The plant has been an important source of medicine since antiquity. The oldest known record of the plant being used for a therapeutic purpose is found in Egyptian medical papyrus written in the fourteen century.\cite{1} Since then, preparations of plant materials in the form of decoction, infusion, powder, or paste have been used in traditional medicine for prevention and treatment of different diseases and for improving the general well-being. According to the World Health Organization (WHO), about 80% of people living in Africa and Asia use the traditional medicine to help meet some of their primary health-care needs.\cite{2} People in Europe, Australia, and North America increasingly embrace the use of herbal medications to complement orthodox medicine.\cite{3} In this regard, Averrhoa bilimbi Linn. is one of the important medicinal plants of many tropical and subtropical countries of the world which has been widely used in the traditional system of medicines for the treatment of a variety of ailments, particularly as an antidiabetic, antihypertensive, and antimicrobial agent. The key emphasis of this review is to accumulate and organize literature based on traditional claims and correlate those with current findings on the use of A. bilimbi in the management of different ailments. Through interpreting already published scientific manuscripts (1995 through 2015) retrieved from the different scientific search engines, namely Medline, PubMed, EMBASE, and Science Direct databases, published articles and reports covering traditional and scientific literature related to A. bilimbi’s potential role against various ailments have been thoroughly evaluated, interpreted, and discussed. Several pharmacological studies have demonstrated the ability of this plant to act as antidiabetic, antihypertensive, thrombolytic, antimicrobial, antioxidant, hepatoprotective, and hypolipidemic agent. A. bilimbi holds great value in the complementary and alternative medicine as evidenced by the substantial amount of research on it. Therefore, we aimed to compile an up-to-date and comprehensive review of A. bilimbi that covers its traditional and folk medicine uses, phytochemistry, and pharmacology. Hence, this paper presents an up-to-date and comprehensive review of the ethnomedicinal uses, different chemical constituents, and pharmacological activities of A. bilimbi. So far, the biologically active agents have not been isolated from this plant and this can be a good scientific study for the future antidiabetic, antihypertensive, and antimicrobial implications. Hence, this review targets at emphasizing the diverse traditional claims and pharmacological activities of A. bilimbi with respect to carrying out more scientific studies to isolate active principles through advanced technology.

**ABSTRACT**

Averrhoa bilimbi Linn. is principally cultivated for medicinal purposes in many tropical and subtropical countries of the world. Literature survey about this plant shows that A. bilimbi is mainly used as a folk medicine in the treatment of diabetes mellitus, hypertension, and as an antimicrobial agent. The prime objective of this review is to accumulate and organize literature based on traditional claims and correlate those with current findings on the use of A. bilimbi in the management of different ailments. Through interpreting already published scientific manuscripts (1995 through 2015) retrieved from the different scientific search engines, namely Medline, PubMed, EMBASE, and Science Direct databases, published articles and reports covering traditional and scientific literature related to A. bilimbi’s potential role against various ailments have been thoroughly evaluated, interpreted, and discussed. Several pharmacological studies have demonstrated the ability of this plant to act as antidiabetic, antihypertensive, thrombolytic, antimicrobial, antioxidant, hepatoprotective, and hypolipidemic agent. A. bilimbi holds great value in the complementary and alternative medicine as evidenced by the substantial amount of research on it. Therefore, we aimed to compile an up-to-date and comprehensive review of A. bilimbi that covers its traditional and folk medicine uses, phytochemistry, and pharmacology. Hence, this paper presents an up-to-date and comprehensive review of the ethnomedicinal uses, different chemical constituents, and pharmacological activities of A. bilimbi. So far, the biologically active agents have not been isolated from this plant and this can be a good scientific study for the future antidiabetic, antihypertensive, and antimicrobial implications. Hence, this review targets at emphasizing the diverse traditional claims and pharmacological activities of A. bilimbi with respect to carrying out more scientific studies to isolate active principles through advanced technology.

**KEY WORDS:** Averrhoa bilimbi Linn., pharmacological activities, phytochemistry, traditional uses
utilitarian side and medicinal characteristic of *A. bilimbi* and turn that into a drug for future diabetic and hypertensive patient’s management. The methodology followed was to methodically collect, organize, and chart the recent advances in the use of *A. bilimbi* in different chronic disorders. Data were retrieved from Medline, PubMed, EMBASE, and Science Direct databases covering traditional and scientific literature related to *A. bilimbi*’s potential role for the treatment of various diseases that have been thoroughly evaluated and discussed. Moreover, this review aims at highlighting the diverse traditional claims and pharmacological activities of *A. bilimbi*.

### Averrhoa bilimbi Linn.

*A. bilimbi* (common name: Bilimbi) is a medicinal plant belonging to the family Oxalidaceae. The genus *Averrhoa* was named after an Arab Philosopher, physician and Islamic Jurist Ibn Rushd often known as Averroes (1126-98).[6] *A. bilimbi* is closely related to *Averrhoa carambola* (carambola, starfruit). It originated in the Southeast Asia and is claimed as a native of the West Malaysia and the Indonesian Moluccas.[5] It is cultivated throughout Malaysia, Indonesia, Singapore, Philippines, Thailand, Bangladesh, Myanmar, and India. It also extends to other countries like the US, Argentina, Australia, Brazil, Colombia, Ecuador, Puerto Rico, Tanzania, and Trinidad and Tobago. The other common names of *A. bilimbi* are bilimbi, cucumber tree, tree sorrel, pickle tree (English); kamias, camias, and pias (Philippines); t'aling pling (Thai); huang gua shu (Chinese); bilimbim, biri-biri, limao de caiena, and azedinhia (Brazil); vilimbipuli, irumpanpuli, and bilimbi (India); khe tay (Vietnamese); taling pling (Thailand); and belimbing buluh and blimbing asam (Malaysia).[6]

*A. bilimbi* is a small tree which grows up to 15 m high with sparsely arranged branches. It has compound leaves with twenty–forty leaflets each and 5–10 cm long.[7] The leaves are hairy with pinnate shapes and form clusters at the end of branches.[6,8] The tree is cauliflorous with 18–68 flowers in twenty–forty leaflets each and 5–10 sparsely arranged branches. It has compound leaves with close related to *Averrrhoa bilimbi* - *gua shu* camias, and pias - *bilimbi* (Vietnamese); *taling pling* (Chinese); *bilimbim, biri* (Brazil); *vilimbipuli, irumpanpuli, and bilimbi* (Philippines); *ta ling pling* (Thai); *huang gua shu* (Chinese); *bilimbim, biri-biri, limao de caiena, and azedinhia* (Brazil); *vilimbipuli, irumpanpuli, and bilimbi* (India); *khe tay* (Vietnamese); *taling pling* (Thailand); and *belimbing buluh* and *blimbing asam* (Malaysia).[6]

### Ethnomedicinal Uses

*A. bilimbi* has been used in the traditional medicine for the treatment of a variety of ailments. Infusions and decoctions of the leaves are used as an antibacterial, antiscorbutic, astringent, postpartum protective medicine, in the treatment of fever, inflammation of the rectum, and diabetes.[9] The paste of leaves is used in the treatment of itches, boils, skin eruptions, bites of poisonous creatures, rheumatism, cough, cold, mumps, and syphilis.[10,11] Grated fruits, with a little salt added, are applied on the face to treat pimples.[12] Fruit juice is employed in the treatment of scurvy, bilious colic, whooping cough, hypertension, obesity, and diabetes.[10,12,13]

### Phytochemical Constituents

**Fruits**

In an analysis conducted on Malaysia’s *A. bilimbi* fruits, 53 different components were identified as the volatile constituents. Aliphatic acids constitute 47.8% of the total volatiles. The main constituents were hexadecanoic acid [palmitic acid] (20.4%), 2-furaldehyde (19.1%), and (Z)-9-octadecenoic acid (10.2%). Twelve of the compounds identified were esters among which butyl nicotinate (1.6%) and hexyl nicotinate (1.7%) were present in higher quantities.[14]

In another study, Pino et al. investigated the volatile constituents of *A. bilimbi* that is grown in Cuba. The fruit pulp had approximately 6 mg/kg of total volatile components from which 62 compounds were identified. The major compounds were nonanal (2.7 mg/kg), (Z)-3-hexenol (0.48 mg/kg), hexadecanoic acid (0.31 mg/kg), octane (0.29), tricosene (0.27 mg/kg), (E)-2-decanal (0.26 mg/kg), nonanoic acid (0.25 mg/kg), (Z)-9-pentacosene (0.24 mg/kg), 2-furfural (0.18 mg/kg), and (Z)-9-tricosene (0.11 mg/kg). The remaining compounds were present in infinitesimal quantities (<0.1 mg/kg). The series of C-9 compounds: Nonanal, nonanoic acid, and (E)-2-nonenal provide the *A. bilimbi* fruit with its characteristic fatty and green notes. The second most dominant compound, namely (Z)-3-hexenol is also believed to contribute to the green notes of the fruit.[15] Preliminary phytochemical studies of the fruit extracts using chemical methods and thin layer chromatography revealed the presence of carbohydrates, proteins, amino acids, flavonoids, tannins, bitter principles, essential oil, valepotriatres, coumarin, and terpenes. The fruits are also rich in Vitamin C and oxalic acid.[16,17] The isolation of 2,4-dihydroxy-6-((4-methylpentyloxy) methyl) benzaldehyde from the fruit extract has also been reported.[18]

### Leaves

The preliminary phytochemical screening of the leaves extracts revealed the presence of alkaloid, tannins, saponins,
flavonoids, cardiac glycosides, glycosides, triterpenes, phenols, and carbohydrates.\textsuperscript{[10,20]} Gunawan \textit{et al.} reported the isolation of seven compounds from the leaves methanol extract of \textit{A. bilimbi}. These include squalene, 3-(6,10,14-trimethylpentadecan-2-yl) furan-2 (5H)-one, 2,3-bis (2,6,10-trimethylundeca-1,5,9-trienyl) oxirane, phytol, 3,4-Dihydroxyhexanedioic acid, malonic acid, and 4,5-Dihydroxy-2-methylhexahydrobenzaldehyde.\textsuperscript{[18]}

\textbf{Pharmacology}

The traditional claims, as well as roles for the efficacy of \textit{A. bilimbi} in the treatment of various infectious and noninfectious diseases, have been confirmed by several relevant scientific studies. Numerous pharmacological investigations including \textit{in vitro} and \textit{in vivo} (animal) studies have been carried out on the leaves and fruits of \textit{A. bilimbi}. A wide range of pharmacological activities such as antidiabetic, antihypertensive, antithrombotic, hypolipidemic, hepatoprotective, cytotoxic, antimicrobial, wound healing, anthelmintic, and antioxidant have been reported by different researchers so far.

\textbf{Role of \textit{Averrhoa bilimbi} as an Antimicrobial Agent}

Antimicrobial agents are among the most frequently used drugs in human medicine and veterinary practices. The widespread development of antimicrobial resistance in recent years had led to a renewed search for newer antimicrobial agents for the treatment of infectious diseases. The leaves ethanol extract of \textit{A. bilimbi} was reported to exhibit appreciable antimicrobial activity against six pathogenic microorganisms, namely two Gram-positive bacteria (\textit{Bacillus cereus} and \textit{Bacillus megaterium}), two Gram-negative bacteria (\textit{Escherichia coli} and \textit{Pseudomonas aeruginosa}), and two fungi (\textit{Aspergillus ochraceous} and \textit{Cryptococcus neoformans}).\textsuperscript{[21]} The aqueous and chloroform extracts of \textit{A. bilimbi}’s leaves and fruits (100 mg/ml) showed a positive antibacterial activity against \textit{Staphylococcus aureus}, \textit{Staphylococcus epidermis}, \textit{Bacillus cereus}, \textit{Salmonella typhi}, \textit{Citrobacter freundii}, \textit{Aeromonas hydrophila}, \textit{Proteus vulgaris}, and \textit{Kocuria rhizophila}.\textsuperscript{[22]} Whole bilimbi fruit and blended bilimbi juice (not filtered) at a concentration of 1:2 and 1:4 w/v, respectively, displayed a significant activity against \textit{Listeria monocytogenes} Scott A and \textit{Salmonella typhimurium} in an \textit{in vitro} antibacterial assay. The fruit preparations were also found to reduce the microbial load of \textit{L. monocytogenes} Scott A and \textit{S. typhimurium} on raw shrimps after washing and during storage (4°C). This demonstrated the potential of \textit{A. bilimbi} fruits to be adopted as a natural method of decontaminating shrimps just before preparation and consumption.\textsuperscript{[21]} In another study, fruits and roots extracts of \textit{A. bilimbi} were also found to exhibit the positive activity against \textit{Mycobacterium tuberculosis} with MIC of 1600 μg/ml.\textsuperscript{[24]} The leaves extracts have also been reported to display moderate antifungal activity against \textit{Blastomyces dermatitidis}, \textit{Candida albicans}, \textit{Cryptococcus neoformans}, \textit{Pityrosporum ovale}, and \textit{Trichophyton spp.} with MIC values ranging from 15.65 to 62.50 μg/ml.\textsuperscript{[25]}

\textbf{Role of \textit{Averrhoa bilimbi} as an Antioxidant Agent}

Antioxidants are compounds that interact with and neutralize free radicals, thus preventing them from causing cellular damage. The therapeutic potential of antioxidants in diseases associated with oxidative stress (e.g. cancer, diabetes mellitus [DM], and neurodegenerative disorders) has gained much attention in recent years. Abas \textit{et al.} studied the antioxidant properties and the effect on nitric oxide production in lipopolysaccharide-activated macrophages of \textit{A. bilimbi} and 11 other Malaysian traditional vegetables.\textsuperscript{[24]} The result obtained revealed that \textit{A. bilimbi} leaves extract (0.02% w/v) displayed moderate antioxidant activity in ferric thiocyanate and thiobarbituric acid methods while it was found to be inactive in 2,2-diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl (DPPH) assay. Unlike the leaves, the fruits extracts showed a strong DPPH radical scavenging activity with \textit{IC}$_{50}$ value of 20.35 μg/ml. It also displayed remarkable total antioxidant capacity (417.09± 6.577 mg/g in an ascorbic acid equivalent).\textsuperscript{[26]} This finding was further confirmed by other researchers who conducted similar studies.\textsuperscript{[27,28]} Precious \textit{et al.} studied the photoprotective effect of leaves ethanol extract of \textit{A. bilimbi} against the ultraviolet (UV) light (200–400 nm)-induced oxidative damage in albino mice. The study revealed that topical application of extract (4%) decreased the effect of UV light-induced photo-aging in mice skin by decreasing malondialdehyde level by up to 50% compared to an irradiated control group. The extract treated animals also showed minimal signs of histological changes and dermatitis compared with the untreated group. This finding suggests that the leaves may possess some anti-aging agents.\textsuperscript{[29]}

\textbf{Role of \textit{Averrhoa bilimbi} as a Hepatoprotective Agent}

The liver is a vital organ in the body which performs a major role in the metabolism, secretion, storage, and detoxification of chemical substances. Hepatoprotective activity is the ability of a compound or extract to prevent liver damage. The methanol extract of \textit{A. bilimbi} leaves exhibited appreciable hepatoprotective activity against carbon tetrachloride (CCL$_4$)-induced liver toxicity in Wistar rats. Thamizh \textit{et al.} reported that methanol extract of \textit{A. bilimbi} (250 and 500 mg/kg, p.o.) significantly (\textit{P} < 0.01) prevented CCL$_4$-induced elevation of levels of some biomarkers for liver damage which include serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase and alkaline phosphatase, total protein, and bilirubin in rat.\textsuperscript{[30]} Moreover, the fruits extracts at a dose of 250 mg/kg body weight and 500 mg/kg body weight have also been reported to demonstrate significant hepatoprotective activity against acetaminophen-induced liver damage in Wister rat.\textsuperscript{[31]}

\textbf{Role of \textit{Averrhoa bilimbi} as an Anticancer Agent}

Cytotoxicity assays are used to determine whether a compound or extract is toxic to cells. Cytotoxicity testing methods are
routine used in the screening of antitumor drugs. Ethanol extract of A. bilimbi leaves has been shown to possess moderate cytotoxic activity (LC$_{50}$ 5.81 μg/ml) in brine shrimp lethality assay.[20] In another study, the methanol extract of fruits and its CCl$_4$ and petroleum ether fractions demonstrated a significant cytotoxic potential (LC$_{50}$ of 0.005 μg/ml, 1.198 μg/ml and 0.781 μg/ml, respectively) compared to vincristine sulfate (with LC$_{50}$ of 0.859 μg/ml). In another similar study, the LC$_{50}$ values of chloroform and aqueous soluble fractions were found to be 5.691 and 6.123 μg/ml, respectively.[32]

Role of Averrhoa bilimbi as a Wound Healing Agent

Several medicinal plants have been shown to possess a significant healing effect. In this regard, the use of A. bilimbi in treating oral injuries has been scientifically investigated as well. Iga conducted a study to evaluate the effect of A. bilimbi leaves extract on the healing of the gingival wound. The result obtained showed that application of ethanol extract of A. bilimbi leaves (10% concentration)-enhanced gingival wound healing which was indicated by significant increase in the number of fibroblast in the rat gingival wound compared to untreated group.[31]

Role of Averrhoa bilimbi as an Antidiabetic Agent

DM affects hundreds of millions of people across the world. DM is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. It is a major public health problem that affects over 400 million people worldwide.[16] Scientific investigations revealed that A. bilimbi possesses antidiabetic properties. Pushparaj et al. evaluated the hypoglycemic and hypolipidemic effects of A. bilimbi leaves extract in streptozotocin (STZ)-induced diabetic rats. In this study, it was observed that the leaves ethanol extract (125 mg/kg twice daily p.o.) significantly lowered blood glucose and triglyceride levels when compared with the vehicle.[31] In another study, Pushparaj et al. examined the possible mechanism of the hypoglycemic action of hexane, ethyl acetate, butanol, and aqueous fractions of A. bilimbi’s leaves ethanol extract in STZ-diabetic male Sprague-Dawley rats. The hypoglycemic property of different fractions was assessed at a dose of 125 mg/kg body weight in STZ-diabetic rats. Results obtained showed that an oral administration of the aqueous fraction to STZ-induced diabetic rats significantly enhanced insulin secretion and improved glucose tolerance, while hepatic glucose-6-phosphatase activity was lowered. The resultant increase in serum insulin level was presumed to be the possible mechanism of action of the plant.[30] In a similar study conducted by Tan et al. in a high-fat diet (HFD) fed STZ-induced diabetic rats, aqueous fraction and butanol fractions of leaves ethanol extract resulted in significant hypoglycemic and hypotriglyceridemic effects.[32] In another in vitro study against digestive enzymes, leaves ethanol extract was reported to show α-glucosidase inhibitory activity and the same extract was found to be inactive against α-amylase enzyme.[30,39] Moreover, Pan investigated the effect of A. bilimbi on insulin signaling pathway. It was observed that different leaves extracts exhibit strong inhibition of protein tyrosine phosphatase 1B (PTP1B) in an in vitro enzyme assay at 10 μg/ml. The diethyl ether extract demonstrated the strongest inhibition with 0.7% residual PTP1B activity followed by petroleum ether extract with 5.7%, while butanol and water extracts displayed relatively less potency with residual PTP1B activity of 34.9% and 35.0%, respectively.[40]

Role of Averrhoa bilimbi as an Antihyperlipidemic Agent

The lipids in the body are mainly represented by cholesterol, triglycerides, and phospholipids. Elevated blood lipid levels are the major risk factors for the development of cardiovascular diseases, coronary artery disease, cerebrovascular disease, and peripheral vascular disease. These conditions often lead heart attacks and strokes. Several medicinal plants have been scientifically evaluated for their lipids-lowering property with respect to control aforementioned disorders. Pharmacological investigations have revealed that A. bilimbi possesses lipid-lowering property. Pushparaj investigated the hypoglycemic and hypolipidemic activities of an ethanol extract of leaves. It was observed that repeated administration of the ethanol extract of leaves (250 mg/kg/day) significantly lowered blood triglyceride by 130% when compared with the vehicle in STZ-induced diabetic rats. The treatment significantly increased the antiatherogenic index and high-density lipoprotein cholesterol to total cholesterol ratio.[35] The leaves extract has also been shown to cholesterol-uptake inhibition in an in vitro assay using the Caco-2 cells model of intestinal absorption. The fruit (125 mg/kg) as well as its aqueous extract (50 mg/kg) was also found to be effective in lowering lipids in the HFD fed rats.[41]

Role of Averrhoa bilimbi as an Antihypertensive Agent

Hypertension is considered a major risk factor for several cardiovascular diseases such as atherosclerosis, heart failure, stroke, coronary artery disease, and renal insufficiency. According to WHO, about one-third of the world’s population suffers from hypertension, and the incidences have been increasing at an alarming rate owing to the unique lifestyle modification. Recently, attention has been greatly concentrated on the use of herbal preparations as alternative agents to cure and prevent cardiovascular complications. Ethnobotanical surveys of various medicinal plants indicate their vast use in the treatments of cardiovascular disorders. Traditionally, the fruits and leaves of A. bilimbi have also been efficaciously used for blood pressure symptom. In this regard, Bipat et al. scientifically investigated the antihypertensive potential of aqueous extract of A. bilimbi’s leaves together with other plants using an in vitro isolated organ model. It was observed that the leaves aqueous extract significantly decreased the contractility of the norepinephrine-stimulated guinea pig aorta without affecting their beating frequency.[42] The leaves extract also demonstrated a significant antihypertensive effect in an in vivo experiment using cats revealing the ability of leaves extract to become a potential antihypertensive drug.[43]
Role of *Averrhoa bilimbi* as an Antithrombotic Agent

Anticoagulant herbs are used as an antithrombotic agent. Anticoagulant herbs are efficaciously used in angina, hepatitis, coronary artery disease, dysmenorrhea, rheumatoid arthritis, traumatic injury, tumors, depression, renal failure, stroke prevention, and poststroke syndrome. The anticoagulant activity of *A. bilimbi* was reported by Daud *et al.* in normal and alloxan-induced diabetic rats.[44] In their experiments, they found that oral administration of ethanol extracts of leaves and fruits (250 mg/kg) for 14 days were able to cause significant anticoagulant effect as observed by increased prothrombin time. In another similar study, crude methanol extract and partitioned fractions of leaves demonstrated significant thrombolytic activity (17.06–27.72%) in an *in vitro* assay.[45]

Toxicity

*A. bilimbi*’s fruit contains a large amount of oxalic acid. Excessive consumption of the fruit juice can lead to increased serum oxalate level and accumulation of calcium oxalate crystals in renal tubules which can cause acute kidney failure. Bakul *et al.* reported a series of cases from five hospitals in the State of Kerala (India) who developed an acute renal failure after drinking the fruit juice (100–400 ml/day). All the patients had severe renal failure with serum creatinine ranging from 5.5 to 12.3 mg/dl, and kidney biopsy showed an acute tubular necrosis with calcium oxalate crystals. Seven out of the ten patients required hemodialysis, but fortunately all of them recovered to normal conditions after 2–6 weeks of treatment.[46] Nair *et al.* further reported two additional cases of acute nephropathy with tubular oxalate deposition following ingestion of fruit juice.[47]

Bioprocessing of *Averrhoa bilimbi*

Since time immemorial, medicinal plants have been the reliable source for the herbal and traditional medicine practitioners to treat various disorders without even knowing about the presence of active principles responsible for the assuagement of symptoms of the disease in the plants. However, recent significant advancements in technology have played crucial roles in health care setting in which medicinal plants have been set forth to different scientific evaluations to find out a variety of more efficacious and safe biologically active agents responsible for the various pharmacological activities of the medicinal plants. Hence, many phytoconstituents exhibiting encouraging and potent biological effects have been patented for the commercial pharmaceutical purposes to cure many disorders. Moreover, a particular plant of medicinal quality needs to be processed very carefully to preserve the pharmacological activity and threshold amount of the bioactive compounds from pre- and post-harvesting stress such as ultraviolet light, heat, chemical exposure, microorganisms attack, and moisture.[48] *A. bilimbi* is traditionally used as a fresh juice, decoction, infusions, or dried powder as wound healing, antidiabetic, antihypertensive, antihyperlipidemic agent, etc.[49] It is commercially found in many herbal products in different countries. Different types of organic solvents (dichloromethane, chloroform, ethyl acetate, acetone, ethanol, methanol, etc.) are extensively used to extract pharmacological active compounds from the plants of medicinal significance. However, these organic solvents have also been feasibly associated to generate cancer or other deleterious toxicities in the human body. Therefore, this reason alone rescinds the potential of herbal preparations that are prepared using toxic organic solvents.[48] Hence, it is necessary to extract the medicinal plants using a green technology (toxic organic solvents-free extraction methods) to control the process and produce nonhazardous herbal preparations so that the pharmacological effect of medicinal plant remains intact. With the enormous advancement of latest technology to be utilized and the effect of various extraction techniques yet to be properly studied on the medicinal plants, hence, there is still a large unexplored area to be explored meticulously. For instance, the supercritical fluid extraction (SFE) technique might be used to make toxic solvent free *A. bilimbi*’s antidiabetic or antihypertensive fractions that could have good commercialization prospect after appropriate scientific studies.[49,49] Currently, SFE technique has become refined and sophisticated enough to yield controlled particles, particle generation from supercritical solution or suspensions, microencapsulation using antisolvent techniques.[10] Such advanced and sophisticated analytical techniques can be successfully used to develop the bioactive fractions into pharmaceutical grade products in order to cure various disorders efficaciously.[51] As SFE is an organic solvent-free technique and is able to produce stable extracts that could be effectively employed as a good prospect to change a common medicinal plant into an efficacious drug at a cost-effective and a healthy way. Likewise, other extraction alternatives such as microwave assisted extraction (MAE) and ultrasonic-assisted extraction (UAE) might also be used to recognize the better extraction method for this plant.[52]

It is apparent from the extensive literature review that *A. bilimbi* possesses antidiabetic, antihypertensive, antithrombotic, hypolipidemic, hepatoprotective, anticancer, and wound healing effects due to its strong antioxidant, anti-inflammatory, and antimicrobial properties. It was found to show significant hypoglycemic as well as its antioxidative property which can be used against the oxidative stress and consecutive heart disease, stroke, cancer, and liver damage. The antihyperlipidemic property can be used against hyperlipidemia. It possesses different pharmacological assets which can be efficaciously exploited for the management of many current global threats such as DM, cardiovascular disorders, and cancer. Moreover, it is a promising alternative to treat DM and its related complications all together in one shot and since this plant is abundant in nature, therefore, bioprocessing can be effectively and easily done using current green extractive methods such as SFE, MAE, or UAE to get high quality, organic trace free fractions, and bioactive compounds that can be promising and potent new antidiabetic, antihypertensive, or anticancer agents in the therapeutic managements of DM, hypertension, or cancer as well as other chronic syndromes.
Conclusion

*A. bilimbi* is an important medicinal plant used in traditional medicine for the treatment of various ailments and in maintaining good health and well-being. Extensive pharmacological research conducted over the years have proven the scientific bases for the therapeutic uses of *A. bilimbi*’s leaves and fruits in the treatment of several diseases including DM, hypertension, and microbial infections. In contrast to several pharmacological investigations, few preliminary phytochemical studies have been reported on this plant and the compounds identified so far are mainly volatile oils, fatty acids, and long-chain hydrocarbons with weak medicinal value. Despite the beneficial use of *A. bilimbi* in complimentary medicine and its scientifically proven pharmacological activities, there is a paucity of information on the bioactive compounds present in this plant. Given its interesting pharmacological profile, there is an urgent need to identify and isolate the bioactive constituents of this plant responsible for various biological activities. Isolation and characterization of bioactive compounds of different parts of *A. bilimbi* will provide an insight into the biochemical mechanism action of this plant. Knowledge of bioactive constituents will provide the bases for developing a new drug from the plant either as a pure compound or standardized extracts using advanced and sophisticated technology. The pure compounds exhibiting different pharmacological effects may also serve as lead for future drug development.

Financial support and sponsorship

Corresponding author is grateful to Fundamental Research Grant Scheme (FRGS13-089-0330) approved by the Department of Higher Education, Malaysia.

Conflicts of interest

There are no conflicts of interest.

References

1. Bryan CP. The Papyrus Ebers: Translated from German Version. London: The Garden City Press LTD.; 1930.
2. WHO. World Health Organization Fact sheet No. 134: Traditional Medicine. 2003. p. 2-4.
3. Ekor M. The growing use of herbal medicines: Issues relating to adverse reactions and challenges in monitoring safety. Front Neurol 2014;4:177.
4. Quattrocchi U. CRC World Dictionary of Plant Names: Common Names, Scientific Names, Eponyms, Synonyms, and Etymology. Vol. 3. New York, USA: CRC Press; 1999.
5. Veldhuijzen JF. Bilimbia (Lichenes) resurrected. Lichenologist 2004;36:191-5.
6. Orwa C, Mutua A, Kindt R, Jamnadass R, Anthony S. Agroforestree Database:a tree reference and selection guide version 4.0. 2009. Available from: http://www.worldagroforestry.org/treedb/AFTPDFS/ Averrhoa_bilimbi.PDF. Last accessed on 2015 Jul 05.
7. De Lima VL, Mélo ED, Lima LD. Physicochemical characteristics of bilimbi (*Averrhoa bilimbi*) L. Rev Bras Frutic 2001;23:421-3.
8. Lim TK. Edible Medicinal and Non-Medicinal Plants. Vol. 2. Springer Netherlands; 2012. p. 867-78.
9. Ganders FR. The biology of heterostyly. N Z J Bot 1979;17:607-35.
10. Goh S, Chuah C, Mok J, Soepadmo E. Malaysian Medicinal Plants for the Treatment of Cardiovascular Diseases. Malaysia: Pelanduk Publications; 1995. p. 62-3.
11. Samuel AJ, Kalusalingam A, Chellappan DK, Gopinath R, Radhamani S, Husain HA, et al. Ethnomedical survey of plants used by the Orang Asli in Kampung Bawong, Perak, West Malaysia. J Ethnobiol Ethnomed 2010;6:5.
12. Ong HC, Nordiana M. Malay ethno-medico botany in Machang, Kelantan, Malaysia. Fitzoterapia 1998;70:502-13.
13. Alsarhan AN, Sultana N, Kadir MR, Aburuj T. Ethnopharmacological survey of medicinal plants in Malaysia, the Kangkar Pulai region. Int J Pharmacol 2012;8:679-86.
14. Wong KC, Wong SN. Volatile constituents of *Averrhoa bilimbi* L. fruit. J Essent Oil Res 1996;7:691-3.
15. Pino JA, Marbot R, Bello A. Fruit grown in Cuba. J Essent Oil Res 2004;16:241-2.
16. Hasanuzzaman M, Alii MR, Hossain M, Kuri S, Islam MS. Evaluation of total phenolic content, free radical scavenging activity and phytochemical screening of different extracts of *Averrhoa bilimbi* (fruits). Int J Pharm Res 2013;2:92-6.
17. Patil AG, Koli SP, Patil DA. Pharmacognostical standardization and HPTLC fingerprint of *Averrhoa bilimbi* (L.) fruits. J Pharm Res 2013;6:145-50.
18. Gunawan CA, Paano A. Structure Elucidation of Two New Phytol Derivatives, a New Phenolic Compound and Other Metabolites of *Averrhoa bilimbi*. Research Congress, De La Salle University Manila; 2013. p. 1-8.
19. Siddique KJ, Muhammad M, Uddin N, Islam S, Pavin S, Shahriar M. Phytochemical screenings, thrombolytic activity and antimicrobial properties of the bark extracts of *Averrhoa bilimbi*. J Appl Pharm Sci 2013;3:94-6.
20. Karan B, Ibrahim M, Mahmodo A, Huq MA, Chowdhury MM, Hossain A, et al. Preliminary antimicrobial, cytotoxic and chemical investigations of *Averrhoa bilimbi* Linn. and *Zizyphus mauritiana* Lam. Bangladesh Pharm J 2011;14:127-31.
21. Mackeen MM, Ali AM, El-Sharkawy SH, Manap MY, Saleh KM, Laijs NH, et al. Antimicrobial and cytotoxic properties of some Malaysian traditional vegetables (Ulam). Pharm Biol 1997;35:174-8.
22. Zakaria ZA, Zaiton H, Henie EF, Jais AM, Zainuddin EN. *In vitro* antibacterial activity of *Averrhoa bilimbi* L. leaves and fruits extracts. Int J Trop Med 2007;2:96-100.
23. Norhana MN, Azman MN, Poole SE, Deeth HC, Dykes GA. Effects of bilimbi (*Averrhoa bilimbi* L.) and tamarind (*Tamarindus indica* L.) juice on *Listeria monocytogenes* Scott A and *Salmonella typhimurium ATCC 14028* and the sensory properties of raw shrimps. Int J Food Microbiol 2009;136:58-94.
24. Mohamad S, Zin NM, Wahab HA, Ibrahim P, Sulaiman SF, Zaharinuddin AS, et al. Antituberculosis potential of some ethnobotanically selected Malaysian plants. J Ethnopharmacol 2011;133:1021-6.
25. Nazmul MH, Salmah I, Syahid A, Mahmood A. *In vitro* screening of antifungal activity of plants in Malaysia. Biomed Res 2011;22:28-30.
26. Ahmad F, Lajis NH, Israif DA, Khozirah S, Kalsom YU. Antioxidant and nitric oxide inhibition activities of selected Malay traditional vegetables. Food Chem 2006;95:566-73.
27. Sabiha SC, Golam MU, Nazia M, Mokarram H, Raquibul HS. *In vitro* antioxidant and cytotoxic potential of hydromethanolic extract of *Averrhoa bilimbi* L. fruits. Int J Pharm Sci Res 2012;3:2263-8.
28. Asna ANI, Norham A, Antioxidant activity and bioactive components of *oxalidaceae* fruit extracts. Malays J Anal Sci 2014;18:116-26.
29. Precious LA, Coren JP, Celestine LA, Mary RM, Janina CE, Rheinmark LS, Mizna M,  Kuri MS . Preliminary cytotoxic activity of different extracts of *Averrhoa bilimbi* Linn. leaves crude extract prevents UVB-induced oxidative damage in albino mice. The STETH 2012;6:29-41.
30. Dnyaneshwar MN, Shikkar BY, Shajesh SW, Juvekar R. Hepatoprotective effect of *Averrhoa bilimbi* Linn. against carbon tetrachloride induced hepatic damage in rats. Pharmacologyonline 2010;3:1-6.
31. Thamizh SN, Santhi PS, Sanjayakumar YR, Venugopalan TN, Vasanthakumar KG, Swamy G. Hepatoprotective activity of *Averrhoa bilimbi* fruit in acetaminophen induced hepatotoxicity in wistar albino rats. J Chem Pharm Res 2015;7:335-40.
32. Ali R, Hossaina M, Runa JF. Preliminary cytotoxic activity of different extracts of *Averrhoa bilimbi* (fruits). Int J Pharm Res 2013;2:83-4.
33. Igae H. Topical application of ethanol extract of starfruit leaves (*Averrhoa bilimbi* Linn.) increases fibroblasts in gingival
wounds healing of white male rats. Indones J Biomed Sci 2012;6:35-9.
34. Aguiree F, Brown A, Cho NH, Dahlquist G, Dodd S, Dunning T, et al. IDF Diabetes Atlas. 6th ed. Basel, Switzerland: International Diabetes Federation; 2013.
35. Pushparaj P, Tan CH, Tan BK. Effects of Averrhoa bilimbi leaf extract on blood glucose and lipids in streptozotocin-diabetic rats. J Ethnopharmacol 2000;72:69-76.
36. Pushparaj PN, Tan BK, Tan CH. The mechanism of hypoglycemic action of the semi-purified fractions of Averrhoa bilimbi in streptozotocin-diabetic rats. Life Sci 2001;70:535-47.
37. Tan BK, Tan CH, Pushparaj PN. Anti-diabetic activity of the semi-purified fractions of Averrhoa bilimbi in high fat diet fed-streptozotocin-induced diabetic rats. Life Sci 2005;76:2827-39.
38. Ali H, Houghton PJ, Soumyanath A. Alpha-Amylase inhibitory activity of some Malaysian plants used to treat diabetes; with particular reference to Phyllanthus amarus. J Ethnopharmacol 2006;107:449-55.
39. Lawag IL, Aguinaldo AM, Naheed S, Mosihuzzaman M. α-Glucosidase inhibitory activity of selected Philippine plants. J Ethnopharmacol 2012;144:217-9.
40. Pan S. Natural Products and Insulin Signalling; Aspects of the Metabolic Syndrome; Testing in in vitro and Cell Based Assays. Doctoral Dissertation Uniwein; 2011. p. 35-64. Available from: http://www.othes.univie.ac.at/16111/1/2011-09-16_0325745.pdf. [Last accessed on 2015 May 04].
41. Pattamadiok D, Niumsakul S, Limpeanchob N, Ingkaninan K, Wongsinkongman P. Screening of cholesterol uptake inhibitor from Thai medicinal plant extracts. J Thai Tradit Altern Med 2015;8:146-51.
42. Bipat R, Toelsie JR, Joemmanbaks RF, Gummels JM, Klaverweide J, Jhanjan N, et al. Effects of plants popularly used against hypertension on norepinephrine-stimulated guinea pig atria. Pharmacogn Mag 2008;4:12-9.
43. Winarti C, Marwati T. Effect of bilimbi leaf extracts on decrease blood pressure. J Pascapanen 2009;6:54-61.
44. Daud N, Hashim H, Samsulrizal N. Anticoagulant activity of Averrhoa bilimbi Linn. In normal and alloxan-induced diabetic rats. Open Conf Proc J 2013;4: (Suppl 2, M6):21-6.
45. Ramjan A, Hossain M, Runa JF, Md H, Mahmodul I. Evaluation of thrombolytic potential of three medicinal plants available in Bangladesh, as a potent source of thrombolytic compounds. Avicenna J Phytoled 2014;4:430-6.
46. Bakul G, Unni VN, Seethaleksmy NV, Mathew A, Rajesh R, Kurien G, et al. Acute oxalate nephropathy due to ‘Averrhoa bilimbi’ fruit juice ingestion. Indian J Nephrol 2013;23:297-300.
47. Nair S, George J, Kumar S, Gracious N. Acute oxalate nephropathy following ingestion of Averrhoa bilimbi juice. Case Rep Nephrol 2014;2014:240936.
48. Huie CW. A review of modern sample-preparation techniques for the extraction and analysis of medicinal plants. Anal Bioanal Chem 2002;373:23-30.
49. Raskin I, Ribnicky DM, Komarnytsky S, Ilic N, Poulev A, Borisjuk N, et al. Plants and human health in the twenty-first century. Trends Biotechnol 2002;20:522-31.
50. Mohamed RS, Mansoori GA. The use of supercritical fluid extraction technology in food processing. London, UK: Featured Article in Food Technol Magazine, The World Markets Research Centre; 2002.
51. Smelt JPPM, Rijke GGF. High pressure treatment as a tool for pasteurization of food. In: Balry C, Hayashi R, Heremans K, Masson P, editors. High Pressure Biotechnology. Vol. 224. Colloque INSERM N John Libbey; 1992. p. 361-4.
52. Grigonis D, Venskutonis PR, Sivik B, Sandahl M, Eskilsson CS. Comparison of different extraction techniques for isolation of antioxidants from sweet grass (Hierochloe odorata). J Supercrit Fluids 2005;33:223-33.