

REVIEW

Zinopin[®] – the Rationale for its Use as a Food Supplement in Traveller's Thrombosis and Motion Sickness

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Venous thrombo-embolism (VTE) has been associated with periods of prolonged immobility during air, sea and road travel. Motion sickness (MS) has also been reported during both long and short journeys. Current prophylactic therapies for both these indications are generally associated with side effects.

Physiological profiles of Pycnogenol[®] and Standardized Ginger Root Extract (SGRE) representing active constituents of Zinopin[®] have been described and reviewed in relation to their activities involved in the pathophysiology of VTE (Traveller's Sickness) and MS and their safe use as food supplement, in traveller's thrombosis and motion sickness. The patho-physiology of VTE and MS is discussed in light of epidemiological data and risk factors associated with these conditions.

Rationale of development of Zinopin[®] and its mechanism of action are discussed based on physiological synergy of Pycnogenol[®] and SGRE. Conclusions are made in light of preliminary clinical findings obtained in an open controlled clinical trial. Further clinical study on Zinopin[®] on these lines is suggested. Copyright © 2004 John Wiley & Sons, Ltd.

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INTRODUCTION

Venous thrombo-embolism (VTE) has been associated with prolonged immobility during travel involving aeroplanes, buses, trains and cars. The recognition that VTE was associated with prolonged flight or travel was first reported by Homans in 1954. This was then described as 'Economy Class Syndrome' in 1988 (Cruikshank *et al.*, 1988). Seventeen to twenty-five percent of patients with VTE admitted to two Honolulu hospitals had had a recent history of air travel (Eklöf *et al.*, 1996; Mercer and Brown, 1998). Others have looked at this association in relation to travel by car, bus, truck or train (Tardy *et al.*, 1993; Ferrari *et al.*, 1999). The mean duration of trip was 14.2 h and the first symptom occurred in less than a week after the journey in 75% of the cases (Tardy *et al.*, 1993). Prolonged travel in the seated position causes venous stasis, and it is venous stasis that is associated with VTE. This is consistent with Virchow's classic postulate that venous stasis contributes to VTE. The present evidence regarding air travel is circumstantial, and could be misleading given that VTE is a very common disorder, with an annual incidence of 1 per 1000 population suffering with a deep vein thrombosis (Ferrari *et al.*, 1999).

When travel times are greater than 12 h there was a greater incidence of thrombo-embolism – 76.5% cases

correspond to more than 12 h flight (Clerehugh and Caillard, 1999). The incidence rate as recorded at the airports of Paris was 0.5 per million of passengers, with an important prevalence in females (Clerehugh and Caillard, 1999). Out of 11 in-flight deaths from pulmonary embolism there were ten with an incidence of thrombo-embolism (Mercer and Brown, 1998).

Simulated or real long flights have been reported to bring about blood changes including high fibrinogen levels, haemo-concentration and low fibrinolytic activity (Sarvesvaran, 1986; Kraaijenhagen *et al.*, 2000). It has been shown in healthy subjects that 1 h sitting position, there appears a net diminution of flow to legs, 30% increase in haematocrit and 40% increase in plasma proteins (Kraaijenhagen *et al.*, 2000). Other factors including dehydration (Carruthers *et al.*, 1976) stress, climatic change, and activation of blood clotting (Simon and Krol, 1996) may contribute additional risk factors to venous stasis in the development of VTE. Immobility, hypoxia and a decrease in atmospheric pressure was shown to alter fibrinolytic activity and cause release of venous wall factors leading to deep vein thrombosis (Gertler *et al.*, 1993; Landgraf *et al.*, 1994; Bendz *et al.*, 2000). In an independent study in healthy volunteers, hypoxia and decrease in pressure has been demonstrated to raise clotting factors (Bendz *et al.*, 2000). These blood changes may contribute to the development of a deep vein thrombosis.

The majority of clots are asymptomatic, with only those extending into the femoral and pelvic veins giving rise to classic symptoms of pain and swelling. Asymptomatic DVT occurs in 3–10% of air travellers.

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Scurr and his colleagues (2001) demonstrated 'ultrasound detected thrombus' in up to 10% of people travelling long distance. Patients with known risk factors had already been excluded. Only a few go on to develop swelling of the legs, or signs and symptoms of pulmonary embolism including death. The development of a deep vein thrombosis is generally associated with risk factors. The more risk factors, the greater is the chance of developing a deep vein thrombosis. The condition is not confined to people with cardiovascular disease, or even previous thrombo-embolic episodes, but can affect young healthy people. Many people who have suffered a deep vein thrombosis had no obvious risk factors other than travel. Any deep vein thrombosis is potentially life threatening. The development of a DVT will predispose to a future DVT, and larger DVTs are associated with an increased risk of pulmonary embolism. Small clots cause difficulty in breathing. Large clots may prove fatal.

Although asymptomatic DVTs may resolve, valvular damage may occur, predisposing people to further episodes of deep vein thrombosis and the development of a chronic post-thrombotic limb.

The LONFLIT study (Belcaro *et al.*, 2001) demonstrated 3% of travellers developing clots on long flights, most are silent or asymptomatic, but still potentially posing a threat of recurrent deep vein thrombosis. With US Airlines carrying 600 million passengers, 50% making journeys over 4 h with up to 10% developing clots, this would suggest that up to 1.8 million travellers develop deep vein thrombosis. In studies where patients presenting with deep vein thrombosis and pulmonary embolism were studied, up to 66% had a deep vein thrombosis attributed to air travel (Simon and Krol, 1996). A similar figure of around 50% has been obtained by Mercer and Brown (1998). In Honolulu, Eklof *et al.* (1996) found 254 patients with deep vein thrombosis, of whom 20% had developed clots during air travel. The incidence of deep vein thrombosis was found to be 6% in a study made by Ferrari *et al.* (1999) in Nice. There is a considerable range, and the true incidence of deep vein thrombosis following air travel remains unknown. Further studies by the WHO addressing the epidemiology of venous thrombosis will assist.

RISK FACTORS

In the absence of properly controlled clinical studies, most of our information relating to risk factors comes from hospital-based studies, looking at patients admitted to hospital to undergo surgical treatment (Lowe *et al.*, 1992; Scurr *et al.*, 1998). Immobility, a past history of deep vein thrombosis, recent surgery or injury, and an underlying thrombophilia remain the most important factors. Cancer, chronic heart disease, diabetes, and obesity are also included as risk factors. Pregnancy, oestrogen-containing oral contraceptives, and women on hormone replacement therapy, are also thought to have an increased risk. No single risk factor is likely to cause a deep vein thrombosis, but a combination of several risk factors increases the risk. Identifying risk factors will identify passengers who are at increased risk during periods of travel. Unfortunately other pas-

sengers with no risk factors can also develop deep vein thrombosis. With 7–10% of the population suffering from a thrombophilia, often unknown and undiagnosed, it is not difficult to see why up to 10% of people travelling will develop an asymptomatic deep vein thrombosis.

Frequency of travel and duration of travel are also important risk factors.

CURRENT TREATMENT AND PROPHYLAXIS FOR VENOUS THROMBO-EMBOLISM

Most of the studies relate to hospitalised patients. Mechanical methods of prophylaxis including elastic compression stockings and intermittent pneumatic compression have been proven to reduce the incidence of deep vein thrombosis (Tardy *et al.*, 1993; International Consensus Statement, 1997; Anonymous, 2000; Belcaro *et al.*, 2001). By extrapolation reduce the incidence of deep vein thrombosis is thought to reduce the risk of pulmonary embolism. A number of pharmacological approaches have been evaluated, including low dose unfractionated heparin, low molecular weight heparin, low dose Warfarin, and aspirin. There are many studies looking at the effects on reducing deep vein thrombosis, and un-fractionated low dose heparin, low molecular weight heparin, low dose Warfarin, and aspirin have been seen to have some beneficial effects. Currently, low molecular weight heparin is the treatment of choice. Studies using unfractionated heparin, and more recently, low molecular weight heparin, have demonstrated a reduction in the incidence of pulmonary embolism (Belcaro *et al.*, 2001; Cesarone *et al.*, 2002; Belcaro *et al.*, 2002; Scurr, 2002). There are as yet few properly controlled clinical studies looking at the effect of prophylaxis on air travel. Several studies have shown a beneficial effect of wearing compression stockings in both preventing asymptomatic and the symptoms of leg swelling.

Aspirin has some proven benefits in the arterial circulation, but the effects on the venous circulation remain controversial with an associated increased risk of gastrointestinal bleeding, making it difficult to recommend aspirin on a routine basis (Llyod and Bochner, 1996; International Consensus Statement, 1997). Thus research investigators are encouraged to develop new anti-platelet agents that are equivalent or superior to aspirin, but with less or no adverse effects. Currently, for most passengers, DVT prophylaxis consists of advice, exercises before, during, and after the flight, the avoidance of excessive alcohol and sleeping tablets, and advice to report symptoms at an early stage. None of these methods of prophylaxis have yet been scientifically evaluated.

PATHOPHYSIOLOGY OF VENOUS STASIS OEDEMA AND CHRONIC VENOUS INSUFFICIENCY

Venous stasis and the inability to reduce venous pressure during exercise give rise to chronic venous insufficiency with increased capillary permeability (Wenner

et al., 1980). An experimental model using the rat tail (Nordmann and Gulati, 1980; Nordmann *et al.*, 1982) has been used to assess the effects of hydroxyethylrutosides (Paroven®) in chronic venous insufficiency. These models were validated using plethysmography, thermography, fluorescence angiography and radioactive microspheres techniques. Paroven was a venotonic drug showing significant inhibition of the oedemogenic response in the acute and chronic phases of experimentally induced chronic venous insufficiency.

It is postulated that venous stasis leads to endothelial damage, the incorporation of inflammatory cells, with a release of oedemogenic and/or inflammatory mediators. Endothelial damage leads to increased venous permeability in the post-capillary venules (Gulati *et al.*, 1983a; 1983b). The same group showed oedemogenic mediators, including histamine, leukotriene C₄ and leukotriene D₄ and inflammatory mediators like cytokines, prostaglandins, causing increased vascular permeability leading to fluid leaving the intravascular compartment for the extra-cellular spaces. This process was further aided by increased venous pressure, in particular, the ability to be unable to reduce it. The accumulation of fluid in the extra-cellular compartment has an osmotic effect increasing oedema further. With increased local inflammation of the veins, red blood cells leave the circulation and form part of the process ultimately giving rise to lipodermatosclerosis.

PATHOPHYSIOLOGY OF DEEP VEIN THROMBOSIS

Virchow (1856) noted that venous stasis, combined with damage to the venous endothelium, plus changes in the blood's ability to coagulate, would predispose to the development of a deep vein thrombosis. In actual situation, following long travels by air, bus car, truck or train, the mechanisms include tendency to clot formation in the legs secondary to the reduced venous return induced by the sitting position with direct compression of popliteal and femoral veins, and secondary to dehydration and haemoconcentration (Tardy *et al.*, 1993). Immobility remains an important factor. Damage caused to the endothelial lining by oxidative stress, and changes in the ability of the blood to coagulate, are not only important in the process of forming a deep vein thrombosis (Gertler *et al.*, 1993; Landgraf *et al.*, 1994; Bendz *et al.*, 2000), but also important because we can influence these changes, reducing the risk of deep vein thrombosis. Platelets are the smallest cellular components in the blood stream existing as a α -nuclear disc-shaped cells in their resting state and they travel singly as discoidal particles. (Rao, 1993; Rao and Rao, 1994). Any insult to the vascular endothelium will make it thrombogenic, with platelets binding to fibrinogen, aggregating to the area and among themselves giving rise to microthrombi. The microthrombi release platelet activating factors (PAFs, including adenosine diphosphate (ADP) and serotonin. ADP and arachidonic acid (AA) metabolite act as endogenous platelet activator, thromboxane A₂ (TxA₂), intensifying the extent of platelet aggregation. These substances act in positive feedback loops, producing a vicious circle (Llyod and Bochner, 1996). Venous stasis leads to slowing of

the blood flow, with the development of intravascular thrombosis. Thrombokinase is released from microthrombi converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin, forming the basic skeleton of a clot. As platelets and red blood cells get intercalated, the clot develops.

PATHOPHYSIOLOGY OF MOTION SICKNESS

Motion sickness (MS) is an illness triggered by sensory conflicts involving the vestibular system, occurring when sensory inputs regarding body position in space are contradictory or different from those predicted from experience.

Gastric dysrhythmias (tachygastria) has been associated with the patho-physiology of motion sickness (Stern *et al.*, 1987; 1989). Quantitative analyses showed that tachygastria index correlated with intensity of nausea, which in turn, correlated positively with plasma vasopressin levels (Koch *et al.*, 1990). Vasopressin is released from neurohypophysis during motion sickness, which mediates nausea. Elevated plasma vasopressin levels demonstrate a close temporal relationship with the development and resolution of nausea evoked by circularvection (Koch *et al.*, 1990; Xu *et al.*, 1993; Kim *et al.*, 1997; Koch, 1999). Elusory self-motion orvection evokes nausea, dysrhythmia and vasopressin release in motion sickness-susceptible subjects via cholinergic – prostaglandin independent pathways (Kim *et al.*, 1997). The effect is centrally mediated and not peripheral action of vasopressin. Selective vasopressin antagonists have been shown to abolish symptoms of motion sickness in primates (Cheung *et al.*, 1994).

Nausea associated with motion sickness is unpleasant. Current anti-motion sickness medication includes antimuscarinics and antihistamines. These agents produce incomplete symptom control and elicit significant side effects such as dry mouth, lethargy and drowsiness.

BIOLOGICAL PROFILE OF PYCNOGENOL®

Biological profile of Pycnogenol® and its clinical activities have been reviewed by Packer and his co-workers (1999) and Rohdewald (1999; 2002). For the purpose of this review we will consider those studies, which are relevant to the product Zinopin® in context with the rationale of its development.

The most obvious feature of Pycnogenol® is its strong antioxidant activity owing to the basic chemical structure of its components procyanidins and phenolic acids. Various studies have addressed its antioxidant capacity in simplified assay systems *in vitro*, cultured cell models (Rong *et al.*, 1995; Wei *et al.*, 1997; Virgili *et al.*, 1998a; Bayeta *et al.*, 2000), *in vivo* in animals (Blazso *et al.*, 1994; 1995; 1997) and in clinical studies (Devraj *et al.*, 2002). The antioxidant activity of two major metabolites [σ -(3, 4 dihydroxyphenyl)- γ -valerolactone] and [σ -(3-methoxy-4 hydroxyphenyl)- γ -valerolactone] of Pycnogenol® has also been shown in an independent *in vitro* study (Grimm *et al.*, 2004).

Interestingly Nelson *et al.* (1998) studied the capacity of Pycnogenol® to protect the low density lipoprotein

(LDL) fraction of human plasma from copper-induced oxidation and have reported a dose-dependant decrease in lipid peroxide. Pycnogenol[®] exhibited a concentration dependent inhibition of oxidative burst triggered by zymosan in murine macrophages *in vitro*. Furthermore, it significantly minimized the cleavage of DNA caused by hydroxyl radicals, induced by exposure of pBR 322 plasmid DNA to iron/ascorbic acid system and measured by agarose gel electrophoresis (Nelson *et al.*, 1998). Chida and his co-workers (1999) studied Pycnogenol[®] among different known antioxidants and found Pycnogenol[®] to be many fold more potent than vitamin C, E and grape seed extract in the lipid peroxidation model using bovine retinal cell model. Increase in antioxidative enzyme system (GSH reduction enzymes, SOD and catalase) has been demonstrated in two independent studies *in vitro* (Wei *et al.*, 1997; Maritim *et al.*, 2003).

Interestingly, a strong correlation between antioxidant activity *in vivo* and anti-inflammatory activity *in vivo* has been demonstrated indicating the role of oxidative stress in inflammation and anti-inflammatory mechanism of Pycnogenol[®] working through its antioxidant activity (Blazso *et al.*, 1994).

Anti-inflammatory activity of Pycnogenol[®] is well documented (Blazso *et al.*, 1994; 1995; 1997). One of the molecular features of the UV induced inflammatory response is the activation of the transcription factor NF- κ B which in turn, regulates the expression of different inflammatory cytokines and triggers the inflammatory response. Pycnogenol[®] has been shown to significantly inhibit this activation (Peng *et al.*, 2000). Furthermore, Pycnogenol[®] dose dependently inhibited tumour necrosis factor- α (TNF- α) – induced activation of NF- κ B and inhibited TNF- α – induced release of superoxide and hydrogen peroxide ions from human vascular endothelial cells *in vitro*. Adhesion molecules are needed for penetration of inflammatory cells into tissues. At the transcriptional level, the expression of the adhesion molecule (iCAM-1) is inhibited by pre-incubation of Pycnogenol[®] in human vascular endothelial cells (Peng *et al.*, 2000). Pycnogenol[®] reduces production of reactive oxygen and nitrogen species in activated immune cells (Virgili *et al.*, 1998a; 1998b). The oxidative burst of macrophages releasing superoxide and hydroxyl radical including hydrogen peroxide is inhibited by Pycnogenol[®] *in vitro* (Virgili *et al.*, 1998a; Nelson *et al.*, 1998). Furthermore the production of the pro-inflammatory interleukin-1 β is inhibited by Pycnogenol[®] in the same cell system (Cho *et al.*, 2000). Pycnogenol[®] down regulates Interferon- γ – induced adhesion of T cells to human keratinocytes by inhibiting inducible ICAM-I expression (Bito *et al.*, 2000). Pycnogenol[®] has been shown to provide protection against UV induced damage to skin *in vitro* as well as *in vivo* in animals and in humans (Guochang, 1993; Saliou *et al.*, 2001; Sime and Reeve, 2004).

Another interesting feature of Pycnogenol[®] is its anti-thrombosis profile, relevant to the subject matter of this review. Pycnogenol[®] inhibits platelet reactivity induced by cigarette smoking, without producing any adverse effect on the bleeding time that characterises aspirin use (Pütter *et al.*, 1999). Pütter and his collaborators (1999) have observed that in a group of heavy smokers, platelet aggregation was prevented either by

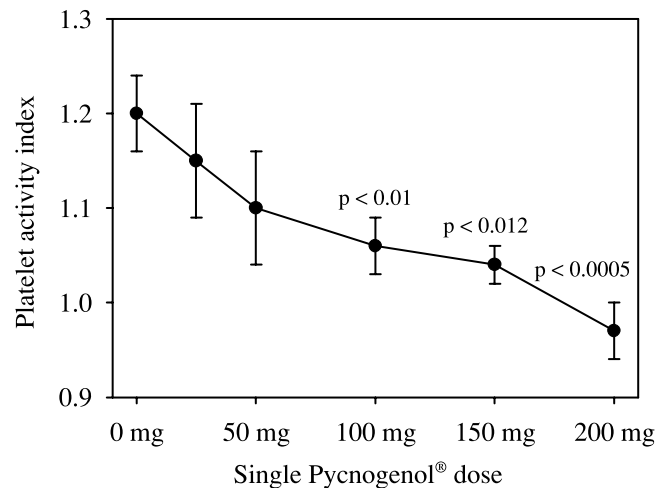


Figure 1. Dose response effects of single Pycnogenol[®] administration on platelet reactivity index in 19 smokers. Statistical significant difference to baseline (0 mg Pycnogenol[®]) was achieved with 100 mg or more Pycnogenol[®]. (Reproduced from Watson, 2003; with permission from the author)

500 mg of acetylsalicylic acid (aspirin) or 100 mg of Pycnogenol[®]. The anti-platelet-reactivity effects were shown to be dose dependent (Fig. 1). At a dose of 200 mg of Pycnogenol[®] the inhibitory effect on platelet reactivity and decreased thromboxane levels in smokers (Araghi-Nicknam *et al.*, 1999). The authors suggest that this activity of Pycnogenol[®] is related to its nitric oxide releasing capacity from the endothelial cells (Minuz *et al.*, 1995; Fitzpatrick *et al.*, 1998), which in turn would inhibit the synthesis of thromboxane A-2. In a clinical study with 60 patients meeting the diagnostic criteria of coronary heart disease, it was reported that Pycnogenol[®] administered for four weeks inhibited the adhesion and aggregation of platelets, enhanced the capillary diameter and improved the microcirculation (Wang *et al.*, 1999). The cardiovascular profile of Pycnogenol[®] has been reviewed by Watson (1999, 2003). Interestingly, Pycnogenol[®] has been shown to decrease the levels of thromboxane in an independent clinical study (Hosseini *et al.*, 2001).

BIOLOGICAL PROFILE OF GINGER ROOT EXTRACT

Ginger root extract has been shown to have anti-platelet aggregation activity *in vitro* (Guh *et al.*, 1995; Venkateshwarlu, 1997; Nurtjahja-Tjendraputra *et al.*, 2003) and *ex vivo* in humans (Verma *et al.*, 1993). In addition to inhibiting platelet aggregation, it also reduces platelet thromboxane synthesis both *in vitro* and *in vivo* (Srivastava, 1984; 1986; 1989; Thomson *et al.*, 2002). Ginger inhibits thromboxane synthesis and stimulates synthesis of prostacyclin (Backon, 1986). Arachidonic acid-induced human platelet serotonin release and aggregation is inhibited (Koo *et al.*, 2001).

Beneficial effects of ginger 0.5 and 1 g ginger in a double blind randomised clinical trial has been shown in nausea and vomiting following surgery (Bone *et al.*, 1990; Phillips *et al.*, 1993; Arfeen *et al.*, 1995) and in morning sickness (Fischer-Rasmussen *et al.*, 1991;

Aiken-Murphy, 1998; Keating and Chase, 2002) motion sickness and sea sickness (Mowrey and Clayson, 1982; Stewart *et al.*, 1991; Lien *et al.*, 1993; Lanner *et al.*, 1995). Ernst and Pittler (2000) made a systematic review of evidence from six randomized controlled trials for and against efficacy of ginger for nausea and vomiting including post-operative patients, subjects with sea sickness, morning sickness and those on the chemotherapy. The results from these studies collectively favour ginger in efficacy over placebo in nausea and vomiting.

Different hypotheses have been put forward:

- Ginger improves the effects of motion sickness through its aromatic, carminative, spasmolytic and possible absorbent properties, which are thought to block gastrointestinal reaction and subsequent nausea feedback (Lien *et al.*, 1993). Unlike anti-motion sickness drugs, it does not reduce vestibular optokinetic nystagmus (Mowrey and Clayson, 1982; Suekawa *et al.*, 1984; Yamahara *et al.*, 1990). The action of ginger is peripheral and not central and thus not associated with general side effects such as drowsiness common to centrally acting anti-emetics.
- It is thought that ginger may act by increasing gastrointestinal motility reducing the feedback from the GI tract to central chemo receptors (Holtman *et al.*, 1989; Qian and Liu, 1992). Ginger juice produce anti-motion sickness by central and peripheral anti-cholinergic and anti-histaminic effects (Mascolo *et al.*, 1989).
- Some researchers believe that ginger produces beneficial effects in motion sickness by preventing the development of gastric dysrhythmias and elevation of plasma vasopressin (Mascolo *et al.*, 1989).
- Ginger has been shown to produce anti-oxidant effects *in vitro* and *in vivo* (Cao *et al.*, 1993; Ahmed *et al.*, 1998).
- Anti-inflammatory actions of ginger have been shown in different animal models. Jana *et al.* (1999) demonstrated that ginger (100 mg/kg) was effective as acetylsalicylic acid (100 mg/kg) in reducing carrageen induced oedema in rats. Similar results have been reported by Mascolo and his colleagues (Jana *et al.*, 1999). The anti-inflammatory action is thought to be due to inhibition of arachidonic acid metabolism and prostaglandin release like other non-steroidal anti-inflammatory drugs, in clinical conditions (Jana *et al.*, 1999).
- Ginger has been shown to increase fibrinolytic activity in human fed with heavy fat diet (Bordia *et al.*, 1997; Verma and Bordia, 2001).

CLINICAL EXPERIENCE WITH PYCNOGENOL®

Rohdewald (2002) has recently reviewed the clinical study data on Pycnogenol®. However, in this review we will focus only on the clinical studies relevant to the subject matter of this review. Five placebo-controlled, double-blind studies involving a total of 149 patients and three double-blind, controlled studies in a total of 231 patients have demonstrated that Pycnogenol® significantly improved pain, occurrence of cramps, heaviness of legs and significantly reduced swelling in the

lower leg and ankle (Gulati, 1999). Two independent studies with 40 patients each confirmed the efficacy of Pycnogenol® in chronic venous insufficiency (Arcangeli, 2000; Petrassi *et al.*, 2000). Another blind study compared the effects of horse chestnut seed extract and Pycnogenol® by measuring the circumference of the lower limb in patients with CVI. A fast onset of action was shown by Pycnogenol® with a significant reduction in leg circumference as compared to horse chestnut extract (Koch, 2002).

RATIONALE OF THE DEVELOPMENT OF ZINOPIN®

Zinopin® is a combination of SGRE and Pycnogenol®. Pycnogenol® is an anti-oxidant and effective anti-oedema anti-inflammatory agent, reducing capillary permeability, and has an anti-thrombotic effect by inhibiting platelet reactivity. Pycnogenol® is effective in decreasing platelet reactivity like aspirin, however, it is devoid of side effect like bleeding. By reducing capillary permeability there is a reduction in oedema formation, reduced endothelial damage, and this combined with its effect on inhibiting platelet activity, has been shown in clinical studies to reduce the clinical symptoms of heaviness of the legs, ankle swelling and a reduction in calf cramps.

Pycnogenol® has been combined with SGRE because ginger is also known to have anti-platelet aggregation activity, fibrinolytic activity and it inhibits thromboxane synthesis. In addition, it is also effective in preventing motion sickness.

It is thought that ginger acts in a peripheral capacity, avoiding the common side effects of centrally acting anti-emetics, which includes drowsiness. Pycnogenol® and ginger both are generally recognized as safe (GRAS) The combination of SGRE and Pycnogenol® therefore, seems to be an appropriate and safe travel supplement. The proposed rationale and mechanism of action of Zinopin® and its active components Pycnogenol® and SGRE has been shown in Fig. 2. It seems both components may act in synergy to produce beneficial effects of Zinopin® in long-haul travel related conditions.

CLINICAL STUDIES OF ZINOPIN®

Zinopin® is currently being taken by travellers that are travelling for more than 8 h, and who are over 18 years of age. There have been no exclusions from this study. Prior to entering the study, a full medical history is obtained, including a history of recent flights and the duration of those flights. Any current medication is noted and passengers are asked to record any use of medication during the study period. No specific advice about travel was given to any passenger, and the passengers took one Zinopin® tablet the day before flight, two on the day of flight, and a further tablet on each of the two following days. On their return, all passengers completed a questionnaire looking specifically for leg and chest symptoms. Passengers took the Zinopin® on both the outward bound and the return flights.

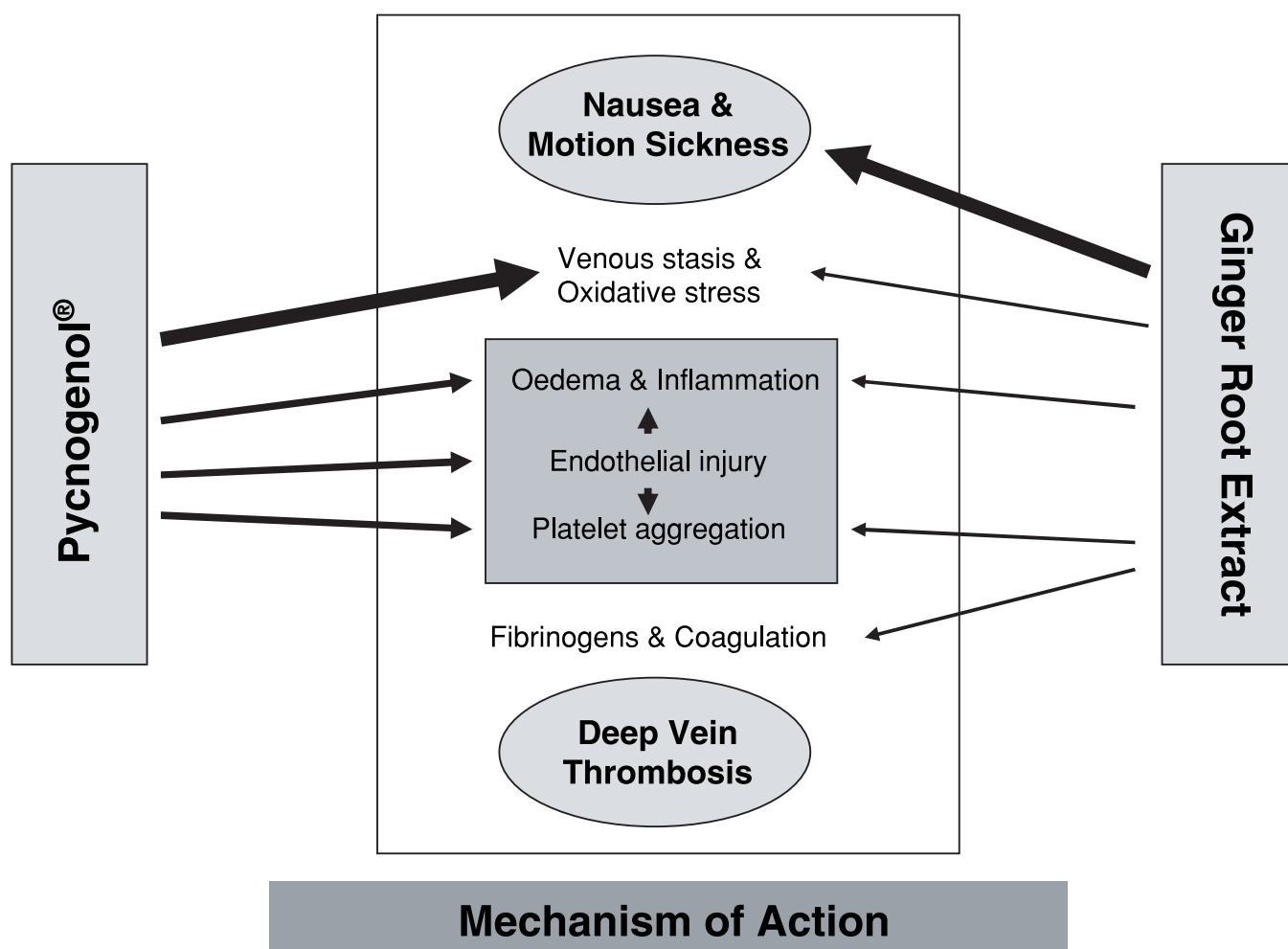


Figure 2. Zinopin®: Pycnogenol® and Standardized Ginger Root Extract (SGRE).

RESULTS

The study is ongoing and passengers are still being recruited. No passenger has developed a symptomatic deep vein thrombosis. More than 50% of the passengers taking Zinopin® commented spontaneously that they had less ankle swelling. This was not objectively measured and is a subjective assessment, but entirely consistent with previous studies using Pycnogenol®.

The results will be analysed on an intention-to-treat basis. It will form the basis of a pilot study, leading to a full double-blind study to assess the benefits of taking a travel supplement Zinopin®.

CONCLUSIONS

Deep vein thrombosis is far more common than was originally appreciated. Whilst in the majority of cases a deep vein thrombosis will resolve with complete reso-

lution, in some people, damage to the vein wall remains, predisposing to further thrombosis episodes. A deep vein thrombosis may be associated with risk factors, but not always. There are occasional episodes of spontaneous deep vein thrombosis in passengers with no obvious risk factors. The deep vein thrombosis may occur two weeks or more after a flight, and may not be associated with travel. There is no evidence to date to suggest that travel-related thrombosis is specific to airline travel, and the current link is simply to one of immobility.

Pycnogenol® has the benefits of aspirin, without having the risk of gastrointestinal bleeding. There are additional benefits of Pycnogenol® in terms of the circulation, reduction of tissue fluid, and the resultant oedema. SGRE similarly has many effects which could be seen to be beneficial in the prevention of venous thrombosis, and in addition to this, an anti-nauseous effect, which makes it an ideal ingredient for any travel supplement. Preliminary studies with the Zinopin® show not only that it is effective; it is well tolerated, and not been associated with any significant side-effects.

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