Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 3, 2013

Review Article

A REVIEW ON THE PHYTOPHARMACOLOGICAL EFFECT OF *SWIETENIA MACROPHYLLA*

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Received: 11 Jun 2013, Revised and Accepted: 19 July 2013

ABSTRACT

Most of the medicinal agents are originated from nature and considered as a rich source for producing drugs including modern drugs. *Swietenia machrophylla* is one of the most important plant of the family, *Meliaceae*. It is planted widely in Southern Asia and in the Pacific region. This review provides information on its traditional uses, phytochemical and medicinal values. The plant extracts and its chemical molecules like limonoids have been accounted to possess Antioxidant, Antimicrobial activity, Anti-inflammatory activity, Anti-HIV activity, Antiulcer activity Antifungal activity Antimalarial and Antidiarrhoeal effects, etc. *S. Macrophylla* activities were proven based on its chemical constituents and traditional uses.

Keywords: *Swietenia macrophylla*, *Meliaceae*, Anti-inflammatory, Anticancer, Anti-HIV.

INTRODUCTION

The species *Swietenia macrophylla* Figure 1, is a member of the family *Meliaceae*. *S. macrophylla* occurs mainly in open rain forest, semideciduous and deciduous forests (which lose their leaves in a partial way or total respectively, during the dry season) [1]. Its fruit seem to point upwards to the sky, therefore, it is commonly known as "sky fruit" [2]. *S. macrophylla* located in more than 40 countries including in Brazil, Bolivia, Mexico, Guatemala, Peru and other central American countries [3,4,2]. The tree of *macrophylla* is usually taller than 30 m, with straight trunk and cylindrical with 100 to 200 cm at breast height. The bark is dark reddish brown, entirely rosy, thick and deeply furrowed. The leaves are alternate with leaflets opposite or occasionally changed. The small flowers yellow-cream colored panicles. The fruit is woody, consisting of capsule, ovoid, color light brown, which opens on 5 shares, with 10 to 14 winged seeds [3,5].

Fig. 1: *Swietenia macrophylla* species.

Chemical constituents

Swietenia macrophylla contained various chemical compounds. A number of limonoids have been reported from the genus *Swietenia* with structures assigned on the basis of spectral data [6]. Hence, limonoids and their derivatives have been identified as major constituents of this plant [7]. Limonoids are derived from tetracyclic triterpenes similar to euphol (H-20b) by a series of oxidative changes at their side chain to a b-substituted furan ring by the loss of four carbon atoms, along with some molecular rearrangements. Therefore, an alternative name, tetranortriterpenoids, with a 4,4,8-trimethyl-17-furanylsteroidal skeleton is used to recognize this compound [8].

Based on the isolation done to the fruit of *S. Macrophylla,* a new phragmalin-type limonoid known as 6-O-acetyl-30-demethylswietephragmin together with 16 known compounds. 6-O-Acetyl-30 demethylswietephragmin, 3,6-O,O-diacetylswietenolide, 3-O-tigloylswietenolide, 3-O-tigloyl- 6-O-acetylswietenolide, swietemahonin, and 6-O-acetylswietemahonin were isolated and identified from its fruit. These compounds exhibited some inhibition of superoxide anion generation by human neutrophils in response to formyl- L-methionyl-L-leucyl-L-phenylalanine (fMLP) [7]. Human neutrophils are known to play a significant role in the host defence against microorganisms and in the pathogenesis of various diseases. Some examples of the diseases are rheumatoid arthritis, asthma, ischemia–reperfusion injury, and chronic obstructive pulmonary disease [7,9].

The understanding of the chemical constituents of the bark of the *S. Macrophylla* was investigated and it was shows that a new phenylpropanoid-subtituted catechin, namely, swietemacrophyllanin-catechin-8,7-7,2-epoxy-(methyl 4,5-dihydroxyphenylpropanoate) was successfully isolated. The other two known compounds were also isolated which are catechin and epicatechin [10]. From *S. macrophylla* seeds, many kinds of limonoids or also known as tetranortriterpenoids were found. These included swietenine, swietenolide (a bitter compound) [10,11], 8,30-epoxy-swietenine acetate, swietenolide diacetate [10,11], augustineolide and 3β,6-dihydroxydihydrocarapin [10,12], as well as five derivatives of the former three compounds [13] were isolated and identified.

Also there are presence of some fatty acids and terpenoids, which isolated from the seeds [10,11] included palmitic acid (12.50%), stearic acid (16.42%), arachidic acid (0.56%), oleic acid (25.30%), linoleic acid (33.87%) and linolenic acid (11.32%). The abundance of polyunsaturated fatty acid especially linoleic and linolenic acid shows that *S. macrophylla* seed oil has the ability to provide benefit to human health [14]. The seeds of *S. macrophylla* were also rich in fat, thus the composition of this seed fat have enhanced the possibility of using this oil [13].

Some chemical constituents were analyzed from the terminal shoots, senescent and mature leaves as the essential oil components in form of fatty acids and terpenoids such as γ-himachalene, germacrene D, germacrene A, cadina-1,4-diene, hexadecanoic acid and ethyl hexadecanoate [10,15]. The percentage of chemical composition of the essential oils of terminal shoots, mature, and senescent leaves of *S. macrophylla* were different except for the main constituent and five other compounds. The major constituent in all samples with concentration 58.5 to 66.5% was germacrene D, while all the oils contained γ-himachalene, germacrene A, cadina-1,4-diene, hexadecanoic acid, and ethyl hexadecanoate, though in different proportions. The most similarity was found in the oils from mature and senescent leaves, both of which contained 10 similar compounds [15].

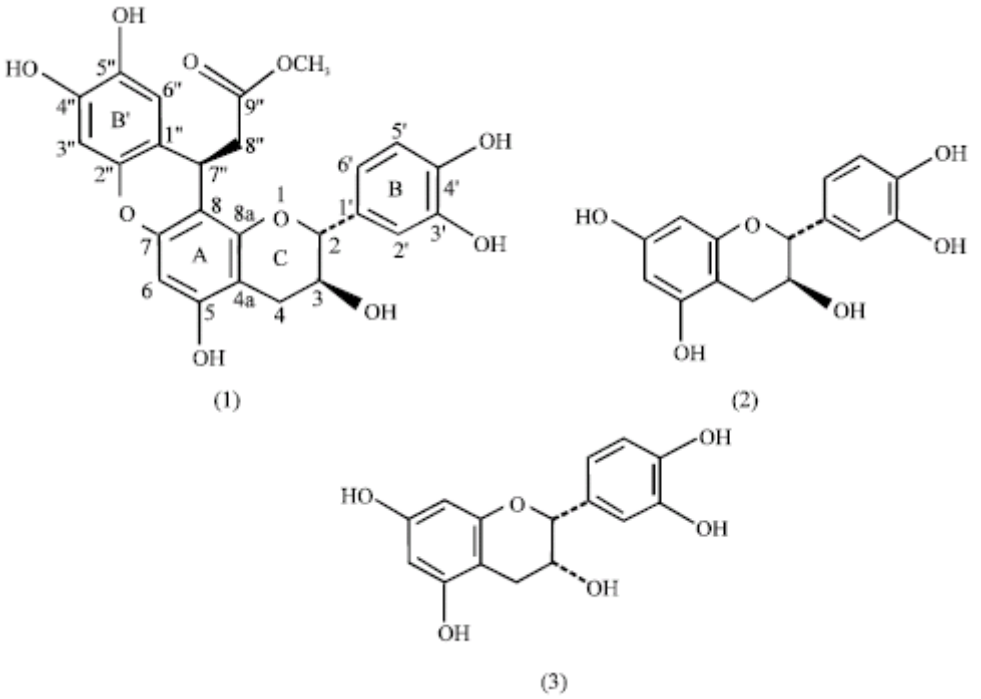

Fig. 2: Chemical constituents isolated from *S. macrophylla* bark. (1) (Pale red amorphous solid) was identified as phenylpropanoid-substituted catechin. (2) (Pale brown amorphous solid) was identified as catechin. (3) (Pale brown amorphous solid) was identified as epicatechin.

Traditional uses

On the basis of traditional use, herbs are selected and combined for their ability to support organ systems which responsible for detoxification and immune function and inhibit microbial growth in various part of the body system. Phytoconstituents such as flavonoids, alkaloids, tannins and triterpenoids are rich source of many medicinal plants such as *S. macrophylla,* which mainly composed of triterpenoids and limonoids [16]. Over the years, medicinal plants have been found useful in the treatment and management of various health problems. About 80% of the world population relies on the use of traditional medicine, which is predominantly based on plant material. Scientific studies available on a good number of medicinal plants indicate that promising phytochemicals can be developed for many health problems [17].

S. macrophylla has been widely used in the common folks communities around the world especially in some countries which have high distribution of this species. Each part of this plant have many uses and beneficial to humans whether as a medicine or other purposes. The fruit, commonly called sky fruit which has been used commercially in healthcare products to improve blood circulation and skin condition [2]. Traditional medicinal plants have been employed successfully by the local communities since long time to treat the disease such as diabetes without adverse effects.

Researches in traditional medicine to find an appropriate natural agents to overcome the diseases (such as hypoglycemic agents) have been focused on plants, especially *S. macrophylla* due to the fact that traditional medicine gives better treatments than drugs [18,19]. Majority of individuals (about 80%) from developed countries use traditional medicine, which contained compounds derived from natural products and medicinal plants. Therefore, more research and investigation should be done in order to approach better understand their properties, safety and efficiency [20].

The traditional practice by chewing and then swallowing the seeds of *S. macrophylla* by natives and the common folks of Malaysia is believed in providing cure to high blood pressure [11], hypertension [11,13,7] and also to relieve pain [2]. Skin ailments and wounds also can be treated using the decoction of the crushed seeds of this tree [21]. Besides, the seeds are also used to reduce the diarrhoea [22,21,2]. Similar to East Midnapore, West Bengal, India, the seeds of *S. macrophylla* are traditionally used by the local healers for curing diarrhoea [22]. In India, *S. macrophylla* King (*Meliaceae*) is used in the treatment of diabetes mellitus, and hypertension [23]. Also the seeds of *S. macrophylla* have been used to treat leishmaniasis [24], which is a disease caused by obligate intra-macrophage protozoa transmitted by phlebotomine sandflies. Poor and neglected populations in East Africa and the Indian subcontinent are particularly affected [25].

For Amazonian Bolivian ethnic group, *S. macrophylla* is used as an abortion medicine [24] also for the treatment of hypertension, diabetes and malaria as a folk medicine in Indonesia [26]. *S. macrophylla* seeds and neem (*Azadirachta indica*) leaves have a beneficial effect on diabetic patients as they were used as traditional plants for the treatment of diabetes. Hypoglycemic effect is observed with neem and *macrophylla* leaves when given to the patients as a leaf extract and seed oil. As stated earlier, the *macrophylla* seeds revealed the presence of triterpenoids, thus these triterpenoids served as potential hypoglycemic agent in *macrophylla* seeds which reduce the glucose level in human's blood stream into an acceptable range [14]. In general, *S. macrophylla* extracts especially the plant seed have many medical efficacy. Which is proven traditionally and scientific as used to cure malaria, anaemia, diarrhoea, fever, dysentery, hypertension, cancer, coughs, chest pains, intestinal parasitism, and anti-ulcer activity [23, 2,27]. On the other hand, *S. macrophylla* leaves can be used for dyeing agent while the bark extract has been used as an astringent for wounds and used occasionally for tanning because of the rich red colour [10].

Macrophylla wood has been used for many purposes even in the architechture, furniture manufacturing, construction and musical instrument. *S. macrophylla* also being used in cabinet making, interior trim, panelling, fancy veneers, musical instruments, boat building, turnery and carving. A part from that, *S. macrophylla* wood also suitable for flooring, automobile bodies and mouldings [28].

Pharmacological activities

Swietenia macrophylla mostly contained the limonoids which have been reported for their responsibility for some of the pharmacological activities such as antifungal [6], antimalarial and insect antifeedant [7]. Many plants have been used because of their antimicrobial traits, which are due to the biological active

compounds synthesized in the secondary metabolism of the plant such as phenols, terpenoids, alkaloids and flavonoids [29]. Some of the pharmacological activities of *S. macrophylla* have been studied including:-

Anti-fungal activity

The enhancement of the plant potential to overcome the pathogenic fungi is actually due to its chemical constituents (triterpenoids) which is present in sufficient concentrations in *S. macrophylla* is an important group of constitutive defense substances [30]. Extracts from seeds of the *S. macrophylla* containing triterpenoidal compounds are known to be effective against plant pathogenic fungi. Antifungal triterpenoids of the *S. macrophylla* include four meliacins from *Chisocheton paniculatus* [31] and nimonol and isomeldenin from *Azadirachta indica* [6,32]. The limonoids of the *S. macrophylla* were tested for anti-fungal activities against the groundnuts rust *Puccinia arachidis*. The results showed an effective reduction of the number of rust pustules on detached ground nuts leaves due to the presence of limonoids content in *S. macrophylla* [6].

Anti-diarrhoeal activity

In developing countries acute diarrhoea is a public health problem, which constitutes a serious problem and is a leading cause of morbidity, malnutrition and mortality among the children [33]. Diarrhoea may result from disturbed bowel function, which cause an increase in bowel transit, excessive secretion of water and electrolytes from intestine, as well as reduction in intestinal reabsorption [34]. Diarrhoea is characterized by wet and watery stool, abdominal pain and frequent increase of bowel movement [35, 16]. In some diarrhoea the secretory component predominates while other diarrhoea is characterized by hypermotility [36].

Despite the emergence of a number of drugs, none has found a place in the routine management of diarrhoea. Therefore, the search for agents which are more safe and effective has been continued to be an important area of research. Since ancient times, medicinal plants or their extracts based on traditional medicine have been used orally in the treatment of diarrhoea [35].

Traditional *S. macrophylla* seed were used for the treatment of diarrhoea and some studies showed that *S. macrophylla* produce a significant anti-diarrhoeal activity when given in a single dose of 100 mg/kg body weight [22, 14]. Anti-diarrhoeal property was investigated in Wister albino rats and showed an activity due to the presence of petroleum ether (PE) extract of *S. macrophylla* seeds.

Powdered seeds of *S. macrophylla* were extracted with petroleum ether using the soxthlet apparatus. The extraction of the seeds was investigated for the anti-diarrhoeal activity of *S. macrophylla* by preparing different grad doses including 25, 50 & 100mg/kg body weight. The study was done in term of reduction in the rate of defecation and consistency of faeces in castor oil induced diarrhoea. The mechanism of its anti-diarrhoeal activity was understood by further evaluatation on intestinal transit and intestinal fluid accumulation induced by castor oil, known as enteropooling [22]. Due to the active metabolite, ricinoleic acid (a hydroxylated fatty acid released from castor oil by intestinal lipases) [37] which stimulates small intestinal peristaltic activity [22,36] and causing the changes in electrolyte permeability in intestinal mucosa castor oil causes diarrhoea [38,22].

At various doses of body weight, 25, 50 and 100mg/kg, the extract showed reduction in the consistency and rate of faeces defecation, which is one remarkable evidence of anti-diarrhoeal activity recorded. These results were then compared to that of standard drug diphenoxylate which was tested to 50 mg/kg body weight. A significant decrease in the severity of diarrhoea and intestinal transit for about 4.45% to 34.60% were shown when 100 mg/kg body weight of *S. macrophylla* extract was adminitrerdorally in a single dose. Extract produced profound also significantly inhibited castor oil induced intestinal fluid accumulation comparable to that of standard drug atropine sulphate at doses of 0.1 mg/kg body weight and 3 mg/kg body weight respectively, which was done through intraperitoneal injection. The percentage inhibition for the number of wet faeces as well as wet mass indicates the presence of anti-diarrhoeal activity in extract as compared with that of control group.

This shows that petroleum ether extract of seeds of *S. macrophylla* possess significant anti-diarrhoeal activity and can be a potent source of anti-diarrhoeal drug in future based on the experimental findings recorded [22].

Hypoglycaemic activity

Diabetes occurs due to inefficiency in the production of insulin or the absence of proper function of insulin to maintain an appropriate glucose level in the body. The excess glucose level in the blood stream will be changed into glycogen by the hormone (insulin). The insulin were produced by the islet of Langerhans located in the pancreas. The failure of the insulin to reduce the glucose level into the acceptable range will cause the diabetes. Thus, the *S. macrophylla* is believed as one of the medicinal plant which contained the anti-diabetic compound. Streptozotocin induced type II diabetic in rat was used to evaluate the anti-diabetic effect of *S. macrophylla* seeds. The extract at the dose of 300 mg/kg body weight is found more effective and it lowered fasting blood glucose level (FBG). FBG levels is statistically significant in diabetic rats at day 12. The same dose of the extract is also significantly reduced the elevated level of serum total triglyceride (10.41%) and cholesterol (18.56%), and increased the reduced liver glycogen level. However, it was found that the extract of both doses improved the body weight of diabetic rat. The increased in glycogenesis and or inhibited glucogenolysis may lead to increase in liver glycogen. The decreased utilization of glucose by tissues is the fundamental mechanism underlying hyperglycemia in the diabetic state which is associated to the excessive hepatic glycogenolysis and gluconeogenesis. This may be due to the lack of or resistance to insulin, which is essential to trigger the activation of glycogen synthase systems.

The test of the extract supplementation on type II diabetic rats shows a significant decrease in the triglycerides and the serum total cholesterol. This is may be due to low level of lipolysis which are under the control of insulin and or low activity of cholesterol biosynthesis enzymes [39]. Another study showed that various types of phytoconstituent are present in *S. macrophylla*. including swietenine, which is identified by physiochemical and spectrometric analysis. Phytoconstituent (swietenine) isolated from the extract of *S. macrophylla* have improved peripheral glucose utilization in diabetic rat due to an insulin mimicking effect of plant [22].

S. macrophylla King (*Meliaceae*) is used to treat diabetes mellitus in Malaysia. Another study was done to evaluate the anti-hyperglycaemic/hypoglycemic potential of petroleum ether (PE), chloroform (CE) and methanol (ME) extracts of *S. macrophylla* seeds, in normoglycaemic (normal rats) and streptozotocin (STZ) induced diabetic rats [23]. Following treatment of normoglycaemic rats with *S. macrophylla* seed extracts, hypoglycaemia and Intraperitoneal Glucose Tolerance Tests (IPGTT) were performed, and the initial blood glucose concentrations were measured respectively. The glucose concentrations of STZ-induced diabetic rats were measured after 1 and 14 days of *S. macrophylla's* extract treatment. Glucose absorption by intestine and glucose uptake by abdominal muscle were tested after treatment with seed extracts. In order to identify the compounds responsible for hypoglycaemic activity, gas chromatography mass spectrometry (GC-MS) analysis was performed on PE of *S. macrophylla* seeds [23].

Within 60 randomly selected normoglycaemic (normal) and diabetic rats undergoing hypoglycaemia tests, none of the extracts had a significant effect on the blood glucose levels. However, only PE have significantly reduced blood glucose levels in half of the randomly selected normoglycaemic rats undergoing IPGTT tests 30–120 minutes after glucose administration. Repeated doses of 1000 mg/kg and 500 mg/kg PE to STZ-induced diabetic rats for 14 days did not reduce blood glucose levels significantly. This shows that PE did not reduce significantly the intestinal absorption of glucose, but significantly increased glucose uptake by abdominal muscle in the absence or presence of insulin. So, eventhough there is no presence or insufficient of insulin, the *S. macrophylla* extracts are still able to

enhance the uptake of glucose by abdonimal mmuscle, thus reduce the blood glucoce level.

This finding has proved that PE extracts of *S. macrophylla* seeds PE showed anti-hyperglycaemic activity on IPGTTs. GC-MS analysis revealed that some of the chemical constituents included diterpenes, triterpenoids, fatty acid, methyl esters, aldehydes, fucosterol, phytosterols and β-sitosterol, may be responsible for these anti-hyperglycaemic properties and glucose lowering effects of PE extracts of *S. macrophylla* [23].

Anti-bacterial activity

The pharmacological activities of *S. macrophylla* are mainly due to the existence of the terpenoids and limonoids. Similarly, two limonoids from *S. macrophylla* are 2 hydroxy 3-swietenolide and 2 hydroxy-3-O-tigloylswietenolide shows significant anti-bacterial activity against eight multi-drug resistant (MDR) bacterial strains [14].

In the other study, *S. macrophylla* King was selected and anti-bacterial activity of extracts from different parts including leaf, fruit cover and seed cover, with various solvents or different fractions of the extracts was studied in laboratory test. Thus, the screening of anti-bacterial activity for a new natural, nontoxic and effective antibiotic from plant extract can be carried out.

In this study, the anti-bacterial activity of these extracts was assessed against two multiple-drug-resistance bacteria strains namely, *Escherichia coli* and *Staphylococcus aureus*. Another bacteria that can be use were *Bacillus subtilis* and *Pseudomonas aeruginosa*, and a fungus, *Candida albicans* [21]. The study was carried using well diffusion method. For the anti-bacterial bioassay, four concentrations of each extract solutions including 10, 50, 100 and 150 µg mL-1 were prepared.

The anti-bacterial activity among extracts was extremely broad against both tested organisms. Extract four from fruit cover shows more inhibitory effects to the bacteria compared to other extracts of the plant's parts. Meanwhile, the ethanol extracts from fruit cover (EFC) displayed overall more effective activity than other parts among solvent crude extracts against both tested bacteria. In contrast, some study found that methanol was more efficient than acetone and ethanol in extracting phytochemicals constituents from plant materials [40]. However, ethanol extracts used in this study showed better inhibition zones against both tested bacteria than acetone and methanol extracts, which means that ethanol extracted more inhibitory principles from those plant parts compared to the other two. The extraction of *S. macrophylla* leaves also can be done using methanol, dicholoromethane, and n-hexane. The extraction using these three chemicals also showed inhibition activities, meaning the components of anti-bacterial activities in *S. macrophylla* are successfully collected [21].

The results obtained from this study show that *S. Macrophylla* King is promising as natural anti-bacterial. The screening process using TLC has successfully showed some bioactive groups, therefore, further researchs to determine the bioactive compounds can be done [20].

Cytotoxic activity

Plant-derived compounds which possessed anti-cancer properties have played an enormous role in cancer treatment over the last thirty years and continue to hold great potential as an important sources of medicines for cancer and various diseases [41,42]. Plant based medicines also received considerable attention in recent years due to their diverse pharmacological properties including cytotoxicity and cancer chemopreventive effects [41].

Most of the current anticancer drugs are derived from plant sources, which act through activation of apoptosis in cancer cells leading to cell cytotoxicity [2]. The vast structural diversity of phytochemicals has given plant-derived cancer drugs a wide range of cancer treating actions [43], and further underlines plants as promising candidates for drug sources and continuing discovery of novel anti-cancer agents of plant origin [44]. The increasing understanding of their biological significance and increasing recognition of the origin and function of targeting plant products study have recently regained the reputation of developing anticancer drug from plants including *S. macrophylla* [45,21].

Recent studies were done to test for the cytotoxic activity of the crude ethanol extract of the seeds of *S. macrophylla.* The seed extracts were fractionated, before assessed to some selected human cancer cells including HCT 116 (colon carcinoma), KB (nasopharyngeal epidermoid carcinoma), Ca Ski (cervical carcinoma) and MCF-7 (breast carcinoma) by using MTT assay.

The cytotoxic activity of the extracts of *S. macrophylla* were tested against these human cancer cells in a dose and time-dependant manner. Then, it was further analysed using flow cytometric analysis to check for its possible mechanisms. The *S. macrophylla* ethyl acetate fraction (SMEAF) showed the most potent activity against HCT116 cell line.

The result of this study highlights the anticancer and cytotoxic potential of seed extract of *S. macrophylla* which suggest that the cytotoxic activity of this plant has been due to its apoptosis inducing properties. This was proved based on the founding of induced apoptosis by SMEAF on treated HCT116. The induced apoptosis of treated HCT116 was further confirmed both by DNA fragmentation and the externalization of phosphatidylserine. Another evidence of cytotoxic and anticancer activity of SMEAF were by depletion of intracellular glutathione, disruption of mitochondrial membrane potential, DNA fragmentation, externalized phosphatidylserine and accumulation of sub-G1 population [21].

Apart from the seed extracts, the study of cytotoxic activity of other parts of *S. macrophylla* including bark and leaf extracts also have been done on KB cells [46].

Anti-inflammatory activity

S. macrophylla also shows an anti-inflammatory activity. The seed extract of *S. macrophylla* inhibits carrageen an induce paw edema by 7.35% at a dose of 50mg/kg, higher dose of 100 mg/kg produce 47.06% that is comparable to the 54.4% inhibition produce by the standard drug ibuprofen. It is well known that there is a close relationship between inflammation and cancer [14].

In the studies on the anti-inflammatory constituents of Formosan plants, many species have been screened for in vitro inhibitory activity on neutrophil pro-inflammatory responses, and *S. macrophylla* has been found to be an active species. Therefore, this study revealed the anti-inflammatory activities of the isolated compounds on human neutrofil. The fruits of *S. macrophylla* were collected and dried before it were pulverised and extracted three times with MeOH for 3 days, then undergo a few steps of extraction using different chemicals [7]. The extractions collected were then undergo a few procedures such as chromatographed on silica gel, and further purified using preparative Thin Layer Chromatography (TLC) before preceed to the Nuclear Magnetic Resonance (NMR) to isolate and identified the compounds including the compounds which responsible to the anti-inflammatory effects.

The anti-inflammatory effects of the isolated compounds from the fruits of *S. macrophylla* were evaluated by suppressing fMet-Leu-Phe (fMLP) induced O_2 generation by human neutrophils. Human neutrophils, which are known to play significant role in the pathogenesis of various diseases taken from the venous blood of healthy adult and as a host defence against microorganisms, were isolated using a standard method of dextran sedimentation prior to centrifugation in a Ficoll Hypaque gradient and hypotonic lysis of erythrocytes, as previously described [7]. The neutrofils will secrete a series of cytotoxin in response to different stimuli, as a precursor of other reactive oxygen species. The induce of inflammatory diseases was carried out by the suppression of extensive or inappropriate activation of neutrophils.

Anti-hepatitis C activity

Hepatitis C virus (HCV) infection is a rapidly increasing global health problem, with approximately 3% of the global population infected. The majority of acute HCV infections become chronic, known as chronic hepatitis C virus often resulting in severe liver disease

including hepatic steatosis, cirrhosis, and hepatocellular carcinoma (HCC) [47,48].

Currently, only half of the patients with HCV treated show a sufficient antiviral response to the only treatment available which consists of a combination of Pegylated interferon alpha (INF-a) and ribavirin. Thus there is a great need for the development of new treatments for HCV infections including development of plant-based drugs [49]. As the standard treatment is not completely efficacious, a safer and more effective agent against HCV infection needs to be developed.

The anti-viral activity-guided fractionation and isolation was performed to screen for anti-HCV components of *S. macrophylla.* The isolation process done using a cell-based HCV replicon system [50]. By using the most potent ethyl acetate extract of *S. macrophylla* stems (SMS), a bioactive compound was successfully isolated and fractionated from the extracts which was identified as 3-hydroxy caruilignan C (3-HCL-C). This compound was responsible in inhibition of HCV replication with no apparent cytotoxicity. Further investigations of anti-HCV activity of *S. macrophylla* extracts were done by combining the 3-HCL-C and IFN-a (HCV enzyme inhibitors) to ensure the development of anti-HCV activity of bioactive compound in SMS [51].

Anti-malaria and Anti-babesia activity

Babesia are classified as apicomplexan parasites which were transmitted by ixodid ticks and infection of the host causes a host-mediated pathology and erythrocyte lysis, resulting in anemia, hyperbilirubinuria, hemoglobinuria, and possibly organ failure [52]. Their symptoms of disease are almost similar to the symptoms showed by malaria disease, which caused by *Plasmodium falciparum*. The similarity of these two diseases is due to the action of the pathogenic protozoan (*Plasmodium falciparum* and *Babesia gibsoni*) which causes the lysis of erythrocytes which lead to the anaemia [53]. In addition, both of these parasites share the same life cycle, thus, it is proposed that an anti-babesial components can be be isolated from the same extracts of plant that was used for treatment of malaria, which is *S. macrophylla* [54,55].

Patients may show up with, non-specific symptoms like fever, flu-like disease, headache, chills, sweats, and myalgia. Babesiosis came into view as a potentially life threatening zoonotic infection in humans as there was some cases of babesiosis have caused fatal [56]. *Babesia microti* infections may persist despite multiple courses of treatment and may be associated with relapsing symptoms for more than a year in immunocompromised individuals as described in a recent case control study, thus a new drug development to treat babesiosis effectively should be in progress [56].

Many samples from plants of traditionallly used for treatment of malaria including *S. macrophylla* were screened for their anti-malarial and anti-babesial activities. Eight plant extract samples showed strong anti-malarial activity which show 89.6 to 100% of inhibition range. Another 15 extracts showed potent anti-babesial activity with an inhibition range from 84.2 to 98.1 %. The extract *of S. macrophylla* showed both strong anti-babesial and anti-malarial activities. Other plant extracts which showed anti-babesial and anti-malarial activities were *Achillea millefolium, Baeckea frutenscens, Brucea javanica, Curcuma xanthorrhiza* and *Strychnos lucida* [57,55]. This finding revealed that *S. macrophylla* contained both anti-malarial and anti-babesial activities. Therefore, further study to produce drug for treatment of malarial and babesiosis can be done using this plant.

Anti-tumor and Anti-mutagenecity activity

Cancer is characterized by rapid and uncontrolled abnormal cells formation which may mass together to form a growth or proliferate throughout the body, and it may progress and can causes death if not treated well [58]. Scientists are interested in investigating medicinal plants which are commonly used by public and derived from folklore information.

A few studies regarding plant-based extracts have been done to find the drugs for cancer treatment. The study on plant parts including seeds of *Gossypium barbadense*, *Ricinus communis*, *Sesamum indicum, Nigella sativa, Vinca rosea* and *Melia azedarah*; fruits of: *Xanthium occidental*; flowers of: *Atriplex nummularia*; barks of: *Cinnamomum zeylanicum*; latex of: *Ficus carica* and rhizomes of: *Curcuma longa* and *Zingiber officinale.*The screening of biological compounds from these plants has enabled the discovery of new medicinal drugs which is more effective for treatment against cancer cells [58].

Another study involving the *S. macrophylla* seeds was done using crude ethanol extract, namely hexane CC14 and methanol . All fractions collected were tested for antimutagenic, and antitumor-promoting activities. The antitumor promoting activity of the crude extract and the solvent fractions were studied using the Epstein-Barr early-antigen (EBV-EA) activation, with 12-0 tetradecanoylphorbol-13-acetate (TPA) as the tumor promoter. The results showed that *S. macrophylla* composed of inhibitory effects on EBV-EA activation which indicating the antitumor-promoting activity [59].

The ethanol extract of *S. macrophylla* was studied using the Micronucleus test to investigate its mutagenicity or anti-mutagenicity. The result showed that at a dosage of 0.02 mg per gram body weight, the extract reduced the number of micronucleated polychromatic erythrocytes induced by mitomycin C, a known mutagen, by almost 50%. This finding revealed that *S. macrophylla* extracts can act as anti-mutagenicity, which is important in the treatment of cancer cells.

Anti-feedant activity

The triterpenoids content in the *S. macrophylla*, from the family *Meliaceae*, in particular, are highly diversified in structure and have been studied extensively for their responsibility as the insect anti-feedant and growth regulating activities [60].

The anti-feedant activity of *S. macrophylla* investigated using the armyworm (FAW), *Spodoptera frugiperda* and striped cucumber beetle (F). The feeding ratios of 0.02 and 0.18 for the ethanol and hexane extracts respectively. The feeding ratio was defined as the percentage of an extract-treated and control leaf disks were eaten by the armyworms and striped cucumber beetles. The extracts were non lethal since no mortality occurred with the hexane extracts, while only 20% mortality was seen with ethanol extracts. However, none of the insects pupated while the larvae were all small. The anti-feedant activity was also exhibited against SCB. The result obtained showed that *S. macrophylla* seed extract was not as potent as the other plant extracts that were also screened [61].

Anti-nociceptive activity

Certain disease or pathological conditions can bring pain sensation. The pain receptor on superficial portions of the skin, known as nociceptors, will detect the pain stimuli and sent the impulse to central nervous system and it was interpreted as pain sensation.

Use of natural products in the management of pain have been widely used from thousands of years ago. Meaning that the plant extract may act as anesthetic drugs. The use of poppy and willow bark by various civilizations to cure fever led to the isolation of morphine and salicylic acid, respectively [62]. These two drugs are still used extensively in modern medical practice. Present trend of the researchers to focus on higher plants has opened up an arena to find bioactive compounds from a source that has been ignored or less explored. It is expected that research on higher plants will continue to rise in the coming days [63]. The research on *S. macrophylla* extracts also led to the foundation of active compounds which responsible for anti-nociceptors activities. The presence of these compounds in *S. macrophylla* have make it possible to help in reduce the pain sensation [64].

CONCLUSION

The genus *Swietenia* is widely used for various purposes. *S. macrophylla* is one of the common trees in China and other tropical areas in the world. It has been reported for its medicinal uses, like in the treatment of hypertension, inflammation, HIV, diabetes, malaria, cancer, amoebiasis, chest pains and intestinal parasitism. Anti-microbial, anti-nociceptive activity and anti-diarrheal activity were

also reported using this plant. Despite the requirement of more detailed research on it, few components have been isolated from *S. Macrophylla*.

REFERENCES

1. Nair KSS. Pest outbreaks in tropical forest plantations: is there a greater risk for exotic tree species. Indonesia: Cent gter for International Forestry Research. 2002.
2. Goh BH, Kadir HA. In vitro cytotoxic potential of *Swietenia macrophylla* King seeds against human carcinoma cell lines. Journal Medicinal Plants Research. 2011;5: 1395-1404.
3. Blundel AG, Gullison RE. Poor regulatory capacity limits the ability of sciences to influence the management of mahogany. Forest Policy and Economics. 2003;5: 395-405.
4. Andre T, Lemes M, Grogan J, Gribel R. Post-logging loss of genetic diversity in a mahogany (*Swietenia macrophylla* King, *Meliaceae*) population in Brazilian Amazonia. Forest Ecology and Management, 2008;255: 340-345.
5. Cornelius JP, Wightman KE, Grogan JE, Ward SE. Encyclopedia of Forest Sciences. *Swietenia* (American *Mahogany*). Burley J, Evans J, Youngquist, JA. (Eds). New York. 2004. p. 1720-1726.
6. Govindachari TR, Suresh G, Banumathy B, Masilamani S, Geetha G, Krishna GNK. Antifungal activity of some b,d-seco limonoids from two meliaceous plants. Journal of Chemical Ecology. 1999;25: 923-933.
7. Chen JJ, Huang SS, Chang HL, Dau CW, Ping JS, Tai CW, Ming JC. A new phragmalin-type limonoid and anti-inflammatory constituents from the fruits of Swietenia macrophylla. Food chemistry. 2010;120: 379–384.
8. Kipassa NT. Structural studies of tetranortriterpenoids from the Congolese species of Entandrophragma angolense. Efficient short step synthesis of Corey's Tamiflu intermediate. Kagoshima Japan: Kagoshima University; 2008. p. 6.
9. Witko-Sarsat V, Rieu P, Descamps-Latscha B, Lesavre P, Halbwachs-Mecarelli L. Neutrophils: Molecules, functions and pathophysiological aspects. Laboratory Investigation. 2002;80: 617–653.
10. Suzuki T, Falah S, Katayama T. Chemical constituents from *Swietenia macrophylla* bark and their antioxidant activity. Pakistan Journal of Biological Sciences. 2008;11(16): 761-795.
11. Chan KC, Tang TS, Toh HT. Isolation of swietenolide diacetate from Swietenia macrophylla. Phytochemistry. 1976;15: 429-430.
12. Mootoo BS, Ali A, Motilal R, Pingal R. Ramlal A. Limonoids from *Swietenia macrophylla* and *S. aubrevilleana*. J. Nat. Prod. 1999;62: 1514-1517.
13. Kojima K, Isaka K, Ogihara Y. Tetranortriterpenoids from *Swietenia macrophylla*. Chem. Pharm. Bull. 1998;46: 523-525.
14. Moumita D, Utpal R, Runu C. Debasish M. Science and culture : Role of diet and plants on diabetic patients - a critical appraisal. Dept. of Food Technology and Biochemical Engineering, Jadavpur University, Kolkata India. NOS. 2011;77: 3–4.
15. Soares MG, Batista-Pereira LG, Fernandes JB, Correa AG, Da Silva MFGF. Electrophysiological responses of female and male of Hypsiphyla grandella (Zeller) to *Swietenia macrophylla* essential oils. J. Chem. Ecol. 2003;29: 2143-2151.
16. Swati P, Richa K. A Review on Antidiarrhoeal Activity of Herbals. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2011;2(3): 1357-1362.
17. Vhuiyan MMI, Israt JB, Moni RS, Muhammad SI. Anti-diarrhoeal and CNS Depressant Activity of Methanolic Extract of *Saccharum spontaneum* Linn. Stamford Journal of Pharmaceutical Sciences. 2008.1(1&2): 63-68.
18. Falah S, Suzuki T, Safithri M, Katayama T. Hypoglycemic Effect of Mahogany (*Swietenia macrophylla* King) Bark Extracts in Alloxan-induced Diabetic Rats. Wood Research Journal. 2010;1(2): 89-94.
19. Rates SMK. Review: Plants as source of drugs. Laboratory of Pharmacognosy, Department of Production of Raw Material, School of Pharmacy, Federal University of Rio Grande do Sul, Av. Ipiranga, 2752 Porto Alegre, Brazil. Toxicon. 2001;39: 603–613.
20. Azhari HN, Abdurahman HN, Jessinta S, Mashitah MY. Antibacterial Activity of Different Extracts of *Swietenia Macrophylla* King. Faculty of Industrial Sciences and Technology, University Malaysia Pahang, Malaysia. 13th Medicinal and Aromatic Plants Seminar (MAPS2012). 2012.
21. Tan S, Osman H, Wong K, Boey P, Ibrahim P. Antimicrobial and antioxidant activities of *Swietenia macrophylla* leaf extracts, As. J. Food Ag-Ind. 2009;2(2): 181-188.
22. Anup M, Subhash CM, Saikat D. In Vivo Evaluation of Antidiarrhoeal Activity of the Seed of *Swietenia macrophylla* King (*Meliaceae*). Pharmacognosy and Phytotherapy Research Laboratory, Division of Pharmacognosy, Department of Pharmaceutical Technology, Jadavpur University, Kolkata-700032, India. Tropical Journal of Pharmaceutical Research. 2007;6(2): 711-716.
23. Mohd AH, Mun FY, Sook YH, Chung PL, Mohd ZA, Amirin S. Anti-hyperglycaemic activity of *Swietenia macrophylla* king (*meliaceae*) seed extracts in normoglycaemic rats undergoing glucose tolerance tests. Chinese Medicine. 2013;8: 11.
24. Bourdy G, De Walt SJ, Chavez De Michel LR, Roca A, Deharo E. Medicinal plants uses of the tacana, an amazonian bolivian ethnic group. J. Ethnopharmacol. 2000;70: 87-109.
25. Francois C, Shyam S, Asrat H, Hashim G, Suman R, Rosanna WP, Jorge A, Marleen B. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control. Nature Publishing Group. 2007. p.14.
26. Kadota S, Marpaung L, Kikuchi T, Ekimoto H. Constituents of the seed of *Swietenia mahagoni* JACQ. I. isolations, structures and ^{1}H and ^{13}C nuclear magnetic resonance signal assignment of new tetranortriterpenoids related to swietenine and swietenolide. Chem. Pharm. Bull. 1990;38: 639-651.
27. Al-Radahe S, Ahmed K, Salama S, Abdulla A, Amin Z, Al-Jassabi S, Hashim H. Anti-ulcer activity of Swietenia mahagoni leaf extract in ethanol-induced gastric mucosal damage in rats, Journal of Medicinal Plants Research, 2012;6(12): 2266-2275.
28. Krisnawati H, Kallio M, Kanninen M. *Swietenia macrophylla* King: ecology, silviculture and productivity. CIFOR, Bogor, Indonesia: International Forestry Research; 2011.
29. Jeyachandran R, Baskaran X, Cindrella L. Screening of Phytochemical and Antibacterial Potential of Four Indian Medicinal Plants. Libyan Agriculture Research Center Journal International 2010;1(5): 301-306.
30. Grayer RJ, Harborne JB. A survey of antifungal compounds from higher plants 1982-1993. Phytochemistry 1994;37: 19-42.
31. Bordoloi M, Saikia B, Mathur RK, Goswami BN. l,2-Dihydro-6Aacetoxyazadirone, a new antifungal meliacin from the fruit of *Chisocheton paniculatus.* Phytochemistry 1993;34: 583-584.
32. Suresh G, Narasimhan NS, Masilamani S, Partho PD, Geetha G. Antifungal fractions and compounds from uncrushed green leaves of *Azadirachta indica.* Phytoparasitica 1997;25: 33-39.
33. Ching FP, Omogbai EKI, Ozolua RI, Okpo SO. Antidiarrhoeal activities of aqueous extract of *Stereospermum kunthianum* (Cham, Sandrine Petit) stem bark in rodents. African Journal of Biotechnology. 2008;7: 1220-1225.
34. Gurgel LA, Silva RM, Santos FA, Domingos, Martins TO. Studies on the Antidiarrhoeal Effect of Dragon's Blood from *Croton urucurana.* Phytotherapy research. 2001;15: 319–322.
35. Sunil KJ, Mukesh KD, Ajay KV, Sanjib D, Vijaykumar M, Chandana VR. Evaluation of iridoid glycosides from leave of *Barleria Prionitis* as an Anti-diarrhoeal Activity: an Ethnopharmacological study. International Journal of Pharmaceutical Sciences. 2010;2: 680-686.
36. Havagiray RC, Ramesh C, Sadhna K. Studies on anti-diarrhoeal activity of Calotropis gigantea R.BR. in experimental animals. J. Pharm Pharmaceutical Sciences. 2004;7: 70-75.
37. Sorin T, Till FA, Rolf MN, Martin D, Stefan O. Castor oil induces laxation and uterus contraction via ricinoleic acid activating prostaglandin EP3 receptors. aDepartment of Pharmacology, Max-Planck-Institute for Heart and Lung Research, Bad Nauheim, Germany. PNAS. 2012;109(23): 9179–9184.
38. Ammon PJ, Thomas, Philips S. Effects of oleic and recinoleic acids net jejunal water and electrolyte movement. J. Clin. Invest 1974;53: 374- 379.
39. Sereday MSD, Gonzalez C, Giorgini D, Loredo LD, Braguinsky J, Cobenas C. Diabetes Metab. 2004;30: 335-339.
40. Cowan MM. Plant products as antimicrobial agents. Department of Microbiology, Miami University, Oxford, Ohio. Clinical Microbiology Review. 1999;(12): 564–582.

41. Gonzales GF, Valerio LG. Medicinal plants from Peru: A review of plants as potential agents against cancer. Anticancer Agents Med. Chem. 2006;6(5): 429-444.
42. Daniel R. *In vitro* Evaluation of Potential Anti-Inflammatory Agents from Peruvian Medicinal Plant Extracts. 2012.
43. Shoeb M, MacManus SM, Jaspars M, Trevidadu J, Nahar L, Thoo-Lin PK, Sarker SD. Montamine, a unique dimeric indole alkaloid, form the seeds of Centaurea Montana (Asteraceae), and its in vitro cytotoxic activity against the Caco2 colon cancer cells. Tetrahedron. 2006;62: 11172-11177.
44. Cragg GM, Newman DJ. Plants as a source of anticancer agents. Ethnopharmacol. 2005;100: 72-79.
45. Conforti F, Loele G, Statti GA, Marrelli M, Ragno G, Menichini F. Antiproliferative activity against human tumor cell lines and toxicity test on Mediterranean dietary plants. Food Chem. Toxicol. 2008;46(10): 3325-3332.
46. Camacho MR, Philipson JD, Croft SL, Solis PN, Marshall SJ, Ghazanfar SA. Screening of plant extracts for antiprotozoal and cytotoxic activities. J. Ethnopharmacol. 2003;89(2&3): 185-191.
47. Rodney KL, David CK, Selena MS, David RB, Yanouchka R, Adrian FP, Sunney X, Albert S, John PP. Direct imaging of the disruption of hepatitis C virus replication complexes by inhibitors of lipid metabolism. Virology. 2009;394: 130–142.
48. Carcamo, Wendy C, Cuong QN. Advancement in the Development of Models for Hepatitis C Research. Journal of Biomedicine and Biotechnology. 2012; Article ID 346761: 7.
49. Ansar M, Usman AA, Imran S, Muhammad TS, Tariq J, Sidra R, Sajida H, Sheikh R. Inhibition of full length Hepatitis C Virus particles of 1a genotype through small interference RNA. Virology Journal. 2011;8: 203.
50. Keril JB, Jane AM, Joseph M, Charles MR. Efficient Replication of Hepatitis C Virus Genotype 1a RNAs in Cell Culture. Journal of virology. 2003;77(5): 3181–3190.
51. Wu SF, Lin CK, Chuang YS, Chang FR, Tseng CK, Lee JC. Anti-hepatitis C virus activity of 3-hydroxy caruilignan C from *Swietenia macrophylla* stems. Journal of Viral Hepatitis. 2011;10: 1365-2893.
52. Hunfeld KP, Hildebrandt A, Gray JS. Babesiosis: Recent insights into an ancient disease. International Journal for Parasitology. 2008;38: 1219–1237.
53. Nicholas JW. Antimalarial drug resistance. 1Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. Centre for Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, United Kingdom. The Journal of Clinical Investigation. 2004;113(8): 1084-1092.
54. Homer MJ, Aguilar-Delfin I, Telford SM, Krause PJ, Persing DH. Clinical Microbiology review. 2000;13: 451-469.
55. Murnigsih T, Subekti HM, Takahashi K, Yamasaki M. Evaluation of the inhibitory activities of the extracts of indonesian traditional medicinal plants against *Plasmodium falciparum* and *Babesia gibsoni*. J Vet Med Sci. 2005;67: 829-831.
56. Herwaldt BL, Caccio S, Gherlinzoni F, Aspock H, Slemenda SB, Piccaluga P, Martinelli G, Edelhofer R, Hollenstein U, Poletti G, Pampiglione S, Loschenberger K, Tura S, Pieniazek NJ. Molecular characterization of a non-Babesia divergens organism causing zoonotic babesiosis in Europe. Emerg Infect. 2003;9: 942–948.
57. Soediro I, Padmawinata K, Wattimena JR, Rekita S. Study of the active antimalarial methanolic extract of *Swietenia macrophylla* King (*Meliaceae*). Acta Pharmaceutica Indonesia. 1990;15(1): 1-13.
58. Amara AA, El-Masry MH, Bogdady HH. Plant crude extracts could be the solution: Extracts showing *in vivo* antitumorigenic activity. Pak J Pharm Sci. 2008;21(2): 159-171.
59. Guevera AP, Apilado A, Sakarai H, Kozuka M, Tokunda H. Antiinflammatory, antimutagenecity and antitumor activity of mahagony seeds, *Swietenia macrophylla* (*Meliaceae*). Phill J Sc. 1996;125: 271-278.
60. Champagne DE, Koul O, Isman MB, Scudder GGE, Towers GHN. Biological activity of limonoids from the Rutales. Phytochemistry. 1992;31: 377-394.
61. Mikolajczak KL, Reed DK. Extraction of seeds of the *Meliaceae*: Effects on Spodoptera frugiperda, Acalymma fitatum and Artemia salina Leach. Journal of Chemical Ecology. 1987;13(1): 829-831.
62. Sneader W. Drug Discovery: A History. School of Pharmacy University of Strathclyde Glasgow, England: UKJohn Wiley & Sons; 2005.
63. Shilpi JA, Islam ME, Billah M, Islam KMD, Sabrin F, Uddin SJ, Nahar L, Sarker SD. Antinociceptive, Anti-Inflammatory, and Antipyretic Activity of Mangrove Plants: AMini Review. Advances in Pharmacological Sciences. 2012, Article ID 576086:7.
64. Das A, Sunilson JAJ, Gopinath R, Radhamani S, Nilugal K. Antinociceptive Activity of the Fruits of *Swietenia macrophylla* King. J Pharm Res. 2009;2(9): 1367-1369.