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Evaluation of hepatoprotective effects of aqueous extract of *Piper betel*

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Abstract

Now a day's traditional treatment in the form of medicinal plant is widely used by the population. The therapeutic using plant that found in nature a part from having no side effects and adverse effect can be long duration of time. It is highly an abundant and inexpensive therefore improving further research industrialization development including in the food and pharmaceutical company [7]. The health benefits bonded with piper betel (local name Paan) belong to family Piperaceae, it has been an important herb distributed throughout of worldwide. Pharmacological profile reveals Piper Betel to have a potential for treating various diseases and condition such as chronic [8].

Piper Betel may have the antioxidant properties and blocked lipid peroxidation in Carbon Tetrachloride induced hepatic damages. Atherosclerosis and diabetes mellitus [4]. This review also provides a list of phytochemical compound compounds in piper betel leaves extracts and their pharmacological advantages mainly how it is hepatic protective [2].

Keywords: *Piper betel*, chavicol, chavibetol, hepatoprotective, antioxidant

Introduction

Piper Betel Linn. (Local name 'Paan') family *Piperaceae* found in Asian region, the leaf surface is green and slippery, while the tree trunk is slightly brownish green with a wrinkled skin surface and rough.

There are various types of leaves, the most popular being: Calcutta, Banarasi, Magahi, Magahi, etc. In Faridpur, Jessore, Bangladesh, and Braise area's producing the most betel [4].

The term Betel was derived from the Malayalam word Vettila via Portuguese. Since antiquity, Piper Betel. Linn, commonly known as Betel vine, has been used as a religious, recreational and medicinal plant in Southeast Asia. The leaves, which are the most commonly used plant part, are pungent with aromatic flavour and are widely consumed as a mouth freshener. It is carminative, stimulant, astringent and is effective against parasitic worms. Experimental studies have shown that it possess diverse biological and pharmacological effects, which includes antibacterial, antifungal, larvicidal, antiprotozal, anticaries, gastroprotective effects, free radical scavenging, antioxidant, anti-inflammatory hepatoprotective, immunomodulatory, antiulcer and chemo preventive activities. The active principles hydroxychavicol, allylpyrocatechol and eugenol with their plethora of pharmacological properties may also have the potential to develop as bioactive lead molecule. In this review, an attempt is made to summarize the religious, traditional uses, phytochemical composition and experimentally validated pharmacological properties of Piper betel. [6]Emphasis is also placed on aspects warranting detail studies for it to be of pharmaceutical/clinical use to humans [3].

Taxonomical classification**Kingdom:** Plantae**Division:** Magnoliophyta**Class:** Magnolipsida**Order:** Piperales**Family:** Piperaceae**Genus:** Piper**Species:** Betel



Fig 1: Piper Betel

Anatomy and physiology of Liver

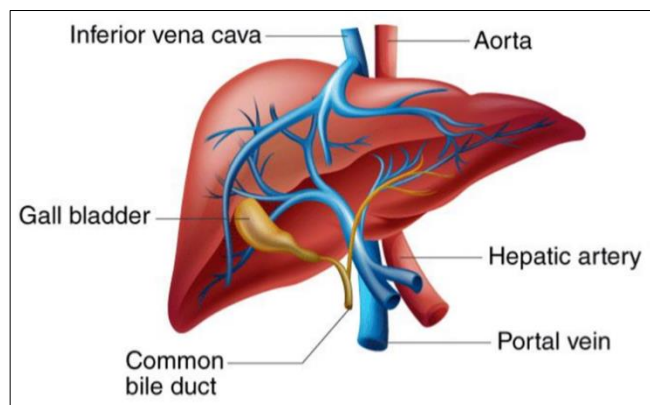


Fig 2: Anatomy of Liver

- The liver is an organ located in the upper right part of the belly (abdomen). It is beneath the diaphragm and on top of the stomach, right kidney, and intestines.
- Shaped like a cone, the liver is a dark reddish-brown organ that weighs about 3 pounds. There are 2 distinct sources that supply blood to the liver, including the following:
 - Oxygenated blood flows in from the hepatic artery
 - Nutrient-rich blood flows in from the hepatic portal vein.

The liver is reddish-brown organ weighing about 1200-1500g which is the largest human internal organ and is the second largest organ after skin. It performs around 500 different vital body functions which are helpful in performing, maintaining and regulating homeostasis of the body [32].

It is responsible in carrying out functions like digestion, sugar and fat metabolism and storage, protein synthesis, detoxification of drugs and other toxins, hormones metabolism and excretion of bilirubin and also body's immune defense (Gorre *et al.*, 2011) [27].

The liver synthesizes products like glucose, plasma protein, clotting factor and urea which are released into the blood stream and bile is excreted to intestinal tract [19].

Many of the synthesized products like glycogen, fat and fat soluble vitamins are stored in liver parenchyma (Pandit *et al.*, 2012) [33].

The Liver is a resilient organ and is maintenance-free which can be ignored until something gets wrong to it. Liver has wide range of responsibilities so it often comes under attack by viruses, toxic substances (including alcohol), contaminants and disease.

The liver is very slow to complain even if its two third is damaged by scarring (cirrhosis) and still it keeps on working.

[34]. Mostly due to few symptoms people are unaware of liver problem.

On having many major advances for the treatment liver diseases still there is no cures and so it's important to carry out preventive steps to avoid liver diseases like making healthy lifestyle and to get immunized against liver disease causing viruses [40].

The liver is divided into left and right lobes by the aciform ligament, but a functional division is into the right and left hemi livers depending upon the hepatic blood supply which is more useful.

These both hemi livers are further again divided into total of eight segments in accordance with subdivisions of the hepatic and portal veins [35].

Each segment has its own branch of the hepatic artery and biliary tree which are used clinically to describe the position of liver tumours on radiological imaging.

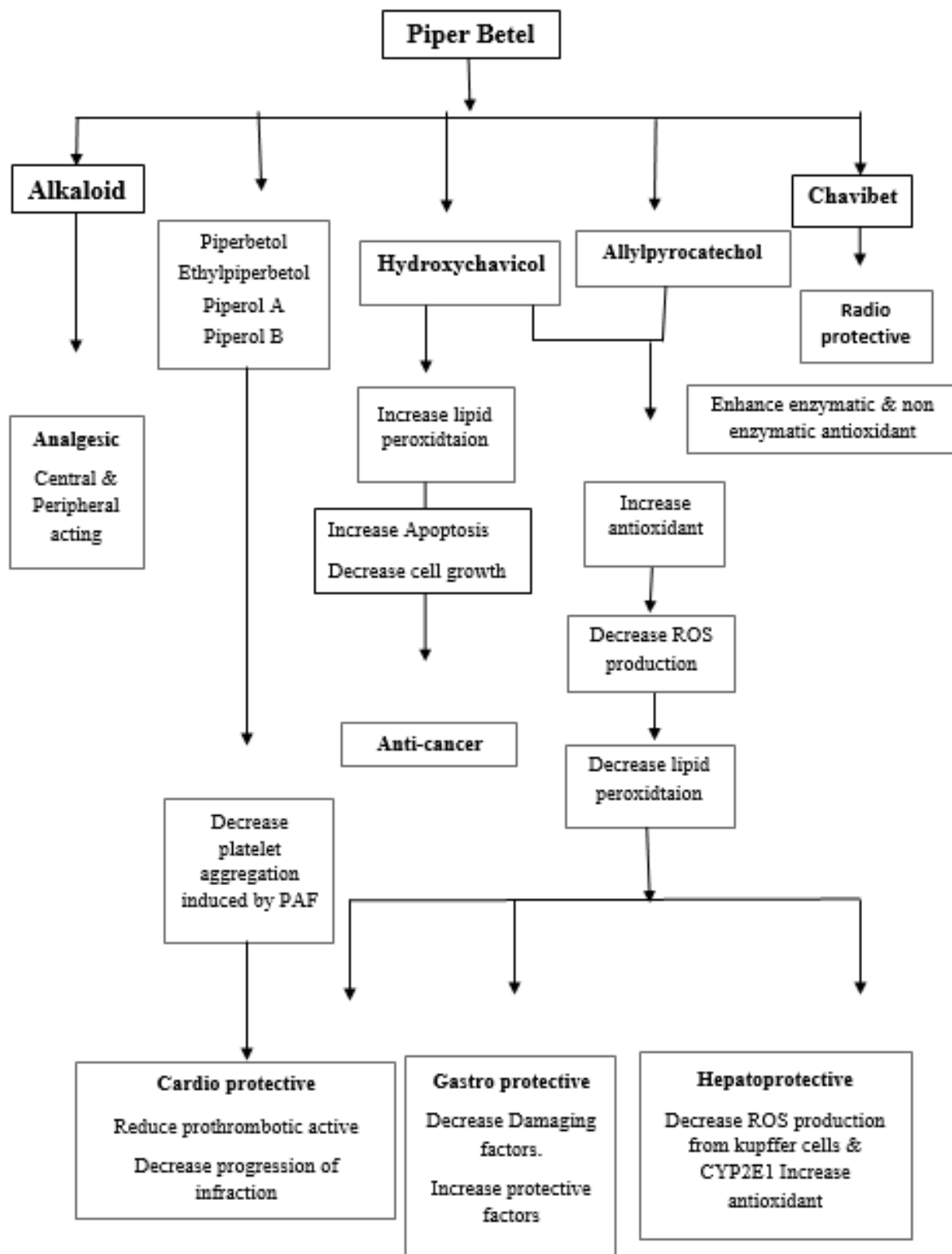
A liver segment is made up of number of smaller units known as lobules, comprised of a central vein, radiating sinusoids separated from each other by single hepatocyte cell plates, and peripheral portal tracts [36]. The hepatic sinus is the functional unit of the liver.

Hepatotoxicity

- Hepatotoxicity implies chemical-driven liver damage. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ.
- Chemicals that cause liver injury are called hepatotoxins. Hepatotoxicity is defined as an injury to the liver that is associated with impaired liver function caused by exposure to a drug or another non-infectious agent. (Victor *et al.*, 2006) [24].
- Hepatotoxicity implies chemical driven liver damage (Pandit *et al.*, 2012). The differentiation between injury function is important as it is mainly when function is impaired that symptoms and clinically significant disease follow (Victor *et al.*, 2006) [24].
- Some medicinal agents when taken in overdose and sometimes even introduced within therapeutic ranges may damage the organ. Other chemical agents like those which are used in laboratories and industries, natural chemicals (e.g. Microcystins) and herbal remedies can also induce hepatotoxicity [20].
- Chemicals that cause liver injury are called hepatotoxins. (Pandit *et al.*, 2012) [26].
- Drug induced hepatotoxicity is frequently a major safety issue for an investigational new drug which may occur as an unexpected idiosyncratic reaction to an otherwise nontoxic drug or it may be an expected consequence of the intrinsic toxicity of a drug, taken in sufficiently large dose to cause liver injury (Yeong-Liang *et al.*, 2003) [22].
- Idiosyncratic reactions are characterized or described by a variable delay or latency period, ranging from 5 to 90 days from the initial administration of the drug and are mostly fatal if the drug is continued once the reaction has started (Lee, 2003) [40].
- In many of the cases, there is no effective treatment other than stopping the drug and providing general supportive care. Prompt uses of N- acetyl cysteine after acetaminophen overdose and intravenous carnation for valproate induced mitochondrial injury are exceptions (Victor *et al.*, 2006) [24].

- Drug related hepatotoxicity may not occur during clinical trials, which are usually limited to a few thousand participants only. However, after approval of a drug for use and subsequent marketing, large numbers of patients are exposed, and rare toxic effect may emerge (Victor *et al.*, 2006) [24].
- Due to increase in the importance of drug induced researchers and regulators have vigorously gained basic knowledge about hepatotoxicity, including types and mechanisms, the circumstances under which hepatic injury occurs, and measures to reduce the occurrence of this untoward side effect (Yeong-Liang *et al.*, 2003) [27].

Hepatoprotective Action of Piper Betel



Piper Betel on hepatic marker enzymes and tissue antioxidant status in ethanol-treated Wistar Rats: Results indicate P. Betel

provide a significant hepatoprotective and antioxidant effect. Hepatoprotective/Chemopreventive/Anti-Liver Fibrosis.

Protection effect of piper betel leaf extract against carbon tetrachloride-induced liver fibrosis in rats [41]. Study supports a chemo preventive potential of PB leaves against liver fibrosis [31]. The hepatoprotection is a compound that functions to protect the liver. Methotrexate (MTX) and folate are folate antagonists that are currently used as first-line therapy for autoimmune diseases such as rheumatoid arthritis and psoriasis. Still, their use is limited because they can cause hepatotoxicity or liver poisoning [9]. The ethanol extract of betel leaf (Piper Betel) can reduce hepatotoxicity in methotrexate (MTX) induced rats. Mice induced with extra betel leaf ethanol intraperitoneally with a concentration of 50 or 100 mg kg⁻¹ bw showed hepa to protective activity in mice given a single dose of MTX of 20 mg kg⁻¹, bw, intraperitoneally and had more hepatic protective properties. Higher compared to folic acid at a concentration of 1mg kg⁻¹ BB, IP [18].

Chemical Constituents of *Piper betle*

Table 1: Chemical Constituents of *Piper betle*

Component	Percentage of components
Chavibetol	53.1
Caryophyllene	3.71
Chavibetol acetate	15.5
Allylpyrocatechol diacetate	0.71
Chavibetol, methyl ether	0.48
Campene	0.48
f-pinene	0.21
Eugenol	0.32
u-limonene	0.14
a-pinene	0.21
1,8-cineol	0.04
Sarobe	0.11
Allylpyrocatechol monoacetate	0.23

Chavibetol

1. Fragrance - Fragrances or odour agents, can be used in home products.
2. Decor, candle - Chemicals detected in substances or products.
3. Similar industrial products; usage indicated when known; more specific modifiers included when known.
4. It is used an air freshener.
5. It is also used as the cleaning [1].

Caryophyllene

1. Caryophyllene, occurring in many essential oils, particularly oil of cloves.
2. It has a role as a non-steroidal anti-inflammatory drug, a fragrance, a metabolite and an insect attractant.

Chavibetol Acetate

Chavibetol and other phenylpropanoids compounds are reported as fungicides, protecting photosensitization-mediated lipid peroxidation (LPO) of rat liver mitochondria and antioxidants [11].

Chavibetol methyl ether

1. Methyleugenol is used as a flavouring agent in jellies,
2. It is used in chewing gums.
3. It is also used in candy and ice creams.

Campene

Camphene is used in the preparation of fragrances and as a food additive for flavouring. These include isobornyl acetate.

F-pinene

1. The F-pinene compounds for the treatment of bladder,
2. The F-pinene compounds are using in the treatment of kidney and urinary stones.

Eugenol

1. Eugenol is useful for treatment of skin infections, skin lesions and inflammatory disorders.
2. It is used asa flavouring for foods and teas and as an herbal oil used topically to treat toothache and more rarely to be taken orally to treat gastrointestinal and respiratory complaints.

U-Limonene

1. Limonene's uses, potential benefits, side effects, and dosage.
2. This citrus compound is also used as an aromatic oil for its calming and therapeutic properties [38].
3. Limonene is a popular additive in foods, cosmetics, cleaning products, and natural insect repellents. For example, it's used in foods like sodas, desserts, and candies to provide a lemony flavour.

1, 8-Cineol

1, 8-Cineole has also shown therapeutic benefits in inflammatory airway diseases, such as asthma and chronic obstructive pulmonary disease.

Saprobe

1. Saprobies are the group of fungi that act as decomposers
2. It helps dispose of organic waste.

Allylpyrocatechol monoacetate

Allylpyrocatechol monoacetate is a natural product found in *Alpinagalanga* with data available. LOTUS - the natural products occurrence database [17].

Advantages of Piper Betel in Liver

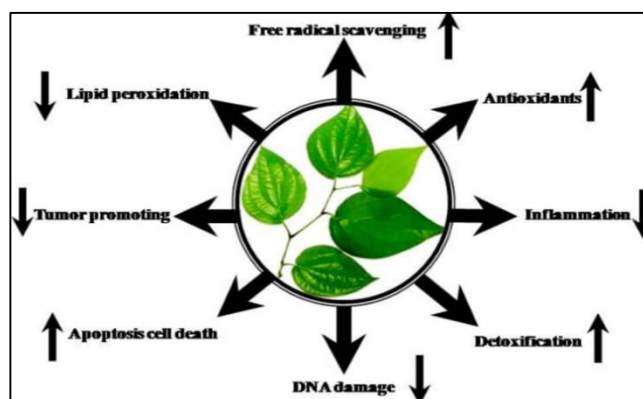


Fig 3: Advantages of *piper betel*

1. Potential use of betel leaves for headache

Betel leaves may have cooling and analgesic (relieve pain) properties. It may be used to relieve pain from severe headaches [39]. Further studies on animals and humans are required to check the effect of betel leaves on headaches. If you experience a prolonged headache or unbearable pain, you must consult your doctor.

2. Potential use of betel leaves for cancer

Betel leaves may have anti-cancer properties and may protect the body against cancer. Studies showed that phenolic-related compounds in betel leaf extract may possess the capacity to inhibit the growth of cancerous cells.¹ However, further studies are required to check the use of betel leaves on cancer. Cancer is a dangerous disease; therefore, you must get proper treatment instead of self-medicating ^[14].

3. Potential use of betel leaves for fungal infection

Betel leaves may be used for fungal infections which, contain a bioactive compound Hydroxychavicol (polyphenol) and it may inhibit the growth of fungus. Betel leaves are used as an antifungal agent for topical infections or as gargle mouthwash for oral fungal infections. ¹ However, further evaluation of the antifungal activity of betel leaves is required in humans. If you suspect a fungal infection, you must consult your doctor and get proper treatment before the infection becomes severe ^[12].

4. Potential use of betel leaves for gastric ulcers

Betel leaves may be used in gastric ulcers due to their gastro protective properties. Due to their antioxidant characteristics, betel leaves may increase enzymatic activity which may be advantageous for gastric ulcers. Betel leaves may increase the mucus content on the stomach lining and inhibit the volume of gastric acid, thereby acting against gastric ulcers.¹ However, further studies on humans are required to check the activity of betel leaves for gastric ulcers. You must get proper treatment instead of self-medicating if you have painful ulcers over time ^[30].

5. Potential use of betel leaves for diabetes

There may be a possible betel leaf health benefit for diabetes. Studies on rats showed that betel leaves might decrease blood

sugar levels.¹ However, further studies are required to evaluate the activity of betel leaves for diabetes. If you are a diabetic patient, you must be diagnosed with diabetes and consult a doctor for proper treatment in case of high blood sugar levels.

6. Potential use of betel leaves for allergies

Betel leaves may be used in case of allergies and *in vitro* studies were done on human lung epithelial cell lines to check the production of allergic mediators by mast cells. The results suggested that the production of allergy mediators may be inhibited by betel leaves. Allergic mediators are biochemical substances in the body that are produced in response to allergens and show allergic symptoms. Further studies on humans are required to evaluate the action of betel leaves against allergies. If you have an allergic reaction, you must consult your doctor.

7. Potential use of betel leaves for healing wounds

Betel leaves may have the ability to heal wounds and studies on male albino rats showed that betel leaves might reduce the healing time and increase the repair mechanism. Studies showed that betel leaves may help to heal wounds due to epithelialization (the process of formation of an epithelial layer over the injured surface).¹ However, further studies are required on humans to check the ability of betel leaves on wound healing. You must immediately consult your doctor if you suffer from a severe or painful wound ^[15].

8. Potential use of betel leaves for constipation

Betel leaves may be used in case of constipation. A suppository made from the stalk of betel leaves (along with castor oil) inserted into the rectum may relieve constipation.¹ However, further studies on humans are required to evaluate the activity of betel leaves for constipation ^[16].

Sr. No.	Piper extract	Activity/ Action	Result	Reference
1)	Aqueous extra of the fresh Piper beetle leaves.	Antimicrobial activity/Various microorganisms /disc diffusion method.	Aqueous extracts showed effective inhibitory action microorganisms	Shame EM Pasha MD (2013) ^[21]
2)	Aqueous extract of the fresh <i>Piper betle</i> Leaves.	Antioxidative & antihemolytic activity/Microorganisms (Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas Aeruginosaa & Escherichia coli).	The ant oxidative & antihemolytic activities were attributed to the high concentration & combined activity of flavonoids & polyphenols	Chakra borty Devjan I; (2011)
3)	Aqueous and ethanol extract of the Piper Beetle leaves.	Antibacterial Activity/Gram positive (Bacillus subtilis, Staphylococcus aureus & Micrococcus luteus) & Gram negative (Escherichia coli & Pseudomonas aeruginosa) bacteria/Agar diffusion method.	The study reveals that both the aqueous and Alcoholic extracts be active beside the strains of bacteria which are common cause of infections.	Kaveti Balaji (2011)
4)	The <i>Piper betle</i> leaf extract.	Antihepatotoxic effect/ethanol & carbon tetrachloride (CCl ₄) induced liver injury in a rat model.	The histological examination shows that <i>Piper betle</i> leaf extract secluded liver from the damage induce by CCl ₄ by declining alpha smooth muscle acting (alpha-sma) expression.	Young S.C (2007)
5)	The ethanolic extract of Piper beetle leaf.	Radioprotective activity/Rat liver mitochondria and pBR 322plasmid DNA.	The extract of <i>Piper betle</i> effectively prevented γ -rayinduced lipid Peroxidation.	Bhattacharya S; <i>et al.</i> (2005)

Need of Work

The liver is one of the most important organs in the body, performing a fundamental role in the regulation of diverse processes, among which the metabolism and detoxification. Piper Betel have a potential for treating various diseases and condition such as chronic diseases like alcoholic fatty liver, liver cirrhosis etc.

This review also provides a list of phytochemical compounds in piper betel leaves extracts and their pharmacological advantages as hepatoprotective, Anti-inflammatory and Antioxidant.

Future Scope

To study Hepatoprotective effect of Betel leaf formulation in Experimentally Induced Hepatotoxicity in rat.

Creates opportunities and formulate new dosage form by using novel techniques.

Piper Betel polyherbal formulation of plant extracts accelerates protective effect on liver by proliferation and mobilization So Piper Betel extract is very useful in future as a hepatoprotective.

Herbal Medicinal Products are gaining acceptance among people across the worldwide because it shows minimal side effects.

Conclusion

Results suggests that the hepatoprotective effects of aqueous extract of Piper Betel might be useful for liver protection due to its own effectiveness. Used as potent source for novel therapeutically value. Further studies of betel plant are also recommended to focus on the variety of metabolic activities in human, thus, improving its usage medically that will be beneficial to human beings.

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