Bidens pilosa Linn.: Beautiful Weed for the Healthy Mouth – A Mini Review

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Abstract. *Bidens pilosa* L. can be found everywhere in warm and humid regions. The plant has been used as a food and drink supplement, and as medicinal herbs for a long time by people from various places. The assortment of activities of *B. pilosa* in treating diseases gives a remarkable possibility to explore and develop its utilization for various medicinal purposes. In this mini-review, we explored the application of *B. spilosa* as herbal medicine for mouth health, specifically mouthwash. Until now, there is no information about the application of this plant for mouthwash. The use of alcohol, cetyl pyridinium, chlorhexidine, and triclosan as active ingredients in mouthwash can control plaque. However, the long-term use of these compounds may show side effects, for instance, changes in taste, and teeth and oral stains. Based on the result, it can be concluded that the *B. spilosa* plant contains diverse groups of compounds, such as polyacetylenes, flavonoids, and tannins, which are responsible for its various activities. The *B. spilosa* extracts are non-toxic and have potential active compounds in mouthwash formulation, due to their antimicrobial action against a wide range of microbes, particularly oral microbes and it has additional activities such as anti-inflammation, analgesic, and antioxidant.

Keywords: Environmentally friendly, medicinal plants, mouthwash, supplement

1 Introduction

Bidens pilosa L. is a perennial herb belonging to the Asteraceae family. The plant is thought to be originated in South America and then spread all over the world. *B. pilosa* is scattered widely over the tropical, subtropical, and warm temperate regions of the world, such as Asia, Africa, and South America. The seed has a burr that adheres to human clothes or animal fur or feather. As the seed is laid and covered by humid soils, it will soon germinate. In this way, the seeds can be spread easily over the lands. The plant is regarded as a weed because of its invasiveness tendencies [1–4].

B. spilosa is known by vernacular names, such as Ketul, Ajeran (Indonesia); Uqadolo (Southern Africa); Amor Seco (Peruvian); Ottrancedi (India); Picãopreto, Cuamba (Portuguese); Kinehi / Ko'oko'olau (Hawaii); Guizhencao (Demon Spike Grass or Ghost Needle Weed) , Xian Feng Cao (Abundant Weed) (Chinese); Has Kung Chia, Han Feng (Taiwan); Bidenthérissé, Bident poilu, Herbed'aiguille, Herbevillebague, Piquants noirs

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(French); Ko-sendangusa (Japan); Piripiri (Tahitian); Farmer's friends, Cobbler's pegs (Australia); Spanish needles (Barbados); Te de Coral (Mexico); Z'Herbe Zedruite, Z'Herbe Z'Aiguille (Dominica Republic); Beggar's ticks (USA); Devil's needles, Broomstick, Blackjack, Railway Daisy, Pitchforks (English) [2–6]. The synonym names of *B. pilosa* are *B. sundaica* var. *minor Blume*, *B. pilosa* var. *bimucronata*, *B. pilosa* var. *minor* [1].

The plant has ethnobotanical uses as a food and drinks supplement [1, 2]. All parts of the plants are eaten as food: Leaves, flowers, stems, and whole plants. In South Africa, the leaves and young shoot of the plant are used as food. The leaves and young shoot can be cooked as soups or stews ingredients or added to salads. In many countries, young shoot tips and/or leaves are used to prepare beverages or juices or dried to make tea [3]. For example, Ladakhi tea in Himalayan regions [7].

This plant is more known as a medicinal herb for a long time by people from various places: India, Africa, China, Cuba, Uganda, Middle America, Hong Kong, Zulu, Taiwan, Bafia, Brazil, Venezuela, Hawaii, Japan, Trinidad, Tobago, and many others [1–3]. All parts of the *B. pilosa* plant such as leaves, flowers, seeds, stems, aerial parts, and/or roots are used as components of herbal medicine. In folklore, *B. pilosa* is suggested to treat various ailments and disorders with indications that can be varying between populations or regions. The following examples are diseases to be cured: Yellow fever and common fever, colds, influenza, sore throat, cough, diarrhea, enteritis, dysentery, constipation, acute appendicitis, eye infection, catarrh, conjunctivitis, otitis, pharyngitis, diabetes, hepatitis, malaria, intestinal worms, acute nephritis, diuretic, stomach ache, colic, wound, nosebleed, ulcer illnesses, rheumatoid arthritis, sprain, insect and scorpion sting, pruritus, anti-inflammatory, asthma, pulmonary tuberculosis, dysmenorrhea, obesity, ant yeast, hemorrhoids, and bacterial infections in renal and gastrointestinal tracts. To obtain high effectiveness for illnesses treatment, locals people make such preparation of the herb in the forms of decoctions, macerations, juices, fresh leaves squeezed, or directly consumed [1–4, 8–11].

The properties are no longer folklores because many studies have been proven the activities *in vitro*, *in vivo,* and *ex vivo* assays [3, 7, 9, 12–23]. Currently, the plant become a market commodity, such as dried plant powder, *B. pilosa* tea, extracts, and tinctures. The products are sold as food supplements, refreshments, or herbal medicines with indications to improve the health of humans, domestic plants, and animals. For example, the plant extracted with ethanol-water is sold as "*B. pilosa* Extract" (Hunan Nutra Max), with indications for the broad-spectrum antimicrobial agent; toning, strengthening, protecting, and detoxifying liver; for arthritis, rheumatism, and other inflammatory conditions; for diabetes; and for stomach ulcers and digestive disorders. In Uganda, *B. pilosa*, known as Obukura, is sold by 12 % of industries and with the lowest market price as recorded in 2013 [24]. In Taiwan, the dried whole plant is processed into capsules, decoctions, and tinctures are sold approximately 700 t yr^{-1} of fresh weight for diabetes treatment. Other product of *B. pilosa* is Clear Guard™, an anti-allergic product [7].

The assortment of activities of *B. pilosa* in treating diseases give a remarkable possibility to explore and develop its utilization for various medicinal purposes. Furthermore, the plant can easily be found everywhere in Indonesia by local people, in such a warm and humid region. The use of *B. pilosa*, specifically for mouth health, is a promising candidate for natural resources. The plant showed remarkable biological properties and is the potential for making good mouth-health preparations and formulations. In mouthwash formulation, it gives advantages of its antimicrobial, anti-inflammatory, anti-infection, antioxidant, analgesic, and sprue-curing activities. Moreover, this plant is commonly consumed by people as food or as an herbal tea drink. So far, this herb and the extracts are proven as non-toxic. Based on the facts, the use of the plant as mouthwash is

very promising. Until now, there was little information about the application of this plant for mouth health formulation, specifically for mouthwash.

An oral cavity is an ideal place for bacterial growth. If not cleaned properly, the leftover food becomes a place for bacteria to grow. The main bacteria that cause plaque is *Streptococcus mutans* Clarke 1924, a normal inhabitant of the oral cavity. These bacteria can develop to be pathogens when met with a supportive environment. The *S. mutans* can produce lactic acid that will destroy tooth enamel and eventually cause dental caries [25]. Maintaining oral and dental hygiene by regularly removing plaque accumulated on the tooth surface is an effective way to prevent dental and periodontal caries [26]. Brushing and flossing are not enough to clean the teeth, particularly for people in specific conditions. Gargling with mouthwash gives a therapeutic effect over the entire tooth surface including areas that cannot be reached by a toothbrush [27]. Mouth washing gives other benefits to oral health due to the anti-inflammatory, anti-microbial, and analgesic actions of the content [28].

The use of alcohol, cetyl pyridinium, chlorhexidine, and triclosan as active ingredients in mouthwash can control plaque. However, long-term use of these compounds showed side effects, such as changes in taste, formation of calculus supragingival, desquamation of the oral mucosa and can cause teeth and oral staining [19]. The use of herbal materials is an alternative to overcome the negative impacts caused by synthetic materials. Various plants extracts have been used in mouthwash formulations and proved to reduce bacterial counts. *B. pilosa* extracts have anti-microbial properties which are effectively used to maintain good oral hygiene.

In this mini-review, we performed a literature study on the application of *B. pilosa* as herbal medicine for mouth health, specifically mouthwash. The components and bioactivity of this plant and its extracts make this plant interesting to be explored. The advantage of adding *B. pilosa* in mouthwash and its safety are discussed here.

2 Ethnomedical uses of *B. pilosa* in the world

B. pilosa has a long tradition uses as medical herb globally. All parts of the plants are believed to have an activity to cure many diseases with varying indications from one nation to the other. Every nation has its own story for the purposes of plants utilization, as listed in Table 1. Some of the effects have been proven experimentally.

Table 1. The use of *B. pilosa* as herbal medicine among people from various regions.

Regions and applications	Reference
Africa	
Bafia: Headache, Hypotensive, and Dysmenorrhea	[3]
Cameroon: Headache, Hypotensive, Dysmenorrhea	[3]
Ghana: For allergies, bleeding, earaches, eye infections, hives	[2]
Uganda: Colds, diarrhea, eye infection, influenza, nose bleeds, sore throat, stomach ulcers, yellow fever, a blood-clotting agent, headache, ear infection, kidney problems, and Flatulence.	[6, 3]
Zulu, Africa: Antirheumatic, Enema for abdominal pain, and Arthritis/malaria	[3]

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Table 1. Continued

Regions and applications	Reference
Africa	
South Africa: To treat headaches, ear infections, kidney problems, tuberculosis, malaria, flatulence, diarrhoea, hangover, poison antidote, stomach and mouth ulcers	[9, 29]
Africa–commonly Antiseptic, bleeding, blood clots, burns, cataracts, colitis, malaria, pneumonia, tuberculosis, otitis, pharyngitis, conjunctivitis, skin problems (Cuts, burns, wounds, and other), respiratory infections, diarrhea, sores, dysentery/bacillary dysentery, enteritis, stomach pains, eye disorders, earache, inflammation, constipation, haemorrhages, food poisoning, postpartum haemorrhage, hyperemesis gravidarum (morning sickness), rheumatism, worms, and yaws	[2, 3]
Europe	
Astringent, diaphoretic, and diuretic properties. Roots, leaves, and seeds possess antibacterial, anti-dysenteric, antimalaria, antiseptic, anti-cancer, anti-inflammatory, antipyretic, anti-diabetic, liver-protective, blood-lowering, hypoglycaemic, diuretic, and hepatoprotective effects	[7, 9]
America	
Central America: Wounds	[3]
Middle America: Choleretic, colds, diuretic, eye infection, eye irritation, influenza, nose bleeds, sore throat, stomach ulcers, scarlatina infections, and yellow fever	[3, 7]
Amazonia: For angina, chills, diabetes, dysentery, toothache, malaria, headache, eye disorders, oedema, hepatitis, jaundice, laryngitis, sore throat, menstrual disorders, parasites, sore mouth, wounds stomach-ache, worms, urinary insufficiency	[2]
Bahamas: For tumour, cancer, fever, heat-rash, itch, intestinal gas, wounds, skin sores, lacerations, water retention	[2]
Brazil: For breast engorgement, fungal infections, pharyngitis, skin problems (cuts, burns, wounds, and others), malaria, cough, diabetes, diaper rash, dysentery, gonorrhoea, vaginal infections, sore throat, vaginal discharge, lung disorders urinary infections, urinary insufficiency, hepatitis, toothache, tonsillitis, fever, inflammation, haemorrhoids, insect bites, jaundice, lactation aid, liver tonic, liver obstructions, parasites, wounds, rheumatism, sclerosis (glands), scurvy, ulcers, astringent and as an antiseptic	[2, 3]
Cuba: Anti-inflammatory, asthma, anti-tumour, catarrh, renal infection, pulmonary tuberculosis, the coolness of the uterus, cough, diabetes, gastritis, menstrual irregularities, stomach ulcers	[3]
Dominican Republic: For chest problems, toothaches, and to promote milk production, salivation, urination, and menstruation	[2]
Haiti: For angina, foot-and-mouth disease, stomatitis, vomiting, tonsilitis, milk production, mental disorders, nervous shock, diabetes, catarrh	[2]
Hawaii: Wounds	[3]

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Table 1. Continued

Regions and applications	Reference
Amerika	
Mexico: For blood clots, chest problems, diabetes, fever, gastroenteritis, hemorrhoids, inflammation, jaundice, kidney, liver disorders, mouth blisters, nervous problems, snakebite, stomach disorders, and as an antiseptic and diuretic	[2]
Panama: For colds, headache, intestinal disorders, prostate tumours, rheumatism	[2]
Peru: For abscesses, wounds, angina, anuria, baldness, bile stimulation, parasites, childbirth, chills, conjunctivitis, cystitis, inflammation, diabetes, mouth sores, dysentery, oedema, foot–and–mouth disease, fever, fungal infections, headache, haemorrhage, hepatitis, sores, sore throat, jaundice, lacerations, laryngitis, liver problems, liver support, menstrual disorders, nephritis, nervous system disorders, pain, obesity, rheumatism, tonsilitis, toothache, urinary infections, urinary insufficiency, venereal diseases, weight loss, worms	[2]
Tobago and Trinidad: Antimicrobial, bacterial infections in gastrointestinal tracts, cuts, burns, and skin problems	[3]
Venezuela: Cuts, burns, and skin problems	[3]
Asia	
China: Anti-inflammatory, asthma, colds, colic's, conjunctivitis, enteritis, cough, dysentery / bacillary dysentery, influenza, malaria, yellow fever, otitis, nose bleeds, pharyngitis, pulmonary, wounds, skin problems (cuts and burns), snake bites, sore throat, tuberculosis,	[3, 7]
Hong Kong: Acute appendicitis, haemorrhoids, antirheumatic,acute infectious hepatitis, pruritus.	[3]
India: Acute or chronic hepatitis, colds, flu, glandular sclerosis, wounds, urinary tract infections and stomach-ache,	[3]
Taiwan: Diabetes	[3]
Japan: For livedo reticularis with summer ulceration, a cutaneous disease, anti-inflammatory, and anti-allergic properties,	[7]
Elsewhere	
For abortions, bleeding, blood cleansing, boils, bronchitis, styptic, cancer, candida, colds, colic, colitis, conjunctivitis, coughs, cuts, diabetes, diarrhea, dysentery, eye problems, fever, flatulence, flu, food poisoning, gout, hair loss, hepatitis, hyperglycemia, stomach disorders, liver diseases, hypertension, inflammation, respiratory infections, intestinal infections, parasites, worms, wounds, and as antiseptic, urinary infections, urinary problems, skin problems, menstrual promotion, rheumatism, ulcers, ulcerative colitis, burns astringent, snakebite, sweat promotion, toothache, thrush, diuretic,	[2, 3]

Based on Table 1, there are several common uses of this plant by people in many nations. The following are the intended uses at most:

1. Antimicrobial (infections of gastrointestinal, respiratory, pulmonary, urogenital, renal, ear, eye, tooth, and pulmonary tuberculosis); and as antiseptics
2. For skin problems, such as cuts, burns, wounds, and itch

3. For kidney problems such as diuretics
4. Anti-inflammatory: Skin, colon, intestine, eye, etc
5. For stomach pains and ulcers
6. For haemorrhages
7. Anti-diabetic
8. Headaches
9. Pharyngitis and otitis
10. Anti-malarial
11. Anti-rheumatic
12. Cold, fever, and influenza
13. Menstrual disorders and dysmenorrhea
14. Poison antidote
15. Antivirus: Yellow fever, and hepatitis
16. Anti-parasites, worm
17. Anti-tumours and anticancer

Besides the above usages, in a few countries, the plant is applied to cure cataracts, pneumonia, asthma, hypotensive, allergies, and obesity.

3 Bioactive compounds of *B. pilosa* plant parts

B. pilosa contains diverse groups of compounds that affect their biological activities. Two compound groups, flavonoids, and polyacetylenes, are found in plenty of amounts in *B. pilosa*. Other groups that are also detected in *B. pilosa* are phenolics, pheophytins, fatty acids, and phytosterols [9, 7].

The flavonoids and their derivatives are compounds that are found in most plant parts of *B. pilosa*. There are twenty kinds of flavonoids glycosides, twelve kinds of aurone glycosides, sixteen kinds of okanin chalcone glycosides, and ten kinds of other flavonoids. Many of the flavonoids are found in leaves, aerial parts, or whole plants. Some are only found in the upper parts of the plants, for example, the aurone glycosides. Other examples of flavonoids found in the leaves, flowers, and aerial parts of *B. pilosa* are okanin chalcone glycosides. The presence of these compounds causes this plant to acquire the following activities: Antioxidant, anti-inflammatory, antimalarial, hepato-and mucous-protection, cytotoxic, anti-allergic, inhibits platelet aggregation, anti-hypertension, antibacterial, anti-leishmanial, anti-listeria, antiviral activity against HIV and Flavivirus [7, 9, 23]. The isoquercitrin; vitexin; astragalin; 5,6,7,4'–tetra methoxyl flavone; 5,3',4'–trihydroxy–3,7–dimethoxylfla–vone; and quercetin are flavonoids which showed antioxidant and anti-proliferative activity against RKO cells [30].

The polyacetylenes are found in *B. pilosa* in large amounts, both in quantity and in types. There are at least 1 400 polyactylenes and its derivative; 37 types of them can be found in *B. pilosa*. The only polyacetylene reported being detected in all plant parts of *B. pilosa* is phenylheptatriyne (1–phenylhepta–1,3,5–triyne). The subsequent compounds are example of polyacetylenes with known effects: 1,2–dihydroxytrideca–5,7,9,11–tetrayne and 1,3–dihydroxy 6(E)–tetradecane–8,10,12–triyne [31]; Phenylheptatriyne (1–phenylhepta–1,3,5–triyne);1–Phenyl–1,3–diyn–5–en–7–ol–acetate;2–b–D Glucopyran-osyloxy–1–hydroxyl– 5(E)–tridecene–7,9,11–triyne; 2–β–d–(R)–1,2–dihydroxytrideca–3,5,7,9,11–pentayne and 2–β–d–glycopyrasyloxy–1– hydroxytrideca– 3,5,7,9,11–pentayne; 1–phenyl–1,3–diyn–5–en–7–ol–acetate 2–O–â–D– glucosyltrideca–11E–en–3,5,7,9 –tetrayn–1,2–diol; 1–phenylhepta–1,3,5–triyne and so on. Extraction methods influence the polyacetylenes isolated because the compounds are very sensitive, unstable, and polymerized when concentrated. The change can cause loss of their biological activities [7].

The polyacetylenes have been associated with the following effects: Anti-inflammatory, antioxidant, cytotoxic activity, antibacterial, anti-fungal, anti-malarial activity, diabetes, nematocidal activities, anticancer, anti-proliferative and/or pro-apoptotic, anti- hyperglycaemic effects inhibit adipogenesis, antiulcer, and anti-obese [9, 23, anti- angiogenic activities and the ability to regulate the expression of cell cycle mediators 31]. The photo-activated form of polyacetylenes is more effective to inhibit and eliminate pathogenic bacteria [9].

Besides flavonoids and polyacetylenes, the phenolics compounds also give important effects on *B. pilosa*, such as quinic acids and chlorogenic acid also act as an antioxidant. Ethyl caffeate is an ester of hydroxycinnamic acid, belongs to a polyphenolic compound, involve in the anti-inflammatory process. O-caffeoylquinic acids have an Anti-Respiratory Syncytial Virus (RSV) [7]. Other compounds with significant effects can also be found in *B. pilosa*. Linoleic acid cause cytotoxicity activity is anti-viral against herpes, influenza, sendai, sindbis, antibacterial, and anti-malarial [32, 33].

In traditional uses, the plants are consumed as fresh or dried simplices or are prepared in water as decocts or infuse, in alcohol as tinctures [2]. The ethnobotanical applications of *B. pilosa* are proven to be effective as shown by many studies' results. All parts of the plants extracted in both solvents were investigated thoroughly and exhibited the same effects as the traditional applications. The extracts contain active compounds that are related to their activity. The polyacetylenes and flavonoids present in both extracts are important in the inhibition of various pathogenic organisms, reduction of gastric acid secretion, and activity against chemical-and bacteria-induced gastric lesions and ulcers [7]. Flavonoids are responsible for antibacterial activity against sensitive and resistant strains [34]. The acetylene and flavonoid are also responsible for antimalarial activity. The polyacetylenes can also reduce inflammation, probably mediated by different mechanisms. *B. pilosa* also contained triterpenes and essential oils which may contribute to the observed therapeutic action of the herb, and photo-activated polyacetylenes that can act as antimicrobial and anticancer [7].

The aqueous extract of *B. pilosa* contains polyacetylenes; flavonoids; flavonols; terpenoids; tannins; phlobatannins; alkaloids; saponins; steroids; sterols; cardiac glycosides; Phenol, 2, 4–Bis (1, 1–Dimethylethyl) and other phenolic compounds [18, 35, 29, 36]. These compounds might play a role in the activities of the extracts, such as antimicrobial activity against Gram-positive and negative bacteria [29], analgesic activity [18]; anti-inflammatory [5]; hepatoprotective activity [37]; anti-plasmodial activity, [35]; anti-obesity [36]; and alleviate the dry-eye symptoms [20].

The alcoholic extracts have active compounds, such as polyacetylene, flavonoid, alkaloids, tannins, saponins, phenol, quinones, glycosides, methyl ester; Dodecanoic acid; 10,13–Octadecadienoic acid, methyl ester; 9,12,15–Octadecatrienoic acid, methyl ester(Z,Z,Z)–; Tetradecanal; 2–Methyl–Z,Z–3,13–octadecadienol; 13–Octadecenal, (Z)–; Oleic Acid etc. [3, 13–19, 22, 38]. The alcoholic extracts inhibited the growth of Gram-positive and Gram-negative bacteria [16, 17, 19, 38]; even toward drug resistance bacteria [21], and *Mycobacterium* [17]; yeast, and fungi [3, 16, 17, 19]. Other effects are also proven, including analgesic activity [18]; anti-inflammatory [3, 13, 14]; antioxidants [3, 13, 19, 22]; antiplasmodial activity [3, 15]; larvicidal activity [19]; haematopoietic strength and modulator of white blood cell differential count [3, 12]; anticancer and antipyretic activity [3, 19, 20]; antiallergic activity, hypotensive effects, gastric antisecretory and antiulcer activities [3].

In some regions, the plant is consumed fresh directly as or as dried simplices. Studies in chicken showed that the plant contained three polyynes that act as an anti-coccidia [40] and as a prebiotic to enhance the growth of probiotics in animal guts [41]. In this way, it seems that the growth of chickens can be optimal, and the immune system

improves. In rats, feeding this plant can suppress oxidative stress, prostaglandin production, and inflammation [42]. Application of distilled oil from the whole plants had an antioxidant activity which might be the effect of á1-pinene 14.7 %; β-ocimene 12.8 %; ε-caryophyllene 13.5 %; cadinene 10.1 % [43]. Feeding of mice and chicken with whole plant powder of *B. pilosa* suppressed gut pathogens which can improve the immune system and growth of animals [44].

Nowadays, commercial products of *B. pilosa* are available in the market, such as powders, tinctures, or dried plants. These products were also proven to be effective as anti-inflammatory agent for gastrointestinal disorders [45], for treating neurodegeneration symptoms [46], and to reduce adipogenesis [47].

4 Toxicity studies of B. *pilosa*

A long history of medicinal and traditional uses indicates that B. *pilosa* is safe for human consumption. Many populations in many regions have experience using B. *pilosa* for various purposes. The plant efficacy as believed by the local population was proven effective without any visible toxicity [9].

Recent toxicity studies of the plant, including on acute, sub-chronic and chronic, have proven that all plant parts and its extracts are non-toxic to cell culture [35, 48]; mosquito larvae [33, 49]; mice [44, 14]; chicken [44]; rats [3, 36, 37]; and human [50, 7].

For medical uses, it is important that the raw plant and its extracts are non-toxic. Several toxicity studies *in vivo* and *ex vivo* showed no obvious toxicity in diverse cells or organisms treated with water extracts [3, 35–37]; hydroethanolic extracts [14, 21, 48, 49]; or oral administration of dried plants [44, 50]. These studies were performed using dried plants or extracted in non-toxic solvents Table 2 as applied by people traditionally.

The doses of this herbal plant in common medication are below the limit doses of toxicity based on an experimental study using some parameters. Common doses are between 15 g d^{-1} to 60 g d^{-1} [9]. The following are the doses used by the investigators that showed no obvious toxicity to the animals, or volunteers. Consumption of whole plants at 15 g kg^{-1} BW d^{-1} or less, were not toxic in mice and chicken [44], or 1.2 g d^{-1} for 90 d in humans [50]. The whole groundmass of the plant appeared more safe compared to the water and ethanol extracts of B. *pilosa* [44]. Treatment of rats or mice using B. *pilosa* water extracts is still safe up to 10 g kg^{-1} BW once a day [3], or up to 2 g kg^{-1} BW using hydroethanolic extracts [14].

Table 2. *Cytotoxicity* studies of B. *pilosa*

Plant parts or extracts	Non-toxic dose	Length of treatment	Experimental subjects	References
Water extract of aerial part	Up to ≤ 2 000 μg mL^{-1}	72 h	Vero cells and RAW 264.7 cells	[32]
Water extract of leaves	CC_{50} = 76.11 ± 3.21 for L929; and 73.23 ± 1.22 for HEPG2	48 h	Animal cell lines fibroblast L929 and Hella cells	[35]
Hydroethanolic extract of leaves	Up to 100 μg mL^{-1}	72 h	A549 human tumor cell line	[48]
Hydroethanolic extracts of leaves and roots	Less than 5 mg mL^{-1}	48 h	*Aedes albopictus* (Skuse, 1894) larvae	[21]

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Table 2. Continued

Plant parts or extracts	Non-toxic dose	Length of treatment	Experimental subjects	References
Hydroethanolic extracts of stem, flower, and root	5 mg mL^{-1}	48 h	*A. albopictus* larvae	[49]
Hydroethanolic extract of aerial parts	Up to 2 g kg^{-1} BW	Information not available	mice	[14]
Whole plants	Consumption at 5 % or less once a day, or equal to 15 g kg^{-1} BW d^{-1} or less	24 wk	mice and chicken	[44]
Water extract of leaves	at 10 g kg^{-1} BW once a day	4 wk	rats	[3]
Water extract of whole plant	1 g kg^{-1} BW d^{-1}, once a day	4 wk	rats	[3]
Water extract of leaves	1 g kg^{-1} BW once a day	4 wk	Wistar rats	[37]
Water extract of leaves	0.8 g kg^{-1} BW d^{-1}, once a day, orally	4 wk	Wistar rats	[36]
Formulation, commercial product	Consumption of 400 mg, three times a day	7 mo	Human volunteers	[50]

Although some studies proved that this plant is safe for human consumption and medication, however, further research is still needed to establish its efficacy and safety. A complete toxicological study has not been completed for humans. Clinical trials involving a high number of participants are required to determine the efficacy and toxicology of *B. pilosa* in humans preceding to subsequent medical use [50].

The drug interactions of *B. pilosa* with other drugs are unknown. Further safety verification and clinical trials should be performed before *B. pilosa* L. can be considered for medicinal use [7]. Using ethanolic extracts of *B. pilosa* against human tumor cells, an antiproliferative compound of *B. pilosa*, the polyacetylene, showed an apoptotic effect on human umbilical vein endothelium cells, but not on normal cells [51, 7]. However, Wu *et. al*. predicted that it has a potent cytotoxic effect based on the IC_{50} value of 43.53 μg mL^{-1} of ethyl acetate fraction of *B. pilosa* [52]. Long-term consumption of dry or fresh of this plant is thought to be the cause of oesophageal cancer in South African people [7, 53]. This assumption might be based on a study by Mirvish that thymidine incorporation to the rat oesophageal epithelial genome is increased by the addition of boiled *B. pilosa* [54]. The result is supported by Costa (2008) that tea made from the aerial parts of *B. pilosa* caused DNA damage at a dose of 40 µL mL^{-1} of cell culture [53]. Upon contact with the plant, sun-exposed skin may experience irritation, skin burning, swelling and other detrimental effects [1]. The heating process generates the toxicity effect of the plant to the skin. Photo-activation of polyacetylenes has been associated to cytotoxic and antimicrobial activity [22], and anticancer activity [7].

Attention should be paid when harvesting the plants for medical use. Phytochemical contents in plants are influenced by environmental conditions, such as weather conditions,

soils contents, and extraction methods [14, 7]. In certain regions, such as in Brazil, people collect the plants before 10 a.m. or after 4 p.m. The plants, then are air-dried in a cool, dark, and well-ventilated place [23]. *B. pilosa* can accumulate Cd and exclude As. In the case that As and Cd contents in soil are high, then the metals are accumulated in the tissues of *B. pilosa* and it will be toxic to humans [7]. Therefore, collecting and sampling this plant for medical use should be done from non-polluted regions and in the proper way.

Based on the facts, it can be said that the plant or its extract is non-toxic for consumption and medical uses under these considerations. The dose for oral administration of *B. pilosa* dried plant is less than 15 g kg^{-1} BW d^{-1} [44]; the hydroethanolic extract is less than 2 g kg^{-1} BW [14], and water extract is less than 10 g kg^{-1} BW [3]. The plant shall be collected at times with less sunlight, and dried under shading from sun rays or strong light [23]. For antimicrobial and anti-insecticidal purposes, sun exposure to the plant might be considered for optimum activity [22]. The plant is better harvested from soil that is free of heavy metal pollution.

5 Application of *B. pilosa* for mouth health formulations

The oral cavity can be a host for various microbes [55]. Bacteria from saliva may adsorb onto the tooth surface and grow mature into dental biofilm or dental plaque. The first bacterial settler, mostly streptococci, plays an important role in the properties of dental plaque. Dental plaque and oral microorganisms can cause dental caries, periodontal diseases, and severe or chronic infectious diseases [25]. Management of oral health can be done by toothbrushing and flossing, and then by mouth washing. Mouthwashes help reduce plaque and periodontal diseases due to the antibacterial contents [56].

Mouthwashes (mouth rinses) are liquids or solutions used for removing oral debris, refreshing breath, reducing bacteria in the mouth, and freshening mouth cavity with a pleasurable taste [57]. Mouthwashes are expected to wash away the food residue from gum or teeth, covering and neutralizing halitosis, creating a good taste and sense of freshness in the mouth, and have antiseptic. Preferable that mouthwash has anti-inflammatory, antimicrobial, and analgesic action [58]. There are three types of mouthwashes can be found in the market nowadays: Antiseptic, fluoride rinse, or a combination of the two [59]. Based on its functions, mouthwashes can be classified as cosmetic and therapeutic [27]. Therapeutic rinses contain an additive ingredient, that help protect against periodontal diseases, bad breath, and tooth decay.

5.1 Herbal mouthwash formulation

The components of mouthwashes vary from product to product. In general, mouthwashes contain basic components such as surface-active agents, flavouring agent, sweeteners, coloring agents, preservatives, water, and active ingredient. Each ingredient has a different role and affects the characteristics of the final mouthwash product. Surfactant is needed to the dispersed water-insoluble component through the liquid, such as essential oils. Sodium lauryl sarcosinate is a common surfactant which are less irritating to the oral mucosa. Sodium lauryl sarcosinate also has antimicrobial activity by interfering with membranes and a variety of biological processes in microorganisms [60] and is effective in acid and alkaline solutions and in hard water. The flavouring agents used in mouthwashes are spearmint, peppermint, eucalyptus, menthol, and volatile essential oils. Flavouring agents can be added to give a sweet taste and attractive appearance. The most commonly used sweeteners are sodium saccharin, sorbitol, and glycerol. Xylitol is a sweetener that is also claimed to provide anti-caries activity because it inhibits glycolysis and cannot be fermented by oral microorganisms [61]. Sorbitol is a less-fermented

sweetener [62]. The preservative is a compound added to the formulation to prevent the growth of microorganisms in the product. The common preservatives are sodium benzoate, methylparaben, propylparaben and/or alcohol. Alcohol is a preservative and a semi-active ingredient, usually added at a concentration of 5 % to 27 % [63].

The active compounds are the important ingredients in mouthwash, which give anti-bacterial and antiseptic activities of the mouthwash to treat the mouth and teeth. The commercially available mouthwashes commonly contain antiseptic agents with activity to reduce plaque and gingivitis such as alcohol, Cetylpyridinium chloride, sodium fluoride, chlorhexidine, and triclosan. Other agents are sometimes added to give the therapeutic effects: Anticaries agents, anti-plaque agents, and anti-halositosis. Cetylpyridinium Chloride (CPC) is cationic quaternary ammonium. Chlorhexidine is the "gold standard" of antiplaque mouthwashes. Chlorhexidine is effective against both Gram-positive and Gram-negative bacteria, and some viruses. The chlorhexidine reduces pellicle formation, bacterial absorption and/or attachment to teeth, causes lysis of bacterial cell wall and caused an interaction with the viral protein cap. Triclosan is a non-ionic chlorinated phenolic agent with broad-spectrum efficacy on Gram-positive and most Gram-negative bacteria, mycobacterium, anaerobic bacteria, and against the spores and fungi of the *Candida* species. Triclosan also has an anti-inflammatory effect and reduces oral mucosal irritation caused by sodium lauryl sulfate. Halitosis or bad breath or halitosis is due to the retention of anaerobic, Gram-negative bacteria from the oral cavity. Metabolism of sulphur-containing amino acids by these bacteria produce unpleasant smell Volatile Sulfur-containing Compounds (VSC). The VSC production can be inhibited by the presence of zinc [56, 63–68].

Active compound that is often used in conventional mouthwash have an activity to reduce or prevent plaques and gingivitis, however, they have certain disadvantages. Excessive and regular alcohol rinse was reported may cause side effects on mucous membrane, lungs, kidneys, intestines, and in certain cases, the brain may also get affected, such as xerostomia. There is an association between excessive alcohol mouthwash usage or alcohol drinking with oral-pharyngeal cancer which is mainly caused by a higher level of acetaldehyde in the oral cavity, the product of alcohol metabolism [69, 63]. Chlorhexidine may cause side effects such as the burning mouth and severe stains on the teeth, tongue, and restorative materials [66]. Cetylpyridinium chloride is also reported may cause teeth and oral cavity stained as its side effects. The side effects of triclosan were taste alterations and mucosal irritations. All the compounds reported gave the same side effects, such as taste disturbances, altered oral sensations, and feelings of sickness [70].

Recently, a great concern has been focused on developing the formulation with natural resources compounds. Some herbal mouthwashes contain various herbal extracts, such as *Piper betle* L., clove oil [*Syzygium aromaticum* (L.) Merr. & L.M.Perry.], essential oils, green tea, *Aloe vera* (L.) Burm.f., *Punica granatum*, Oak husk of *Quercus brantii* Lind. and essential oif extracted from leaves of *Zataria multiflora* Boiss. [71], and white oak bark (*Quercus alba* L.) have shown therapeutic effects in the oral cavity with lower side effects. The extract can be formulated with other ingredients such as propylene glycol, polyethylene glycol 400, glycerin and water [71]. Formulation of *Ocimum gratissimum* L. in mouthwash containing triethanolamine, alcohol, water, nipagin 0.2 %, glycerin 2.5 % and aspartame, showed a good result and acceptance of volunteer, without any abscess formation, ulcerations or allergic reactions; no pigmentation and taste disturbance [72]. Polyherbal mouthwash also showed comparable effect as commercial mouthwashes [73, 74, 60]. Chowdhury *et al.* developed a free-alcohol herbal mouthwash which totally contained water and herbal extracts, *i.e*., guava (genus *Psidium*) leaves, betel leaves, ajwain [*Trachyspermum ammi* (L.) Sprague ex Turrill], peppermint oil (*Mentha* × *piperita* L.), and clove oil. The mouthwash showed antiseptic properties, and specific favorable flavors; the

microbiological and physicochemical properties were stable however the appearance change upon 7 d storage at ambient temperature [57].

In herbal mouthwash formulation, plants extracts, or natural compounds are added as active compounds, instead of ethanol or other synthetic compounds [71, 57]. Antiseptic effect in mouthwash formulation is gained by the presence of constituents of plants extracts such as essential oils, polyphenols, and tannin are known to have antimicrobial actions. To avoid the adverse effects of chlorhexidine, World Health Organization (WHO) suggested that the herb and plant extracts are added in natural mouthwash to inhibit dental plaque and gingivitis. Unfortunately, meta data analyses from paper published up to April 2017 showed that the natural products were reported to cause teeth and oral cavity stained after 14 wk used [70]. The contents of the herb and extracts may cause different effect and properties of the herbal mouthwashes. Therefore, improvement is still needed to develop the better-quality product with less side effects.

5.2 *B. pilosa* as active compounds in mouthwash formulation

B. pilosa extracts have been recognized to possess various functional properties. The plant compounds give beneficial effect that isimportant for mouthwash formulation. As a mouthwash, it may be recommendedto have antimicrobial, topical anti-inflammatory, and analgesics activities. Todays, new approaches are being pursued to create formulas with natural sources. Herbs can be added in formulation as active compounds because many plants have antimicrobial, preservatives agents, flavouring agents, and sometimes as antioxidants activities.

The *B. pilosa* extracts were reported to inhibit and kill pathogenic microorganisms. The extracts showed antimicrobial activities although it is extracted using water or ethanol. Both solvents are the same solvents used by local people traditionally. All parts of plants exhibited antimicrobial activity against Gram positive- and negative- bacteria, for instance *Staphylococcus aureus* Rosenbach 1884, *Streptococcus faecalis* Schleifer and Kilpper-Bälz, 1984, *Escherichia coli* Castellani and Chalmers 1919, *Salmonella enteritidis* (genus Lignières 1900) , *Shigella* spp. (Table 3). Moreover, the leaves and flowers extracts of *B. pilosa* showed antibacterial activities against drug-resistant bacteria, such as oxacillin resistant *S. aureus*, methicillin-resistant *S. aureus* and resistant *Pseudomonas aeruginosa* Migula 1900 [34, 21]. Evidence from an experimental study showed that hexane fraction of root had antimycobacterial against *Mycobacterium tuberculosis* Zopf 1883 strains (drug sensitive and resistant) [16]. For antimicrobial purposes, it revealed that hydroethanolic extract were more potent compared to water extracts [38, 75]. The extracts derived from leaves were reported active against wide range of microbes [17, 19, 38, 29, 49]. The *B. pilosa* extracts were also exhibited antifungal activity [16, 17, 19, 49] and antiviral activity [32].

Based on the activities, the *B. pilosa* extract is a potential candidate to be added as an active agent in mouthwash formulation. The extracts exhibited antimicrobial action against wide range of microbes (Table 3). Moreover, the aqueous and ethanolic extracts have antibacterial effect towards oral microbes isolated grom HIV/AIDS patients, such as *S. mutans*, *Streptococcus pneumoniae* Chester 1901, *E. coli*, *S. aureus*, *Staphylococcus saprophyticus* Shaw et al. 1951, *Bacillus cereus* Frankland & Frankland 1887, non-haemolytic *Streptococcus*, *Salmonella pullorum* (genus Lignières 1900) and *Klebsiella pneumonia* Trevisan 1887 with an averange range of MICs from (0.01 ± 0.04) μg mL^{-1} to (1.00 ± 0.00) μg mL^{-1} [75]. Essential oil of the leaves *B. pilosa* has activity to reduce the fungal count on *Bambara groundnut* (L.) Verdc. [76]. Although the plant extracts have excellent antimicrobial actions, no toxicity were exhibited towards cells cultures, animals, and human (Table 2).

Table 3. Microorganisms inhibited by extracts of *B. pilosa* plant parts

Microorganism	Leaf	Stem	Root	Flower
S. aureus	+	+	+	+
Staphylococcus epidermidis	+	–	+	–
S. saprophyticus	+	–	–	–
non–haemolytic *Streptococcus*	+	–	–	–
S. mutans	+	–	+	–
Enterococcus faecalis	+	–	+	–
Micrococcus luteus	+	+	–	+
Micrococcus kristinae	–	–	+	–
Bacillus subtilis	+	–	+	–
B. cereus	+	–	+	+
E. coli	+	+	+	+
P. aeruginosa	+	+	+	–
S. enteritidis	+	+	+	–
Salmonella tyhpi	+	+	+	–
Salmonella paratyphi	+	+	+	–
Salmonella typhimurium	+	+	+	+
Salmonella arizonae	+	+	+	–
Salmonella choleraesuis	+	+	+	–
S. pullorum	+	–	–	–
Shigella spp.	+	+	+	–
Shigella flexinerii	+	–	+	–
Enterobacter cloacae	+	–	–	+
K. pneumonia	–	–	+	–
Proteus mirabilis	+	–	–	+
Serratia marcescens	+	–	+	+
Candida albicans	+	+	–	+
Saccharomyces cerevisae	+	+	–	+
Rhizopus sp.	+	–	–	–

Note: + means active against the microbe; – means no activity or no available data. Sources: [16, 17, 19, 29, 50, 76, 78, 79]

Many compounds have been isolated from *B. pilosa* Previous studies have shown that *B. pilosa* contains compounds involved in antimicrobial activity of this plant. Polyacetylenes are the secondary metabolite commonly found in the plants, and the most intense in leaves [22, 6]. When used as antiseptic or antimicrobial in formulation, the photoactivation of polyacetylene by sun- or fluorescent-light prior to use will enhanced the antimicrobial power [9]. The other groups are also involved in antimicrobial action, for instance flavonoids [34], saponins, alkaloids, polyphenols, sterols, triterpenoids, and tannins [14, 16, 21]. The tannins, or tannic acids, are categorized as a Generally Recognized As Safe (GRAS) for human but toxic to microbial cells. Mechanisms action of tannins in microbial cells occurred by complexation of tannin with enzymes or other compounds, by its action on microbial membrane, and by complexation with metal [79].

The *B. pilosa* plant is widely used traditionally for treating inflammation [2]. The anti-inflammatory effect has been proven in laboratory animals of colitis [13], or induced inflamed by chemical and mechanical [80], induced gastric ulcer, liver inflammation, or arthritis-type swelling [9]. The analgesic effect of the plant was proven to reduce oral paint of HIV/AIDS patients [18]. This can be potential for future application to treat users suffering of oral lesion or oral ulcers. The aqueous extracts showed anti-inflammatory effect on mice [5]. Compounds predicted to be related to the activities

were flavonoids, such as quercetin and iso-okanin [80], friedelin and friedelan–3β–ol [6], centaurein and centaureidin [23] and others compounds such as oleic acid and n–hexadecanoic acid [13], and polyacetylenes such as 2–O–â–D–glucosyltrideca–11E–en–3,5,7,9–tetrayn–1,2–diol [23]. The polyacetylenes and flavonoids are predominantly found in *B. pilosa*, which might correspond to antibacterial, antifungal, antioxidant and anti-inflammation and analgesic activities; tannin, alkaloid, terpenoids and saponin which are related to anti-inflammatory activity [14].

The *B. pilosa* are known to be rich of compounds that have free radical scavenging activity or antioxidant activity [19]. The leaves and flowers contain essential oil which have the highest antioxidant potential as compared to other parts of the plants [22, 19]. The aqueous infusion of *B. pilosa* has very active antioxidant and employs its protective effect at low amounts at IC_{50} of 1.19 mg mL^{-1} DW of infusion [3]. The IC_{50} antioxidant value of plants might be reported a bit difference from one to other places due to variation in the plant growth environment, the harvesting season, the physiological stage of the harvested plant and extraction method [22, 38, 34]. The antioxidant activity has been connected to the presence of flavonoids, such as quercetin [30], and polyacetylenes [23, 30], tannins [81], polyacetylenes [23], polysaccharides, carotenoids, amines, lactones, mineral elements, and coumarins. Tannins derivatives, such as caffeic acid derivatives and flavonoids are potent antioxidant [7].

The presence of compounds with effective antioxidant can give value to mouthwash formulation since it will protect the product from oxidation and damage by microbe's activity. Study by Goudoum *et al* showed that essential oil of *B. pilosa* has antioxidant activity which give indication that the essential oil can serve as preservative against pest attack [43].

Based on the facts, *B. pilosa* plant and the extracts are potential to be used as active agents in mouthwash formulation. First, because of antimicrobial action against wide range microbes, bacteria, fungi, and virus. Second, it has antibacterial effects toward oral microbes [75]. Third, the extracts contain compounds which have antioxidant, analgesic, and anti-inflammation. Although antioxidant, analgesic, and anti-inflammation activities of the *B. pilosa* extracts have been proven in many studies, however further investigation still be needed because the effect gained by oral administration of the extracts not just by gargling it. In the antimicrobial assays performed in these studies, bacterial and fungal cells had close contact with extract during longer time (around 24 h) compared to mouthwash application times (30 s to 60 s). Although few papers described about minimum bactericidal concentration, however the cells were in contact with extract for 24 h instead of minutes time. By gargling, the mouthwash has contact with microbes in only few minutes. The assay for this herbal mouthwash is better performed by considering time contact using other methods [82].

5.3 Important points concerning *B. pilosa* as active agents in mouthwash formulation

B. pilosa extracts are potential candidate to be formulated in mouthwash based on the antimicrobial, anti-inflammation, analgesic and antioxidant activities, and non-toxic properties. *B. pilosa* extracts may have better properties as mouthwash since the plant has been used by people for a long time without any obvious side effects as shown by synthetic compounds. No reported about stained teeth and other mouth unpleasant after long time of consumption. In accordance to the application of the extracts, few thing that need to be considered is described here. The active compounds of *B. pilosa* plant could be extracted using safe solvents, particularly 70 % to 80 % ethanol. The semipolar extract of *B. pilosa* has better action than water extract. The extract shall be formulated with suitable

ingredients in such a way to form a mouthwash with good properties. Contemplating the bioactive compounds in *B. pilosa* extracts, the following items are important things that need to be considered for formulating a mouthwash with *B. pilosa* as active ingredient. The items are the organoleptic properties of mouthwash in the presence of tannin, the formulation of water in-soluble extract in mouthwash and the activation of polyacetylenes in formulation.

Tannins are polyphenol compounds which have antimicrobial activity. However, the presence of tannin in solution gives a bitter taste and yellow to brown colour [83]. Usually, the colour is unfavourable. Upon several usage, the colour of mouthwash can become darker.

Since the hydroethanolic extracts contain more bioactive compound important for antimicrobial and antioxidant, then the formulation may contain ingredients to maintain the consistency of liquid. Beside tannins and polyacetylenes, other active compounds might be unstable in liquid during storage. Emulsifying and suspending agent or other medicinal plant can be added, such as gum and *Aloe vera* [3]. However, the compounds added shall not be antagonist or lowering the *B. pilosa* activity.

As mentioned before, the antimicrobial of polyacetylenes is more potent upon photoactivated. This should be considered when formulating herbal mouthwash. Generally, the plant extracts are added to preserve the product from microbial growth and damages. However, the heating process may change the appearance and stability of the product due to polyphenol browning upon heating or oxidation.

6 Conclusions

In can concluded that the *B. pilosa* plant contain diverse groups of compounds, such as polyacetylenes, flavonoids, tannins, cardiac glycosides, saponin, alkaloid, terpenoid, and steroid. The diverse compounds are responsible for various activities of the plant and its extracts. The *B. pilosa* extracts are non-toxic and has potential active compound for mouthwash formulation, due to its antimicrobial action against wide range microbes, particularly toward oral microbes, and its additional activities such as antioxidant, anti-inflammation, and analgesic.

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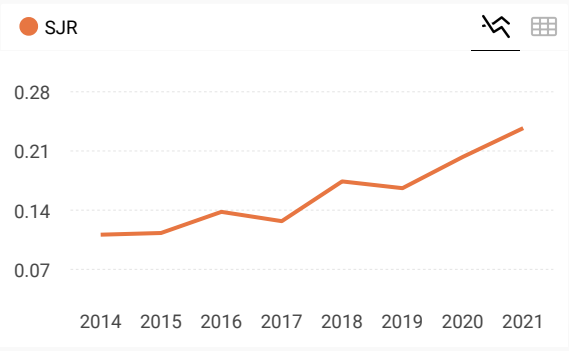

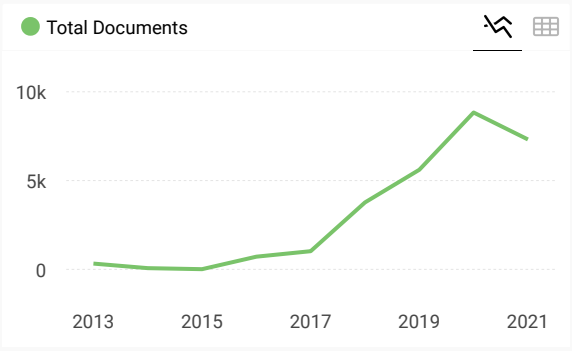

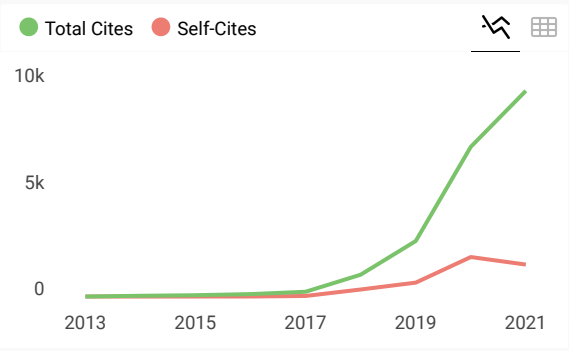

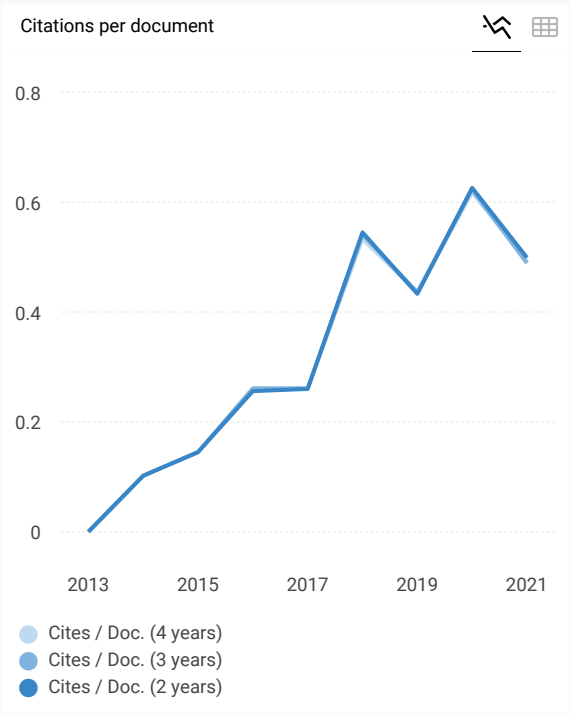

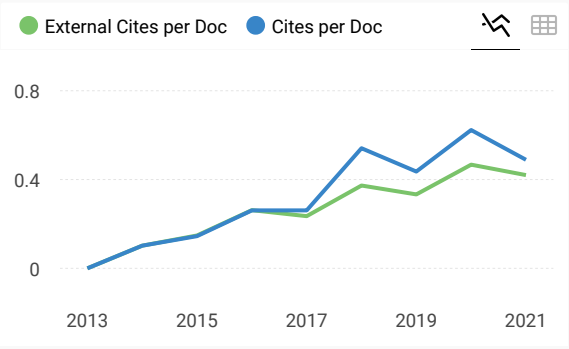

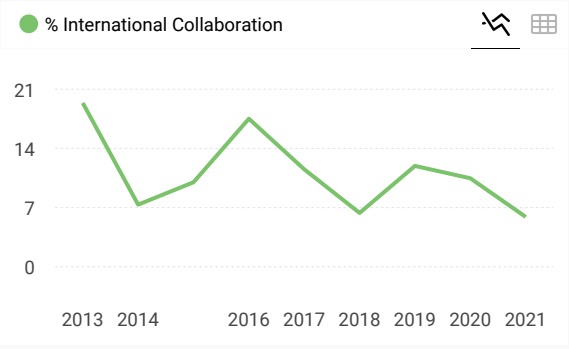

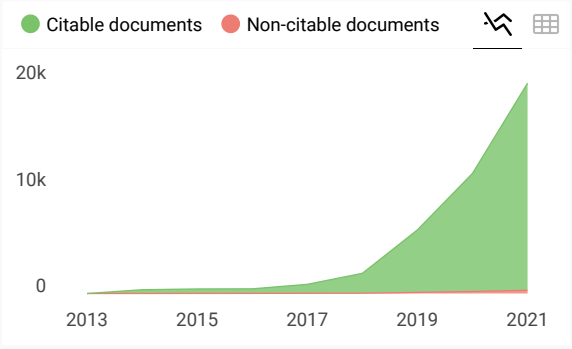

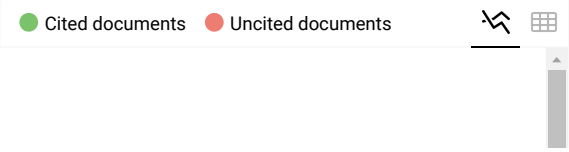

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Tjie Kok, Natasha Florenika, Mangihot Tua Gultom, Popy Hartatie Hardjo and Muhannad Illayan Massadeh

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eISSN: 2267-1242

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UNIVERSITAS SURABAYA

FAKULTAS EKNOBIOLOGI

NRLS INTERNATIONAL CONFERENCE ON NATURAL RESOURCES AND LIFE SCIENCES

VIRTUAL CONFERENCE ON NATURAL RESOURCES AND LIFE SCIENCES

THEME :
GREEN TECHNOLOGY TO PROMOTE SUSTAINABLE CLEAN ENERGY, ENVIRONMENTAL WELLNESS, AND HEALTHY LIFE

ABSTRACT'S SUBMISSION DEADLINE
(POSTER AND ORAL PRESENTATION)
18TH July 2020

NOTIFICATION OF ACCEPTANCE
31ST July 2020

REGISTRATION DEADLINE
31ST April 2020 (Early Bird)
28TH August 2020 (Normal)

INTERNATIONAL CONFERENCE
23TH - 24TH September 2020

WORKSHOP
Drug Development for Fighting Covid-19
25TH September 2020
Virtual Workshop in Bioinformatics
Will be Held on September 25TH, 2020.

CONFERENCES WILL BE HELD VIRTUALLY

SUB THEME
1. Clean Energy and Environmental Sustainability
2. Sustainable Agriculture
3. Health Care

NRLS 2020

INVITED SPEAKERS :

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University of Heidelberg, Germany
Healthcare

Prof. Yashwant Pathak
University of South Florida, USA
Food Security and Nutrition

Prof. Kyung-Min Kim, Ph.D.
Kyungpook National University, South Korea
Agriculture and Aquaculture

Heny Budi Utari, Ph.D.
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Agriculture and Aquaculture

Dr. rer. nat. Theresia Desy A.
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Energy and Renewable Resources

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E3S Web of Conference or International Journal :
Annals of Tropical and Public Health
and Coffee Science

ORGANIZING COMMITTEE
Faculty of Biotechnology, University of Surabaya

Active Participant Must Submit Their Presentation Video With Maximal Duration 7 Minutes
The video must be submitted no longer than August, 8TH 2020

	Early Bird	Normal price
Student	IDR 150.000	IDR 200.000
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PREFACE: the 3rd International Conference on Natural Resources and Life Sciences (NRLS) 2020

Nowadays, the sustainability of energy generation and environmental wellness are two of the big challenges in the world. Ecological disturbance and depletion of non-renewable energy in most countries urge the need for development and exploration of sustainable bioenergy resources. A proper approach to implement biotechnology for converting and conserving resources will be of great importance. Ideally, the conversion of natural resources into a certain form of energy should be parallel with the bioproduction of valuable compounds. Furthermore, environmental wellness does encourage us to employ proper habits that promote a healthy environment for a healthy life.

The bioproduction of valuable compounds originating from renewable resources and carbon-neutral waste materials as substrates is a promising approach for a sustainable environment and healthy life. Recent studies on genetic, epigenetic, protein and metabolic engineering offer significant improvement strategies in the bioproduction of many valuable compounds, such as biosurfactants, biofuels, bioinsecticides, bioplastic precursors, biopharmaceuticals, functional food, etc. Hence, in the 3rd International Conference on Natural Resources and Life Sciences (NRLS) themed Green technology to promote sustainable clean energy, environmental wellness, and healthy life, we will highlight the latest developments in biotechnological research and its applications, consisting of Clean Energy and Environmental Sustainability, Sustainable Agriculture, and Health Care.

Following the successful program of the 1st & 2nd NRLS, we intend to make the two-day meeting followed by a one-day workshop in the 3rd NRLS, as a global forum for scientific and industrial communities to discuss the recent advances in biotechnological research and its application. It is our great pleasure to welcome you to the virtual 3rd NRLS from September 23rd to 24th, 2020.

After a rigorous selection process, the Scientific & Editorial Board (S.E. Board) of the virtual 3rd NRLS decided to publish 40 papers in the E3S Web of Conferences, an open-access proceeding

in environment, energy, and earth sciences, managed by EDP Sciences, Paris, France, and indexed on Scopus, Scimago, Conference Proceedings Citation Index-Science (CPCI-S) of Clarivate Analytics's Web of Science, and DOAJ (Directory of Open Access Journals). As a result, E3S Web of Conferences is a conference proceeding with the highest SJR (Scopus and Scimago) score compared to other conference proceedings.

The proceeding of the 3rd NRLS comprises 40 selected papers compiled by 253 authors from 72 institutions. To improve the quality of manuscripts, S.E. Boards apply for a "guidance program" for several manuscripts. The impact there is joint research by Indonesian and overseas scholars. In the collaboration research, 22 institutions were involved, of which were from abroad Indonesia. The overseas institutions are from Germany, India, Jordan, Pakistan, the Republic of Korea, Latvia, Lithuania, Malaysia, the Netherlands, Poland, Taiwan - ROC, Thailand, Timor Leste, the United Kingdom, and Vietnam. Each manuscripts submitted in the E3S Web of Conferences was reviewed by at least two experts using the double-blind system (list of the experts in S.E. Board). As a result, the published articles have passed all necessary improvement requirements following the Web of Conferences standard, reviewer's comments, S.I. (*Système International d'Unités*), similarity tests by the Turnitin program (with the highest threshold of 20 %), meet the standard value of 85 % of the Premium Grammarly program, amount 90 % of references must be at least dated from 15 years and reflected on Google, as well as editing procedures by professional editors from five countries (Indonesia, Estonia, Georgia, Pakistan, and the United Kingdom).

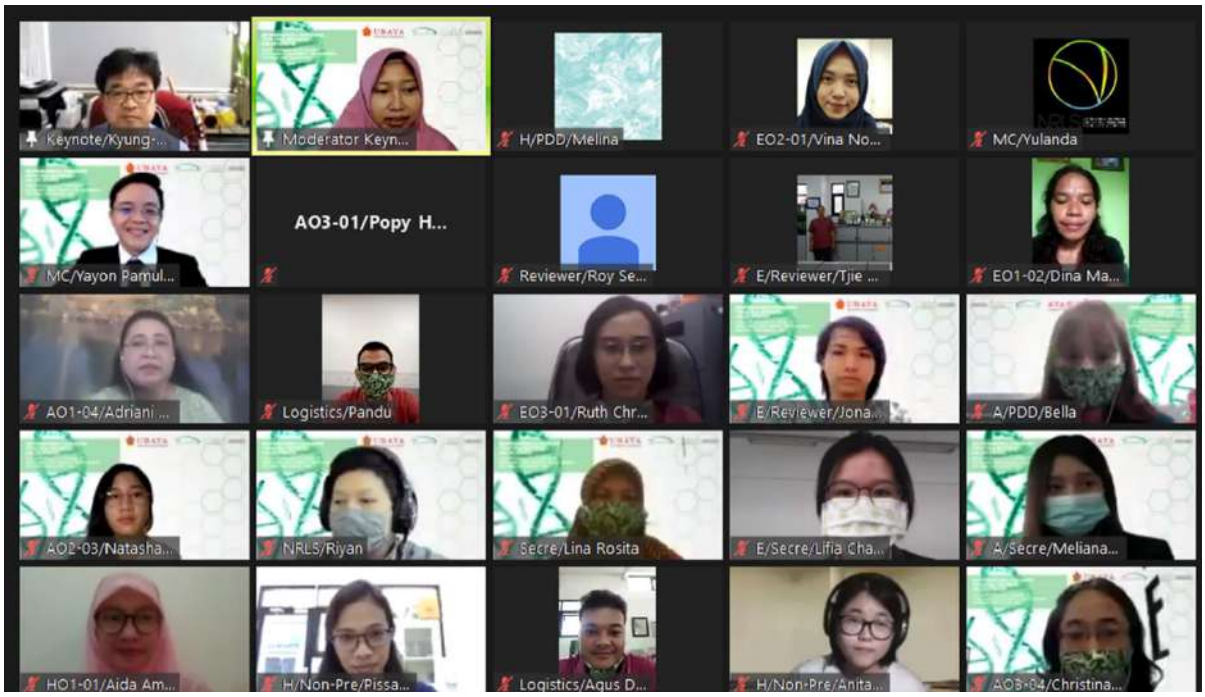
We thank all presenters and attendees for the rigorous participation in this conference to share scientific ideas, inspire new studies for closer co-operations. We hope you are encouraged for further collaboration in order to explore natural resources and life sciences in future. We look forward to inviting you for the next 4th NRLS.

Surabaya, Februari 28, 2023

Dr.rer.nat. Theresia Desy Askitosari, S.Si., M.Biotech.
3rd NRLS Chairwoman

Scientific and Editorial Board

The VIRTUAL 3rd NRLS: CONFERENCE PHOTOS



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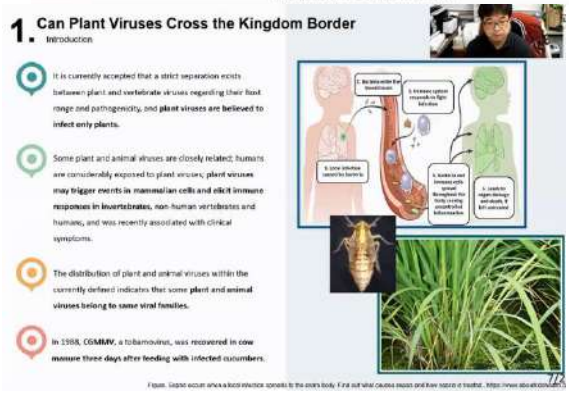
Bioelectrochemical System Application: An Insight into Green Technology

THERESIA DESY ASKITOSARI



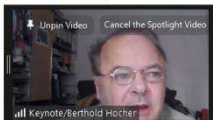
Ruprecht-Karls-Universität Heidelberg

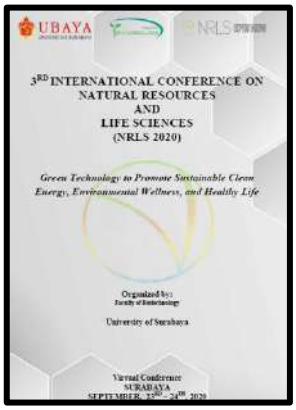
Fetal Programming - from Epidemiology to Epigenetics

Berthold Hocher

E-Mail: berthold.hocher@medma.uni-heidelberg.de

Department of Medicine (Nephrology/Endocrinology/Rheumatology), University Medical Centre Mannheim, University of Heidelberg, Heidelberg, Germany
School of Medicine, Hunan Normal University, Changsha, China; Reproductive Genetic Hospital of CITIC-Xiangya, Changsha, China;





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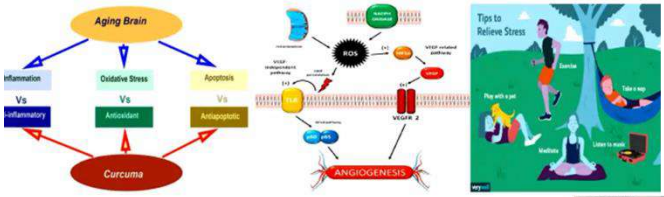
Understand the pathways of the stress



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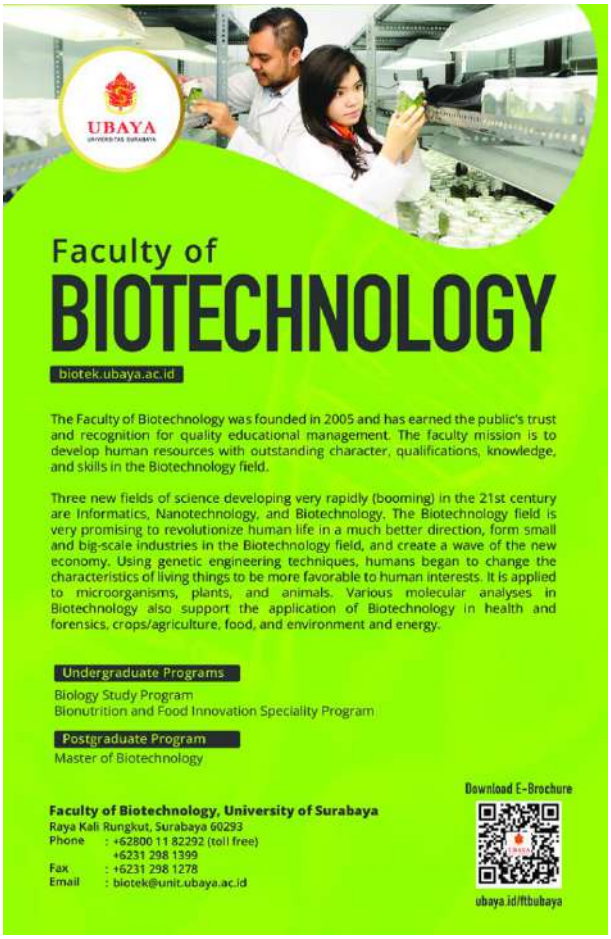

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The proceeding of the 3rd NRLS comprises 40 selected manuscripts compiled by 253 authors from 72 institutions. In addition, 22 institutions outside Indonesia were involved in collaboration research, i.e., Germany, India, Jordan, Pakistan, the Republic of Korea, Latvia, Lithuania, Malaysia, the Netherlands, Poland, Taiwan - ROC, Thailand, Timor Leste, the United Kingdom, and Vietnam.

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Title: The 3rd International Conference on Natural Resources and Life Sciences (NRLS) 2020
Date: September 23rd to 24th, 2020.
Place: Virtual.
Website: https://www.youtube.com/watch?v=YvnRnLbwI7s
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Date and editor's signature

Malang, Indonesia, Februari 22, 2023
Dies Cinerum/Ash Wednesday,

(**Roy Hendroko Setyobudi**)
Ps. Thank you to our God because E3S has been covered again by Scopus. Congrats!

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CERTIFICATE

THIS CERTIFIES

Dr. Dra. Mariana Wahjudi, M.Si.

ORAL PRESENTER

at Virtual International Conference on Natural Resources and Life Sciences (NRLS)2020
Themed "Green Technology to Promote Sustainable Clean Energy, Environmental Wellness, and Healthy Life"
Faculty of Biotechnology, University of Surabaya, September 23RD - 24TH 2020
Surabaya, East Java, Indonesia.

Dean of Faculty of Biotechnology
University of Surabaya

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Natural Resources and Life Sciences 2020

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