Sys Rev Pharm 2022; 13(8): 775-781
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453 / DOI: 10.31858/0975-8453.13.8.775-781

Review Article

Overview Discussion on Various Pharmacological Effects of *Selenicereus undatus* Plant Parts and Precise Focus on Hepatic Disorders and Treatment Options: A Concise Review

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Article History: *Submitted: 02.08.2022* *Accepted: 26.08.2022* *Published: 02.09.2022*

ABSTRACT

The current discussion focuses on *Selenicereus undatus* pharmacological effects on various physiological systems. This plant contains high amount of polyphenols thus showing antioxidant activity, influences the p-450 enzyme mechanism either by inhibiting or inducing the metabolic activity of enzymes thus, used for the treatment of hepatotoxicity. Also, *Selenicereus undatus* is known for its radical scavenging activity due to the presence of phenolic content. Onitin and luteolin isolated from the methanolic extract of *Selenicereus undatus* showed superoxide scavenging effects and DPPH free radical scavenging activity hence can also be used in cancer treatment. The antioxidant activity and phenolic composition of three different extracts (ethanol, n-butanol and water) of *Selenicereus undatus* were investigated by measuring the total reducing power expressed by Ascorbate Equivalent Antioxidant Capacity-AEAC, inhibition of lipid peroxidation, and free Radical Scavenging Capacity (RSC) towards 2,2-diphenyl-1- picrylhydrazyl (DPPH radical) and Nitric Oxide (NO).The influence of different extracts during lipid peroxidation of sunflower oil induced by the lipophilic azo-initiator 4,4′-azobis(4- cyanovaleric acid) and soybean phosphatidylcholine liposomes induced by the hydrophilic azo-initiator 2,2′-azobis(2-amidinopropane) dihydrochloride was investigated in this study. Hepatoprotective activity-guided fractionation of the methanol extract of *Selenicereus undatus* showed that Onitin and luteolin possessed Hepatoprotective activities on tacrine-induced cytotoxicity in human liver-derived Hep G2 cells. This plant also possesses sedative and anticonvulsant activity. The hydro alcoholic extract of stem from *Selenicereus undatus* shows antinociceptive and anti-inflammatory effects. Studies say that *Selenicereus undatus* can also produce a diuretic effect. The extract of *Selenicereus undatus* produced a dose-dependent inhibition of thrombin and ADP-induced platelet aggregation with in fact proofs that plant has many pharmacological activities.

Keywords: *Selenicereus undatus*, Radical scavenging, Hepatoprotective, Cytotoxicity, Antinociceptive

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INTRODUCTION

The process of evolution has made the survival of organisms by regulating metabolism and various other functions by an organ called liver. The basic functional unit of liver is called as hepatocytes which possess various mechanisms to deal with reactive oxygen species and its effects (Abraham G, 2014). Among the functions of liver include induction of antioxidant proteins such as superoxide dismutase, catalase, and glutathione peroxidase. There is also an enzymatic antioxidant system such as Cu-Zn, Mn, catalase, and glutathione reductase functions by direct or sequential removal of reactive oxygen species, thereby terminating their activities. An imbalance between the oxidative forces and antioxidant defense systems causes oxidative injury, which has been implicated in various diseases, such as atherosclerosis, diabetes, cancer, liver cirrhosis, etc.

The reactive oxygen species is generated continuously at physiological conditions and eliminated by various intracellular and extracellular antioxidant systems (Halliwell B and Gutteridge J, 1984). An uncontrolled production of reactive oxygen species can damage cellular macromolecules like DNA, proteins other antioxidant molecules. The most important species are the superoxide anion radical O_2^-, hydrogen peroxide (H_2O_2), alkoxyl (RO), peroxyl (ROO), hydroxyl radical (OH), and hypochlorous acid (HOCl). There are non-oxygen species that possess reactive nitrogen species as Nitric oxide (NO) and peroxynitrite also have important bioactivity (Jakus V, 2000). Free radical reaction is an important pathway in a wide range of unrelated biological systems. Among many ways of chemical-induced injury, the critical class of reaction is production of free radical intermediates which trigger a network of multifarious disturbances (Jaeschke H, *et al.*, 2002).

There are several hepatotoxic chemicals that damage the liver cells caused by lipid peroxidation and many other oxidative damages. Liver possesses a unique metabolism and plays a pivotal role in the removal of substances from the portal circulation due to which it is susceptible to toxicity of drugs, xenobiotics, and oxidative stress. The two distinct pathways in liver metabolism occur *via* cytochrome p-450 and glutathione-peroxidase. Cytochrome p-450 enzymes play a very important role for the metabolism of all the foreign chemical constituents as well as the natural products that organism consumes (Xu J, *et al.*, 2003). These enzymes are specific to several moieties that enter the body and helps in specific metabolism. However, many times the presence of other drugs will affect the metabolic process either by increasing the metabolism like potentiating process or by decreasing the metabolism like inhibiting the metabolic process. An example is the presence of grape fruit juice will inhibit the metabolism of other drugs and similarly, metabolism inhibition by warfarin kind of compounds on others. The current treatment for hepatotoxicity includes drugs which influence the p-450 enzyme mechanism either by inhibiting (amiodarone, cimetidine, ciprofloxacin, etc.) or inducing (rifampicin, carbamazepine, phenobarbital, phenytoin) the metabolic activity of enzymes (Oh H, *et al.*, 2004).

Recent studies have been focussed on investigating the hepatoprotective function of naturally occurring compounds and their mechanisms of action. Chemical-induced toxicity in HepG2 cells

represents a suitable *in vitro* model for hepato toxicological assessment of drugs, through analysis of different cytotoxic endpoints. HepG2 cells have been used to investigate the metabolism and toxicity of drugs, since these cells retain many specialized functions that are characteristic to normal human hepatocytes, including synthesis and secretion of plasma proteins (D'Agostino M, *et al.*, 1984).

In the absence of reliable modern hepatoprotective drugs, there are a number of traditional medicines recommended for treatment of liver diseases. Many herbs such as *Silybum marianum*, *Tridax procumbens*, and *Andrographis paniculata* have been reported to possess hepatoprotective activity (Malar HV and Bai SM, 2009). Plants contain wide variety of bioactive molecules including terpenoids, steroids, phenols, and flavonoids. In addition to their nutritional value these phytoconstituents exhibit a wide array of pharmacological properties such as anti-inflammatory, antiviral, anti-proliferative, and anti-carcinogenic. Plant derived phenolic, flavonoid, and polyphenolic compounds are considered to contribute to the prevention of diseases associated with oxidative stress (Malar HV and Bai SM, 2009).

There are several reported studies that evaluated the hepatoprotective activity of natural herbal extracts namely *Phyllanthus emblica* Linn. (Euphorbiaceae), *Camellia sinensis* Linn. (Theaceae), *Punica granatum* Linn. (Punicaceae), *Mangifera indica* Linn. (Anacardiaceae), and *Acacia catechu* Linn. (Mimosaceae) on t-BH induced liver toxicity using HepG2 cells (Santos AR, *et al.*, 1995).

Dragon fruit stems are scandent (climbing habit), creeping, sprawling or clambering, and branch profusely. There can be four to seven of them, between 5 and 10 m (16 and 33 ft) or longer, with joints from 30 to 120 cm (12 to 47 in) or longer, and 10 to 12 cm (3.9 to 4.7 in) thick; with generally three ribs; margins are corneous (horn-like) with age, and undulate (Galisteo M, *et al.*, 2000).

Areoles, that is, the small area bearing spines or hairs on a cactus, are 2 mm (0.079 in) across with internodes 1 to 4 cm (0.39 to 1.57 in). Spines on the adult branches are 1 to 4 mm (0.039 to 0.157 in) long, being acicular (needle-like) to almost conical, and grayish brown to black in color and spreading, with a deep green epidermis (WebMD, 2005).

The scented, nocturnal flowers are 25 to 30 cm (9.8 to 11.8 in) long, 15 to 17 cm (5.9 to 6.7 in) wide with the pericarpel 2.5 to 5 cm (0.98 to 1.97 in) long, about 2.5 cm (0.98 in) thick, bracteoles ovate, acute, to 2.5 to less than 4 cm (1.6 in) long; receptacle about 3 cm (1.2 in) thick, bracteoles are linear-lanceolate, 3 to 8 cm (1.2 to 3.1 in) long; outer tepals lanceolate-linear to linear, acuminate (tapering to a point), being 10 to 15 cm (3.9 to 5.9 in) long, 10 to 15 mm (0.39 to 0.59 in) wide and mucronate (ending in a short sharp point). Their colour is greenish-yellow or whitish, rarely rose-tinged; inner tepals are lanceolate (tapering to a point at the tip) to oblanceolate (i.e. more pointed at the base), up to 10 to 15 cm (3.9 to 5.9 in) long about 40 mm (1.6 in) wide at widest point, and mucronate, unbroken, sharp to acuminate (pointed), and white. Stamens 5 to 10 cm (2.0 to 3.9 in) long, are declinate, inserted in one continuous zone from throat to 35 mm (1.4 in) above the pericarpel and cream. The style (bearing the stigma) to 17, they are 5 to 24.5 cm (2.0 to 9.6 in) long, stout, 6 to 8 mm (0.24 to 0.31 in) thick, cream, and up to 26 stigma lobes, they can be whole or sometimes split at the top, cream, about 25 mm (0.98 in) long. Nectar chambers are 30 mm (1.2 in) long. The fruit is oblong to oval, 6 to 12 cm (2.4 to 4.7 in) long, 4 to 9 cm (1.6 to 3.5 in) thick, red with large bracteoles, with white pulp and edible black seeds (Schweitzer A, *et al.*, 2015).

Selenicereus undatus is lithophytic or hemiepiphytic. It is widely distributed through the tropics in cultivation. Like all true cacti, the genus originates in the Americas, but the precise origin of the species *S. undatus* is uncertain and it may be a hybrid. It is a sprawling or vining, terrestrial or epiphytic cactus *(Figure 1)*. They climb by use of aerial roots and can reach a height of 10 meters (32.8 feet) or more growing on rocks and trees. This species is closely related to *S. ocamponis* and *S. escuintlensis*. *Selenicereus undatus* was described by (Haw.) Britton and Rose and published in Flora of Bermuda 256, 1918. In 2017, DR Hunt groups the genus *Hylocereus* within the genus *Selenicereus*. This has been supported by a phylogenetic analysis of the Hylocereeae tribe, therefore this species is consigned under the name *Selenicereus undatus* (Dény P, 2006).

Figure 1: Various parts of *Selenicereus undatus* plant (https://www.nparks.gov.sg/florafaunaweb/flora/1/4/1419)

LITERATURE REVIEW

Hepatic disorders

Liver: The liver is the largest internal organ of the human body, weighing approximately 1.5 kg. It develops from the foregut and it spans the upper right and part of left abdominal quadrants. Anatomically the liver consists of four lobes: Two larger ones (right and left) and two smaller ones (quadrate and caudate) (Hirschfield GM and Gershwin ME, 2013).

The liver, as an organ, receives blood from two different sources. The major one is *via* the hepatic portal vein (75%), which carries venous blood from the intestines, pancreas and spleen. Despite the lack of oxygen, this blood contains high amount of nutrients, endocrine secretions, broken down erythrocytes, but also ingested toxins. The second major source is *via* the hepatic artery (25%), which brings oxygenated blood to the liver. Together with the bile duct, the hepatic portal vein and hepatic artery form the portal triad. Those structures supply blood to the sinusoids and the hepatocytes, subsequently draining into the central vein followed by the sub-lobular veins. The second drainage pattern is *via* the hepatic veins, which end up in the inferior vena cava. The blood vessels travelling through the portal canals are called interlobular vessels, which send blood into the sinusoids, either directly or by branching into distributing vessels first, which in turn empty into the sinusoids *via* inlet vessels. The blood drains into the central vein from sinusoids, which occupies the central axis of the classic liver lobule. The endothelial cells forming the central veins are surrounded by a small quantity of connective tissue fibres (Chu J and Sadler KC, 2009).

As they travel through the parenchyma, the central veins become larger, subsequently emptying into the sub-lobular veins. The endothelial lining of the sub-lobular veins is surrounded by a high quantity of connective tissue fibers, consisting of a layer of both collagenous and elastic fibres. Several sub-lobular veins then converge into larger and valve less hepatic veins, which ultimately empty into the inferior venacava. In histological terms, the liver consists of a large number of microscopic functional units that work in unison to ensure the overall, proper activity of the entire organ. There are three possible ways of describing one such unit, as given below: Hepatic (classic) lobule, Portal lobule, Liver acinus.

Hepatocytes: These large and polyhedral (six surfaces) cells make up 80% of the total cells of the liver. They can contain between two and four nuclei, which are large and spherical, occupying the centre of the cells. Each nucleus has at least two nucleoli. The typical lifespan of a hepatocyte is five months. The adjacent hepatocytes leave a very small space between them

known as bile canaliculi which are almost 1.0-2.0 μm in diameter. The cell membranes near these canaliculi are joined by tight junctions.

Hepatic cirrhosis: This condition is characterized by aggregates of regenerated hepatic cells that are separated by bands of scar tissue (deposited collagen tissue). These two processes take place in response to some extent of hepatocyte destruction, resulting in their damage and subsequent death. Some causes include: Chronic alcoholism, Hepatitis B or C infection, certain autoimmune conditions some genetic metabolic diseases that result in an excessive storage of copper and iron. The scar tissue negatively impacts the blood flow from the sinusoids to the hepatocytes, resulting in a decrease in function. As a result, portal hypertension develops because the blood cannot drain from the portal vein. Cirrhosis often has no signs or symptoms until liver damage is extensive. When signs and symptoms do occur, they may include: Fatigue, easily bleeding or bruising, loss of appetite, swelling in your legs, feet or ankles (edema), weight loss, itchy skin, yellow discoloration in the skin and eyes (jaundice), fluid accumulation in your abdomen (ascites), spiderlike blood vessels on your skin, redness in the palms of the hands, confusion, drowsiness and slurred speech (hepatic encephalopathy). A wide range of diseases and conditions can damage the liver and lead to cirrhosis.

Some of the causes include:

- Iron build up in the body (hemochromatosis)
- Cystic fibrosis
- Copper accumulated in the liver (Wilson's disease)
- Poorly formed bile ducts (biliary atresia)
- Alpha-1 antitrypsin deficiency
- Inherited disorders of sugar metabolism (galactosemia or glycogen storage disease)
- Genetic digestive disorder (Alagille syndrome)
- Liver disease caused by your body's immune system (autoimmune hepatitis)
- Destruction of the bile ducts (primary biliary cirrhosis)
- Hardening and scarring of the bile ducts (primary sclerosing cholangitis)
- Infection, such as syphilis or brucellosis
- Medications, including methotrexate or isoniazid

Some of the risk factors include:

- Drinking too much alcohol- Excessive alcohol consumption is a risk factor for cirrhosis.
- Being overweight- Being obese increases your risk of conditions that may lead to cirrhosis, such as non-alcoholic fatty liver disease and non-alcoholic steato-hepatitis.
- Having viral hepatitis- Not everyone with chronic hepatitis will develop cirrhosis, but it's one of the world's leading causes of liver disease.

Jaundice: This condition classically manifests itself as a yellow discoloration of tissues, which is due to excessive levels of bilirubin (hyper bilirubinaemia) and deposited bile pigments. Jaundice can have a variety of causes, two common ones being hepatic and biliary tract diseases.

If the ability of the liver to excrete conjugated bilirubin is exceeded, pre-hepatic jaundice takes place. This type is related to diseases characterized by a high amount of red blood cell breakdown, like sickle cell anemia (a major source of bilirubin is red blood cell breakdown).

If the liver is damage such that it cannot effectively metabolize and excrete bilirubin, hepatic jaundice occurs. In contrast to the pre-hepatic type, this kind of jaundice exhibits both conjugated and unconjugated hyper bilirubinaemia.

Post-hepatic (obstructive) jaundice is due to a chemical blockage in the biliary system, mostly due to gallstones (Suzuki K, *et al.*, 2008).

Hepatitis: It is a common condition of liver inflammation. The major reason being the viral infections are hepatitis A, B, C, D, and E. These can be sexually transmitted. The viruses in the family Herpesviridae such as the herpes simplex virus may cause hepatitis. Chronic (rather than acute) infection with hepatitis B virus or hepatitis C virus is the main cause of liver cancer. Globally, about 248 million individuals are chronically infected with hepatitis B (with 843,724 in the US), and 142 million are chronically infected with hepatitis C (with 2.7 million in the US). Globally there are about 114 million and 20 million cases of hepatitis A and hepatitis E respectively, but these generally resolve and do not become chronic. Hepatitis D virus is a "satellite" of hepatitis B virus (can only infect in the presence of hepatitis B), and co-infects nearly 20 million people with hepatitis B, globally.

Hepatic encephalopathy is caused by an accumulation of toxins in the bloodstream that are normally removed by the liver. This condition can result in coma and can prove fatal. Budd-Chiari syndrome is a condition caused by blockage of the hepatic veins (including thrombosis) that drain the liver. It presents with the classical triad of abdominal pain, ascites and liver enlargement. Many diseases of the liver are accompanied by jaundice caused by increased levels of bilirubin in the system. The bilirubin results from the breakup of the hemoglobin of dead red blood cells; normally, the liver removes bilirubin from the blood and excretes it through bile.

Other disorders caused by excessive alcohol consumption are grouped under alcoholic liver diseases and these include alcoholic hepatitis, fatty liver, and cirrhosis. Factors contributing to the development of alcoholic liver diseases are not only the quantity and frequency of alcohol consumption, but can also include gender, genetics, and liver insult. Liver damage can also be caused by drugs, particularly paracetamol and drugs used to treat cancer. A rupture of the liver can be caused by a liver shot used in combat sports.

Primary biliary cholangitis is an autoimmune disease of the liver. It is marked by slow progressive destruction of the small bile ducts of the liver, with the intralobular ducts (Canals of Hering) affected early in the disease. When these ducts are damaged, bile and other toxins build up in the liver (cholestasis) and over time damage the liver tissue in combination with ongoing immune related damage. This can lead to scarring (fibrosis) and cirrhosis. Cirrhosis increases the resistance to blood flow in the liver, and can result in portal hypertension. Congested anastomoses between the portal venous system and the systemic circulation can be a subsequent condition.

There are also many pediatric liver diseases, including biliary atresia, alpha-1 antitrypsin deficiency, alagille syndrome, progressive familial intrahepatic cholestasis, Langerhans cell histiocytosis and hepatic hemangioma a benign tumor the most common type of liver tumor, thought to be congenital. A genetic disorder causing multiple cysts to form in the liver tissue, usually in later life, and usually asymptomatic, is polycystic liver disease. Diseases that interfere with liver function will lead to derangement of these processes. However, the liver has a great capacity to regenerate and has a large reserve capacity. In most cases, the liver only produces symptoms after extensive damage.

The liver is the only human internal organ capable of natural regeneration of lost tissue; as little as 25% of a liver can regenerate into a whole liver. This is, however, not true regeneration but rather compensatory growth in mammals. The lobes that are removed do not regrow and the growth of the liver is a restoration of function, not original form. This contrasts with true regeneration where both original function and form are restored. In some other species, such as zebra fish, the liver undergoes true regeneration by restoring both shape and size of the organ. In the liver, large areas of the tissues are formed but for the formation of new cells there must be sufficient amount of material so the circulation of the blood becomes more active.

This is predominantly due to the hepatocytes re-entering the cell cycle. That is, the hepatocytes go from the quiescent G_0 phase to the G_1 phase and undergo mitosis. This process is activated by the p75 receptors. There is also some evidence of bipotential stem cells, called hepatic oval cells or ovalocytes, which are thought to reside in the canals of Hering. These cells can differentiate into either hepatocytes or cholangiocytes. Cholangiocytes are the epithelial lining cells of the bile ducts. They are cuboidal epithelium in the small interlobular bile ducts, but become columnar and mucus secreting in larger bile ducts approaching the portahepatis and the extrahepatic ducts. Research is being carried out on the use of stem cells for the generation of an artificial liver (Tietz PS and LaRusso NF, 2006).

The preliminary phytochemical analysis showed that the plant contained alkaloids, carbohydrate, proteins and amino acids, phytosterols, saponins, sterols, ascorbic acid, silicic acid, phenol, tannin flavonoids and triterpenoids. The plant contained silicic acid, tartaric acid, methyl esters of protocatechuic, caffeic acids isoquercitrin, apigenin and kaempferol as phenolic compounds. Stem contained silicic acid and silicates (5%-8%), calcium (1.3%), potassium (1.8%) and other minerals such as aluminum, sulphur, phosphorus, sodium, zinc, magnesium and manganese. Alkaloids such as nicotine, palustrine and palustrinine were isolated from the plant. The total phenolic content of n-butanol, ethyl acetate and water extracts were 96.4, 26.4 and 15.4 mg/g of dry extracts, respectively. The plant contained 0.6% to 0.9% flavonoids including apigenin-5-0-glucoside, genkwanin-5-O-glucoside, kaempferol-3,7-di-0-glucoside, kaempferol-3-0-(6'-0- malonylglucoside)-7-0-glucoside, kaempferol-3-O-sophoroside, luteolin-5-O-glucoside, quercetin-3-O-glucoside. It was also contained caffeic acid ester (up to 1% including chlorogenic acid, dicoffeoyl-meso-tartaric acid), 5%-7.7% silicic acid and pyridine alkaloids, and styrolpyroneglucosides. Equisetumoside A (3- methoxy-11,12-dihydroxy-phenylhexane-9-one-4-O-β-D-glucopyranoside), equisetumoside B(3-methoxy-4,11-dihydroxy-phenylhexane-9-one-12-O-β-D-glucopyranoside), equisetumoside C (cis-ferulic acid potassium salt 4-O-β-D- glucopyranoside), uridine, inosine, 2′-deoxyinosine, 2′-deoxycytidine,tryptophan,thymidine, 5-carboxy-2′-deoxyuridine, coniferin, and kaempferol 3-O-β-D-sophoroside-7-O-β-D-glucopyranoside were isolated from the water-soluble extract of fertile sprouts of *Selenicereus undatus*. The volatile constituents of the sterile stems of *Selenicereus undatus* were investigated using GC, Gas Chromatography-Mass Spectrometry (GC/MS) and carbon-13 Nuclear Magnetic Resonance (NMR) spectroscopy (^{13}C-NMR). Twenty-five compoundswere identified. Hexahydrofarnesyl acetone (18.34%), cis-geranyl acetone (13.74%), thymol (12.09%) and trans-phytol (10.06%) were the major constituents (Kawarada Y, *et al.*, 2000).

Pharmacological actions

The plant contained high amount of polyphenols. Antioxidant activity (ABTS assay) was estimated to be 98.13 ± 3.84 (μM Trolox equivalents/g dry weight). The total phenol content, total antioxidant capacity and silicic acid amount were found to be 18.67%, 123 mg gallic acid/g dry weight extract, 1608 μM TEAC/mg dry weight extract and 0.0049 mg silicic acid/mg dry weight extract, respectively. Aqueous and ethanol extract from top and body portions of field horsetail were tested for antioxidative activity using four different methods. The ethanol extract fractions of each portion were richer in total phenolic components than water extracts. These fractions had remarkable antioxidative activities, similar to that of 5 mM ascorbic acid. Water extracts of both portions showed high superoxide anion radical-scavenging activities. Hydroxyl radicals were effectively scavenged by ethanol extracts. Rich in vitamin C, E and contained high levels of copper, zinc. These were essential elements, for superoxide dismutase to act against active oxygen species (Clemens J, 2003). The antioxidative activity of different horsetail (*Selenicereus undatus*) extracts was studied by the electron spin resonance spectroscopy–spin trapping method. The influence of different horsetail extracts during lipid peroxidation of sunflower oil induced by the lipophilic azo-initiator 4,4'-azobis(4-cyanovaleric acid) and soybean phosphatidylcholine liposomes induced by the hydrophilic azo-initiator 2,2'-azobis(2-amidinopropane) dihydrochloride was investigated. The results of electron spin resonance analysis confirmed that the extracts suppressed the formation of lipid peroxyl radicals in both systems investigated, in a dose-dependent manner. The results indicate that n-butanol, methanol, ethyl acetate, and water extracts had significant peroxyl radical scavenging activity (Clemens J, 2003). The antioxidant activity and phenolic composition of three different extracts (ethanol, nbutanol and water) of *Selenicereus undatus* were investigated by measuring the total reducing power (expressed by Ascorbate Equivalent Antioxidant Capacity-AEAC), inhibition of lipid peroxidation, and free Radical Scavenging Capacity (RSC) towards 2,2-diphenyl-1- picrylhydrazyl (DPPH radical) and Nitric oxide (NO). The anti-oxidative activity of horsetail extracts was tested by measuring their ability to scavenge stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) and reactive hydroxyl radicals by electron spin resonance spectroscopy. The results demonstrated that the free radical scavenging activity (versus both DPPH and hydroxyl radicals) depended on the type and concentration of applied extracts; the highest DPPH (EC_{50}=0.65 mg/ml) and hydroxyl radical scavenging activities (EC_{50}=0.74 mg/ml) were obtained in the case of n-butanol extract. The radical scavenging activity of extracts significantly correlated with total phenolic content. Onitin and luteolin isolated from the methanolic extract of *Selenicereus undatus* showed superoxide scavenging effects (IC_{50}=35.3 ± 0.2 mM and 5.9 ± 0.3 mM, respectively) and DPPH free radical scavenging effect was (IC_{50} of 35.8 ± 0.4 mM and 22.7 ± 2.8 mM, respectively).

Anticancer effect: The antiproliferative activity of different horsetail (*Selenicereus undatus*) extracts was studied using the sulforhodamine B colorimetric assay on the human cancer cell lines HeLa, HT-29, and MCF7. The antiproliferative of the extracts was depended on cell line, type of extract, and extract concentration. Ethyl acetate extract exhibited the most prominent antiproliferative effect, without inducing any cell growth stimulation on human tumor cell lines. Mouse fibroblasts cell culture (NCTC cell line clone L929) was used to study the effect of polyherbal extract (70% ethanolic extract: 4 g *Selenicereus undatus*, 3 g *Achillea millefolium*, 2.5 g *Echinacea purpurea* and 0.5 g *Hyssopus officinalis* on collagen secretion. Cells were supplemented with 5% Fetal Calf Serum (FCS), containing different concentrations of polyherbal extract (35-140 μg/ml). The results showed a significantly ($P<0.05$) increase of collagen synthesis in the culture medium of fibroblasts treated with 70 and 140 μg/ml polyherbal extract, after 48 h and 72 h of cultivation. It was observed that the collagen synthesis was almost 2 times higher in cultures treated with 140 μg/ml polyherbal extract, for 72 h, compared to the value obtained in the control group. The water extract from sterile stems of *Selenicereus undatus* exerted dose dependent cytotoxic effects on human leukemic U 937 cells. DNA fragmentation, externalization of phosphatidylserine and the collapse of mitochondrial trans membrane potential were all observed in cells cultured for 48 h with the herb extract. The authors concluded that the cytotoxicity of *Selenicereus undatus* water extract against U 93 7 cells was due to apoptosis. The antiproliferative effect of *Selenicereus undatus* extract was tested on melanoma B16 cells. At a concentration of >0.5 mg/ml, it showed significant antiproliferative effect. The cytotoxicity of the methanolic extract of the dried aerial part of *Selenicereus undatus* was tested against various cancer cell lines including cervical adenocarcinoma, lung fibroblast, breast adenocarcinoma, and human embryonic kidney cells. After 72 hours treatment, the cells were assayed to determine the relative percentages of dead and live cells. The extract induced death on the four tested cell lines with the greatest effect on human embryonic kidney cells followed by breast adenocarcinoma. However, the extent of toxicity varied depending on the cell type and the concentration of the used extract. Compared to untreated cells, the plant extract had a profound cytotoxic effect on the breast cancer cell line. This effect was concentration- dependent, where 50 μg/ml had

a larger effect than 20 µg/ml. A cytotoxic effect was also observed on the embryonic kidney cell line, 50 µg/ml showed more activity than 20 µg/ml. On HeLa cells, only a very slight difference was observed when extract-treated cells were compared to untreated cells (Philip D, 1994). The crude *Selenicereus undatus* protein extract inhibited cancer cell proliferation in cell culture of L-1210 (mouse derived leukemia cells), 3T3 (mouse derived SV-transformed fibroblasts) and HMV-1 (human derived melanin producing melanoma cells). It also caused life prolongation in mice in an *in vivo* study using L-1210 and B16F1 (mouse melanoma cells). Concentrations range between 100-3000 µg/ml were tested for the first trial to determine IC_{50} value, which was appeared as 500 µg/ml in 48 hour. For this concentration, viability was determined as 49.61%. Cytotoxic evaluation of IC_{50} for 24, 48 and 72 hour was compared with total phenol content and antioxidant activity of the extracts. Strong correlation was recorded between cytotoxic activity and antioxidant activity and total phenol content. A significantly higher cytotoxic activity was processed with extraction medium containing 90% ethanol for 12 hour, while extracts obtained with 10% ethanol for 2 hour did not decrease the viability upon exposure to fibroblast cells.

Antimicrobial effect: The methanolic extract of the aerial parts of *Selenicereus undatus* displayed antibacterial activity against *Escherichia coli* at high concentration (1 g/ml) (Tietz NW, 1976). *Selenicereus undatus* extracts showed antimicrobial activity against *Staphylococcus epidermidis* and *Escherichia coli*, but it possessed no effect against *Candida albicans*. A disk diffusion method was used for the evaluation of the antimicrobial activity of volatile constituents of *Selenicereus undatus* against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Salmonella enteritidis*. The antifungal activity of the oil was studied against *Aspergillus niger* and *Candida albicans*. The 1:10 dilution of the essential oil of *Selenicereus undatus* possessed a broad spectrum and very strong antimicrobial activity against all the tested bacteria and fungi. The antibacterial activity of ethanolic and aqueous extract of *Selenicereus undatus* was screened against selected urinary tract pathogens (*E. coli*, *Klebsiella pneumonia*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Staphylococcus saprophyticus* and *Enterococcus faecalis*) using disc diffusion technique. Both the extracts at different concentration exhibited antibacterial activity against all the tested bacterial strains. Ethanolic extract exhibited comparably a high degree of activity than the aqueous extract. The ethanolic extract was more effective against *E. coli*, *Proteus mirabilis* and *Staphylococcus saprophyticus* with a zone of inhibition of 24 mm, 23 mm and 24 mm diameter (at concentration of 1000 µg) respectively and was least effective against *Pseudomonas aeruginosa* with zone of inhibition of 11 mm (at concentration of 1000 µg). Among the other studied bacterial species, *Klebsiella pneumoniae* and *Enterococcus faecalis* showed a zone of inhibition of 18 mm diameter (at concentration of 1000 µg) and *Staphylococcus aureus* showed inhibition zone of 14 mm diameter (at concentration of 1000 µg) (Henderson AR and Moss DW, 2001). The *in vitro* antibacterial activity of ethanol stem extract (50-400 µg/ml) of *Selenicereus undatus* was studied against two Gram positive (*Bacillus subtilis* and *Micrococcus luteus*) and four Gram negative (*Vibrio cholerae*, *Escherichia coli*, *Shigella flexneri* and *Shigella dysenteriae*) bacteria. Out of six bacterial species (except *Shigella dysenteriae* and *Vibrio cholera*), four were found to be very sensitive to plant extract at all concentrations. The mean zone of inhibition for the extract against Gram positive and Gram negative bacteria increased with the increasing concentration of the extract. The highest mean zone of inhibition (32 mm) was recorded against *Escherichia coli*. The water extract of aerial parts of *Selenicereus undatus* possesses inhibitory effect on HIV-1 induced cytopathy. Effect on smooth muscles: The vasorelaxant activities of dicaffeoyl- meso-tartaric acid from *Selenicereus undatus* was studied in isolated rat aorta strips. It showed slow relaxation activity against Norepinephrine (NE)-induced contraction of rat aorta with/without endothelium. This compound did not affect contraction induced by a high concentration of potassium (60 mM K^+), while it inhibited NE-induced vasocontraction in the presence of nicardipine. The results showed that the inhibition of NE-induced vasocontraction was due to a decrease in calcium influx from the extracellular space caused by NE. In addition, dicaffeoyl tartaric acids showed vaso relaxant activity, regardless of their stereochemistry. Dried powdered plant material was extracted with alcohol. The extract obtained after the removal of the alcohol was triturated with petroleum-ether (40°C-60°C) and then charcoaled, filtered and dried under vacuum. A 10 mg/ml solution/suspension of the extract (in distilled water) was added to the bath in 100-800 ug/ml concentrations to study its effect on isolated guinea-pig ileum. The extract of *Selenicereus undatus* antagonized the effect of acetylcholine on the isolated guinea-pig ileum preparation (Tietz NW, 1995).

Central nervous effects: In studying of sedative and anticonvulsant effects of *Selenicereus undatus*, hydroalcoholic extract of *Selenicereus undatus* (200 and 400 mg/kg), it appeared that the extract possessed significant activity on the open field, enhanced the number of falls in the rota-rod reducing the time of permanence in the bar and increased the sleeping time (46% and 74% respectively) in the barbiturate-induced sleeping time. In the pentylene tetrazole seizure, it increased the first convulsion latency, diminished the severity of convulsions, reduced the percentage of animals which developed convulsion (50% and 25% respectively) and protected animals from death. However, in the elevated plus maze, the doses 50, 100 and 150 mg/kg did not affect the evaluated parameters. The ethanolic extract of *Selenicereus undatus* (50 and 100 mg/kg) significantly increased the time-spent and the percentage of the open arm entries in the elevated plus-maze model, the effect was comparable to diazepam. Ethanolic extract (100 mg/kg) prolonged the ketamine-induced total sleeping time and decreased the locomotor activity in mice (US National Plant Germplasm System, 2015). The sedative, pre-anesthetic and anti-anxiety effects of *Selenicereus undatus* were studied in rats. The extract of *Selenicereus undatus* was given at doses of (100, 200, 400 mg/kg, ip) and Diazepam with dose of (0.5 mg/kg, ip). The Hydroalcoholic Extract of *Selenicereus undatus* caused a significant increase in ketamine induced sleep and showed anxiolytic, sedative and preanesthetic effects at a dose of 200 mg/kg ip. The chronic administration of the Hydroalcoholic Extract of stems of *Selenicereus undatus* (HAE) reversed the cognitive impairment in aged rats. Chronic administration of HAE at dose of 50 mg/kg, ip, improved both short- and long term retention of inhibitory avoidance task and ameliorated the cognitive performance in reference and working memory version of the Morris Water Maze. No differences were found between all three groups of young controls, aged controls and HAE-treated animals with regard to the open field and elevated plus maze tests. *In vitro* assays revealed that HAE diminished the thiobarbituric acid reactive substances as well as nitrite formation, but did not alter catalase activity. The authors concluded that the cognitive enhancement effects of the HAE may be attributed, at least in part, to its antioxidant action.

Effect on immune system: The influence of crude *Selenicereus undatus* protein on immune responses was investigated by measuring Interleukin-2 (IL-2) and Interferon-γ (IFN-γ) produced by T helper type 1 (Th1) cells. After 24-hour culture with 0.2 mg/ml of crude *Selenicereus undatus* protein in the presence of 5 µg/ml ConA, 1,434.5 pg/ml of IL-2 was produced, showing 1.7 times greater production than that in the control. In cells cultured for 48 hours, 2,130.9 pg/ml was produced by cells treated with 0.2 mg/ml of crude *Selenicereus undatus* protein in the presence of 10 µg/ml ConA, showing 1.9 times greater production than that in the control. Regarding the IFN-γ production-enhancing effect, 929.3 pg/ml was produced by cells cultured for 24 hours with 0.2 mg/ml of crude *Selenicereus undatus* protein in the presence of 5 µg/ml ConA, suggesting that Th1 cells were activated (Flora of North America, 2015).

Antidiabetic effect: The methanolic extract of *Selenicereus undatus* (50, 100, 250 and 500 mg/kg daily for 5 weeks) was investigated for antidiabetic activity in streptozotocin-induced diabetic rats. The results showed that different doses of methanolic extract significantly lowered blood glucose. Also the weights of methanolic-extract treatment group were significantly higher. Concurrent histological studies of the pancreas of these animals showed comparable regeneration by methanolic extract which were earlier, necrosed bystreptozotocin.

Antinociceptive and anti-inflammatory effects: The antinociceptive and anti-inflammatory effects of Hydroalcoholic Extract of stem from *Selenicereus undatus* were studied in mice. The extract 10, 25, 50 and 100 mg/kg, ip, reduced the writhing induced by acetic acid in 49, 57, 93 and 98%, respectively. In the formalin test, 50 and 100 mg/kg, ip, reduced in 80% and 95% the licking activity in the first phase, but in the second phase only the latter dose diminished the licking time (35%). In both phases, naloxone failed to revert the analgesic effect of the extract. In the hot-plate test, the extract at 100 and 200 mg/kg does not change the latency to licking or jumping. In the carrageenan-induced paw edema, the extract at 50 mg/kg, reduced the paw oedema 2 h (25%) and 4 h (30%) after carrageenan administration. The dose 100 mg/kg caused reduction of the paw edema (29%) only 4 h after carrageenan administration.

Effect on urinary system: The diuretic effect of EADE was assessed clinically by monitoring the volunteers' water balance over a 24 h period. The dried extract of *Selenicereus undatus* (900 mg/day) produced a diuretic effect that was stronger than that of the negative control and was equivalent to that of hydrochlorothiazide without causing significant changes in the elimination of electrolytes. Only rare minor adverse events were reported. The mechanism of action by which ethanol root extract of *Selenicereus undatus* (EA) influences urinary bladder activity in rats was studied. The plant was extracted by hot ethanol (95%). Rats in EA group were treated with a standard diet containing 0.2% of the extract, while rats in the control group were fed with the diet only. After 3 weeks, cystometry with 0.2% acetic acid solution and bladder activity was recorded, blood pressure, body weight and adenosine triphosphate were measured and 0.2% acetic acid solution was infused into the bladder and urinary adenosine triphosphate was determined before and after the stimulation. The results showed that during cystometry with acetic acid, the time interval between urinary bladder contractions was shorter and maximum bladder contraction pressure was much greater in rats in the control group, but in the *Selenicereus undatus* group, the changes were much lower. Furthermore, in the *Selenicereus undatus* group, plasma adrenaline and noradrenaline levels were lower than for the control group. In addition, increase in the levels of urinary adenosine triphosphate was smaller in *Selenicereus undatus* group than in control group. The authors concluded that *Selenicereus undatus* ethanol root extract influences urinary bladder activity by decreasing adenosine triphosphate release (Jinous A and Elnaz R, 2012).

Inhibition of platelet aggregation: The extract of *Selenicereus undatus* produced a dose-dependent inhibition of thrombin and Adenosine diphosphate (ADP)-induced platelet aggregation. The effect of the plant could be related in part to the polyphenolic compounds present in the extract suggesting their involvement in the treatment or prevention of platelet aggregation complications linked to cardiovascular diseases.

Hepatoprotective effect: Hepatoprotective activity-guided fractionation of the methanol extract of *Selenicereus undatus* showed that onitin and luteolin isolated from the methanolic extract of *Selenicereus undatus* possessed hepatoprotective activities on tacrine-induced cytotoxicity in human liver-derived Hep G2 cells, displaying EC_{50} values of 85.8 ± 9.3 mM and 20.2 ± 1.4 mM, respectively, while, Silybin, used as a positive control, showed EC_{50} value of 69.0 ± 3.3 mM.

Side effects, contraindications and toxicity

In acute toxicity the various plant extracts showed no side effects and mortalities in rats. In subacute toxicity study, no body weights changes, cumulative body weight gains, biochemical and hematological side effects were recorded in rats consume 0.3%, 1% and 3% *Selenicereus undatus* powder in diet. In a reverse mutation test, the number of revertant colonies on the plates treated with *Selenicereus undatus* was not increased for *S. typhimurium*. The test substance was not found to have mutagenic potential. In a chromosomal aberration test with Chinese hamster lung cells, the incidence of cells with chromosomal aberrations was lower than 5% both by the short treatment method and the continuous treatment method; the test substance was not found to have chromosomal aberration potential. In the micronucleus test in rats, the incidence of micronucleus was not significantly increased the test substance was not found to have mutagenicity potential *in vivo*. However, the plant was possibly unsafe when taken by mouth long- term. It contained thiaminase, which breaks down the vitamin thiamine. This effect could lead to thiamine deficiency. Some products were labeled (thiaminase-free), but there was no enough information available for their safety. There was no enough information about the safety of taking horsetail in pregnant or breast-feeding woman. It was contraindicated in alcoholic people who, they were generally also thiamine deficient. Therefore, taking horsetail might make thiamine deficiency worse. Horsetail lowered blood sugar levels in people with diabetes. Horsetail might flush potassium out of the body, possibly leading to decrease potassium levels. It used with caution in patient at risk for potassium deficiency. Horsetail was also contraindicated in patients who have edema due to impaired heart and kidney function. A doctor should be consulted when the drug is utilized as a bath additive in cases of major skin lesions, acute skin lesions of unknown origin, major feverish and infectious diseases, cardiac insufficiency and hypertonia. Toxicity was recorded in animals, symptoms of *Selenicereus undatus* poisoning were seen primarily in young, rapidly growing horses, cows and sheep. The symptoms of *Selenicereus undatus* poisoning developed slowly. These included scruffy physical appearance, diarrhea and slight incoordination. Untreated poisoning will developed to loss of muscular control, staggering gait and nervousness. Animals may lie down and not be able to get up, may complain seizure and die within 1-2 weeks. Treatment should be oriented to remove the source of poisoning, Equisetum should not present inhay. Thiamine (vitamin B1) may be administered initially intravenously, then intramuscularly for several days. The acute hepatotoxicity of *Selenicereus undatus* (30, 50, and 100 mg/kg for 14 days) was evaluated in rats. Blood samples were obtained to determine TGO, TGP, FA, DHL and GT-gamma activities. Hepatic tissue samples were collected for the anatomopathologic analysis. The anatomopathologic exam of the hepatic tissue showed lobular structure, however, there was no significant change in the activities of the hepatic enzymes when compared to control group.

DISCUSSION AND CONCLUSION

The hepatoprotective activity of *Selenicereus undatus* was studied in albino Wistar rats by inducing hepatotoxicity using paracetamol. The haematological parameters have shown a increase in liver enzymes in blood after liver damage and become to normal after giving the treatment. A high dose compared to low dose was found more effective in attaining hepatoprotection. The histopathological studies were observed in microscopic examination, which confirmed the liver damage with paracetamol and a recovery of healthy hepatocytes after the treatment for 7 days. Thus it is concluded that the plant powder from *Selenicereus undatus* may be consisting of an active constituents which can improvise the health status of hepatocytes in damaged liver and also can protect the liver from damaging. Still further confirming studies are required for identifying the exact mechanism of action as well as identifying the lead molecule from the plant that is essential for hepatoprotective activity.

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