Review

Clin Ter 2014; 165 (5):269-277. doi: 10.7417/CT.2014.1758

A Review of the Use of *Piper Betel* in Oxidative Stress Disorders

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Abstract

Increase in prevalence of disease related oxidative stress disorders have been on the rise in the entire world since the past decades. Significant positive effects with few antioxidant properties in the modern drugs pave for the alternative medicines in managing the disease. *Piper betel* (*P. betel*), a herb, is known to possess high anti-oxidant, anti-diabetic, anti-atherosclerosis, anti-hyperlipidemic, anti-cancer and neuroprotective property. This review focused on the effect of *P. betel* on diabetes mellitus, atherosclerosis and chronic kidney disease, Alzheimer's disease and breast cancer. *P. betel* proved to show positive effects with specific outcomes towards these diseases. Moreover, the promising effect of *P. betel* in vitro studies was also highlighted in the present review. It is believed that the findings obtained in this review will draw the attention of the medical professionals and general public towards *P. betel* and it will open the door for further detailed research.
Clin Ter 2014; 165(5):269-277. doi: 10.7417/CT.2014.1758

Key words: *anti-oxidant, herbs, oxidative stress disorders, piper betel*

Introduction

Piper betel (P. betel)

Betel vine or scientifically known as *Piper betel (P. betel)* belongs to *Piperaceae* family is commonly found in South East Asia. *P. betel* is commonly known as daunsirih (Malaysia), paan (India), maluu (Khmer), Plue (Thailand) and tanbol (Arabic) (1) .It is believed that *P. betel* is a blessed to have heart-shaped as in its leaves. It was found by anthropologists that *P. betel* was widely used in developing countries including Thailand, Malaysia and India since the time period from 5500 – 7000 BC (2). In another anthropology search, it was revealed that skeleton found with black teeth in Indonesia may be due to prolonged use of *P. betel* (3). *P. betel* is native to Malaysia and was taken to cultivate throughout other part of Malaysia, tropical Asia, Madagascar, East Africa and West India as its represent a social status (4). For cultivation it needs deep, well-drained, friable loamy and clayley soils which rich with organic matter and pH 7–7.5. It thrives best under tropical forest condition with more than 179 cm rainfall which gives enough humidity and with enough shade. *P. betel* plant is a climber type and heart shaped leaves with varies size. It is yellowish green to dark green in color (5-7).

Phytochemically, the leaves contain alkaloids, carbohydrate, amino Acids, tannins and steroidal components (8). Phenol and terpene can be found in the leaves which give a specific strong pungent smell (9). The quality of the leaves is determined by its level of phenol. The higher level of the phenol the betters the leaf quality (10). *P. betel* leaf contains water (85-90%), proteins (3-3.5%), carbohydrates (0.5-6.1%), minerals (2.3-3.3%), fat (0.4-1%), fibre (2.3%) essential oil (0.08.02%) and tannin (0.1-1.3%). Moreover, *P. betel* leaf also contains different vitamins and minerals such as vitamin A, vitamin C, thiamine (B1), riboflavin (B2), nicotinic acid (B3), calcium, iron, iodine, phosphorus and potassium.

Traditionally, *P. betel* leaves are used in many ways such as chewing, eye drop solution, topical cream and remedy. In addition to that *P. betel* is commonly used in chewing to provide cardiotonic effect, regulates irregular heart's beat and blood pressure. *P. betel* also accelerates the salivation and enhances the gastric juice by helping digestion process. It is believed that it has good effect in preventing bad breath (halitosis), improving the vocalization, hardening the gum, conserving the teeth and sweetening the breath (11). *P. betel* has been used to treat cough, bad mouth smell, ozoena, bronchitis, clears throat, vulnery and styptic. Furthermore, it is also used to treat alcoholism, asthma, leprosy and dyspepsia (12).

Recently, many studies have been conducted to prove the therapeutic use of *P. betel*. The aqueous extract of *P. betel* and *Psidium guajava* significantly reduced the cell-surface hydrophobicity of *Streptococcus sanguinis, Streptococcus mitis* and *Actinomyces sp* in vitro. These bacteria interact strongly with the experimental pellicle by their hydrophobic feature which results in the formation of plaque. *P. betel* is

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ISSN 0009-9074

able to alter the interaction between these bacteria and the tooth surface (13, 14). The active compound sterol in *P. betel* helps to reduce the acid producing activity by targeting the structure and function of the bacterial cell and membranes (15). The leaves have also been tested against *Streptococcus pyogenes, Staphylococcus aureus, Protues vulgaris and Escherichia coli* and proved to possess antibacterial activity. A group of researchers also documented that *P. betel* contain flavonoids and polyphenols which provide anti-oxidative activity (13). It has been pointed out that oral administration of *P. betel* showed significant decrease in oxidative stress markers and a significant increase in antioxidant enzymes in experimental animal models (16, 17). It is also agreed by the other researchers who noted that *P. betel* is enriched with antioxidant activity by investigating on DPPH scavenging assay. The effect of *P. betel* on diseases related to the oxidative stress disorders were tabulated (Table 1).

Oxidative Stress Disorders

The reactive oxygen species (ROS) is an atom or molecule formed from the double oxygen (O_2) that is relatively stable at its ground state until partial reduction causes it to lose an electron. ROS holds an unpaired electron and capable of engaging with other molecules and then destabilize them which in turn generates many more free radicals (18-20). Various forms of ROS has been mentioned in the previous literatures which include singlet oxygen, hydrogen peroxide and superoxide anion and hydroxyl with the special affinity towards lipids, proteins and nucleic acids (21). These ROS produces toxicity and exert oxidative damage to the cells and various tissues. In oxidation, ROS is being generated in the cells through the electron transport chain and also from the enzymes like xanthine oxidase, aldehyde oxidase and cytochrome P450 mono-oxygenase (22).

Antioxidant mechanism in the healthy body serves as an integrated defense network which will scavenge the toxic radicals and convert it to less reactive species. However, when this mechanism is impaired, there is an imbalance between the production and elimination of the free radicals which causes the oxidative stress disorder (Fig. 1).

Increase ROS production is precipitated by the physical environmental factors such as radioactivity and ultraviolet irradiation, metabolism of drug and xenobiotic, chronic metabolic disorder, antioxidant enzyme deficiency and genetic disorder related to electron transport chain (23). The expanding evidences in the current literature shows that oxidative stress plays a pivotal role in the various diseases like diabetes mellitus, atherosclerosis, chronic kidney disease, Alzheimer's diseases and breast cancer (24-26).

Oxidative stress disorders are of growing importance as it contributes to growing mortalities and morbidities. Diabetes mellitus was reported to be on a rising trend in most of the developed countries including even the developing and newly industrialized countries (27). It accounted for 285 million cases in 2010, and estimated to be increased to 439 million by the year of 2030 (28). On the other hand, cardiovascular disease in its various forms is the leading

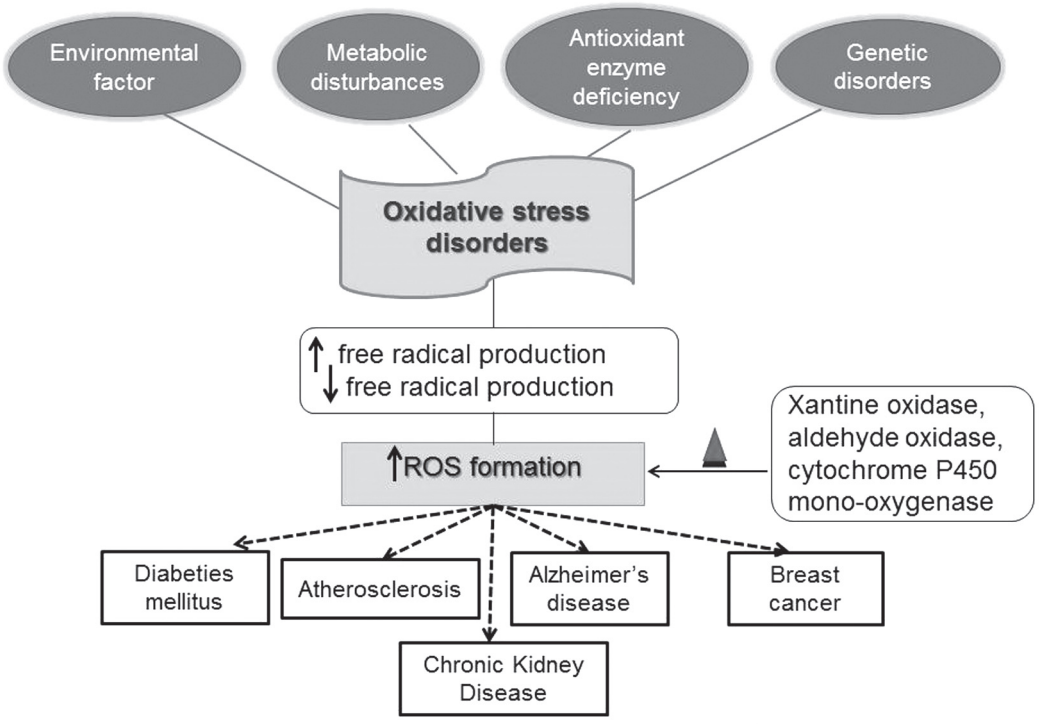

Fig. 1. Schematic diagram showing the mechanism of oxidative stress disorder and its associated diseases. ▲= stimulate, ↑= increase, ↓= decrease.

Table 1. Effect of Piper betel towards oxidative stress disorders.

No.	Dose	Extract	Combination with other herbs	Compound extracted	Properties	Type of study	Results/findings	Disease/ cell culture/ Organism	Duration of treatment	Reference
1.	100mg/ml	Crude aqueous extract	Psidium guajava	NA	Anti-bacterial Anti-adhesive	In vitro	Significantly reduce the cell-surface hydrophobicity of Strep. sanguinis, Strep. mitis and Actinomyces sp.	Dental plaque	24 hours	13
2.	1,2,5,10 mg/ml	Aqueous extract	NA	hydrophobic compound	Anti-bacterial	In vitro	Significantly reduced the growth, adherence activity, glycosyltransferase activity and cell surface hydrophobicity of S. mutans	Streptococcus mutans	24 hours	15
3.	75mg/ kg body weight	Aqueous extract	NA	NA	Anti-oxidant	In vivo	Significantly increase TBARS, hydroperoxides in plasma, liver and kidney GSH, SOD, CAT and GPx in liver and kidney	Diabetes mellitus	30 days	16
4.	150 mg/ kg body weight	Ethanolic extract	NA	NA	Anti-oxidant property, free radical scavenging activity	In vivo	Significantly increased SOD and catalase activity, mucus and total gastric tissue sulfhydryl group	NSAID-induced peptic ulcer	10 days	18
5.	50µg/ml	NA	NA	phenolic compounds (chavibetol and 4-allylpyrocatechol)	Anti-oxidant, Inhibitory effect on photosensitization-induced damages to lipids and proteins	In vitro	Decrease TBARS, increase SOD in mitochondria of animal liver, significantly reduced protein carbonyl	Photosensitization-induced liver damage	30-60 min	40
6.	100, 200, 300 and 1500 mg/ kg body weight	Hot water extract and cold ethanolic extract	NA	NA	Anti-diabetic property	In vivo	Significantly lowered the blood glucose level and markedly reduced the external glucose load in glucose tolerance test	Type 1 diabetes mellitus	42 consecutive days	43
7.	50 mg/ kg body weight	Aqueous extract	NA	NA	Anti-oxidant and anti-diabetic property, improve delayed wound healing	In vivo	Increase total protein content and wound contraction rate	Wound healing in type 1 diabetes mellitus	10 days	44
8.	75, 150, and 300 mg/ kg body weight	Hydromethanolic extract	NA	NA	Cardioprotective activity	In vivo	Significant decrease in systolic, diastolic, mean arterial pressure, heart rate, restored SOD, CAT, GSH, and GPx, reduced the leakage of CK-MB isoenzyme and lactate dehydrogenase along with decreased lipid peroxidation in the heart	Isoproterenol-induced cardiotoxicity	30 days	52
9.	16.513 g/100 ml	Ethanolic extract	Catharanthus roseus [L] G.Don), Dendropthoe petandra L. Curcuma mangga Val	Quercetin	antioxidant and antiproliferative property	In vitro	Significant decrease in cell viability of T47D cells	Human breast cancer T47D cell line	1 day	57

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10.	High dose	Aqueous extract	NA	NA	Anti-tumour activity	In vivo	Inhibited the emergence of tumors in initial phase	7,12-dimethyl-benzan-thracene (DMBA)-induced mammary carcinoge-nesis	8 weeks	64
11.	20 mg/ml	Aqueous extract	Psidium guajava L.	NA	Potent anti-proliferative and cytotoxic activity	In vitro	Significantly increased in IC50 values towards KB cells	human nasopha-ryngeal epider-moid carci-noma (KB) and HeLa cell lines	72 hours	66
12.	400 mg/ kg body weight	Alcoholic extract	NA	NA	Antioxidant and anti- hyperlipi-daemic effect	In vivo	Significantly increase in the plasma TBARS, lipid hydroperoxides, and a decrease in vitamin C, vitamin E and reduced glutathione concentra-tions. Significantly incre-ased in VLDL and LDL, significantly decreased in HDL, increase in the levels of total cholesterol, phospholipids, triglyce-rides, free fatty acids in the plasma and tissues of liver and kidney	D-galac-tosamine-induced hepatitis	20 days	80
13.	25-1000µg/ml	Aqueous extract	Chlorella vulgaris, Momor-dica charantia	NA	Neuroprotective effect	In vitro	50% reduction of free radical at DPPH scaven-ging activity, significan-tly decreased in the number of cytotoxic cells, significant increase in the number of Viable neurone cells	Human neuro-blastoma SH-SY5Y cell	72 hours	85
14.	200mg/ml	Crude aqueous extract	Brucea javanica	NA	Anti-adhesive	In vitro	Drastically reduced the adherence of C. tropica-lis, Candida albicans and C. krusei	Oral candi-dasis	24 hours	86

cause of death in both developed and developing countries. According to the recent World Health Organization (WHO) data, more than 80% of the death was due to cardiovascular disease (29). It was also noted that chronic kidney disease was becoming more prevalent worldwide. In a recent report by the United States Renal Data System, it was estimated that nearly one-half million of patients were treated for end-stage renal disease (ESRD) in year 2004 and by the year 2010, the figure was expected to increase by approximately 40% (30, 31). Another oxidative stress disorder which may cause high mortality rate among women is the breast cancer. It is the most common cause of death among women globally, comprising 16% of all female cancers. It is estimated that 519, 000 women died in 2004 due to breast cancer, and although breast cancer was thought to be a disease of the developed world, a majority (69%) of all breast cancer deaths occured in the developing countries, as well (32).

Diabetes Mellitus

Diabetes mellitus is a disease characterized by chronic hyperglycemia associated with disruption of carbohydrate, fat and protein metabolism secondary to the defect in pancreas insulin secretion, insulin action, or both and is accompanied by long-term complications (33). Several symptoms may be presented in diabetes mellitus which include polydipsia, polyuria, blurring of vision, weight loss and in severe state with diabetic ketoacidosis. It can be classified into insulin dependent type (IDDM), known as Type 1 diabetes mellitus due to insufficient or absence of insulin production and the non-insulin dependent type (NIDDM), known as Type 2 diabetes mellitus due to insulin resistance in peripheral tissue and relative insulin deficiency with beta-cells secretary defect. Gestational diabetes mellitus (GDM) may also be taken into the account under diabetes mellitus

as it defined as any degree of glucose intolerance with onset or first recognition during pregnancy (34). Long-standing diabetes mellitus can bring about specific complications such as retinopathy, nephropathy, neuropathy accompanied with increased risk of food ulcer, amputation and Charcot joints, increase cardiovascular risk and autonomic dysfunction (35). Evidence of oxidative stress precipitated by diabetes mellitus can be found in the polyol pathway, formation of advance glycosylated end products (AGEs), increase in reactive oxygen species and superoxide production (36-38). Increase oxidative stress in diabetic mellitus leads to oxidative damage to various tissues and thus all sorts of complications arise (39). Diabetes mellitus requires life-long treatment. Oral hypoglycemic agents such as metformin, glipizide, roziglitazone and alpha glucosidase inhibitor are the various choices of drugs for the treatment in type 2 diabetes mellitus. Growing evidence has shown that diabetes mellitus and its complications are much related to oxidative stress in our body. However, currently used drug in the treatment of diabetes mellitus have little or no antioxidant properties and is unable to improve the complications related to the disease (40). In addition to that modern drugs are costly expensive and having side effects which create the pavement for the alternative medicines. Proper diet and regular exercise have been introduced as alternative ways to treat diabetes mellitus. Yet another, significant failure rates were observed with this treatment regimen due to discontinuity in following the standard protocol. Therefore, herbal medicine has been used as an alternative supplement to manage the disease. Since the past few decades, it is believed that the herb possess the active compounds with lesser side effects and potential role in antioxidant activity. *P. betel* possesses antioxidant, antidiabetic, anti-inflammatory, antimicrobial and immunomodulatory activities (41, 42). Several in vitro and in vivo studies have been carried out concerning *P. betel* leaves. During an in vivo study, *P. betel* leaves were proved to have antioxidant effect by its free radical scavenging activity and can prevent lipid peroxidation (16). In the year 2003, it was proved that hot water extract (HWE) and cold ethanolic extract of *P. betel* (75 mg/kg body weight) showed antidiabetic effect on normoglycemic and streptozotocin (STZ)-induced diabetic rats with 30 days of treatment (43). Furthermore, a group of researchers discovered a potent antioxidant property of *P. betel* in vivo, when 75 mg/kg of *P. betel* suspension was administered to STZ-induced diabetic rats. This suggested that antioxidant property of *P. betel* leaves plays a protective role in diabetes (44). It was also documented that topical application of *P. betel* 50 mg/kg body weight for 10 days in experimental diabetic rats showed improvement in the wound healing (45).

Atherosclerosis

Atherosclerosis is a major cause of cardiovascular disease. Atherosclerotic disease remains the most important cause of death in developed and developing countries despite the availability of advance medical and surgical intervention (46). Atherosclerotic plaque is a lesion that is covered by a fibrous cap that overlies a core lipid and necrotic tissue (47). Cycles of accumulation of macrophages, migration and proliferation of smooth-muscle cells and formation of fibrous tissue lead to further enlargement and restructuring of the lesion (48). Series of events in relation to the atherosclerosis are triggered by endothelial injury which is closely related to oxidative stress. Possible causes of endothelial injury leading to atherosclerosis are elevated and modified LDL, free radicals caused by cigarette smoking, hypertension, diabetes mellitus, genetic alterations, elevated plasma homocysteine concentrations, and infection (49). Oxidized LDL increases level of lipid peroxides and facilitates the accumulations of cholesterol ester leading to formation of foam cells. In addition, it is also chemotactic which can aggravate the inflammatory response resulting in more extensive endothelial injury (50). Among the factors that cause endothelial injury, ROS play a crucial role in compromising endothelial function. Studies have shown that antioxidant increases the resistance of human LDL to oxidation ex vivo in proportion to the vitamin E content of the plasma (51). Yet another, vitamin E intake was found to be inversely correlating with the incidence of myocardial infarction (52). Furthermore, supplements including herbal plants with antioxidant properties are also explored to modify the disease. In an in vivo study of cardioprotective potential of *P. betel*, it was documented that myocardial antioxidants like superoxide dismutase, catalase, reduced glutathione and glutathione peroxidase are significantly restored in rats with isoproterenol (ISP)-induced myocardial infarction pre-treated with 150mg/kg and 300mg/kg of *P. betel* leaf extract (53). Another group of researchers found out that hyproxychavicol (HC), active compound in *P. betel* leaves, could be a potential therapeutic agent for prevention and treatment for atherosclerosis due to its antioxidant property. Arachidonic acid stimulates platelet ROS production which enhances platelets aggregation is inhibited by HC, thus supporting HC as a ROS scavenger by suppressing the ROS-induced chemiluminescence and DNA breaks (54, 55).

Breast Cancer

Breast cancer is a malignant tumour that starts in the cells of the breast. A malignant tumour is a group of cancer cells that can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. The disease occurs almost entirely in women, but men can get it, too (56). Breast cancer is the most common cancer among women and the second leading cause of cancer deaths in women after lung cancer (57, 58). The aetiology of breast cancer involves genetic, hormonal, and dietary factors. Cancer prevention by using dietary or natural substances is considered as an approach to reduce the increasing incidence of cancer (59, 60). Increased exposure to estrogen is an establish risk factors for the development of breast cancer in both young women and postmenopausal taking hormone therapy (HT). Although, estrogens play an important role in the development of normal mammary glands, however, they are also implicated in the development of breast cancer by stimulating cell proliferation and gene expression via the estrogen receptor (ER) and by causing DNA damage potentially via their genotoxic catechol estrogen metabolites. The fact that ERs are expressed in breasts of most women. However, not all get estrogen-induced cancer suggests that an alternative pathway which counteracts the carcinogenic

effects of estrogens may be active in them and lack of this pathway may make women more susceptible to estrogen induced breast cancer (61). Diets rich in grains, fruits, and vegetables are able to reduce cancer risk, and to implicate edible plants as potential sources of anticancer agents. A variety of compounds produced by edible plants has demonstrated anticancer activity (62, 63). Fruits and vegetables contain high polyphenols and significantly reduce risks for cancers in many types. The leading effects of polyphenols on cancer cells are concentrated on growth, differentiation and apoptosis (64).

Several studies were conducted on the effect of *P. betel* in reducing various types of tumors. The aqueous extract of *P. betel* prevented formation of tumors when fed to rats in the initiation phase of induced-mammary carcinogenesis but not significantly inhibit tumor growth when fed to rats with induced mammary carcinogenesis (57, 65). Furthermore, the leaves of *P. betel* have strong anti-tumor promoting activities at a concentration of 40μg/ml in Raji cells (66) whereas the aqueous extract from dried *P. betel* and *P. guajava* leaves of 20 mg/ml was reported to exhibit anti-proliferative action towards kB cells, indicating their potential in treating oral cancer (67). There is paucity of studies on *P. betel* towards anti-carcinogenic property. Since *P. betel* contains high antioxidant activities, it can potentially exhibit anti-proliferative effects. The status of the antioxidants such as superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), glutathione peroxidase (GPx) and glutathione-S-transferase (GST) also reflect the oxidative state of the tissue. The antioxidants CAT and SOD are able to act as anticarcinogens, *i.e.* inhibitor at the initiation and promotion/transformation stage of carcinogenesis. Cellular injury caused by superoxide as well as DNA strand scission caused by the xanthine/xanthine oxidase may be prevented by SOD and CAT (68). *P. betel* aqueous extract presented antioxidant activity with an IC50 of 0.3%. These findings are similar to previous research reports that showed *P. betel* ethanolic extract to possess high antioxidant properties (67).

Chronic Kidney Disease

Chronic kidney disease (CKD) in a condition in which the kidneys are damaged and cannot functioning as normal (69). It is a condition that causes reduced kidney function over period of time and cause accumulation of waste in the body and leads to develop the complications. The symptoms may include fatigue, headaches, pruritus, nausea and drowsiness, confusion and numbness in its severe state. CKD is present when a patient's glomerular filtration rate remains below 60 milliliters per minute for more than 3 months or when a patient's urine albumin-to-creatinine ratio is over 30 mg of albumin for each g of creatinine (30 mg/g) (70, 71).

Based on statistics from the United States Renal Data System's 2010 Annual Data Report and 2011 Annual data report, the prevalence of CKD is growing most rapidly in people with 60 yrs and older with the increase in percentage from 18.8% to 24.5% (72). While In Malaysia, prevalence of diabetes has increased from 6.3% in 1986 to 8.3% in 1996. Adults with Diabetes Mellitus (DM) and hypertension are at an increasing risk to develop CKD. Besides that, adults with obesity, elevated cholesterol and family history of CKD are prone to develop CKD. The final stage of CKD is known as end-stage renal disease (ESRD) in which the kidneys are no longer able to remove waste and excess fluids in the body. At this point, dialysis or kidney transplantation is the only survival. About 110,000 patients in the United States started treatment for ESRD in 2007 and incidence is greater among adults older than 65 years (73).

Impaired oxidative balance in CKD is a result from reduced erythrocyte superoxide dismutase (SOD) (106), reduced plasma thiol groups (74), diminished plasma glutathione, and glutathione peroxidase function (75) which is characterized by functional as well as structural abnormalities. There is thickening of basement membranes, mesangial expansion, hypertrophy and glomerular epithelial cell (podocyte) loss which results in functional impairment (76, 77).The current state of antioxidant therapies for CKD is one of the promises, but not without controversy. Studies carried out by Small DM and Gobe GC showed that some of the antioxidant therapy can benefit the management of CKD patients (78, 79).

The study conducted by Pushpavalli et al. (2010) using alcoholic leaf-extract of 200 mg/kg body weight *P. betel* for 20 days in D-galactosamine induced intoxicated male albino Wistar rats observed that there was increase in TBARS, lipid hydroperoxides, and a decrease in vitamin C, vitamin E and reduced glutathione concentrations (80). Very low density lipoprotein cholesterol and low density lipoprotein cholesterol increased significantly while high density lipoprotein cholesterol decreased. Furthermore, increase in the levels of total cholesterol, phospholipids, triglycerides, free fatty acids in the plasma and tissues of liver and kidney were observed in D-GalN-treated rats. It showed that administration *P. betel* leaves extract decreased the oxidation and improved the condition of the disease (80). From the results, it was suggested that the constituent of *P. betel* extract had the antioxidant effect to manage the oxidative stress disorder in CKD patients.

Alzheimer's disease

Alzheimer disease (AD) is a neuro-degenerative disease of the brain that causes changes in brain function. Alzheimer's disease was first identified more than 100 years ago, but research into its symptoms, causes, risk factors and treatment has gained momentum only in the last 30 years (81). AD usually affects people over the age of 65 years, with a progressive decline in memory, thinking, language and learning capacity. Age is the strongest predictor for the development and progression of AD and with the rapidly aging population of the society. In United Stated, Millions of Americans have Alzheimer's disease and other dementias. Based on the new study by U.S Census and the Chicago Health and Aging Project (CHAP), an estimated 5.2 million Americans of all ages have Alzheimer's disease in 2013. This includes an estimated 5 million people age 65 and older and approximately 200,000 individuals under age 65 who have younger-onset Alzheimer's (81).

Alzheimer's disease presents with the symptoms such as memory loss, difficulty completing familiar tasks, confusion, problem with words in speaking or writing, poor judgment and changes in mood and personality. As the disease progresses, the individual cognitive and functional abilities is

declined. The pathophysiology of Alzheimer's disease is related to the injury and death of neurons, especially in the area of brain that are involved with memory and learning. The most influential theory to explain the pathogenesis of Alzheimer's disease has been the "Amyloid Cascade Hypothesis" first formulated in 1992 (82) that proposed the deposition of beta-amyloid is the initial pathological event in AD leading to the formation of senile plaques and then to neurofibrillary tangles, neuronal cell death, and ultimately dementia. In addition, some of the researcher focused on oxidative stress mechanism and its importance with relate to the disease pathogenesis. The findings revealed that excessive production of advanced glycation end products, nitration, lipid peroxidation, carbonyl-modified neurofilament protein and free carbonyls. This damage involves all neurons vulnerable to death in Alzheimer's disease. Management of AD is complex and will confront with numerous challenges. At present, there is no cure for AD. The primary goals of treatment are to maximize the patient's ability to function in daily life, maintain quality of life and slow the progression of symptoms.

The dietary antioxidants including vitamin C is considered as the most valuable water-soluble antioxidants in neutralizing ROS before lipid peroxidation is initiated. Vitamin E is a major soluble antioxidant that effective in chain-breaking antioxidant within cell membrane and protects lipid peroxidation. These compounds have the ability to scavenge free radicals by reacting with them directly (83, 84). Moreover, study of effect *P. betel* also has been conducted in the year 2010 showed that *P. betel* has higher radical scavenging activity as shown by DPPH assay. It showed significant protection against BSO-induced cell death. The findings showed that the plant extract with the higher free radical scavenging activity showed neuroprotective effects at (75 mg/kg) in mice and (200 mg/kg) in rats (85).

Conclusion

One can conclude that oxidative stress disorders need a complete attention as it can lead to develop severe complications with multiple organs damage. These types of diseases require lifelong treatment. Increase in financial burden with significant side effects encountered in modern drugs open the door for the herbal medicines in treating the chronic disease. *P. betel* is enriched with anti-oxidant, anti-diabetic, anti-carcinogenic, anti-atherosclerotic and neuroprotective properties. With regard to the oxidative stress disorders like diabetes mellitus, atherosclerosis, chronic kidney disease, Alzheimer's disease and breast cancer, *P. betel* has proven to exhibit positive effects on these diseases. *P. betel* showed significant potential effect in improving the oxidative damage. However, the extended and detailed researches are mandatory to attract the public awareness towards this herb. Further studies focusing on the specific active compounds with its action towards the certain ailments are highly recommended.

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