IJPSR (2014), Vol. 5, Issue 8 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 February, 2014; received in revised form, 11 March, 2014; accepted, 13 June, 2014; published 01 August, 2014

TASKS OF COMPLIMENTARY AND FUNCTIONAL TRIO-MINERALS IN HYPERTENSION

Kannan Eagappan* and Sasikala Sasikumar

Department of Clinical Nutrition and Dietetics, PSG College of Arts and Science, Coimbatore, Tamil Nadu, India

Keywords:

Hypertension, Trio-minerals, mechanism, Dietary intake, Supplements, Nutrient recommendation

Correspondence to Author:

Kannan Eagappan

Associate Professor, Department of Clinical Nutrition and Dietetics, PSG College of Arts and Science, Coimbatore, Tamil Nadu, India

E-mail: dtkannan@gmail.com

ABSTRACT: Micronutrient deficiencies such as potassium, magnesium and calcium are very common in the general population and it is more predominantly present in the individuals with hypertension and cardiovascular patients. These deficiencies will have a massive impact on present and future cardiovascular health outcomes such as hypertension, myocardial infarction, stroke, etc. Recent efforts to reduce the prevalence of hypertension have focused on non-pharmacologic means, specifically diet in order to overcome micronutrient deficiencies. From most of the studies it is evident that an increased intake of minerals such as potassium, magnesium, and calcium by dietary means to reduce blood pressure in patients with hypertension. This article also focuses on how these minerals influence vaso dilation, rennin- angiotension and aldosterone system, natriuresis, sympathetic nervous system nitric oxide production and vascular injury. On the whole, this review will talk about the roles of potassium, magnesium, and calcium in the prevention and treatment of hypertension with specific emphasis on clinical trial evidence, mechanism of action, and recommendations for dietary intake of these minerals.

INTRODUCTION: High Blood Pressure also known as the "silent killer'' affects one billion or one in three adults worldwide, and attributes to about 40% of cardiovascular related deaths; unfortunately more than 50% of hypertensive individuals are unaware of their condition [1]. American heart association defined Hypertension as a systolic blood pressure greater than 140 mmHg and or a diastolic blood pressure greater than 90 mmHg is one of the major risk factors for cardiovascular morbidities including coronary artery disease, myocardial infarction and kidney disease, as well as for mortality [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(8).3322-32

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(8).3322-32

Recent reports indicate that nearly 1 billion adults (more than a quarter of the world's population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 2025 [3].

Hypertension is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries [4]. In India, hypertension is the leading non communicable disease risk and estimated to be attributable for nearly 10 per cent of all deaths [19].

From the studies of Gupta, 2004 and Reddy, 2005 it is evident that adult hypertension prevalence has risen dramatically over the past three decades from 5 per cent to 20-40 per cent in urban areas and 12-17 per cent in rural area [20, 21]. Also, Reddy (2005) reported that the number of hypertensive individuals is anticipated to nearly double from 118 million in 2000 to 213 million by 2025 [25].

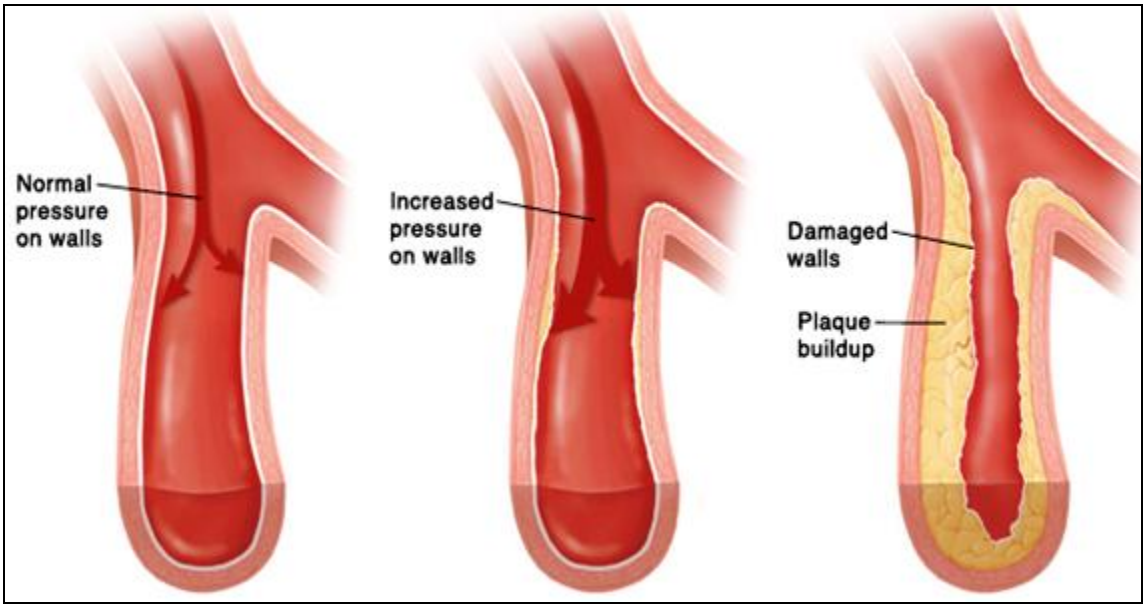

FIGURE 1: PATHOGENESIS OF HYPERTENSION

From the study of Mohan *et al*, 2011, it is understood that 16 per cent of ischemic heart disease, 21 per cent of peripheral vascular disease, 24 per cent of acute myocardial infarctions and 29 per cent of strokes are attributable to hypertension, emphasizing the huge impact of effective hypertension prevention and control in order to reduce the accelerating encumbrance of cardiovascular disease (CVD) [22]. There are number of factors that increase blood pressure such as obesity, insulin resistance, high alcohol intake, high salt intake (in salt-sensitive patients), aging and perhaps sedentary lifestyle, stress, low potassium intake, and low calcium intake [5, 6]. Observational studies have shown that a diet rich in potassium, magnesium, and calcium, present mainly in fruits and vegetables, is associated with lower incidence and mortality from cardiovascular disease [7].

Clinical and population-based studies show that several components of the diet such as sodium, potassium, calcium, magnesium, fiber and fish oil influence blood pressure, and modification of these nutritional factors provide an important strategy to control blood pressure especially in the prehypertensive stage (SBP 120–139mmHg and/or DBP 80–89mmHg) or stage I hypertension (SBP 140–159mmHg and/or DBP 90–99mmHg) [8]. The role of these dietary factors, singly or in combination in blood pressure regulation and to what extent each contributes has been a subject of research for many decades.

Pathophysiology of Hypertension: Even though hypertension is the most prevalent chronic medical conditions, the pathophysiology of hypertensive crises is still poorly understood [9-12]. In addition, not like other disorders the hypertension develops due to a single known entity, rather multifaceted etiological factors could synergistically affect blood pressure. From the studies of Smithburger *et al* (2010) and Varon, (2008), it is clearly implicated that two processes are considered to recklessly induce hypertensive paradigm such as sudden increase in systemic vascular resistance (SVR) and a failure of cerebral blood flow auto regulation, the mechanism that maintains blood flow at an appropriate level during changes in blood pressure [10, 11].

Varon, 2008 reported that hypertensive crisis can also be present without documenting any history of hypertension; the acute nature of these events suggests an underlying hypertensive condition coupled with the presence of an additional seditious factor or event. This was explained by him using an example such as, in the perioperative setting, stimuli such as elevated BP during anesthesia induction, tracheal intubation, and emergence from anesthesia can be the initiating event for the hypertensive crisis [13]. Anesthesia induction alone can cause an increase of 20 mmHg in normotensive patients, and up to 90 mmHg in patients with a pre-existing hypertensive condition[14].

Studies done by Kuppasani and Reddi, 2010; Smithburger *et al.*, 2010; Vaughan and Delanty, 2000, revealed that Vascular endothelial injury may result from repeated instances of acute hypertension, associated with elevated systemic vascular resistance. As blood pressure increases, vessel walls are subjected to stress, which leads to the release of vasoconstrictors resulting in further endothelial damage [9, 10, 15]. Kuppasani and Reddi, 2010 in their study explained that if vascular endothelial injury is not promptly treated, a cycle of clotting cascade activation, arteriole tissue death and accumulation, neurohormonal system upregulation, induction of oxidative stress, and inflammatory cytokines develops [9].

Deposition of platelets and fibrin, vasoconstriction, and thrombosis, as a consequence of vascular injury, result in decreased blood flow and supply to and from organs (hypoperfusion and ischemia) [9, 10]. If this vicious cycle is not concluded, auto regulatory dysfunction becomes imminent [16]. Autoregulation is crucial to maintenance of adequate perfusion of the kidney, heart, and brain. These organs require specific amounts of oxygen to function, and reduced blood flow can lead to ischemia and organ injury. Autoregulation occurs in many body tissues, but has best been studied in cerebral blood flow. When blood pressure is severely elevated there is a right shift in the autoregulation curve, resulting in cerebral blood flow at higher mean arterial pressures [15, 17, and 18].

In order to avoid hyperperfusion of tissues, blood pressure in these patients must be lowered carefully so that hypoperfusion does not occur [17, 18]

In the blood pressure range between 60 mmHg and 140 mmHg, cerebral blood flow is "autoregulated" extremely well. Belsha, 2011 explained in his study that, autoregulation in hypertensive patients occurs with mean arterial pressure (MAP) up to 180 mmHg (shifted to the right), though the blood flow remains constant. During hypertensive crises, the shift in the autoregulatory curve often fails to occur, putting patients at risk for cerebral hyperperfusion. When the corresponding increase in BP crosses the autoregulatory range, compensatory mechanisms end [17]. Vasodilation and endothelial dysfunction occurs, which may lead to cerebral fluid buildup (edema), ultimately followed by cerebral spasm (eclampsia) and ischemia [9].

Continuation of this "vicious" cycle results in the severe, acute elevation in BP.

Impact of Potassium, Magnesium and Calcium on Hypertension:

POTASSIUM: The correlation between potassium and blood pressure has been described in many studies. The mechanism by which potassium intake regulates antihypertensive effects is explained in the **table 1**.

TABLE 1: THE MECHANISMS BY WHICH POTASSIUM INTAKE REGULATES HYPERTENSION

Mechanisms involved	Reference No.
Natriuresis by inhibiting sodium reabsorption in the proximal renal tubules	23
Suppressing renin secretion	24
Normalization of the plasma level of digitalis like substance	25
Increased urinary volume excretion	25
Smooth muscle relaxation by increasing nitric oxide production	26 – 28
Stimulating the rectifier K(+) channels resulting in potential membrane hyperpolarization and subsequently vasodilation	29
Suppression of free radical formation	30
Protection against vascular injury in salt sensitive hypertension	31

Potassium intake was found to be inversely related to both DBP and SBP in a population based study including 685 men and women who were principally Caucasian in Southern California, United States of America (USA) [32]. Similar result was illustrated in the Rotterdam Study [33, 57], a big population- based study in which 3239 participants older than 55 years old were included.

Patients with an increase in potassium intake of 1000mg/day had a 0.9mmHg lower SBP and a 0.8mmHg lower DBP [34].

Priddle (1931) conducted an experiment by giving low sodium, high potassium diet to a group of 45 hypertensives, including some with impaired renal function, and their study results reported a lowering

of blood pressure and an improvement in their general medical condition [35]. Similarly, the rice-fruit diet utilized by Kempner for treatment of hypertension resulted in consistent reductions of blood pressure by reducing the levels of Na^+ intake and the Na^+/K^+ diet ratio by 99% [36].

Several interventional studies have shown the positive effects of potassium supplementation on blood pressure reduction. Cappuccio and MacGregor reviewed 19 clinical trials in which oral potassium supplements significantly lowered SBP (mean of −5.9mmHg, 95% confidence interval (CI), −6.6 to −5.2mmHg) and DBP (mean of −3.4mmHg, 95% CI, −4.0 to 2.8mmHg) [37] . A meta-analysis consisting of 27 potassium trials in adults with a minimum of 2 weeks duration also demonstrated a reduction in blood pressure with increased potassium intake: a mean of −2.42mmHg (95% CI, −3.75 to −1.08mmHg) in SBP and −1.57mmHg (95% CI, −2.65 to −0.50mmHg) in DBP pressure [38].

There are few Japanese studies examining the role of potassium in the regulation of blood pressure[42, 43]. The traditional diet of the Japanese is high in salt (up to 400 mmoles/day in some regions) and this is considered to be causal in the higher mortality from stroke observed in Japan compared to that of Western cultures. In a large epidemiological study, a population from Shimano region where the traditional lifestyle and diet were potted, blood pressure was inversely correlated with urinary potassium excretion and positively correlated with the urinary Na+/K+ ratio, especially in the older age groups [43].

Thus, this study is implicative that the traditional diet comprising of more potassium sources and deprived of novel processed foods containing more sodium helps in the less prevalence of hypertension. A similar relationship was found when two neighbouring regions with markedly different prevalence of hypertension were compared. Individuals from the region with the lower prevalence of hypertension had higher urinary potassium excretions, presumably because of increased consumption of potassium in the form of apples, since the area studied is a region of major apple production [43].

Two recent studies have also assessed the effect of approximately doubling of normal potassium intake (from approximately 60 or 75 mM/day to 120 or 160 mM/day, respectively) on blood pressure in essential hypertensive who maintained normal intakes of sodium during the period of K+ supplementation. Both studies reported significant reductions of arterial pressure of 10% [44] and which were insufficient to normalize blood pressure in these hypertensive patients.

It has also been stated that apart from K^+ supplementation racism too plays a considerable role in modulating hypertension even with K^+ supplementation. A meta-analysis of all K^+ supplementation clinical trials in the treatment of hypertension demonstrated a racial difference—with black subjects having a more substantial reduction in BP compared with white subjects. A high K intake is most effective in reducing BP in patients with diuretic-induced hypokalemia, in those with a high Na^+ intake [45-47], in patients with salt-sensitive hypertension [47], severe hypertension, or a positive family history [47], as well as in African Americans [47] and Chinese [46]. Alteration of the K^+/Na^+ ratio to a higher level is important for antihypertensive as well as cardiovascular and cerebrovascular effects [46, 48]. High K intake reduces the incidence of cardiovascular and CVAs independent of BP reduction [49-51].

Gu *et al* [46] recently demonstrated for the first time that K supplementation at 60 mmol of KCI per day for 12 weeks significantly reduced SBP _5.0 mm Hg (range, _2.13 to _7.88 mm Hg) (P b .001) in 150 Chinese men and women aged 35 to 64 years. This study confirmed that the higher the initial BP, the greater the response. Finally, it showed that the urinary Na/K ratio correlates best with BP reduction as does the dietary Na/K ratio[48] compared with either urinary Na or K individually [46].

\Based on existing data, the Institute of Medicine has recommended a potassium intake of 4700mg (120mmol) a day as adequate intake for all adults [52]. A similar amount of daily potassium consumption was also suggested by the American Heart Association (AHA) in 2006 to achieve the potential benefit of blood pressure reduction [53].

The 2003 WHO/International Society of Hypertension statement on management of hypertension supported an increased dietary potassium intake although a threshold was not specified [54]. However, the suggested daily intake of potassium might be lower in patients who are prone to develop hyperkalemia such as those with impaired renal excretion of potassium from CKD, CHF, adrenal insufficiency, and medications use (angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), potassium sparing diuretics, trimethoprim, cyclosporine, heparin, etc.)

Apart from drugs influencing the body concentrations of potassium, certain foods may also increase the levels of potassium; **table 2** displays the good natural sources of potassium.

TABLE 2: FOODS HIGH IN POTASSIUM

Food	Serving Size	Potassium (mg)
Apricots, dried	10 halves	407
Avocados, raw	1 ounce	180
Bananas, raw	1 cup	594
Beets, cooked	1 cup	519
Brussel sprouts, cooked	1 cup	504
Cantaloupe	1 cup	494
Dates, dry	5 dates	271
Figs, dry	2 figs	271
Kiwi fruit, raw	1 medium	252
Lima beans	1 cup	955
Melons, honeydew	1 cup	461
Milk, fat free or skim	1 cup	407
Nectarines	1 nectarine	288
Orange juice	1 cup	496
Oranges	1 orange	237
Pears (fresh)	1 pear	208
Peanuts dry roasted, without salt	1 ounce	187
Potatoes, baked, flesh and skin	1 potato	1081
Prune juice	1 cup	707
Prunes, dried	1 cup	828
Raisins	1 cup	1089
Spinach, cooked	1 cup	839
Tomato products, canned, sauce	1 cup	909
Winter squash	1 cup	896
Yogurt plain, skim milk	8 ounces	579

Source: Values were obtained from the USDA Nutrient Database for Standard References, Release 15 for Potassium, K (mg) content of selected foods per common measure.

MAGNESIUM: A high dietary intake of magnesium of at least 500 - 1000mg per day reduces blood pressure in most of the reported epidemiologic, observational and clinical trial [55-64]. A study done by Ahsan (1998), in which 60 essential hypotensive subjects were given magnesium supplements showed a significant reduction in blood pressure over an 8- week period consecutively documented by 24-hr ambulatory blood pressure, home and office blood pressure assessments. From the same study it is well understood that magnesium competes with Na^+ for binding sites on vascular smooth muscles and acts like a calcium channel blocker, it increases PGE, and binds in a necessary cooperative manner with K^+, inducing endothelial vasodilation and thus reducing blood pressure [58].

It is also stated that, magnesium influences blood pressure regulation by modulating vascular tone and reactivity. Vascular effect of magnesium was first suggested in the early 1900s when it was observed in clinical studies that magnesium salt infusion lowers blood pressure via a reduction in peripheral vascular resistance [65] in spite of a slight increase in myocardial contractility [66]. The direct Experimental studies support these clinical observations and confirm that acute magnesium administration induces hypotension through vasodilatory actions [67, 68].

Increased concentrations of extracellular magnesium cause vasodilation, improve blood flow, decrease vascular resistance, increase capacitance function of peripheral, coronary, renal, and cerebral arteries, and attenuate agonist-induced vasoconstriction, whereas, decreased concentrations cause contraction, potentiate agonist evoked vasoconstriction, and increase vascular tone and thus increased blood pressure is possible [69-72].

The relationship between dietary magnesium intake and blood pressure in humans were first demonstrated in the Honolulu Heart study [73] and later by many epidemiological and clinical investigations that supported the hypothesis that increased magnesium intake contributes to prevention of hypertension and cardiovascular disease [73-76]. Data that were obtained from large, prospective studies on nutrition and blood pressure in US and Dutch populations, reported that

magnesium-rich diets may reduce blood pressure levels, especially in older individuals [77, 78]. However, there are seldom studies done in India, on the relationship between these minerals and blood pressure.

Perhaps, some studies worldwide have shown blood pressure lowering after magnesium supplementation. According to Kawano (1998), the administration of magnesium oxide (400 mg daily) for eight weeks in patients with hypertension can reduce blood pressure levels, and this reduction has already been detected in office measurements and by ambulatory blood pressure monitoring [79]. Hatzistavri, (2009), in his study demonstrated that 600 mg of magnesium pidolate per day which was given to 48 subjects was found to reduce blood pressure levels in the supplemented patients when compared to the group with no supplementation [80].

Haenni and colleagues (2002), highlighted positive effects of magnesium supplementation in order to confirm the relationship between the metabolism of this mineral and alteration of endothelial function by showing increased endothelium dependent vasodilatation after magnesium infusion [81]. In this context, Shechter (2000), also showed that chronic magnesium supplementation was able to improve endothelial function in patients with coronary artery disease [82].

In contrary to above mentioned human study, magnesium supplementation had little antihypertensive effect in adult spontaneously hypertensive rat (SHR) with well-established hypertension. In fact, the effect of supplementation was only positive in younger animals, when started in the prehypertensive phase, preventing or at least attenuating the development of hypertension[83]. This finding is highly suggestive of a more protective effect of supplemental magnesium, which may prevent or slow the rise in blood pressure at an early stage of hypertension.

With reference to RAAS, a relationship has also been reported between the rennin-angiotensin system, magnesium, and blood pressure. Hypertensive patients with high renin activity have significantly lower serum magnesium levels than normotensive subjects, and plasma renin activity is inversely associated with serum magnesium [84]. This has been correlated with a finding that hypertensive patients without blood pressure control may have hypomagnesaemia.

When a question of whether acute one day supplementation does it modulate BP, Hatzistavri and colleagues (2009) have shown that magnesium supplementation was associated with slight reduction of 24 h blood pressure levels in patients with mild hypertension [80], which can be evaluated by ambulatory blood pressure monitoring [85]. In connection with the supplementation of magnesium containing foods, the following **table 3** depicts the magnesium content of various food stuffs.

TABLE 3: FOODS HIGH IN MAGNESIUM

Food	Serving Size	Magnesium (mg)
Beans, black	1 cup	120
Broccoli, raw	1 cup	22
Halibut	1/2 fillet	170
Nuts, peanuts	1 oz	64
Okra, frozen	1 cup	94
Oysters	3 oz	49
Plantain, raw	1 medium	66
Rockfish	1 fillet	51
Scallop	6 large	55
Seeds, pumpkin and squash	1 oz (142 seeds)	151
Soy milk	1 cup	47
Spinach, cooked	1 cup	157
Tofu	1/4 block	37
Whole grain cereal, ready-to-eat	3/4 cup	24
Whole grain cereal, cooked	1 cup	56
Whole wheat bread	1 slice	24

Source: Values were obtained from the USDA Nutrient Database for Standard References, Release 15 for Magnesium, Mg (mg) content of selected foods per common measure.

CALCIUM: Over the years, a great number of observational and interventional studies indicated that chronic calcium malnutrition is associated with various diseases and pathologic conditions of unrelated etiology. A proposed mechanism by which calcium intake regulates blood pressure is described in **table 4**.

TABLE 4: THE MECHANISMS BY WHICH CALCIUM INTAKE REGULATES HYPERTENSION

Mechanisms involved	Reference No
Alteration in intracellular calcium which in turn affects vascular smooth muscle contraction	86
Effect of calcium metabolism and regulatory hormones	87-89
Increased natriuresis	90-92
Modulation of the function of the sympathetic nervous system	91

From the studies of Hamet *et al* (1991 and 1992) and Gruchow *et al* (1988), it is evident that people consuming low levels of calcium in their diets, high salt intake is associated with higher blood pressure levels [93-95] and based on this there are studies suggesting that the hypertensive effect of a high sodium intake which can be mitigated by increasing dietary calcium [96, 92, 97, 98]. Resnick also published extensively on the interlinking of the rennin aldosterone system, calcium regulation, and salt sensitivity in modulating blood pressure responses to salt loading, calcium supplementation, and calcium channel blockers [99- 104] . He suggested that these models may provide a targeted approach to identifying and treating hypertensives with calcium supplementation or calcium channel blockers based on their serum renin level and salt sensitivity [105-107].

Despite the above findings, few systemic reviews express that supplementation of Ca^{2+} have modest effect in reducing BP [108, 109]. From the studies of McCarron (1999) and Witteman (1989) it is clearly understood that, individuals receiving >800 mg/d of calcium compared with 400 mg/d achieved a 23% reduction in risk of developing hypertension. [110].

Ascherio and co-workers also demonstrated in more than 30,000 normotensive male health professionals aged 40 to 75 years that men consuming <250 mg/d of calcium had a 50% greater chance of developing hypertension than those who consumed ≥400 mg/d [111].

In a prospective cohort of 28,886 US women older than 45 years, dietary intake of calcium was inversely associated with risk of hypertension; however, no change in BP was observed with calcium supplementation [112].

A review of calcium supplementation during pregnancy for preventing hypertensive disorders concluded that calcium supplementation appears to approximately bisect the risk of preeclampsia and reduces the risk of preterm birth and the rare occurrence of the composite outcome "death or serious morbidity". It is notable that, most women in these trials had a low-calcium diet [113].

Calcium appears to be particularly effective in reducing the age-related increase in blood pressure. Dobnig *et al* (2005) conducted a randomized, double-blind, multi-center study on the effect of daily high-dose calcium supplements in healthy, elderly adults and observed a substantial reduction of systolic and diastolic blood pressure after one year of treatment in individuals who were in the upper third of pre-study blood pressure values [114].

Different intake levels for calcium are recommended by FAO/WHO experts for infants, children and adults [115] to assure optimal whole body calcium retention and consequently adequate development and maintenance of bone mass and mineral density. For children and adolescents between 10–18 years of age, consumption of 1,300 mg per day is recommended, while 1,000 mg per day apply for men between 25–50 years of age and also for women in the same age group, except when higher intake is necessary during pregnancy or after menopause.

Recommended calcium allowance per day for males over 65 years and postmenopausal women is 1,300 mg [115]. Based on existing data, the Indian Council of Medical Research has recommended a calcium intake of 600mg a day as adequate intake for all adults [116].

Table 5 below portrays the calcium content of various foods. However, though we suggest excellent sources of calcium containing foods we should also advise them to be cautious about antinutritional factors such as phytic acids, oxalic acid, EDTA, high amount of fiber etc., which would interfere in their absorption.

TABLE 5: FOODS HIGH IN CALCIUM

Food	Serving Size	Calcium (mg)
Broccoli, raw	1 cup	42
Cheese, cheddar	1 oz	204
Milk, fat free or skim	1 cup	301
Perch	3 oz	116
Salmon	3 oz	181
Sardine	3 oz	325
Spinach, cooked	1 cup	245
Turnip greens, cooked	1 cup	197
Tofu, soft	1 piece	133
Yogurt plain, skim milk	8 oz container	452

Source: Values were obtained from the USDA Nutrient Database for Standard References, Release 15 for Calcium, Ca (mg) content of selected foods per common measure.

SUMMARY AND CONCLUSION: Considering the magnitude of the health and financial consequences of HTN, scientific search for more effective and at the same time more affordable means of tackling HTN has become more than a necessity. Dietary modification has important therapeutic roles in blood pressure control. Increasing evidence indicates that low magnesium, potassium and calcium may play a pathophysiological role in the development of hypertension. The modalities by which these trio-minerals are able to mitigate blood pressure have also been described in this review. Indeed, there are accumulating evidences which show the efficiency of controlling both systolic and diastolic blood pressures but on the other hand there are few studies which claim that non dietary supplements are not effective in controlling BP.

Hence, further constructive studies are needed to rule out that synthetic or organic supplements are not able to attenuate high BP. However, as long as hypertensives and even normotensives who have the risk factor of developing hypertension, If they increase their dietary sources of these trio-minerals, are also benefitted by increased intake of other nutrients too [117]. Similarly, as these minerals are certainly favourable in bringing out a good prognosis, yet much care has to be taken in order to avoid the agents which may be found naturally in food sources or as additives (for e.g. EDTA) from processed foods which may hinder the absorption by binding. Hence dissemination of knowledge on the positive effect of dietary or organic supplements of these minerals in alleviating the development or control of the "silent killer" hypertension is the need of the hour.

REFERENCES:

1. Ostchega, Y., Yoon, S. S, Hughes, J., & Louis, T. (2008). Hypertension awareness, treatment, and control – continued disparities in adults: United States, 2005-2006. NCHS Data Brief, (3), 1-8.
2. American heart association web site.Understanding blood pressure readings. 2011. http:www.heart.org/HEARTORG/conditions/High blood pressure/ about blood pressure/UCM_301764_article.jsp.
3. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365:217–23.
4. Deepa R, Shanthirani CS, Pradeepa R, Mohan V. Is the 'rule of halves' in hypertension still valid?--Evidence from the Chennai Urban Population Study. J Assoc Physicians India 2003; 51 : 153-7.
5. INTERSALT Co-operative Research Group. Sodium, potassium, body mass, alcohol and blood pressure: the INTERSALT study. J Hypertens.1988;6(Suppl 4):S584–6.
6. Sever PS, Poulter NR. A hypothesis for the pathogenesis of essential hypertension:the initiating factors. J Hypertens. 1989;7(Suppl 1):S9–12.
7. K. He, K. Liu, M. L. Daviglus et al., "Magnesium intake and incidence of metabolic syndrome among young adults," *Circulation*, vol. 113, no. 13, pp. 1675–1682, 2006.
8. Ha Nguyen, Olaide A. Odelola, Janani Rangaswami, and Aman Amanullah A Review of Nutritional Factors in Hypertension Management Volume 2013 (2013), Article ID 698940, 12 pages.
9. Kuppasani K, Reddi AS. Emergency or urgency? Effective management of hypertensive crises. JAAPA. 2010;23:44–49.
10. Smithburger PL, Kane-Gill SL, Nestor BL, Seybert AL. Recent advances in the treatment of hypertensive emergencies. Crit Care Nurse. 2010;30(5):24–30. quiz 31.
11. Varon J. Treatment of acute severe hypertension: current and newer agents. Drugs. 2008;68(3):283–297
12. Varon J, Marik PE. Clinical review: the management of hypertensive crises. Crit Care. 2003;7(5):374–384.
13. Awad AS, Goldberg ME. Role of clevidipine butyrate in the treatment of acute hypertension in the critical care setting: a review. Vasc Health Risk Manag.2010;6:457–464.
14. Ahuja K, Charap MH. Management of perioperative hypertensive urgencies with parenteral medications. J Hosp Med. 2010;5(2):E11–E16.
15. Vaughan CJ, Delanty N. Hypertensive emergencies. Lancet. 2000;356(9227):411–417.
16. Polly DM, Paciullo CA, Hatfield CJ. Management of hypertensive emergency and urgency. Adv Emerg Nurs J. 2011;33(2):127–136
17. Belsha CW. Management of hypertensive emergencies. In: Jtfe AL, editor. Clinical Hypertension and Vascular Diseases: Pediatric Hypertension. Berlin, Germany: Springer Science+Business Media; 2011. pp. 559–574.
18. Kessler CS, Joudeh Y. Evaluation and treatment of severe asymptomatic hypertension. Am Fam Physician. 2010;81(4):470–476.

19. Patel V, Chatterji S, Chisholm D, Ebrahim S, Gopalakrishna G, Mathers C, et al. Chronic diseases and injuries in India. Lancet 2011; 377 : 413-28.
20. Gupta R. Trends in hypertension epidemiology in India. 5. *J Hum Hypertens* 2004; *18* : 73-8
21. Reddy KS, Shah B, Varghese C, Ramadoss A. Responding 6. to the threat of chronic diseases in India. *Lancet* 2005; *366* : 1744-9.
22. Mohan S, Reddy KS, Prabhakaran D. Chronic non-7. communicable diseases in India. Reversing the tide. New Delhi: Public Health Foundation of India; 2011
23. M. Brandis, J. Keyes, and E. E.Windhager, "Potassium-induced inhibition of proximal tubular fluid reabsorption in rats," *The American Journal of Physiology*, vol. 222, no. 2,pp. 421–427, 1972.
24. A. J. Vander, "Direct effects of potassiumon renin secretion and renal function," *The American Journal of Physiology*, vol. 219, no.2, pp. 455–459, 1970.
25. M. B. Pamnani, X. Chen, F. J. Haddy, J. F. Schooley, and Z. Mo,"Mechanism of antihypertensive effect of dietary potassium in experimental volume expanded hypertension in rats," *Clinical and Experimental ypertension*, vol. 22, no. 6, pp. 555–569,2000.
26. G. Edwards, K. A. Dora,M. J. Gardener, C. J. Garland, and A.H.Weston, "K+ is an endothelium-derived hyperpolarizing factor in rat arteries," *Nature*, vol. 396, no. 6708, pp. 269–272, 1998.
27. W.Kuschinsky, M.Wahl,O. Bosse, and K.Thurau, "Perivascular potassiumandpHas determinants of local pial arterial diameter in cats. A microapplication study," *Circulation Research*, vol. 31, no. 2, pp. 240–247, 1972.
28. M. S. Zhou, Y. Nishida, H. Yoneyama, Q. H. Chen, and H.Kosaka, "Potassium supplementation increases sodium excretion and nitric oxide production in hypertensive Dahl rats," *Clinical and Experimental Hypertension*, vol. 21, no. 8, pp. 1397–1411, 1999.
29. H. J. Knot, P. A. Zimmermann, andM. T. Nelson, "Extracellular K+-induced hyperpolarizations and dilatations of rat coronary and cerebral arteries involve inward rectifier K+ channels,"Journal of Physiology, vol. 492, no. 2, pp. 419–430, 1996.
30. M. Kido, K. Ando, M. L. Onozato et al., "Protective effect of dietary potassium against vascular injury in salt-sensitive hypertension," Hypertension, vol. 51, no. 2, pp. 225–231, 2008.
31. T. Ishimitsu, L. Tobian, K. Sugimoto, and T. Everson, "High potassium diets reduce vascular and plasma lipid peroxides in stroke-prone spontaneously hypertensive rats," Clinical and Experimental Hypertension, vol. 18, no. 5, pp. 659–673, 1996.
32. K. T. Khaw and E. Barrett-Connor, "Dietary potassium and blood pressure in a population," American Journal of Clinical Nutrition, vol. 39, no. 6, pp. 963–968, 1984.
33. J. M. Geleijnse, J. C. M. Witteman, J. H. Den Breeijen et al., "Dietary electrolyte intake and blood pressure in older subjects: the RotterdamStudy," Journal of Hypertension, vol. 14, no. 6, pp.737–741, 1996.
34. G. G. Krishna and S. C. Kapoor, "Potassium depletion exacerbates essential hypertension," Annals of Internal Medicine, vol. 115, no. 2, pp. 77–83, 1991.
35. 20.Priddle WW: Observations on the management of hypertension Can Med Assoc J 25: 5, 1931.
36. Kempner W: Treatment of hypertensive vascular disease with a rice diet. Am J Med 4: 545, 1957
37. F. P. Cappuccio and G. A.MacGregor, "Does potassium supplementation lower blood pressure? A meta-analysis of published trials," Journal of Hypertension, vol. 9, no. 5, pp. 465–473, 1991.
38. J. M. Geleijnse, F. J. Kok, and D. E. Grobbee, "Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials," Journal of Human Hypertension, vol. 17, no. 7, pp. 471–480, 2003.
39. National Research Council, Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate, The National Academies Press,Washington, DC, USA, 2005.
40. J. A. Whitworth, "2003 World Health Organization (WHO)/ International Society of Hypertension (ISH) statement on management of hypertension," Journal of Hypertension, vol. 21, no. 11, pp. 1983–1992, 2003.
41. M. E.Cogswell, Z. Zhang,A. L.Carriquiry, J. P.Gunn, E.V.Kuklina, S. H. Saydah et al., "Sodiumand potassiumintakes among US adults: NHANES, 2003–2008," American Journal of Clinical Nutrition, vol. 96, no. 3, pp. 647–657, 2012.
42. Yamon Y. Kihara M. Nara Y. Ohtaka M, Hone R. Tsunematsu T. Note S. Hypertension and diet: multiple regression analysis in a Japanese fanninu community. Lancet 1: 1204.1981
43. Sasaki N: High blood pressure and the salt intake of the Japanese. Jp Heart J 3: 313, 1962
44. limura O. Kijima T. Kikuchi K, Miyami A. Ando T. Nakao T, Takigami Y: Studies on the hypotensivc effects of high potassium intake in patients with essential hypertension. Clin Sci 61 (suppl): 77s, 1971
45. Whelton PK, He J, Cutler JA, et al: Effects of oral potassium on blood pressure: Meta-analysis of randomized controlled clinical trials. JAMA 227: 1624- 1632, 1997
46. Gu D, He J, Xigui W, et al: Effect of potassium supplementation on blood pressure in Chinese: A randomized, placebo-controlled trial. J Hypertens19:1325-1331, 2001
47. Barri YM, Wingo CS: The effects of potassium depletion and supplementation on blood pressure: A clinical review. Am J Med Sci 3:37- 40, 1997
48. Hu G, Tian H: A comparison of dietary and nondietary factors of hypertension and normal blood pressure in a Chinese population. J Hum Hypertens 15:487-493, 2001.
49. Villar J, Montilla C, Muniz-Grijalvo O, et al: Erythrocyte Na+-Li+ countertransport in essential hypertension: Correlation with membrane lipid levels. J Hypertens 14:969-973, 1996
50. Khaw K-T, Barrett-Connor E: Dietary potassium and stroke-associated mortality: A 12-year prospective population study. N Engl J Med 316: 235- 240, 1987
51. McCarron DA, Reusser ME: Nonpharmacologic therapy in hypertension: From single components to overall dietary management. Prog Cardiovasc Dis 41:451-460, 1999
52. National Research Council, Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate, The National Academies Press,Washington, DC, USA, 2005.
53. L. J. Appel, M. W. Brands, S. R. Daniels, N. Karanja, P. J. Elmer, andF.M. Sacks, "Dietary approaches toprevent and treat hypertension: a scientific statement from the American Heart Association," Hypertension, vol. 47, no. 2, pp. 296–308, 2006.
54. J. A. Whitworth, "2003 World Health Organization (WHO)/ International Society of Hypertension (ISH) statement on management of hypertension," Journal of Hypertension, vol. 21, no. 11, pp. 1983–1992, 2003.
55. Warner MG: Complementary and alternative therapies for hypertension. Complement Health Pract Rev 6:11- 19, 2000 111. Kotchen TA, McCarron DA: AHA Science

Advisory. Dietary electrolytes and blood pressure. Circulation 98:613-617, 1998
56. Kotchen TA, McCarron DA: AHA Science Advisory. Dietary electrolytes and blood pressure. Circulation 98:613-617, 1998
57. McCarron DA, Reusser ME: Nonpharmacologic therapy in hypertension: From single components to overall dietary management. Prog Cardiovasc Dis 41:451-460, 1999
58. Ahsan SK: Magnesium in health and disease. J Pak Med Assoc 48:246- 250, 1998
59. Weiss D: Cardiovascular disease: Risk factors and fundamental nutrition. Int J Integr Med 2:6 - 12, 2000
60. Widman L, Wester PO, Stegmayr BG, et al: The dose dependent reduction in blood pressure through administration of magnesium: A double blind placebo controlled cross-over trial. Am J Hypertens 6:41- 45, 1993
61. Paolisso G, Gambardella A, Balbi V, et al: Effects of magnesium and nifedipine on insulin action, substrate oxidation and blood pressure in aged subjects. Am J Hypertens 6:920- 926, 1993
62. Kisters K, Krefting ER, Barenbrock M, et al: Na+ and Mg2+ contents in smooth muscle cells in spontaneously hypertensive rats. Am J Hypertens 12:648-652, 1999
63. Sanders GM, Sim KM: Is it feasible to use magnesium sulfate as a hypotensive agent in oral and maxillofacial surgery? Ann Acad Med Singapore 27:780-785, 1998
64. Altura BM, Altura BT, Carella A: Magnesium deficiency–induced spasms of umbilical vessels: Relation to preeclampsia, hypertension, growth retardation. Science 221:376-378, 1983
65. K.D. Blackfan, B. Hamilton, Boston Med. Surg. J. 193 (1925) 617–621.
66. C. Vigorito, A. Giordano, P. Ferraro, P. Supino, M. De Pasquale, B. Giordano, F. Lionetti, F. Rengo, Am. J. Cardiol. 67 (1991) 1435–1437.
67. B.H. Ji, P. Erne, W. Kiosky, F.R. Buhler, P. Bolli, J. Hypertens. 1 (1983) 368–371.
68. L.M. Resnick, R.K. Gupta, B. DiFabio, M. Barbagallo, S. Mann, R. Marion, J.H. Laragh, J. Clin. Invest. 94 (3) (1994) 1269–1276.
69. P. Tammaro, A.L. Smith, B.L. Crowley, S.V. Smirnov, Cardiovasc. Res. 65 (2) (2005) 387–396
70. R.M. Touyz, G. Yao, J. Cell Physiol. 197 (3) (2003) 326–335.
71. P. Laurant, R.M. Touyz, E.L. SchiVrin, Can. J. Physiol. Pharmacol. 5 (1997) 293–300.
72. M. Yoshimura, T. Oshima, H. Matsuura, T. Ishida, M. Kambe, G.Kajiyama, Circulation 95 (11) (1997) 2567–2572.
73. M.R. JoVres, D.M. Reed, K. Yano, Am. J. Clin. Nutr. 45 (1987) 469– 475.
74. P.K. Whelton, M.J. Klag, Am. J. Cardiol. 63 (1989) 26G–30G.
75. E.M. Van Leer, J.C. Seidell, D. Kromhout, Int. J. Epidemiol. 24 (1995) 1117–1123.
76. D.G. Simons-Morton, S.A. Hunsberger, L. Van Horn, B.A. Barton, A.M. Robson, R.P. McMahon, L.E. Muhonen, P.O. Kwiterovich, N.L. Lasser, S.Y.S. Kimm, M.R. Greenlick, Hypertension 29 (1997) 930–936.
77. A. Ascherio, C. Hennekens, W.C. Willett, F. Sacks, B. Rosner, J. Manson, J. Witteman, M.J. Stampfer, Hypertension 27 (5) (1996) 1065– 1072.
78. J.M. Geleinjoise, J.C. Witteman, J.H. den Breeijen, A. Hofman, P.T. de Jong, H.A. Pols, D.E. Grobbee, J. Hypertens. 14 (6) (1996) 737–741.
79. Y. Kawano, H. Matsuoka, S. Takishita, and T. Omae, "Effects of magnesium supplementation in hypertensive patients: assessment by office, home, and ambulatory blood pressures," *Hypertension*, vol. 32, no. 2, pp. 260–265, 1998.
80. L. S. Hatzistavri, P. A. Sarafidis, P. I. Georgianos et al., "Oral magnesium supplementation reduces ambulatory blood pressure in patients with mild hypertension," *American Journal of Hypertension*, vol. 22, no. 10, pp. 1070–1075, 2009.
81. A. Haenni, K. Johansson, L. Lind, and H. Lithell, "Magnesium infusion improves endothelium-dependent vasodilation in the human forearm," *American Journal of Hypertension*, vol. 15, no. 1, part 1, pp. 10–15, 2002.
82. M. Shechter,M. Sharir, M. J. Labrador et al., "Oralmagnesium therapy improves endothelial function in patients with coronary artery disease," *Circulation*, vol. 102, no. 19, pp. 2353– 2358, 2000.
83. R. M. Touyz and F. J. Milne, "Magnesium supplementation attenuates, but does not prevent, development of hypertension in spontaneously hypertensive rats," American Journal of Hypertension, vol. 12, no. 8, part 1, pp. 757–765, 1999.
84. L. M. Resnick, J. H. Laragh, J. E. Sealey, and M. H. Alderman, "Divalent cations in essential hypertension: relations between serum ionized calcium, magnesium, and plasma renin activity," The New England Journal ofMedicine, vol. 309, no. 15, pp. 888–891, 1983.
85. Y. Kawano, "Role of blood pressure monitoring in nonpharmacological management of hypertension," Blood Pressure Monitoring, vol. 7, no. 1, pp. 51–54, 2002.
86. M. C. Houston and K. J. Harper, "Potassium, magnesium, and calcium: their role in both the cause and treatment of hypertension," Journal of ClinicalHypertension, vol. 10,no. 7, pp.3–11, 2008.
87. D. A. McCarron, "Role of adequate dietary calcium intake in the prevention andmanagement of salt-sensitive hypertension," American Journal of Clinical Nutrition, vol. 65, no. 2, pp. 712S– 716S, 1997.
88. H. Yamakawa,H. Suzuki, M.Nakamura, Y.Ohno, and T. Saruta, "Disturbed calcium metabolism in offspring of hypertensive parents," Hypertension, vol. 19, no. 6, pp. 528–534, 1992.
89. P. Lijnen and V. Petrov, "Dietary calcium, blood pressure and cell membrane cation transport systems in males," Journal of Hypertension, vol. 13, no. 8, pp. 875–882, 1995.
90. K. Saito, H. Sano, Y. Furuta, and H. Fukuzaki, "Effect of oral calcium on blood pressure response in salt-loaded borderline hypertensive patients," Hypertension, vol. 13, no. 3, pp. 219–226, 1989.
91. D. C. Hatton and D. A. McCarron, "Dietary calcium and blood pressure in experimental models of hypertension: a review," Hypertension, vol. 23, no. 4, pp. 513–530, 1994.
92. J. R. Sowers, M. B. Zemel, P. C. Zemel, and P. R. Standley, "Calcium metabolism and dietary calcium in salt sensitive hypertension," American Journal of Hypertension, vol. 4, no. 6, pp. 557–563, 1991.
93. P. Hamet, E. Mongeau, J. Lambert et al., "Interactions among calcium, sodium, and alcohol intake as determinants of blood 11 pressure," Hypertension, vol. 17, no. 1, supplement, pp. I150–I154, 1991.
94. P. Hamet, M. Daignault-Gelinas, J. Lambert et al., "Epidemiological evidence of an interaction between calcium and sodium intake impacting on blood pressure. AMontreal Study," American Journal of Hypertension, vol. 5, no. 6, pp. 378–385, 1992.
95. H.W.Gruchow,K.A. Sobocinski, and J. J. Barboriak, "Calcium intake and the relationship of dietary sodium and

potassium to blood pressure," American Journal of Clinical Nutrition, vol. 48, no. 6, pp. 1463–1470, 1988.
96. D. A. McCarron, "Role of adequate dietary calcium intake in the prevention andmanagement of salt-sensitive hypertension," American Journal of Clinical Nutrition, vol. 65, no. 2, pp. 712S– 716S, 1997.
97. T. A. Kotchen and D. A. McCarron, "Dietary electrolytes and blood pressure: a statement for healthcare professionals from the American Heart Association Nutrition Committee," Circulation, vol. 98, no. 6, pp. 613–617, 1998.
98. M. H. Weinberger, U. L. Wagner, and N. S. Fineberg, "The blood pressure effects of calcium supplementation in humans of known sodium responsiveness," American Journal of Hypertension, vol. 6, no. 9, pp. 799–805, 1993.
99. L. M. Resnick, F. B. Muller, and J. H. Laragh, "Calciumregulating hormones in essential hypertension: relation to plasma renin activity and sodium metabolism," Annals of Internal Medicine, vol. 105, no. 5, pp. 649–654, 1986.
100. L. M. Resnick, J. P. Nicholson, and J. H. Laragh, "Calcium metabolism in essential hypertension: relationship to altered renin system activity," Federation Proceedings, vol. 45, no. 12, pp.2739–2745, 1986.
101. L. M. Resnick and J. H. Laragh, "Renin, calcium metabolism and the pathophysiologic basis of antihypertensive therapy," American Journal of Cardiology, vol. 56, no. 16, pp. H68–H74, 1985.
102. L. M. Resnick, J. P. Nicholson, and J. H. Laragh, "Alterations in calcium metabolism mediate dietary salt sensitivity in essential hypertension," Transactions of the Association of American Physicians, vol. 98, pp. 313–321, 1985.
103. L. M. Resnick, J. H. Laragh, J. E. Sealey, and M. H. Alderman, "Divalent cations in essential hypertension. Relations between serumionized calcium, magnesium, and plasma renin activity," The New England Journal of Medicine, vol. 309, no. 15, pp. 888– 891, 1983.
104. L.M. Resnick and J. H. Laragh, "The significance of calciumand calcium channel blockade in essential hypertension," Journal of Hypertension, vol. 3, no. 3, pp. S541–S544, 1985.
105. L. Resnick, "Calcium metabolism, renin activity, and the antihypertensive effects of calcium channel blockade," The American Journal of Medicine, vol. 81, no. 6, pp. 6–14, 1986.
106. L. M. Resnick, "The effects of sodium and calcium in clinical hypertension: mediating role of vitamin D metabolism," Advances in Second Messenger and Phosphoprotein Research, vol. 24, pp. 535–541, 1990.
107. L.M. Resnick, "Alterations of dietary calcium intake as a therapeutic modality in essential hypertension," Canadian Journal of Physiology and Pharmacology, vol. 64, no. 6, pp. 803–807, 1986.
108. . Birkett NJ: Comments on a meta-analysis of the relation between dietary calcium intake and blood pressure. Am J Epidemiol 148:223- 228, 1998 152.
109. Griffith L, Guyatt GH, Cook RJ, et al: The influence of dietary and nondietary calcium supplementation on blood pressure: An updated meta-analysis of randomized clinical trials. Am J Hypertens 12:84- 92, 1999
110. McCarron DA, Reusser ME. Nonpharmacologic therapy in hypertension: from single components to overall dietary management.*Prog Cardiovasc Dis*. 1999;**41**:451–460.
111. Ascherio A, Rimm EB, Giovannucci EL, *et al.* A prospective study of nutritional factors and hypertension among US men.*Circulation*. 1992;**86**(5):1475–148
112. Wang L, Manson JE, Buring JE, *et al.* Dietary intake of dairy products, calcium, and vitamin D and the risk of hypertension in middle-aged and older women. *Hypertension*. 2008;**51**:1073–1079
113. Appel LJ, Moore TJ, Obarzanek E, et al: A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 336:1117- 1124, 1997
114. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2010; (8):CD001059.
115. Dobnig, H.; Pfeifer, M.; Begerow, B.; Suppan, K. Calcium, Not Vitamin D Decreases Blood Pressure Effectively in Elderly Subjects with Low Vitamin D Levels: A Randomized, Double-blind, Multi-center Study. In Abstracts of the 87th Annual Meeting of the Endocrine Society, San Diego, California, USA, 4–7 June 2005.
116. Indian Council of Medical Research. In: Gopalan C, Rama Sastri BV, Balasubramanian SC. Nutritive value of Indian foods. Hyderabad: National Institute of Nutrition; 2010.
117. Karanja N, Morris CD, Rufolo P, et al: The impact of increasing dietary calcium intake on nutrient consumption, plasma lipids and lipoproteins in humans. Am J Hypertens 59:900- 907, 1994.

How to cite this article:
Nimbark S and Gorrepati R: *In vivo* stabilization studies on Indian Cobra (*Naja naja*) venom for its toxicological activity (LD_{50}) in mice. Int J Pharm Sci Res 2014; 5(8): 3322-32.doi: 10.13040/IJPSR.0975-8232.5(8).3322-32