine of calcium currents at mouse motor nerve endings. *Brain research***524**(1)**:** 112-118.

[46] Xu SZ, Zhang Y, Ren JY, Zhou ZN (1997). Effects of berberine of L- and T-type calcium channels in guinea pig ventricular myocytes. *Zhongguo yao li xue bao = Acta pharmacologica Sinica***18**(6)**:** 515-518.

[47] Zamponi GW, Bourinet E, Nelson D, Nargeot J, Snutch TP (1997). Crosstalk between G proteins and protein kinase C mediated by the calcium channel alpha1 subunit. *Nature***385**(6615)**:** 442-446.

[48] Zhan X, Graf WM (2012). Harmaline attenuates voltage--sensitive Ca(2+) currents in neurons of the inferior olive. *Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques***15**(5)**:** 657-668.

[49] Zhang L, Geng Y, Duan W, Wang D, Fu M, Wang X (2009). Ionic liquid-based ultrasound-assisted extraction of fangchinoline and tetrandrine from Stephaniae tetrandrae. *Journal of separation science***32**(20)**:** 3550-3554.