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RESEARCH ARTICLE

HIGH ALTITUDE RESEARCH IN INDIA AND NEIGHBOURING COUNTRIES

***Mallika Manral, Prasanna Reddy, M. and SomNath Singh**

Defence Institute of Physiology and Allied Sciences, Lucknow Road, Timarpur, Delhi 110054 India

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ABSTRACT

Each year millions of people including Armed Force personnels, mountaineers, tourists are exposed to high altitude. Hypoxia, cold and intense solar radiations at high altitude can exert a significant impact on physiology of the human beings. China, India, Pakistan and Nepal are countries in vicinity of Himalayas. Over the years studies have been carried out to understand various aspects of high altitude acclimatization.This review attempts to estimate quantity, scope and quality of high altitude research in these four countries. A systematic search of literature was carried out in electronic databases viz. www.sciencedirect.com and www.pubmed.com with acclimatization; oxygenation; SaO_2; pulmonary function; altitude maladies (acute mountain sickness, chronic mountain sickness, High Altitude Pulmonary Oedema (HAPE/HAPO)); therapeutic agents (diamox, herbal remedies, *Ginkgo biloba, Panax ginseng, Hippophae rhamnoides*); nutrition and genetic variation as keywords.
It was observed that maximum numbers of studies on high altitude research have been carried out by China followed by Nepal, India and Pakistan. Amongst the different research areas of high altitude research, highest numbers of studies have been carried out on acclimatization followed by pulmonary function and acute mountain sickness.

INTRODUCTION

Strategic location of Himalayas and expedition curiosity of mankind has lead high altitude (HA) research in the regional countries and also all over the world for mountaineering as sport. Over the years considerable literature has accumulated on the subject of high altitude research in China, India, Pakistan and Nepal because of the location of Himalayan Alpine range in these Asian countries and to vigil their borders at high altitude. From the literature it is evident that physical as well as mental performance at high altitude decreases in comparison to sea level and proper acclimatization is must which takes few days to weeks depending on the altitude. In China, the construction of the Qinghai-Tibet railroad made the way to high altitude more easily accessible to the researchers and this is leading to a spurt in high altitude research in China. In the recent past, six studies (Wu *et al*., 2007a,b; Fan *et al*., 2004; Yu-jing *et al*., 2010; Qi *et al*., 2009; Wu *et al*., 2009) have been reported on workers involved in construction of Qinghai-Tibet railroad and one study (Wu *et al*., 2010) has been reported on passengers of the same railroad. The high altitude literature is a fragmented corpus and scholars from a diversity of disciplinary backgrounds study a variety of parameters, work on different population groups in order to investigate, analyze and report on a phenomenon that is complex and multidimensional. More specifically, this diversity is reflected in the multitude of approaches and the different parameters. Within the literature main emphasis is given to acclimatization response, etiology of diseases like High Altitude Pulmonary Oedema (HAPE /HAPO), Acute Mountain Sickness (AMS), and Chronic Mountain Sickness (CMS), pulmonary functions and oxygenation; treatment with diamox and herbal remedies. Recently, genetic variation is a focus of studies in different populations. Within the literature on high altitude; acclimatization, acute mountain sickness, chronic mountain sickness, HAPE/HAPO, oxygenation, SaO_2, nutrition, pulmonary function, genetic variation, diamox, herbal remedies like *Ginkgo biloba*, *Panax ginseng*, maladies, seabuckthorn are frequently studied. The review was outlined by articulating the terms of high altitude aspects of acclimatization addressing the issue of high altitude research carried out in the country and neighbouring countries viz., China, Pakistan and Nepal.

Corresponding author: mallikach2@rediffmail.com

METHODOLOGY

In order to search the literature, search was done in electronic databases www.sciencedirect.com and www.pubmed.com with acclimatization, oxygenation, SaO_2, HAPE/HAPO, pulmonary function, maladies, acute mountain sickness, chronic mountain sickness, diamox, herbal remedies, *Ginkgo biloba, Panax ginseng, Hippophae rhaminoides* (a high altitude plant with various bioactive compounds), nutrition, genetic variation as the keywords alongwith the names of four countries viz., India, China, Pakistan and Nepal. Search in the electronic databases were carriedout in December 2011. The results of the electronic database search have been depicted in Fig 1 and Fig 2. The abstracts obtained in the pubmed search with 60 combinations of keywords were shortlisted on the basis of affiliation. e.g. in the studies pertaining to India only those studies have been reviewed where the authors have Indian affiliation.

DISCUSSION

High Altitude Research in INDIA

Acclimatization

Pubmed database search with the keywords, high altitude + India + acclimatization revealed 58 studies. Amongst these, authors of 52 studies had Indian affiliation. Among these 52, five studies had been conducted on animals, one was on plants, one was a review

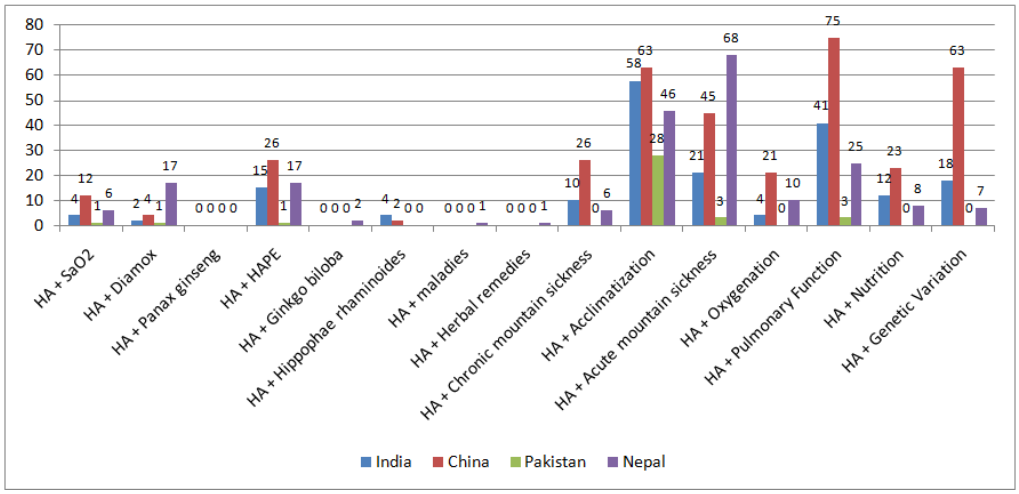

Figure 1. Number of studies on different aspects of high altitude research in China, India, Pakistan and Nepal as reflected in search on www.pubmed.com

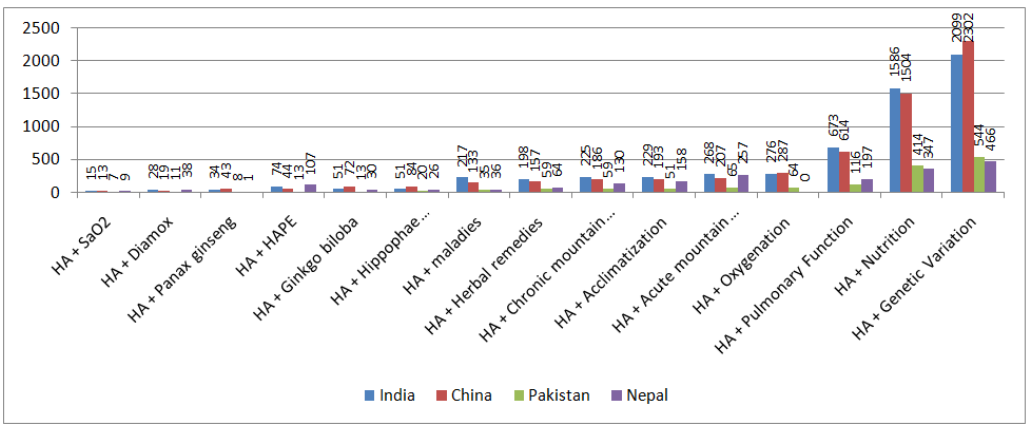

Figure 2. Number of studies on different aspects of high altitude research in China, India, Pakistan and Nepal as reflected in search on www.sciencedirect.com

(Paralikar and Paralikar, 2010) and one was a case study (Nair *et al*., 2008). In the human studies, comparison between lowlanders and native high landers (Sinha *et al*., 2009; Basu *et al*., 2007; Passino *et al*., 1996; Srivastava *et al*., 1975; Shivastava and Malhotra, 1974), natives and sojourners (Sinha *et al*., 2009; Vij *et al*., 2005), natives and acclimatized lowlanders (Sinha *et al*., 2009; Apte and Rao, 2005), sojourners and acclimatized lowlanders (Shukla *et al*., 2005; Sawhney and Malhotra, 1991), Indians and Krygis (Basu *et al*., 2007) have been made . Maximum number of studies have been carried out on pulmonary function (Basu *et al*., 2007; Apte and Rao 2005; Bhaumik *et al*., 2003; Myers *et al*., 2008; Wood *et al*., 2003; Guleria *et al*., 1971; Apte, 2004; Basu *et al*., 1996b), followed by biochemical variables (Basu *et al*., 2007; Srivastava *et al*., 1975; Shivastava and Malhotra, 1974; Vij *et al*., 2005; Singh *et al*., 2003), hormones (Shukla *et al*., 2005; Sawhney and Malhotra 1991; Basu *et al*., 1995; Basu *et al*., 1997; Anand *et al*., 1993), body composition (Amitabh *et al*., 2009; Ray and Selvamurthy, 1998; Bhardwaj and Malhotra, 1974), vitamin status (Sridharan *et al*., 2004; Purkayastha *et al*., 1999), antioxidant status (Sinha *et al*., 2009; Sinha *et al*., 2010). There were single studies reporting acclimatization and pupil dynamics (Wilson *et al*., 2008); nail growth (Sawhney, 2002), physical performance (Purkayastha *et al*., 2000), body fluid status (Singh *et al*., 1990), skinfold thickness (Zachariah *et al*., 1987), chemoreceptor sensitivity (Mathew *et al*., 1983), incidence of disease (Singh *et al*., 1977), role of beta-2-adrenergic receptor gene haplotype in HAPE (Stobdan *et al*., 2010), effect of prolonged stay at high altitude on platelet aggregation and fibrinogen (Vij, 2009). Sachidhnandan *et al*. (2010) conducted a study to examine possible age and ethnic variation in plasma pro (ANP1-98) levels in men after 3 to 4 weeks at high altitude and found that ethnicity but not age variation is associated with plasma pro ANP (1-98) under high altitude stress. In another study by Sachidhnandan *et al*. (2009) effect of age and ethnicity on impact of prolonged high altitude exposure on plasma prolactin in men were studied. Sinha *et al*. (2010) studied protein nitration, lipid peroxidation and DNA damage at high altitude in acclimatized lowlanders and native highlanders and results indicated that oxygen consumption was positively correlated with nitrosative and oxidative stress markers irrespective of environmental condition and adaptation levels. Sinha *et al*. (2009) in their study on antioxidant and redox status after maximal aerobic exercise at high altitude in acclimatised lowlanders and native highlanders reported that high altitude natives were more susceptible to oxidative stress when subjected to high intensity exercise than lowlanders. In a study (Amitabh *et al*. 2009) on the body composition and cardiovascular functions in healthy males acclimatized to desert and high altitude it was found that lower physical fitness index at high altitude could be attributed to a combination of factors viz., higher resting pulse rate, increased blood pressure and body fat. Basu *et al*. (2007) studied the erythropoietin levels in lowlanders and high altitude natives at 3450m and concluded that short or prolonged residency at high altitude resulted in increased secretion of erythropoietin. Sawhney (2002) studied the relationship between high altitude and nail growth and reported that there was decreased nail growth in high altitude areas plausibly due to hypoxic conditions and extreme cold conditions. In a comparative study of Indian and Krygis (Basu *et al*., 2007) it was reported that the major difference between the two populations was larger lung volumes in the Krygis as compared with the Indians. Basu *et al*., (1996a) studied the metabolic responses during initial days of altitude acclimatization

in the eastern Himalayas and reported that acclimatization to a mid-altitude of 3445m could be safely avoided in cases where rapid ascent to higher altitude is required.

Oxygenation

Four studies were found in Pubmed search with high altitude + India + oxygenation as keywords. Two studies (Stobdan *et al*., 2010; Ahsan *et al*., 2005) were on gene polymorphism in relation with high altitude adaptation. The other was a cell culture study (Kolluru *et al*., 2008). Prasad (2011) conducted a study to evaluate ENT morbidity at high altitude and concluded that diseases of ear, nose and throat contribute significantly to high altitude morbidity.

SaO_2

Four studies were found in Pubmed search with high altitude + India + SaO_2 as keywords and three of these had Indian affiliation. Amongst three, one was a case study (Ahmad *et al*., 2006). One study (Kumar *et al*., 2004) was on gene polymorphism and the other study (Basu *et al*., 1996b) was on acclimatization to high altitude and these have been discussed under the heading genetic variation and acclimatization, respectively.

HAPE

Pubmed database search with the keywords, high altitude + India + HAPE revealed 15 studies and all these had Indian affiliation. Out of 15 studies two studies were on cell culture, one was an animal study, one was a case study (Ahmad *et al*., 2006), and four were reviews (Paralikar and Paralikar, 2010; Norboo *et al*., 2004; Pasha and Newman, 2010; Paintal, 1995). There were three studies on gene polymorphism viz., NOS3 polymorphism (Ahsan *et al*., 2006); ACEI/D polymorphism (Kumar *et al*., 2004); A1 and A2 genes (Saxena *et al*., 2005). There were studies on role of beta2-adrenergic receptor (ADRB2) in pulmonary oxygenation (Stobdan *et al*., 2010), comparison of erythropoietin levels in lowlanders and high-altitude natives at 3450 m (Basu *et al*., 2007).

Ahmad *et al*. (2011) investigated the *plasma*, proteome using 2-gel electrophoresis and matrix assisted laser desorption ionization tandem time of flight from patient with HAPE. Stobdan *et al*. (2011) studied the association of RAS polymorphisms with HAPE and reported a significant relationship of D allele of ACE and M allele of AGT with HAPE. Another study (Ahsan *et al*., 2006) reported contribution of heterozygotes of NOS3 polymorphisms in reduced nitrogen oxides in high altitude pulmonary oedema. Saxena *et al*., (2005) studied the association of polymorphisms in pulmonary surfactant protein A1 and A2 genes with high altitude pulmonary oedema and reported that polymorphisms in SP-A1 (C1101T, T3192C and T3234 C) and Sp-A2 (A3265C) could be one of the genetic factors contributing to susceptibility to HAPE.

Pulmonary Function

Pubmed search with high altitude + India + pulmonary function revealed 41 abstracts and 36 of these had Indian affiliation. Among these, four were conducted on animals and two others were on cell cultures. Two of the abstracts were of review articles (Sarkar *et al*., 2003; Selvamurthy and Basu, 1998). There were studies on exercise response to trekking (Bhaumik *et al*., 2008), erythropoietin levels (Basu *et al*., 2007), clinical anthropometry of changes in eye (Bali *et al*., 2005), maximum expiratory flow volume of loop (Apte and Rao, 2005), pulmonary artery pressure (Apte, 2004), hypoxic ventilatory response (Bhaumik *et al*., 2003), metabolic responses (Basu *et al*., 1996a), respiratory changes during acclimatization (Basu *et al*., 1996b, Malik and Pandey, 1993). There have been studies on peak expiratory flow rates (Kashyap *et al*., 1992), respiratory illnesses (Norboo *et al*., 1991), cardiopulmonary functional changes (Rupwate *et al*., 1990), adult subacute mountain sickness (Anand *et al*., 1990), abnormalities of blood coagulation (Singh and Chouhan, 1972), pulmonary diffusing capacity (Guleria *et al*., 1971), fibrinolytic activity in HAPE (Singh *et al*., 1969). Sharma (1990) studied clinical, biochemical, electrocardiographic and non invasive hemodynamic assessment of cardiovascular status in natives at high to extreme altitudes (3000m-5500m) of the Himalayan region and observed that with increase in altitude, there was an increase in HDL cholesterol but a decrease in the LDL cholesterol, total cholesterol/HDL cholesterol ratio and LDL cholesterol/HDL cholesterol ratio. Patial (1999) carried out a study on high altitude koilonychias. There have been studies exclusively on adolescents (Malik and Pandey, 1993), children (Kashyap *et al*., 1998) and mountaineers (Rupwate *et al*., 1990). There were studies on gene polymorphism viz., NOS3 (Ahsan *et al*., 2006), ACE I/D (Kumar *et al*., 2004), pulmonary surfactant protein A1 and A2 genes (Saxena *et al*., 2005). Bhaumik *et al*., (2008) studied the maximum exercise responses of men and women mountaineering trainees on induction to high altitude (4350m) by trekking and concluded that the decrement of maximum aerobic capacity at 4350m was less in women than in men. Kolluru *et al*., (2008) studied nitric oxide cGMP protection for endothelial cells from hypoxia mediated leakiness and reported that hypoxia induced cytoskeletal rearrangements and membrane leakiness were associated with the low nitric oxide availability under hypoxia. Bali *et al*., (2005) carried out a case controlled study in clinical ocular anthropometry of changes in the eye and reported that hypoxia, ultraviolet radiations and persistent snow cover at high altitude could affect the anthropometry of the eye. Apte, (2004) studied the pulmonary artery pressure in Ladakhi men on exposure to acute hypoxia after a stay at sea level and found that natives of Ladakh were adapted to hypoxia and not merely acclimatized. In a study (Apte and Rao, 2005) on maximum expiratory flow volume loop in natives of Ladakh and acclimatized lowlanders it was found that forced vital capacity and forced expiratory volume were significantly higher in the natives but the flow rates at larger lung volumes were similar in the two groups. In a study (Bhaumik *et al*, 2003) on hypoxic ventilatory response changes in men and women 6 to 7 days after climbing from 2100m to 4350 m altitude and after descent it was found that gender did not influence chemosensitive response measured during induction to high altitude.

Basu *et al*. (1996a) studied metabolic responses during initial days of altitude acclimatization in the eastern Himalayas and observed that acclimatization to a mid-altitude of 3445 could be safely avoided where immediate ascent to higher altitude was required. In another study by Basu *et al*, (1996b) on the respiratory changes during initial days of acclimatization to increasing altitudes it was found that ventilation, tidal volume and respiratory rate showed significant increases on arrival at high altitude and remained high during entire period of observation. Malik and Pandey, (1993) studied the respiratory adaptation to high altitude in adolescent Bod girls of the Western Himalayas and reported that high altitude Bod girls were shorter and lighter and the difference was more pronounced in weight and especially after 14 yrs of age. In a study on peak expiratory flow rates of healthy tribal children living at high altitudes in the Himalayas it was concluded that peak expiratory flow rates of these children could be compared with children of the West as well as with children of North Indian urban areas. In a study on domestic pollution and respiratory illness in a Himalayan village, no significant associations between winter pollution levels and the presence of chronic symptoms were reported. Rupwate *et al*., (1990) studied the cardiopulmonary changes in acute acclimatization to high altitude in mountaineers and observed that proper acclimatization could prevent health problems and improve performance. Anand *et al*., (1990) reported a novel type of adult subacute mountain sickness- a syndrome of congestive heart failure in man at very high altitude. The characteristics of this type of mountain sickness were severe congestive heart failure with oedema and ascites after 10.8 weeks at altitudes of 5800-6700m.

Maladies

Pubmed database search with the keywords, high altitude + India + maladies revealed two studies and both of these had Indian affiliation.

Among these, one was a study on animals. Another study (Singh *et al*., 2003) was on blood gases, hematology and renal blood flow during prolonged mountain sojourns it was reported in this study that renal function had an important role in the acclimatization process and was also an important factor in providing protection to body against severe hypoxia.

Acute Mountain Sickness

Pubmed search with keywords high altitude + India + acute mountain sickness revealed 24 studies and 22 of these had Indian affiliation. There were four reviews (Paralikar and Paralikar, 2010; Norboo *et al*, 2004; Pasha and Newman, 2010; Meena *et al*, 2010) and one case study (Ahmad *et al*, 2006). There was a paper on gastrointestinal problems (Anand *et al*., 2006). Three studies (Poduval, 2000; Mistry *et al*., 1993; Purkayastha *et al*., 1995) were exclusively on acute mountain sickness. Acute mountain sickness had been studied in relation with erythropoietin levels (Basu *et al*., 2007), acclimatization (Basu *et al*., 2002b), oxidative stress (Vij *et al*., 2005), pulmonary artery pressure (Apte, 2004), cardiopulmonary functional changes (Rupwate *et al*., 1990), congestive heart failure (Anand *et al*., 1990), acclimatization (Purkayastha *et al*., 1995), glucocorticoids (Basu *et al*., 2002a; Basu *et al*., 2002b) and zinc and copper concentration (Hayat *et al*., 2006). Anand *et al*., (1990) studied adult subacute mountain sickness, a syndrome of congestive heart failure in mammals at very high altitude.

Chronic Mountain Sickness

There were ten studies in Pubmed search with keywords high altitude +chronic mountain sickness + India. Nine studies had Indian affiliation. One was a review of high altitude problems (Norboo *et al*., 2004) while five studies had been carried out in animals. Pasha and Newman, (2010) in their article have discussed high altitude disorders, pulmonary hypertension, pulmonary vascular disease. Vij, (2009) investigated the effect of chronic hypobaric hypoxia on platelet function and fibrinogen concentration and concluded that increased platelet activity could not be responsible for prevention of thrombotic phenomenon during prolonged stay at high altitude but increased availability of substrate for coagulation could favour procoagulant tendencies. Meena *et al*., (2010) have discussed a herbomineral drug, *Shilajit* for high altitude problems.

Diamox

Two studies were found in Pubmed search on high altitude + diamox + India. Paralikar and Paralikar, (2010) have discussed various high altitude drugs like acetazolamide, dexamethasone, nifedipine etc. Ghosh *et al.*, (2010) conducted a study to examine genotoxic activity of marketed medicines used in management of high altitude sickness.

Herbal remedies

No study was found in Pubmed search on high altitude + herbal remedies + India.

Ginkgo biloba

No study was found in Pubmed search on high altitude + *Ginkgo biloba* + India.

Panax ginseng

No study was found in Pubmed search on high altitude + *Panax ginseng* + India

Hippophae rhaminoides

Pubmed search with high altitude + ***Hippophae*** *rhaminoides* + India showed 4 abstracts and all of these had Indian affiliation. However, none of these had been conducted on human subjects.

Nutrition

Twelve articles were found in Pubmed search with high altitude + India + nutrition and 11 of these had Indian affiliation. There were three studies on rats and one was a review article (Srivastava and Kumar, 1992). Human studies have been reported on vitamin status during consumption of tinned rations (Sridharan *et al*, 2004); zinc and copper concentrations (Rawal *et al*., 1999), human taste intensity and hedonics (Singh *et al.*, 1997) and epidemiology and prevention of low birth weight babies (Tibrewala *et al*., 1980). Kumar *et al*., (2011) did a population based cross sectional study to investigate the prevalence and risk factors of gastrooesophageal reflux disease in a high altitude area and reported 18.7% prevalence of gastrooesophageal reflux disease. Dutta *et al*., (2009) studied the prevalence of undernutrition among children in Garhwal Himalayas and found that the majority of children were severely stunted and wasted indicating a high prevalence of both chronic and acute malnutrition. Tripathy and Gupta, (2007) studied the growth among Tibetans at high and low altitudes in India and reported that Tibetans at high altitude were taller and heavier compared to Andean highlanders. In a study on the vitamin status at high altitude (3660m) in acclimatized human subjects during consumption of tinned rations it was reported that additional vitamin supplementation was not required after acclimatization at high altitude and for 30 days when consuming tinned rations (Sridharan *et al*., 2004).

Srivastava and Kumar, (1992) studied human nutrition in cold and high terrestrial altitudes and observed that hypoxia and cold resulted in loss of appetite and thereby resulting in a need for special foods for these conditions. Rawal *et al*., (1999) studied the effect of time exposure to high altitude on zinc and copper concentration in human plasma and found that under hypoxic stress plasma zinc was transported into organs and tissues so its level in the plasma changed but circulating levels of copper remained unchanged indicating that extra supplementation of copper was not required for hypoxic stress. Singh *et al*., (1997) studied high altitude effects on human taste intensity and hedonics and observed that hedonic responses changed due to hypoxic stress resulting in increased palatability for sweetness plausibly due to anorexia-linked nutritional stress.

Genetic Variation

Pubmed search with keywords high altitude + genetic variation + India showed 19 abstracts and 16 of these had Indian affiliation. Three studies had animals or plants as subject and one was a review article on high altitude adaptation (Stobdan *et al*., 2010). There have been studies exclusively on highlanders (Trivedi *et al*., 2002; Tripathy and Gupta, 2005) as well as on lowlanders (Kumar *et al*., 2004; Ahsan *et al*., 2006; Kumar *et al*., 2003). Further, there were studies that compared highlanders and lowlanders (Ahsan *et al*., 2005; Rajput *et al*., 2006a; Rajput *et al*., 2006b). Saxena *et al*. (2005) carried out study on lowlanders, highlanders and sojourners. The studied genes were endothelial pulmonary surfactant protein A1 and A2 genes (Saxena *et al*., 2005), nitric oxide synthase gene (NOS3) (Zhao *et al*., 2007); CYP11B2 (Rajput *et al*., 2006a); endothelin-1 (Rajput *et al*., 2006b), surfactant protein A1 and A2 genes (Saxena *et al*., 2005), NOS3 G894T (Glu298Asp) and 4B/4A polymorphisms (Ahsan *et al*., 2005), ACE I/D gene (Kumar *et al*., 2004). Pasha and Newman (2010) in their article have discussed high altitude disorders, pulmonary hypertension, pulmonary vascular disease.

In a study on the rennin angiotensin aldosterone system (RAAS) and the possible association of angiotensin converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism in the development of HAPE in Indian men it was found that RAAS participated in the development of HAPE in low altitude natives, but there was no association of ACE I/D gene polymorphism with HAPE (Kumar *et al*., 2003; Kumar *et al*., 2004). Tripathy and Gupta (2005), studied birth weight among Tibetans at different altitudes in India and reported that birth weights were higher in Tibetans than other ethnic

groups, at high as well as low altitude. Rajput *et al.*, (2006a) studied the predominance of interaction among wild-type alleles of CYP11B2 in Himalayan native associates with high altitude adaptation and concluded that over representation of wild-type-344T allele, genotype combinations and haplotypes of CYP11B2, and their correlation with lowser aldosterone levels was associated with high altitude adaptation in the highlanders and this allelic presentation in sojourners could help them cope with high altitude. In another study by Rajput *et al.* (2006a) on association of endothelin-1 gene with adaptation to hyopobaric hypoxia in high altitude natives it was found that there was over-representation of Longer-repeats, G allele, and wild-type genotype combinations in high altitude natives and presence of such alleles could help sojourners in acclimatization. Aggarwal *et al*. (2010) reported a link between high-altitude adaptation and common variations rs 47920 (C/T) and rs 480902 (T/C) in the EGLN1 gene and found that EGLN1 polymorphisms were associated with high altitude-adaptation and a genotype rare in highlanders but overrepresented in a sub group of normal low landers discernible by methods used in Ayurveda may have increased risk for HAPE. In a case-control study the association between eight single nucleotide polymorphisms and disease was examined and it was found that haplotypes of ADR32 consisting of the SNP, 46 A/G and 79 C/G had a greater potential for predicting HAPE (Stobdan *et al*., 2010).

High Altitude Research in China

Acclimatization

Pubmed search with keywords high altitude + China + acclimatization revealed 64 studies. Out of these, 32 studies have been conducted by China. Amongst these 32 studies, 21 studies have been carried out on humans. Two studies have reviewed the work on physiological responses of Tibetans at extreme altitudes (Wu and Kayser, 2006; Wu *et al*., 2005) and have reported that Tibetans are better adapted to high altitude as compared to other ethnic groups as the former have greater hypoxic and ventilatory responsiveness, larger lung volumes, better lung function, and greater lung diffusing capacity than lowlanders. Three studies were genetic studies (Liu *et al*., 2010a; Liu *et al*., 2010b; Yi *et al*., 2010). Some studies (Chen *et al*., 1997; Niu *et al*., 1995; Ge *et al*., 1994; Sun *et al*., 1990; Zhongyuan *et al*., 1979) have compared different population groups for high altitude adaptation. One study (Niu *et al*., 1995) compared the effects of long term acclimatization in lowlanders who migrated to high altitude with high altitude residents and found that at high altitude the lowlanders were able to regain much of the aerobic capacity that they had lost initially but their mechanical efficiency was found to be lower than Tibetans. In a similar study (Ge *et al*., 1994) a comparison between Tibetans and Han newcomers has been made and it was reported that exercise performance and anaerobic threshold was higher in Tibetan natives. Tibetans had a higher VO_2 max than the Hans and that implied an increased capacity for O_2 transport to the working muscle (Sun *et al*., 1990).

One study each on children (Wu and Miao, 2002) and adolescents (Chen *et al*., 1997) have been reported. Studies have been reported on heart disease (Wu and Miao, 2002), obesity (Ge *et al*., 2005), SaO_2 and heart rate (Ge *et al*., 2005; Luo *et al*., 2005) and exercise performance (Chen *et al*., 1997; Ge *et al*., 1994). Studies with larger sample size have been conducted on chronic disease and work at altitude (Wu *et al*., 2007a; Fan *et al*., 2004; Huang *et al*., 2006). In a study (Wu *et al*., 2007b) on chronic disease and work at high altitude it was reported that deterioration in a pre-existing health condition at high altitude could be prevented by evaluation of preexisting chronic illness. Further, it was observed that overweight subjects were more prone to weight loss than normal subjects. Fan *et al*., (2004) conducted a study on construction workers at high altitude and found that exposure to high altitude environment could cause abnormal blood pressure, increase in WBC, RBC, Hb alongwith headache, dizziness, loss of appetite and insomnia. In a retrospective clinical study of chronic high altitude disease it was reported that risk of acute high altitude disease increased by about five times in (CHAD) patients (Huang *et al*., 2006). Wu *et al*., (2010) quantified the occurrence of altitude illness in Qinghai-Tibet railroad passengers and found that acute mountain sickness incidence was 31% in non-acclimatized Han compared to 16% in Han altitude residents and 0% in Tibetans. In a study (Zhou *et al*., 1997) on the structural modifications of brain in acclimatization to high altitude it was found that high altitude acclimatization was associated with brain structural modifications including the loss of regional cortical grey matter accompanied by changes in the white matter which could underlie the physiological adaptation of residents at high altitude. Chen *et al*., (1997) reported that exposure to high altitude from birth to adolescence resulted in an efficient O_2 transport and a greater aerobic exercise performance that could facilitate easy adaptation to high altitude. Luo *et al*., (2005) in their study reported that oxygen enrichment through a respirator could improve the capacity of workload under altitude hypoxic environment.

Oxygenation

Twenty one studies were found in Pubmed search with China + oxygenation + high altitude as key words and fourteen of these had Chinese affiliation. Eight studies had been conducted on animals and three had been conducted on cell cultures (Luo *et al*., 2011; Huang *et al*., 2006; Gao *et al*., 2005). Study by Zhao *et al*., (2007) compared the placental mitochondrial respiratory function in neonates borne by native Tibetan women and by immigrant Han women and reported that the mitochondrial oxidative phosphorylation activity was significantly higher in the former than in the latter, implying that Tibetans could utilize much more oxygen under hypoxic conditions at high altitude and the same could be the reason for better adaptation of Tibetans to hypoxic environment at high altitude. Study by Fan *et al*., (2004) measured oxygenation indices in construction worker's health at high altitude and found that high altitude environment could cause abnormal blood pressure that lead to increase of WBC, RBC, Hb.

SaO_2

There were 12 studies in Pubmed search with China + SaO_2 + high altitude as keywords and seven of these had Chinese affiliation. These studies had been conducted on effects of oxygen increased respirator on blood oxygen saturation (SaO_2) (Luo *et al*., 2005); exaggerated respiratory chemosensitivity and association with SaO_2 level in obesity (Ge *et al*., 2005); increasing arterial oxygen saturation by healthy exerciser under hypoxia (Zhou *et al*., 1997); SaO_2 during sleep in patients with chronic mountain sickness (Sun *et al*., 1996). Wei *et al*., (2007) investigated the effects of a nutritional supplement on nutritional status and hypoxia endurance in young adults living at high altitude and the results of the survey revealed that the ratio of three macronutrients was not adequate and intakes of calcium, vitamin A, vitamin B_2 were lower than average nutrient intakes by Chinese population and the supplement could be successfully used to improve nutritional status and increase the hypoxia endurance in young adults living at high altitude. Acute mountain score to some extent could be assessed by assessing physiological responses to short-term hypoxia and breath holding at sea level (Huang *et al*., 2004).

Mou *et al*., (2004) evaluated hemodynamic effects of aminophylline and nifedipine in patients with high altitude pulmonary oedema and found that both the drugs could attenuate pulmonary hypertension in patients with HAPE but aminophylline had better effect than nifedipine. Luo *et al*., (2005) studied the effect of oxygen increased respirator on SaO_2 heart rate under plateau environment and observed that oxygen increased respirator could improve the capacity of workload under altitude hypoxic environment and thereby help in acclimatization to high altitude. Ge *et al*., (2005) investigated the association of obesity with changes in respiratory chemosensitivity and association with SaO_2 level in healthy obese individuals and found them at potential risk of desaturation during sleep at high altitude. Zhou *et al*., (1997) carried out a study on increasing arterial

oxygen saturation by healthy exerciser under hypoxia and reported that the use of exerciser could increase the SaO_2 and the same could be used to prevent or treat acute hypoxic response. Sun *et al*., (1996) studied breathing and brain blood flow during sleep in patients with chronic mountain sickness and found that sleep disordered breathing and episodes of unexplained desaturation lowered nocturnal SaO_2 and CaO_2 which decreased brain oxygen delivery in chronic mountain sickness patients during notable period of night.

HAPE

Twenty six studies were found on Pubmed search with keywords as HA + China + HAPE and twenty four of these studies had Chinese affiliation. There were 21 human studies. One was a meta analysis (Qi *et al*., 2011) while four studies have reported case studies (Zhang *et al*., 2011, Zhou *et al*., 2007b, Wu, 2004b; Li *et al*., 1990). Studies have been reported on gene polymorphism (Yu-jing *et al*., 2010), VEGF (Yang *et al*., 2000), multiple organ dysfunction (Zhou *et al*., 2007a; Yang *et al*., 2009; Zhou *et al*., 2007b), gastrointestinal dysfunction (Yang *et al*., 2009), severe acute mountain sickness (Zhou *et al*., 2007a; Yang *et al*., 2009; Zhou *et al*., 2007b; Wei *et al*., 2009), high altitude disease (Zhou *et al*., 2007a; Huang *et al*., 2003). There have been studies on chronic disease and work (Wu *et al*., 2007 b); leucocytosis (Zhou *et al*., 2007a); ataxia (Wu *et al*., 2006), plasma fibrinolysis system (Yu *et al*., 2003), antioxidative capacity (Fu *et al*., 2002), pulmonary diffusing capacity (Chen *et al*., 2000). Incidence of HACE and HAPE was reported to be 0.28% and 0.49% in altitude workers involved in construction of Qinghai-Tibet railroad, respectively (Wu *et al*., 2007a).

Zhou *et al*., (2011) have discussed various methods and criteria that can be used for early diagnosis and prediction of HAPE. Ran *et al*., (2011) studied the changes of VEGF, TNF-alpha, IL-6 and NO in serum of HAPE patients and concluded that all these studied factors participated in various aspects of pathophysiological process and could have influence on HAPE. In another study (Ren *et al* 2010) incidence of high altitude illness among 3628 unacclimatized persons who had no previous high altitude experience and who travelled to Tibet by air to an altitude of 3600m was surveyed and 1.9% incidence of HAPE was reported. Zhou *et al*., (2007a) conducted a study on clinical significance of leucocytosis and increase in interleukin content in AMS and did not find any difference in differential counts of WBC in HAPE and secondary HAPE. Further, no difference was observed between simple HAPE and HACE. In acute severe mountain sickness, gastrointestinal dysfunction could play a major role in the pathogenesis of multiple organ dysfunction (Yang *et al*., 2009). Yu *et al*., (2003) studied changes of plasma fibrinolysis system and effect of captopril in HAPE and reported that patients with HAPE could have a disturbance of the fibrinolysis system which could be reversed by captopril.

In a study (Fu *et al*., 2002) on the changes of antioxidative capacity and endothelial function before and after treatment among patients with HAPE it was reported that changes of SOD, MDA, GSH, NOs and ET-1 could have a role in HAPE. Chen *et al*., (2000) studied the changes of pulmonary diffusing capacity in subjects with acute mountain sickness and found that decreased pulmonary diffusing capacity indicated the presence of pulmonary gas exchange abnormality which could plausibly be due to subclinical interstitial oedema of lungs. In a retrospective study (Li *et al*., 2006) on acute severe high altitude disease in indigenous Tibetans it was reported that indigenous Tibetans who travelled between the plateau and the plain or to even higher altitude could suffer hypoxic injury and also severe high altitude disease which could be complicated by multiple organ dysfunction.

Pulmonary Function

The pubmed search with keywords high altitude + China + pulmonary function showed 75 abstracts and 61 of these were reported by China. Among these 61 studies, 12 studies were on animals, one was a case study (Duo *et al*., 2010), one was article (Wu *et al*., 2004a), two were review articles (Anonymous, 2006; Ge and Helun, 2001), one was a meta-analysis (Jin *et al*., 2010) and one study was conducted on computer simulated model (Qiu and Bai, 2001). The studies relate to acute mountain sickness (Chen *et al*., 2000), chronic mountain sickness (Pei *et al*., 1989), HAPE (Yu *et al*., 2003; Fu *et al*., 2002; Qi *et al*., 2011), gene polymorphism (Yu *et al*., 2010; Qi *et al*., 2008; Qi *et al*., 2009; Ge *et al*., 2011), pulmonary hypertension (Ge and Helun, 2001; Ge *et al*., 2009), exercise (Ge *et al*., 1994; Ge, 1987) . Single studies were found on leucocytosis (Zhou *et al*., 2007a); cytoglobin (Huang *et al*., 2006); heart disease (Sui *et al*., 2001); nitric oxide (Hoit *et al*., 2005), pulmonary diffusing capacity (Chen *et al*., 2000). Studies with parameters such as pulmonary arterial pressure and vasodilation (Sun, 1993), lung capacity (Droma *et al*., 1991), oxygen uptake and vital capacity (Ge, 1987; Sun *et al*., 1990) were also found. Zhu *et al*., (2010) explored the characteristics of the pathogenesis and progression of the acute pancreatitis in high altitude and relationship between acute pancreatitis and plateau erythrocythemia and concluded that deterioration of hepatic, kidney and lung function in acute pancreatitis patients living in plateau was related to high altitude and erythrocythemia. Pang *et al*., (2004) conducted a comparative study of the indexes of pulmonary arterial pressure of healthy children at different altitudes by Doppler echocardiography and found that high altitude hypoxic environment could play a major role in increase of pulse arterial pressure.

In a study (Hoit *et al*., 2005) on nitric oxide and cardiopulmonary hemodynamics in Tibetan highlanders it was reported that nitric oxide (NO) in the lung could help Tibetans at 4200m to compensate for ambient hypoxia with higher pulmonary blood flow and oxygen delivery without the consequences of higher pulmonary arterial pressure. Ge and Helun, (2001) presented review on pulmonary hypertension related high–altitude heart disease in China. Yang *et al*, (2000) determined the benefit of inhaled budesonide for severe asthma at high altitude and reported that high dose of inhaled budenoside combined with terbutaline proved to be an effective therapy for patients with severe asthma at high altitude. Ge *et al*, (2001) studied atrial natriuretic peptide and red cell 2,3-diphosphoglycerate in patients with chronic mountain sickness and reported that overproduction of atrial natriuretic peptide and red cell 2,3-diphosphoglycerate at high altitude could play an important role in the pathophysiology of chronic mountain sickness. In another study by Ge *et al*, (2009) on the changes of cardiac structure and function in pediatric patients with high altitude pulmonary hypertension in Tibet, the results indicated that hypoxia induced infantile high altitude pulmonary hypertension (HAPH) lead to right ventricular hypertrophy in these patients and such structural cardiac changes could result in right ventricular dysfunction and right heart failure. Wu *et al*., (2009) studied acute mountain sickness in Qinghai-Tibet railroad construction workers after repeated 7-month exposures despite 5-month low altitude periods and reported that repetitive 7-month exposures protected lowlanders against acute mountain sickness, even when interspaced with 5 month periods spent at low altitude, however it could not match the level of adaptation of altitude natives.

Zhou *et al*., (2007a) studied the role of white blood cell and interleukins in acute mountain sickness complicated with multiple organ dysfunction and reported that people suffering from acute mountain sickness also had multiple organ dysfunction syndrome which was a major cause of acute mountain sickness and was a critical factor of high altitude diseases and morbidity. Ge *et al*. (1994) reported that the Tibetan natives had higher exercise performance and anaerobic threshold but lower VO_2 max and blood lactate concentration than do acclimatized Han newcomers which indicated the effects of genetic or peripheral adaptation factors in the Tibetan natives. In the study conducted by Droma *et al*. (1991) it was reported that Tibetans like North and South American high altitude residents had larger lung volumes, which could be important for raising lung diffusing capacity and preserving arterial oxygen saturation during

exercise. Sun *et al*. (1990) studied greater maximal O_2 uptakes and vital capacities in Tibetans than Han residents of Lhasa and concluded that the Tibetans achieved a higher maximal O_2 uptake than the Hans implying an increased capacity for O_2transport to the working muscle.

Maladies

No study was found in Pubmed search on high altitude + maladies + China.

Acute Mountain Sickness (AMS)

Pubmed search with keywords high altitude + China + acute mountain sickness showed up 45 abstracts and 31 of these had Chinese affiliation. Amongst 31 studies, four studies had been carried out in animals and one was on plants. Three studies (Wu *et al*., 2007a ; Wu *et al*., 2007b; Wu *et al*., 2009) had been conducted exclusively on railroad construction workers. Pubmed search revealed that acute mountain sickness had been studied in relation with gastro intestinal dysfunction (Yang *et al*., 2009), renal replacement therapy (Wei *et al*., 2009), glomerular filtration rate (Pichler *et al*., 2008) ; leucocytosis and interleukin content (Zhou *et al*., 2007a), high altitude reaction syndrome (Zhang and Luo., 2007), ataxia (Wu and Kayser, 2006), urine acid-base compensation (Ge *et al*., 2006), gene polymorphism (Zhou *et al*., 2005), pulmonary diffusing capacity (Chen *et al*., 2000). There were two papers in which case studies had been presented (Zhou *et al*., 2007b; Li *et al*., 1990); one was a article (Aggarwal *et al*., 2010) and one was a clinical study of high altitude disease (Huang *et al*., 2003). Yang *et al*., (2009) reported that gastrointestinal dysfunction was important in the pathogenesis of multiple organ dysfunction syndrome in acute mountain sickness. Zhou *et al*., (2007a) found that people suffering from acute mountain sickness also had systemic inflammatory response syndrome (SIRS) and the latter played an important part in multiple organ dysfunction syndrome which was a major cause of acute mountain sickness and was a critical factor of high altitude MODS. Wu *et al*., (2007b) studied 14,050 workers involved in the construction of the Qinghai-Tibet rail road and reported an overall incidence of acute mountain sickness upon first time exposure as 51% with obesity being a risk factor for the same. Li *et al*., (2011) conducted a retrospective study on population level determinants of acute mountain sickness among young men and built a multivariate model which could be applied to reduce the effects of acute mountain sickness on young Chinese men. Ge *et al*., (2010) evaluated the body weight loss during acute exposure to high altitude hypoxia in sea level residents and reported that a person with higher body weight during stay at high altitude lost more weight and the heavier individual were more likely to develop acute mountain sickness than leaner individuals during exposure to high altitude hypoxia.

Zhang *et al*., (2010) studied the protective effects of a new compound codonopsis tablets against acute mountain sickness and reported that these tablets could decrease the incidence of acute mountain sickness, could help improve the symptoms of acute mountain sickness and improve breathing function and finger movement function. Effects of inhaled nitric oxide on endothelium-derived angiokinetic factors in patients with acute high altitude disease were studied and it was observed that inhaled NO was effective for treatment of high altitude disease in plateau (Zheng *et al*., 2007). Li *et al*., (2006) described the incidence and clinical characteristics of acute severe high altitude diseases in native Tibetans. Huang *et al*., (2004) explored whether hypoxic response and breath holding at sea level could predict acute mountain sickness and concluded that only limited information could be gained from the same. Li *et al*., (1990) classified 13,403 cases into HAPE, HACE, high altitude children cardiopathy (HACC), high altitude acute response (HAAR), high altitude chronic response (HACR), high altitude erythroblastosis (HAEb), high altitude adult cardiopathy (HAAC), high altitude hypertension (HA Hyper), and high altitude hypotension (HA Hypo).

Wu *et al*. (2007a) studied 13,052 workers involved in the construction of the Qinghai-Tibet rail road and reported an overall incidence of gastrointestinal bleeding as 0.49%, the incidence increased with increasing altitude. Zhou *et al*. (2007b) analysed 3184 cases and found that acute mountain sickness complicated by multiple organ damage (MOD) had an incidence of 2.6%. Ge *et al*. (2006) found that short term low to moderate altitude exposure resulted in a marked acid-base diuresis and renal acid-base compensation was completed by 24h at low to moderate altitude but still incomplete at higher altitude. Kao *et al*., (2002) studied acute mountain sickness in Jade mountain climbers of Taiwan and found that 28% of the Jade mountain trekkers suffered acute mountain sickness. In a study (Chen *et al*., 2000) on the changes of pulmonary diffusing capacity in subjects with acute mountain sickness presence of pulmonary gas exchange abnormality was found which could be due to subclinical interstitial oedema of the lung.

Chronic Mountain Sickness (CMS)

Pubmed search with high altitude + China + chronic mountain sickness showed up 29 abstracts, nineteen of which had Chinese affiliation. Among these 19, two were animal studies, one was a plant study, one was a review article (Ge and Helun, 2001), four were articles(Wu *et al*., 2005; Wu *et al*., 2004a; Pei *et al*., 1989; Wu *et al*., 2001) and two case studies (Wu, 2004b; Li *et al*., 1990). Two studies pertained to genetics (Jiang *et al*., 2012; Wang *et al*., 2011) (have been discussed under heading genetic variation). Studies of chronic mountain sickness in humans were related to chronic disease and work (Wu *et al*., 2007b); high altitude diseases (Huang *et al*., 2003), atrial natriuretic peptide (Ge and Helun., 2001), breathing and brain blood flow (Sun *et al*., 1996). Kong *et al*., (2011) surveyed the sleep quality of individuals with polycythemia at high altitude and determined its association with cognitive abilities. Ge *et al*., (2011) investigated the association between chronic mountain sickness and levels of B-type natriuretic peptide, vascular endothelial growth factor, endothelin-1 and endothelial nitric oxide synthase and concluded that severe chronic hypoxemia and consequent pulmonary hypertension in patients with chronic mountain sickness could stimulate the release of natriuretic peptides and angiogenic cytokines.

Diamox

There were four studies in Pubmed search with high altitude + diamox + China as keywords and three of these had Chinese affiliation. One of the studies was on herbs. One of the studies (Ha *et al*., 2002) was on effect of rhodiola and acetazolamide on the sleep architecture and blood oxygen saturation in men living at high altitude while the other one (Cui *et al*., 2001) was on the effects of Rholida on free radical metabolism and serum creatinine kinase after exercise at plateau. Ha *et al*., (2002) found that Rhodiola and acetazolamide could be used for modulating the sleep architecture and improving the sleep quality in young men living at high altitude. Cui *et al*., (2001) concluded that Rholida, Acetazolamide Xi's capsule could be employed for regulating the disorder of free radical metabolism at plateau.

Herbal Remedies

No study was found in Pubmed search on high altitude + herbal remedies + China.

Ginkgo biloba

No study was found in Pubmed search on high altitude + G*inkgo biloba* + China.

Panax ginseng

No study was found in Pubmed search on high altitude + *Panax ginseng* + China.

Hippophae rhamnoides

Although several nutraceuticals based on seabuckthorn sold in different countries are product of China; there were only two studies on high altitude + *Hippophae rhamnoides* + China as keywords in Pubmed search. However, none of these was a study on humans.

Nutrition

There were 23 studies in Pubmed search as high altitude + nutrition + China and 11 of these had Chinese affiliation. Amongst 11 Chinese studies, 2 were on plants. These studies were on anaemia status in children (Chang *et al*., 2007), childhood growth retardation (Dang *et al*., 2008), dietary iron absorption (Zhou *et al*., 2006), and feeding practice among young Tibetan children (Dang *et al*., 2005). Wei *et al*., (2007) investigated the effects of a nutritional supplement on nutritional status and hypoxia endurance by a nutritional supplement in young adults living at high altitude and reported that nutritional supplements can improve the nutritional status and increase the hypoxia endurance in young adults living at high altitude. Cao *et al*., (2002) conducted an epidemiological survey of fluorosis in three districts of Tibet to explore whether endemic flurosis in Tibet was related local factors and reported that the endemic fluorosis in Tibet was essentially due to heavy consumption of foodstuffs prepared with brick tea; however the high altitude , harsh living conditions and poor nutritional status aggravated fluorosis.

Chen *et al*., (1997) studied the exercise performance of Tibetan and Han adolescents at altitudes of 3417 and 4300 m and found that exposure to high altitude from birth to adolescence resulted in an efficient O_2 transport and a greater aerobic exercise performance that may reflect a successful adaptation to life at high altitude. In a study by Dang *et al*., (2006) epidemiological features of spontaneous abortion among Tibetan women living at high altitude areas were studied and it was reported that high altitude could lead to the increase of spontaneous abortions incidence. In another study by Dang *et al*., (2008) on high altitude and early childhood growth retardation in Tibetan children it was reported that altitude could cause delay in height of younger Tibetan children and the same should be considered for assessing the nutritional status of Tibetan children. In a study on the feeding practice among younger Tibetan children living at high altitude, it was reported that the children were breastfed for long time but complimentary feeding practice of Tibetan children was limited, especially of rural children (Dang *et al*., 2005). In another study by Dang *et al*., (2004) on the nutritional status of younger Tibetan children living at high altitude it was reported that the nutritional status of the entire population was poor and prevalence of malnutrition of children was 39% for stunting, 23.7% for underweight and 5.6% for wasting respectively. Zhou *et al*., (2006) evaluated the dietary iron absorption in Tibetans and reported that dietary iron absorption in adult Tibetan men was relatively high.

Genetic Variation

There were 63 studies that came up when Pubmed search was done with high altitude + China + genetic variation as keywords and 45 of these had Chinese affiliation. Gene polymorphism with respect to high altitude has been studied in a variety of species viz., birds, chicken, horse, yak, shrimps, bacteria, plants, grains etc. Studies in gene polymorphism in humans have been in the areas of HAPE (Qi *et al*., 2008; Qi *et al*., 2009), hypoxic acclimatization (Liu *et al*., 2007 a; Liu *et al*., 2007*b*; Wang *et al*., 2007b). Zhou *et al*., (2005) have reported association of hsp70-2 and hsp-hom gene polymorphisms with risk of acute high-altitude illness in a Chinese population. Wang *et al*., (2011) investigated the origin of Tibetans and genetic basis of adaptation in a rigorous environment by genotyping 30 Tibetan individuals with more than 1 million SNP markers and found that most of the studied genes highly correlated with population specific and beneficial phenotypes such as high infant survival rate and absence of chronic mountain sickness. Ding *et al*., (2011) studied polymorphism of hypoxia related genes in subjects susceptible to acute mountain sickness and reported that VEGFA could have an important role in acute mountain process. Polymorphism of endothelial nitric oxide synthase gene association with susceptibility to HAPE has been reported. Peng *et al*., (2011) performed an analysis of genome wide sequence variation in Tibetans and concluded that observed indicators of natural selection on EPAS1 and EGLN1 suggested that during long term occupation of high altitude areas, functional sequence variations for acquiring biological adaptation to high altitude hypoxia have been enriched in Tibetan populations. Ke *et al*., (2010) investigated the effect of environment induced by altitude on hypoxia inducible factor 1 alpha (HIF1A) gene and reported that the gene could be under hypoxic selection induced by high altitude in the three study groups.

Liu *et al*., (2010b) analysed the Pro 12 ala (C.G) polymorphism in excn 2 and the 161 C>T polymorphism in exon 6 of peroxisome proliferator-activated receptor gamma gene (PPARr) in a Tibetan population and a Han population and reported that PPAR ɣ could be a candidate gene for high altitude adaptation, the Pro 12 Ala (C.G) CC genotype and/or the 161C>TCC genotype are possibly advantageous factors in female Tibetan population. Yi *et al*., (2010) sequenced 50 exomes of ethnic Tibetans and the survey revealed a functionally important locus in genetic adaptation to high altitude. Wang *et al*., (2010) investigated the distinct characters of CAG repeat polymorphism with VO_2 max response to hypoxic training in North China Han men and found that AR CAG repeat polymorphism was associated with exercise performance after aimulated normobaric hypoxi HiHiLo (living high, exercise high and training low) in North China Han men and that the shorter genotypes had a better individual response to hypoxic training.

Luo *et al*., (2010) found that PCR-LDR mtDNA genotyping could be successfully used for mtDNA haplotyping in various applications. Liu *et al*., (2010a) analysed the Pro 12 Ala (C>G) polymorphism in exon B and 161C>T polymorphism in exon 6 of peroxisome proliferator activated receptor gamma gene (PPARG) in Chinese Tajik population living at high altitude and Chinese than population living at altitude and concluded that PPARG was the candidate gene for high altitude adaptation in Chinese Tajik population. Qi *et al*., (2009) reported strong interaction of rs 1061581, rs 1043618 and rs 1008438 polymorphisms with Hsp 70 famiy with susceptibility to HAPE in Chinese. In another study by Qi *et al*., (2008) synergistic effect of the genetic polymorphisms of the rennin-angiotensin-aldosterone system on high altitude pulmonary edema was reported. Liu *et al*., (2007b) studied the association of polymorphisms of 1772 (C- - >T) and 1790 (G- - >A) in HIF1-α gene with hypoxia adaptation in high altitude Sherpas and concluded that polymorphisms of HIF1-α gene 1790 (G - - >A) were associated with hypoxia adaptation in high altitude in Sherpas.

Wang *et al*., (2007a) studied the relationship between adaptation to high altitude hypoxia environment and glucose transport 1 gene polymorphism and found that the frequencies of +22999 polymorphic genotypes and alleles showed statistically significant difference between high altitude group and control group. Genetic single nucleotide polymorphism in GLUT 1 G+ 22999T could be associated with adaptation to high altitude hypoxia. In another study by Wang *et al*., (2007b) on the single nucleotide polymorphism of surfactant protein A gene between Tibet Sherpas and Guangdong Chinese Hans, statistical differences of genotypes and alleles at SP-A2 3265 locus in Hans and Sherpas were reported. SNP in SP-A2 at 3265 could be related to the adaptation of Sherpas to high altitude hypoxia.

High Altitude Research in Pakistan

Acclimatization

Pubmed search on high altitude + acclimatization + Pakistan revealed four abstracts and only one of them had Pakistani affiliation and this was a case control study on the risk factors in high altitude pulmonary

oedema (Rashid *et al*., 2005). In this study it was found that rapid rate of ascent, extreme physical exertion, low height of native dwelling and preceeding respiratory tract infection could make an individual prone to HAPE.

Oxygenation

No study was found in Pubmed search with high altitude + oxygenation + Pakistan as keywords.

SaO_2

There was a single study (Hussain *et al*., 2001) on high altitude + acclimatization + Pakistan as keywords in Pubmed search. The study quantified the relationship between AMS and hypoxemia alongwith evaluating the benefits of acetazolamide dexamethasone chemoprophylaxis during acute ascent. It was reported that the extent of acute mountain sickness depended on hypoxemia and combination of acetazolamide-dexamethasone could prevent acute mountain sickness.

HAPE

There were two Pakistani studies on HAPE (Hussain *et al*., 2001; Hasan *et al*., 1988).

Pulmonary function

There were three studies in Pubmed search with high altitude + pulmonary function + Pakistan and one of these (Hasan *et al*., 1988) had Pakistani affiliation. This study was on HAPE in response to exercise and cold on systemic and pulmonary vascular beds.

Maladies

No study was found in Pubmed search with high altitude + maladies + Pakistan as keywords.

Acute Mountain Sickness

The pubmed search with high altitude + acute mountain sickness + Pakistan revealed three studies and two (Hayat *et al*., 2006; Hussain *et al*, 2001) of them had Pakistani affiliation. Hayat *et al*., (2006) studied the relationship between hyperventilatory capacity and the risk for developing acute mountain sickness and reported that post hyperventilation increase in oxygen saturation at lower altitude could help predict the susceptibility of subjects to develop high altitude sickness.

Chronic Mountain Sickness

No study was found in Pubmed search with high altitude + chronic mountain sickness + Pakistan as keywords.

Diamox

A single study (Hussain *et al.*, 2001) showed up in pubmed search with high altitude + diamox + Pakistan as keywords.

Herbal remedies

No study was found in Pubmed search with high altitude + herbal remedies + Pakistan as keywords.

Ginkgo biloba

No study was found in Pubmed search with high altitude + Ginkgo *biloba* + Pakistan as keywords.

Panax ginseng

No study was found in Pubmed search with high altitude + *Panax ginseng* + Pakistan as keywords.

Hippophae rhaminoides

No study was found in Pubmed search with high altitude + *Hippophae rhaminoides* + Pakistan as keywords.

Nutrition

There was a single study in nutrition (Shah *et al*., 2004) and it assessed obesity and overweight in a high mountain Pakistani population. In the study it was concluded that prevalence of risk factors for non-communicable diseases could increase further in Pakistan depending on the epidemiological, nutritional and demographic changes.

Genetic Variation

There was no study on genetic variation.

High Altitude Research in NEPAL

Acclimatization

Pubmed search with high altitude + Nepal + acclimatization revealed 46 studies. However, only two of these studies had Nepalese affiliation. Other studies had been conducted by other countries viz., UK, USA, France, Italy, Poland, Japan. Basnyat *et al*., (2008) conducted a randomized, double blind placebo controlled trial on the efficacy of acetazolamide in preventing HAPE in trekkers travelling between 4250m (Pheriche)/ 4350 (Dingboche) and 500 m (Lobuje) in Nepal and did not find a single case of HAPE in either group and thus could not determine the efficacy of acetazolamide in preventing HAPE. Bishop *et al.*, (2000) presented a case study of 11 patients documenting the use of ketamine anaesthesia in a hospital at 3900 m by primary care physicians without specialist training in anaesthesia and reported that ketamine with midazolam offered a safe means of anaesthesia at very high altitude without the need for specialist equipment or training by careful clinicians experienced in basic airway management.

Oxygenation

There were ten studies in Pubmed Search with high altitude + Nepal + oxygenation as keywords and two of these had Nepalese affiliation. Basnyat *et al*., (2006) conducted a prospective double blind, randomized placebo-controlled trial reported no significant difference between the efficacy of low dose acetazolamide 125 mg bd (250 mg) as used in Himalayas and 375 mg bd (750mg) of acetazolamide in preventing acute mountain sickness. The other publication (Murdoch, 1992) was on portable hyperbaric chamber for treatment of high altitude illness.

SaO_2

Six studies were found in Pubmed search on high altitude + Nepal + SaO_2 as keywords. However, all of these had been conducted by countries other than Nepal.

HAPE

Seventeen studies showed up in Pubmed search with high altitude + HAPE + Nepal as keywords. Among these, seven studies had been carried out by Nepalese organizations and the other ten were conducted by countries other than Nepal. Amongst the Nepalese studies, one was a case study (Shlim and Papenfus, 1995) and three were reviews (Basnyat, 2005; Basnyat and Murdoch, 2003; Basnyat *et al*., 2000). Basnyat *et al*., (1999) conducted a retrospective study to assess the proportion of acute mountain sickness, HAPE, HACE and found a linear increase in trekkers entering the Himalayas in Nepal but no increase in incidence of HAPE and HACE and this could be attributed to the awareness drives by organizations like Himalayan

Rescuer Association. In an epidemiological study (Basnyat *et al*., 2000) of AMS and HACE in Nepalese pilgrims it was found that high altitude pilgrims especially female pilgrims were very susceptible to HAPE and HACE and preventive measures could save them from the same.

Pulmonary Function

Twenty five studies showed up in Pubmed search with high altitude + pulmonary function + Nepal as keywords however only three of these studies had Nepalese affiliation. One was an article on high altitude sickness (Basnyat and Murdoch, 2003). Basnyat *et al*., (2004) discussed neurological conditions at altitude that are not included in usual definition of altitude sickness. Basnyat *et al*., (1999) carried out a retrospective study on trekkers (tourists, mostly Caucasians and Nepalis (mostly porters and villagers) at the Himalayan Rescue Association medical aid posts for different medical problems including AMS and concluded that there was a linear increase in trekkers entering the Himalayas in Nepal and that HAPE and HACE had not incresead over the years.

Maladies

Only one study was found in Pubmed search with high altitude + Nepal + maladies as keywords and that was not a Nepalese study.

Acute Mountain Sickness

Pubmed search with high altitude + acute mountain sickness + Nepal as keywords revealed forty studies and around half (19) of these studies had Nepalese affiliation. There were six case studies (Litch and Bishop, 2000; Basnyat, 1998; Basnyat *et al*., 2000; Subedi *et al*., 2010; Basnyat, 2002; Basnyat, 1997), two articles (Basnyat and Murdoch 2003; Basnyat *et al*, 2004) and one review (Basnyat *et al*, 2000). Arora *et al*., (2011) evaluated retinal changes associated with altitude illness in young soldiers and reported 58% retinal haemorrhages in soldiers with altitude illness. They also reported significant association of severe grades of high altitude retinopathy with HAPE and HACE. Basnyat *et al.*, (2011) carried out a prospective, double blind, randomized placebo controlled trial to evaluate the efficacy of spironolactone in prevention of acute mountain sickness and concluded that spironolactone (50mg BID) was ineffective as compared to acetazolamide (250mg BID) in prevention of acute mountain sickness in partially acclimatized trekkers. There were other studies also on efficacy of acetazolamide (Basnyat *et al*., 2006; Basnyat *et al*., 2008).

Pradhan *et al*., (2009) studied the incidence and risk factors for acute mountain sickness in native Nepalese children during pilgrimage trip in Nepal (elevation 4380m) and reported no significant correlation between incidence of acute mountain sickness and gender, previous exposure to high altitude or concurrent illness. Basnyat and Litch (1987) assessed the incidence of medical illness among members of trekking groups in Nepal and found that 45% of trekkers experienced medical problems. High altitude pharyngitis/bronchitis (12%) was the most common followed by acute mountain sickness (8%), gastroenteritis (6%), anxiety (3%), cellulitis (3%), scabies (3%), snow blindness (3%), acute alcohol intoxication (2%), conjunctivitis (2%), fever (2%), laceration (2%) and haemorrhoids. Murdoch (1995) conducted a study on symptoms of infection and altitude illness among hikers in Mount Everest region of Nepal and reported that symptoms of infection were common at high altitude and were associated with a higher incidence of acute mountain sickness.

Chronic Mountain Sickness

Six studies were found in Pubmed search with high altitude + Nepal + chronic mountain sickness and all these studies had been conducted by countries other than Nepal.

Diamox

In pubmed search with high altitude + Nepal + diamox as keywords, there were four studies from Nepal. One of these four papers was an article on high altitude illness (Basnyat and Murdoch, 2003). Basnyat *et al.*, (2011) conducted a prospective, double blind, randomized, placebo-controlled trial to study the effectiveness of spironolactone for the prevention of acute mountain sickness and reported that spironolactone (50mg BID) was ineffective in comparison to acetazolamide (250mg BID) in prevention of acute mountain sickness in partially acclimatized western trekkers ascending to 5000m in the Nepal Himalayas. In another (Basnyat *et al*., 2008) randomized, double blind placebo-controlled trial on the efficacy of acetazolamide on partially acclimatized humans it was reported that there was a significant ($p<0.01\%$) difference between the incidence of acute mountain sickness in placebo (21.9%) and acetazolamide group (10.2%)

Herbal remedies

Only one study was found in Pubmed search with high altitude + Nepal + herbal remedies as keywords.

Ginkgo biloba

Two studies were found in Pubmed search with high altitude + Nepal + *Ginkgo biloba* as keywords. One of the studies (Basnyat and Murdoch, 2003) had Nepalese affiliation.

Panax ginseng

No study was found in Pubmed search with high altitude + Nepal + *Panax ginseng* as keywords.

Hippophae rhamnoides

No study was found in Pubmed search with high altitude + Nepal + *Hippophae rhamnoides.*

Nutrition

Eight studies were found in pubmed search on high altitude + Nepal + nutrition as keywords and only one of these had Nepalese affiliation.This was a study on some fetal and pregnancy parameters in Nepal. Ulstein *et al.* (1988) studied 4600 single live biths in a Nepal hospital and reported hemoconcentration in pregnancy was not affected by high altitude.

Genetic Variation

There were seven studies in Pubmed search with high altitude + genetic variation + Nepal as keywords but all of these were from countries other than Nepal.

Conclusion

It was observed that maximum numbers of studies on high altitude research have been carried out by China followed by Nepal, India and Pakistan. Amongst the different research areas of high altitude research highest numbers of studies have been carried out on acclimatization followed by pulmonary function and acute mountain sickness.

On the basis of published literature it is evident that both India and China are working in almost similar lines for high altitude research. The construction of high altitude railway by China has lead to significant increase in research activities, especially in the area of acclimatization and understanding genetic basis of adaptation in Tibetan population. The studies from Nepal are on human subjects

only probably because location of base camps for Himalayan expeditions and involvement of local researchers and clinicians in medical care.

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