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Biswajit Patra
P.G. Department of Environmental Science, Fakir Mohan University, Vyasa Vihar, Balasore, Odisha, India

Mihir Tanay Das
P.G. Department of Environmental Science, Fakir Mohan University, Vyasa Vihar, Balasore, Odisha, India

Surjendu Kumar Dey
P.G. Department of Environmental Science, Fakir Mohan University, Vyasa Vihar, Balasore, Odisha, India

Correspondence
Biswajit Patra
P.G. Department of Environmental Science, Fakir Mohan University, Vyasa Vihar, Balasore, Odisha, India (756020)
Email: patrabiswajit090@gmail.com
Mobile: 09040374481

A review on *Piper betle* L.

Biswajit Patra, Mihir Tanay Das and Surjendu Kumar Dey

Abstract
Betel vine (*Piper betle* L.) belongs to genus *Piper* of the family Piperaceae. Leaves of *Piper betle* posses several bioactivities and are used in traditional medicinal systems. Many research studies on *Piper betle* has reported that it contains important chemical constituents and are acts to arouse action for its medicinal properties like anticancer, anti-allergic, anti-malaria, anti-filarial**,** antibacterial, antifungal study, insecticidal, antioxidant, anti-diabetic, gastro-protective, cyto-toxic, anti-platelet, wound healing activity, chlorophyllase activity, oral hygiene and anti-asthmatic effect. The present paper also focused on diseases of betel vine and their various symptoms.

Keywords: *Piper betle,* activity, diseases

1. Introduction
Medicinal plants are of proven value as potential therapeutics with the increase of resistant pathogens to commonly used antibiotics and the emergence of new infectious diseases. Traditionally ethno-medicines were used everywhere in India due to their low cost, easy accessibility and less side effects [1]. Extracts of the *Piper betle* leaves are seen to be effective against several human pathogens [2]. *Piper betle* is a medicinal plant that has long been used by Indonesian people as an anti vaginal or oral candidiasis. Utilization of bacterial endophytes from medicinal plants had a new way to get the antibacterial compounds without having to directly extract from the medicinal plants [3]. Many research investigations have given a lot of valuable information about *Piper betle* and its activities like anticancer, anti-allergic, anti-malaria, anti-filarial**,** antibacterial, antifungal study, insecticidal, antioxidant, anti-diabetic, gastro-protective, cyto-toxic, anti-platelet, wound healing activity, chlorophyllase activity, oral hygiene, anti-asthmatic effect etc [4, 5, 2]. Solvents like ethanol, methanol, chloroform, n-hexane, ethyl acetate, dichloromethane, acetone, petroleum ether, benzene and distilled water were used for extraction of plant parts of pan [6]. Chemical investigation of *Piper betle* leaf stalk also studied by Dwivedi and Mehta, 2011 and their structures were determined by spectroscopic and chemical methods [7].
The work on *Piper betle* L. in early 70's were investigated by Mishra and Gaur from Bhabha Atomic Research Center, Bombay, India. Their investigations were on "Role of Petiole in the protein metabolism of senescing Betel (*Piper betle* L.) leaves". In normal petiole leaves, the level of chlorophyll and proteins and extent of protein synthesis declined, while the protease activity registered man fold increase with the advancement of senescence. All of these changes were delayed by depetiolation de-midribbing treatments, through without affecting the general pattern of senescence. Thus, the presence of petiole seems to expedite protein degradation [8, 9]. Bhattacharya *et al.,* 2006 analyzed the inhibitory property of *Piper betle* extract against photosensitization induced damages to lipids and proteins. The protective activity of *Piper betle* ethanolic extract against the photosensitization-induced damage to lipids and proteins of rat liver mitochondria was studied and it was found that *Piper betle* ethanolic extract could effectively prevent lipid per oxidation, as assessed by measuring thiobarbituric acid reactive substances, lipid hydro peroxide and conjugated diene [10]. Wahida *et al.,* 2012 discussed about the preservation of *Piper* species by vacuum drying methods and concluded that increasing drying temperature combined with increasing vacuum pressure accelerated the vacuum drying process. The change in colour values was dependent on the drying temperature where higher temperature caused darker product compared to lowest temperature [11].

2. Various proved activities of *Piper betle*

2.1. Anticancer activity

Laboratory and clinical studies have confirmed that chronic inflammation initiated many human diseases, including cancer and tumor [12, 13, 14]. The betel leaf was used as a common household remedy for inflammation in oral cavity [15]. Oral cancer was one of the ten most common cancers with nearly 90% of them being reported from the South East Asia region, where the habits of tobacco chewing and smoking are common. In one of the earliest studied Rao (1984) observed that topical application of betel leaf extract inhibited B(a) P-induced oral tumorigenesis in hamsters [16]. The combination of betel leaf extract with turmeric was also observed to be effective between two dietary agents [17]. Anticancer and free radical scavenging potency of *Catharanthus roseus, Dendrophthoe pentandra, Piper betle* and *Curcuma mangga* extracts in breast cancer cell lines was investigated by Widowati *et al.,* 2013 [18, 2]. Cancer preventive effects of *Piper betle* was reported by Rai *et al.,* 2011 [19]. Supplementation of *betle* leaf extract in drinking water significantly reduced the benzo (a) pyrene-induced forestomach neoplasia in a concentration dependent manner in mice [20]. Thus, the leaf extracts of *Piper betle* have anti proliferative and chemo preventive potential and can be used for the treatment of various ailments including human lung cancer [21].

2.2. Anti-allergic activity

Wirotesangthong *et al.,* 2008 worked on inhibitory effects of *Piper betle* on production of allergic mediators by bone marrow-derived cells and lung epithelial cells. The results suggested that *Piper betle* may offer a new therapeutic approach for the control of allergic diseases through inhibition of production of allergic mediators [22]. The goal of an antiseptic was to eliminated or reduced the number of microorganisms in the surgical field at the time of the surgery. Amalia *et al.,* 2009 tested the *Piper betle* leaf and successfully applied in pre surgery cataract patients [23]. Hajare *et al.,* 2011 applied the *Piper* leaf extract in guinea pig to evaluate the antihistaminic activity [24].

2.3. Anti-malaria activity

Essential oil of *Piper betle* provided better protection from biting of mosquitoes *Anopheles stephensi* and *Culex fatigans* compared to known mosquito repellent citronella oil. *Piper betle* oil provided more than 4 hrs protection against *Anopheles stephensi* and *Culex fatigans* when applied at the rate of 20 µl /cm^2 where as citronella oil provided only 2.2 and 2.6 hrs protection respectively. Thus, mosquito repellent activity of pan were proved [25].

2.4. Anti-filarial activity

Singh *et al.,* 2009 investigated the anti-filarial activity of *Piper betle*. The report described the n-hexane and chloroform fractions of *Piper betle* L. trigger different arms of immune responses in BALB/c mice and exhibit anti filarial activity against human lymphatic filarid Brugia malayi [26, 2].

2.5. Antibacterial activity

The antibacterial properties of the medicinal plants were reported from all over the world and used in the treatment of many diseases like malaria, AIDS, and sexually transmitted diseases [27]. Nalina *et al.,* 2007 reported the crude aqueous extract of *Piper betle* L. and its antibacterial effect towards *Streptococcus mutans*. The focus of antimicrobial effects includes the ultra-structure and acid producing properties of *Streptococcus mutans*. From the micrographs of the transmission electron, it was found that the crude extract of *Piper betle* L. leaves causes plasma cell membrane damage and coagulation of the nucleoid. The extract was found to significantly reduce acid producing properties of the bacteria and changed to the ultra structure of *Streptococcus mutans* [28]. Antimicrobial activity also described by Khan and Kumar, 2011 and Ghosh *et al.,* 2014 [29, 30].

Nair and Chanda, 2008 studied the aquous and methanol extract of the leaves of *Terminalia catappa* L., *Manilkara zapota* L. and *Piper betle* L., for antibacterial activity against 10 Gram positive, 12 Gram negative bacteria and one fungal strain, *Candida tropicalis*, *Piperacillin* and *Gentamicin* were used as standards for antibacterial assay while fluconazole was used as standard for antifungal assay [31].

The antimicrobial activity, mosquito larvicidal activity, antioxidant property and tyrosinase inhibition of *Piper betle* was studied by Ching *et al.,* 2009 [4]. In this experiment the essential oil, methanolic and aqueous extracts of *Piper betle* L. were assayed for the activities. The methanolic and aqueous extracts showed strong activity against yeasts i.e. *C. albicans*, and *M. pachydermatous*. The crude essential oil exhibited a broad-spectrum strong antimicrobial activity against all tested organisms. The strongest activity was observed against *C. albicans,* followed by *S. aureus*, and *M. pachydermatous* [32, 33, 2, 34]. Essential oil from *Vellaikodi* variety of *Piper betle* leaves was extracted by hydro-distillation method in clevenger type apparatus and analysed by gas chromatography and mass spectroscopy. Sixty five components were identified in the oil [35].

Kumar *et al.,* 2010 examined the antibacterial activity and quantitative determination of protein from leaf of *Datura stramonium* and *Piper betle* plants. *Datura* and *Piper betle*, medicinal plants were tested against three standard microorganisms *E. coli, Bacillus amyloliquefaciens* and *Pseudomonas aeruginosa* collected from Chandigarh for antibacterial activity. Among the medicinal plants tested in that study, *Piper betle* showed valuable antibacterial activities. The result showed that *Piper betle* didn't show any antibacterial activity against *Pseudomonas aeruginosa* [36]. Chemical composition and antimicrobial activity of *Vellaikodi* variety of *Piper betle* leaf oil against dental pathogens were reported by Sugumaran *et al.,* 2011 [37].

Four varieties of pan (*Desawari, Desi, Bangladeshi and Jaleswar*) were examined and reported by Agarwal *et al.,* 2012. The results described that the cold aquous, methanolic, ethanolic and ethyl acetate extracts of dried leaves of all the four varieties of *Piper betle* at concentration of 500 mg ml^{-1} were tested against pathogenic microorganisms like *Pseudomonas aeruginosa, Staphylococcus aureus* and *Escherichia coli* using agar well diffusion method [38]. And discussed the antimicrobial screening on leaves of *Piper betle* [39].

Subashkumar *et al.,* 2013 studied the antibacterial effect of crude aqueous extract of *Piper betle* against pathogenic bacteria. Most of the bacteria species were susceptible to the extracts of *Piper betle*. The greatest zone of inhibition among clinical strains tested was demonstrated by the extract obtained from ethanol extraction towards gram positive and gram negative bacteria. While maximum bacterial activity was observed only in *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. It recommended that the extracts of pan were used to treat many of the clinical infections [40]. Shukla *et al.,* 2009 examined the antibacterial activity of fresh leaves of *Piper betle*. Antimicrobial activity of the successive

extract of the fresh leaves of pan was evaluated against both gram positive and gram negative bacterial strains by disc diffusion method. They concluded that all extracts showed effective inhibitory action against *S. aureas*. Ether extracts showed very effective as compared to standard penicillin. Aquous extract was also found significantly effective against *Bacillus* and *P. aeruginosa* as compared to standard penicillin [41].

2.6. Antifungal study

Ali *et al.,* 2010 worked on in vitro antifungal activity of hydroxychavicol, isolated from the chloroform extraction of the aqueous leaf extract of *Piper betle* L., 124 strains of selected fungi were taken for antifungal study [42]. In vitro screening of antifungal activity of plants in Malaysia were studied by Nazmul *et al.,* 2011 and Nazmul *et al.,* 2013. The results concluded that *Piper betle* produced the best result in antifungal susceptibility testing and showed to possess antifungal property against 4 out of 5 strains of fungus. Solid Phase Extraction (SEP) technique was applied to *Piper betle* to achieve initial separation of active antifungal compound in the form of methanol fractions. Thus, *Piper betle* showed the best antifungal activity against *Tichophyton rubrum* [43, 44].

2.7. Insecticidal activity

Insecticidal activities of essential oil from *Piper betle* against storage insect pests were investigated by Cristina *et al.,* 2006. The insecticidal activity of essential oil extracted from the leaves of *Piper betle* L. was evaluated against the been weevil (*Callosobruchus maculatus* F.), corn weevil (*Sitophilus zeamais* M.) and lesser grain borer (*Rhyzopertha dominica* F.) using aged grain assay. The efficiency of treatments was assessed by determining the acute toxicity on adult insects and the extent of preventing or suppressing the production of progenies. Thus, the biological active component of *Piper betle* leaf oil may possess ovicidal properties that inhibited the development of eggs of *C. maculates* into larvae. So, prevented the emergence of the adult stage. The experiment revealed that *Piper betle* leaf oil was a fecundity-reducing agent to adult *S. zeamais* and *R. dominica*. Likewise, the oil's ovicidal effect cannot be discounted. It was suggested that essential oil from *Piper betle* leaves was a promising grain protectant [45].

2.8. Antioxidant activity

The consumption of antioxidant rich foods will help to neutralize the free radicals in the body, thus preventing or delaying the oxidative damage of lipids, proteins and nucleic acids [46]. It has been shown that the antioxidants could reduce mortality rate of cardiovascular diseases [47, 48] and protected against cancer and other chronic diseases [49, 50].

Eukaryotic cells possess antioxidant molecules like glutathione, vitamin E (α-tocopherol), vitamin A (retinol), Vitamin C (ascorbic acid), carotenoidsthioredoxin, lipoic acid, and ubiquinol and the antioxidant enzymes like SOD, GPx and catalase to protect against the free radical-induced damage, mutagenesis and carcinogenesis [51, 52, 47, 13]. Antioxidant activities of *Piper betle* L. extracts with different solvents and extraction times were done by many scientists [53, 54, 55, 56, 57]. Total phenolic content was evaluated according to the Folin-Ciocalteu procedure. The polarity of the plant extract from various solvents was assessed by determining the oil-water partition coefficient by High Performance Liquid Chromatography (HPLC). *Piper betle* leaf phenolics were found to have less polarity than other phenolic antioxidants due to their high value of oil-water partition coefficient. The experiment indicated that the extraction solvent and time are important for the preparation of *betle* leaf extract for use as natural antioxidant. Chakraborty and Shah, 2011 examined four different extracts (water, methanol, ethyl acetate and petroleum ether) of *Piper betle* leaves against four different pathogenic bacteria namely *Streptococcus pyogenes, Staphylococcus aureus, Proteus vulgaris,* and *Escherichia coli*. Further few known and unknown metabolites were isolated from these extracts. Structural analysis were done by different analytical techniques like NMR, Mass and IR spectroscopy. Anti-oxidative studies were done by TBARS and DPPH method. Antioxidant activity of *Piper betle* leaf extract and its constituents are reported by Rathee *et al.,* 2006. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay of the ethanol extracts of three varieties (Bangla, Sweet, and Mysore) of *Piper betle* revealed the Bangla variety to possess the best antioxidant activity that can be correlated with the total phenolic content and reducing powers of the respective extracts. Column chromatography of the extract of the bangla variety led to the isolation of chavibetol (CHV), allylpyrocatechol (APC) and their respective glucosides. The HPTLC analyses of the extracts revealed similar chemical properties of three *Piper betle* varieties [58].

2.9. Anti-diabetic activity

Kaleem *et al.,* 2005 suggested that *Piper betle* used effectively in the treatment of diabetes. The antidiabetic properties of some plants like Bitter gourd (*Momordica charantia*), Neem (*Azadirachta indica*), Tulsi (*Ocimum sanctum*), and Garlic (*Allium sativum*) are known in India. In Piperaceae family *Piper sarmentosum, Piper longum, Piper nigrum* and *Piper betle* are identified as potential antidiabetic agents [59]. These results suggested that oxidative stress played a key role in diabetes and treatment with *Piper betle* leaf extract are useful in controlling glucose and lipid levels of diabetic rats [60, 61, 2]. Hewageegana *et al.,* 2011 and Chandra *et al.,* 2011 also used pan to cure diabetes [62, 63].

Singh *et al.,* 2011 worked on mitochondrial activity of sperm, after treating semen with different concentrations of *Piper betle* and suggested that *Piper betle* has properties to decreased mitochondrial activity in human sperm and also ability to work as contraceptive. The mitochondrial activity was evaluated after subjecting the semen samples for different incubation time periods. Test was done on more than 75% motile semen sample and was found that concentration of extracts increases the mitochondrial activity decreases significantly, similar results were observed when constant concentration of extracts with increasing time intervals [64, 65]. Antifertility effect of alcoholic stalk extract of *Piper betel* on female albino rats are investigated by Santhakumari *et al.,* 2003 [66, 67, 68, 69].

2.10. Gastro protective activity

Arambewela *et al.,* 2004 examined the gastro protective activities of Sri Lankan *Piper betle* leaf extracts in rats. To determined the gastro protective activity of two components, Hot Water Extract (HWE) and Cold Ethanolic Extract (CEE) with three different concentrations (200, 300 and 500 mg kg^{-1}) were fed to rats to induce ulcer. Oral administration of HWE and CEE gave information about an activity which has dependent on dose-age and significant protection against gastric damage caused by absolute ethanol. The HWE significantly increased the mucus content (by 49%) adhering to the wall of the gastric mucosa. In that study, the highest dose of HWE did not cause significant inhibition in acidity

(both total and free) or pH of gastric fluid. Thus, it was concluded that the gastro protective effect of *Piper betle* was not mediated via inhibition of acid secretion in the gastric mucosa but by increasing its mucus content [70, 71, 2]. Leaves of *Piper betle* were used in Chinese folk medicine for the treatment of various disorders. Pan leaves has the biological capabilities of detoxification, antioxidation and antimutation. Young *et al.,* 2007 examined the antihepatotoxic effect of *Piper betle* leaves extract on the carbon tetrachloride (CCL_4)-induced liver injury in a rat model [72, 73]. Prabhu *et al.,* 2012 also tested the pan leaf extract against cadmium-induced oxidative stress and hepatic dysfunction in rats [74].

2.11. Cyto-toxic activity

Cyto-toxic activity of ethanolic extract of *Piper betle* leaves was evaluated using murine (Ehrlich Ascites Carcinoma and Melanoma B-16 cells) and human (Hela, Raji) cancer cell lines by employing MTT assay and Trypan-blue dye exclusion method were examined by Roy and Vijayalaxmi, 2013. The results suggested that there was a concentration-dependent cell death in various cultured cell lines. Even though *Piper betle* displayed cyto-toxicity towards both normal and tumor cell lines, the toxicity on tumor cells was far greater than that on normal cells indicating selective toxic effect of the plant extract on the tumor cells. Thus, the findings concluded that the IC_{50} values for tumor cells were comparatively very low than their normal counterparts, while the percentage inhibition of tumor cells was higher than that of normal cells [75]. Phyto-chemical studies and in vitro cytotoxicity screening of *Piper betle* leaf extract were reported by Chaurasia *et al.,* 2010 [76]. Betel vine landraces genetic diversity were reported by Verma *et al.,* 2004 [77, 78, 79].

2.12. Wound healing activity

Evaluation of wound healing activity of *Piper betle* leaves and stem extract in experimental wistar rats were investigated by Nilugal *et al.,* 2014. Wounds were referred to as disruption of normal anatomic structure and function. Wound healing had a very complex, multifactor sequence of events involving several cellular and biochemical processes. The results showed wound healing and repair, accelerated by applying ointment formulation containing *Piper betle* leaves and stem extract, which was highlighted by the full thickness coverage of the wound area by an organized epidermis. The male albino rats treated with ointment formulation containing 10% *Piper betle* leaves and stem showed significant results when compared with diseased group and control group [80].

2.13. Oral hygiene

Bissa *et al.,* 2007 examined the oral hygiene and concluded that oral microbial population due to synergistic effect of the combination of betel leaf, cadamom and clove. Dental caries had a chronic endogenous infection caused by the normal oral commensally flora. The bacteria primarily responsible for dental decay in human are *Streptococcus mutans*. *Streptococci* belong to four species group: *mutan, salivarius, anginosus*, and *mitis*. In addition to *Streptococcus mutans, Lactobacillus acidophilus* bacteria probably play a minor role in acid production in the plaque [81]. Chu, 2001 investigated the effect of betel chewing on central and autonomic nervous systems [82]. Varunkumar *et al.,* 2014 tested the anticariogenic effect of crude extract of *Piper* by assessing its action on salivary pH [83].

2.14. Anti-asthmatic effect

Misra *et al.,* 2014 worked on the anti-asthmatic effect of *Piper betle* in guinea pigs. Asthma was a hyper responsiveness of the tracheobronchial smooth muscle to a variety of stimuli. Bronchial asthma was an inflammatory condition. Free radical and superoxide may be responsible for bronchial asthma. Histamine may cause broncho-constriction. The effect of Bronchial asthma can be reduced significantly by *Piper betle* extract, though its action had less than that of di-phenyl hydramine. But in humans for asthma, other mediators like leukotriene plays an important role. Thus, effect of *Piper betle* L. on human asthma was not well known, but from that experiment it was concluded that *Piper betle* had the ability to reduce bronchial asthma in guinea pigs [84, 2, 9].

2.15. Chlorophyllase activity

Gender based differences in response to low temperature stress in leaf chlorophyll (Chl) and carotenoids (Car) contents and chlorophyllase (Chlase) activity were monitored in male (*Kapoori vellaikodi* and *Madras pan kapoori*) and female (*Bangla mahoba*, *Desi bangla* and *Kaker*) betel vine landraces. Although female plants contained nearly two fold more Chl than male counterparts, the low temperature induced Chl loss was comparable. Thus, male plants showed higher Chl a/b ratio than females. Chlase activity increased due to cold stress in all the landraces. Male plants always showed higher activities of Chlase, which may be one of the reasons for the rather low Chl contents in male plants [85]. Identification of sex specific DNA markers and RAPD analysis in betel vine have been worked by Ranade *et al.,* 2002 and Samantaray *et al.,* 2012 [86, 87].

2.16. Betel leaf extract on thyroid function

Panda and Kar, 1998 examined that the effects of betel leaf extract (0.10, 0.40, 0.80, and 2.0 g $kg^{-1}day^{-1}$) for 15 days on the alterations in thyroid hormone concentrations, lipid peroxidation (LPO), superoxide dismutase (SOD) and catalase (CAT) were tested in male swiss mice. Administration of betel leaf extract exhibited a dual role, depending on the different doses. While the lowest dose decreased thyroxine (T4) and increased serum tri-iodothyronine (T3) concentrations, reverse effects were observed at two higher doses. Higher doses increased LPO with decrease in SOD and CAT activities. Thus, with the lowest dose effects were reversed. The findings suggested that betel leaf can be both stimulatory and inhibitory to thyroid function, mainly for T3 generation and lipid peroxidation in male mice, depending on the amount consumed [88, 36, 65].

3. Diseases of Betel vine

Pests and diseases of *Piper betle* in India have been worked by many scientists. There was also considerable amount of literature regarding the nomenclature of pathogens of betel vine. Raut and Bhattacharya, 1999 investigated the diseases of betel vine and the findings concluded that the pest and pathogens species are attacked by natural enemies belonging to the *Coleoptera*, *Diptera, Heteroptera, Hymenoptera, Aranea* and *Acari*. The predatory mites *Walzia indiana* and *Proctolaelaps pygmaeus* and the mycophagous mites *Unguizetes clavatus* and *Acarus* sp. seem to have potential to control the insect pests and fungal pathogens [89]. Chowdhury, 1944 surveyed the diseases of pan in Sylhet of Assam [90]. Fungal diseases of betel vine are also surveyed by Maiti and Sen, 1979. They reported that foot rot caused by *Phytophthora palmivora* and *Corticium rolfsii*. Leaf rot caused by

Phytophthora palmivora, and leaf spot and anthracnose caused by *Colletotrichum capsici* are widespread and cause recurrent annual loss to crop yield and quality where rainfall and temperature are favourable for the pathogen. Eleven diseases of minor importance, which may gain epiphytic proportions in specific locations and plantations where they appear, were also described briefly. Technology also used for identifying diseases [91]. Vijayakumar and Arumugam, 2014 used digital image processing techniques and identified *Odium piperis* fungus in *Piper betel* plants. These techniques only apply in the detection of powdery mildew diseases in betel vine [92].

Foot rot caused by *Phytophthora* had considered to be a limiting factor for cultivation of betel vine. An accurate description of the symptoms were given by Dastur, 1931[93]. The diseased plants at this stage show a general yellowing and drooping of the tender shoots. Such plants when pulled out, easily breaks at collar region and underground portions are found in a state of decay. The roots and rootlets become brown to black in dying or dead condition. Long, narrow lines, brown- coloured streaks can be observed in the vascular regions. The fungus enters the stem through roots or rootlets. There was considerable amount of confusion regarding the nomenclature of species of this pathogen. He also carried out an extensive investigation on this disease and found *Pythium* also responsible for the foot rot. He also named it as *Pythium piperinum*. Symptions are similar to the symptoms produced by *Phytophthora*.

Maiti and Sen, 1977 observed two types of symptoms in pan. The disease was characterized by the presence of black or brownish water-soaked spots. In one type the expanded spots are circular, necrotic, deep brown in colour with distant gray-brown zonations. In second type necrotic spots show no zonations [94].

4. Conclusion and Discussion

This review suggests that the leaves of *Piper betle* L. contains number of phytoconstituents and as a source for various therapeutic purposes. Hence, further critical studies on leaf extract should be necessary for improving its uses for various medicine production. During cultivation, betel vine affected by some diseases that causes great loss for farmers. So, disease identification must be necessary at an early stage and preventive action can be taken before the disease starts to spread.

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