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MEDICINAL VALUES OF A FOOD PLANT - *LIMONIA ACIDISSIMA* GROFF

Saravanan Vivekanandarajah SATHASIVAMPILLAI[1]*, Pholtan Rajeev SEBASTIAN[1]

[1]*KnowledgeLink Group, Inc., Waltham, MA 02451, USA*
[2]*Eastern Provincial Herbal Garden Management Center, Department of Indigenous Medicine, Trincomalee, Sri Lanka*

Abstract: *Limonia acidissima* Groff is a tree that fits into the *Rutaceae* family and it is distributed in Asia. This is a food plant and it is also used for medicinal purposes. Its various parts have been using to treat several ailments in ethnomedicines including liver, heart, kidney, eye, and gastric ailments. So far, there is no systematic review available for bioactivities of *L. acidissima* parts. Hence, this work aims to analyze, summarize, and document the bioactivities and bioactive compounds identified from this plant species. Electronic databases including the Web of Science, Scopus, and ScienceDirect were used to detect published articles linked to bioactivities of *L. acidissima* from 1900 to October 2020. To date, only *in vitro* and *in vivo* level of scientific evidence are available for bioactivities. More investigations have been carried out for anticancer, antifungal, and antioxidant activities. Four bioactive compounds have been identified only for antifungal and cardioprotective activities. Only traditional medicinal treatments for tumors, diabetes, diarrhea, heart disorders, urinary tract illnesses, wound healing, and liver diseases have scientific evidence at present. This work analyzed, summarized, and documented the bioactivities of the extracts and compounds isolated from *L. acidissima*.

Keywords: *Limonia acidissima*, *Rutaceae*, Wood apple, Bioactivities, Antifungal, Antioxidant

***Corresponding author:** KnowledgeLink Group, Inc., Waltham, MA 02451, USA
E mail: scloctn@hotmail.com (S.V. SATHASIVAMPILLAI)
Saravanan V. SATHASIVAMPILLAI https://orcid.org/0000-0002-5938-0509
Pholtan Rajeev SEBASTIAN https://orcid.org/0000-0001-9341-5843

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1. Introduction

Limonia acidissima Groff is a tree fit into *Rutaceae* family and it is called Vilaa in Tamil. This plant species is distributed in countries including Sri Lanka, India, Bangladesh, Pakistan, Indonesia, Malaysia, China, Thailand, and Myanmar in Asia (Lim, 2012). *L. acidissima* is used as a food plant as well as for medicinal purposes. Its various parts are used to treat several ailments in ethnomedicines. Fruits are utilized to treat gastric, liver, respiratory, heart, gum, and eye associated diseases, wounds, tumors, and insect bites (Chevallier, 1996; Kirtikar and Basu, 2005; Sastri, 1995; Warrier, 1993). While seeds are applied to cure heart diseases (Jadeja et al., 2005) and bark is employed to heal poisonous injuries (Khare, 2008; Matthew, 1983; Morton, 2013). Leaves are used to treat urinary tract disorders, constipation, skin diseases, heart ailments, vomiting, indigestion, dysentery, and hiccups (Chatterjee, 2000; Krupa et al., 2019; Kyaw et al., 2018; Manohar et al., 2016). On the other hand, roots, resin, and fruits are included in some preparations applied to manage diabetes in Sri Lankan Siddha Medicine (Sathasivampillai et al., 2015; Sathasivampillai et al., 2017; Sathasivampillai et al., 2018).

Quite a few compounds have been isolated from various parts of *L. acidissima*. For example, bark: N-{[p-(3,7-dimethyl-6R,7-dihydroxy-4R-octadecanoyloxy-2-octenyloxy)phenyl]ethyl}benzamide, N-{[p-(3,7-dimethyl-6R, 7-dihydroxy-4R-‴(E)-octadecenoyloxy- 2-octenyloxy)phenyl]ethyl} benzamide, N-{[p-(3,7-dimethyl-6R,7-epoxy-4R-‴(E)-octadecenoyloxy-2-octenyloxy)phenyl]ethyl} benzamide, 13α,14β,17α-lanosta-7,9,24- triene-3β,16α,-diol, 4-methoxy-1-methyl-2 (1H)-quinolinone, 13α,14β,17α- lanosta- 7,24-diene-3β,11β,16α-triol, limodissimin A, osthenol, (2'R)-7-hydroxy-8-(2',3'-dihydroxy-3'-methylbutyl)-2H-1-benzopyran-2-one, columbianetin, seselin, bergapten, psoralen, obacunone, lupeol, (+)-marmesin, obacunone, and acidissimin (Kim et al., 2010, 2009; MacLeod et al., 1989; Wijeratne et al., 1992); fruit: gallic acid, vanillic acid, protocatechuic acid, quercetin, acidissimin, acidissiminol, acidissiminin epoxide, N-benzoyltyramine, dihydroxy acidissiminol, and acidissiminol epoxide (Ghosh et al., 1994, 1991, 1989; Verma et al., 2016); leaf: n-alkanoic acid, α,ω-alkanedioic acid, hydroxyalkanoic acid, dihydroxy alkanoic acid, hydroxy α,ω-alkanedioic acid, p-hydroxy benzaldehyde, heptadecane diol, 9, 16-dihydroxyhexadecanoic acid, 10, 16-dihydroxyhexadecanoic acid, 10,20-dihydroxyicosanaic acid, and 7-hydroxyhexadecane-1,16-dioic acid (Das and Thakur, 1989); root: dihydrosuberenol, apiosylskimmin, acidissimin, bergapten, psoralen, xanthotoxin, osthenol, acidissimin, osthol, aurapten, stigmasterol, isopimpinellin, integriquinolone, and obacunone (Ghosh et al., 1982; MacLeod et al., 1989; Wijeratne et al., 1992);

and other compounds including genistein, daidzein, daidzin, β-pinene, methyl chavicol, myrcene, limonene, linalool, anisaldehyde, p-methoxycinnamaldehyde, sabinene, camphene, ocimene, caryophyllene, glubulol, cadinene, and terpineol (Dash et al., 2015; Syamasundar et al., 2010).

So far, there is no comprehensive review available for bioactivities of *L. acidissima* parts. Hence, this work aims to analyze, summarize, and document the bioactivities and bioactive compounds identified from this plant species. This work would be beneficial to generate an attention to medicinal values of *L. acidissima* to carry out more researches using this plant species.

2. Materials and Methods

Electronic databases (Web of Science, Scopus, PubMed, and ScienceDirect) were used to detect published articles linked to bioactivities of *L. acidissima* from 1900 to December 2020. The binomial scientific name (*Limonia acidissima*) was utilized as a search term. Then the results were refined to the subjects Biology, Chemistry, Agriculture, Molecular Biology, Pharmacology, Toxicology, Biochemistry, and Medicine.

3. Results and Discussion

3.1. Bioactivities of *L. Acidissima*

Bioactivities identified from relevant published articles from the literature search are listed in Table 1. To date, only *in vitro* and *in vivo* level of scientific evidence are available for bioactivities. While, the majority of studies have been conducted in *in vivo* models. Anticancer, antioxidant, immunomodulatory, and cardioprotective activities have both *in vitro* and *in vivo* level of scientific evidence. More investigations have been carried out for anticancer, antifungal, and antioxidant activities. Further, fruits showed a greater number of bioactivities including wound healing, cardioprotective, anticancer, immunomodulatory, antioxidant, hepatoprotective, antidiabetic, antilipidemic, antifungal, and anthelminthic activities. Methanol extract was commonly used in the researches. Four bioactive compounds (2,6-dimethoxybenzoquinone, Psoralene, Xanthotoxin, and Osthenol) have been identified only for antifungal and cardioprotective activities. Osthenol revealed both antifungal and cardioprotective activities. As mentioned above, this plant species is used to treat various ailments in traditional medicines. Anyhow, only treatments for tumors, diabetes, diarrhea, heart disorders, urinary tract illnesses, wound healing, and liver diseases have scientific evidence at present. Only important investigations that used the lowest concentration / dose are discussed below.

3.2. Reported *In Vitro* Evidence

3.2.1. Antibacterial activity

Essential oil distilled from leaves (10 µl) showed antibacterial activities in *Acinetobacter baumannii, Bacillus cereus, Bacillus subtilis, Enterococcus faecalis, Proteus mirabilis, Salmonella enterica* serovar *Typhi*, *Staphylococcus aureus, Streptococcus pyogenes*, and *Vibrio cholerae* assays (Chintaluri et al., 2015).

3.2.2. Anticancer activity

Fruit methanol extract of effective dose 30.6 µg/ml applied in breast cancer cell line (MDA-MB435) exhibited anticancer activity (Pradhan et al., 2012).

3.2.3. Antifungal activity

In a study carried out by Chintaluri et al. (2015) used 10 µl of essential oil distilled from leaves revealed antifungal activity in *Candida albicans* assay. A total of four antifungal compounds (osthenol, psoralene, xanthotoxin, and 2,6-dimethoxybenzoquinone) have been discovered in fruit, bark, and root (Adikaram et al., 1989; Bandara et al., 1988).

3.2.4. Antioxidant activity

Stem bark methanol extract at IC_{50} 18.8 µg/ml showed antioxidant activity in 1,1-diphenyl2-picrylhydrazyl free radical scavenging assay (Shermin et al., 2012).

3.2.5. Cardioprotective activity

Four cardioprotective compounds including (2'R)-7-hydroxy-8-(2',3'-dihydroxy-3'-methylbutyl)-2H-1-benzopyran-2-one, columbianetin, osthenol, and seselin have been identified in bark. Among these compounds, 2',3'-dihydroxy-3'-methylbutyl)-2H-1-benzopyran-2-one exhibited the best cardioprotective activity at 21.6 µM in nitric oxide production inhibition in LPS-activated BV-2 cell assay (Kim et al., 2009).

3.2.6. Immunomodulatory activity

Effective dose of 0.04 mg/ml of methanol extract prepared using fruit unveiled immunomodulatory activity in phagocytic assay (Tripathy and Pradhan, 2014).

3.3. Reported *in vivo* evidence

3.3.1. Anticancer activity

Root methanol extract (200 mg/kg) was orally administered to MCF-7 tumor bearing rats for 14 days exhibited anticancer activity (Gitanjali and Debasish, 2015).

3.3.2. Anticatatonic activity

A study performed by Srivastava et al. (2014), ethanol extract prepared using bark was orally administered to chlorpromazine-induced catatonic rats at 200 mg/kg for 21 days revealed anticatatonic activity.

3.3.3. Antidiabetic activity

Fruit powder (2.5 g) was orally administered to fluoride-exposed rat for 4 weeks reduced elevated blood glucose concentration (Vasant and Narasimhacharya, 2013).

3.3.2. Antidiarrheal activity

Senthilkumar et al. (2010) studied the antidiarrheal activity in rats by orally administrating 200 mg/kg of bark alcohol and aqueous extracts. After 30 minutes, both extracts reduced feces weight and gastrointestinal motility.

3.3.3. Anthelminthic activity

Acetone and methanol extracts (150 mg/ml) prepared using fruit shell unveiled anthelminthic activity in *Paramphistomum cervi* (Islam et al., 2019).

3.3.4. Antilipidemic activity

Dried fruit powder (2.5 g) was orally directed to fluoride-exposed rats for 4 weeks reduced blood cholesterol levels (Vasant and Narasimhacharya, 2013).

3.3.5. Antioxidant activity

An investigation carried out by Chitra (2009), to investigate antioxidant activity in carbon tetrachloride-induced liver damaged rats by orally administrating fruit methanol extract at daily dose of 200 mg/kg for 10 days. The outcomes elevated the activity of catalase antioxidant enzymes.

3.3.6. Cardioprotective activity

Fruit ethanol extract (200 mg/kg) orally directed to isoproterenol-induced myocardial infarction in rats for 15 days improved heart conditions (Manohar et al., 2016).

3.3.7. Diuretic activity

Methanol extract prepared using leaves (200 mg/kg) was orally administered to rats. After 5 hours, it was observed that there was a significant rise in passing urine. Moreover, potassium, sodium, and chloride ions excretion were also elevated. In this study furosemide was utilized as a positive control (Parial et al., 2009).

3.3.8. Hepatoprotective activity

Carbon tetrachloride-induced liver damaged rats were orally directed fruit methanol extract at 200 mg/kg for 10 days improved damaged liver conditions (Chitra, 2009).

3.3.9. Immunomodulatory activity

In a research performed by Sunitha and Mohan (2013), methanol extract prepared using fruits was orally administered to rats and mice developed immunity. However, the authors did not state the duration of the treatment.

3.3.10. Wound healing activity

Fruit methanol extract was orally directed at a dose of 400 mg/kg to dead-space wounded, excision wounded, and incision wounded rats for 21 days healed the wounds and improved the health of the animals (Ilango and Chitra, 2010).

Table 1. Reported bioactivities of L. *acidissima*

	Activity	Part used	Compound	Bioassay / model	Dose	Reference
In vitro	Antibacterial	Leaf	Essential oil	*Acinetobacter baumannii* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Antibacterial	Leaf	Essential oil	*Bacillus cereus* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Antibacterial	Leaf	Essential oil	*Bacillus subtilis* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Antibacterial	Leaf	Essential oil	*Enterococcus faecalis* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Antibacterial	Leaf	Essential oil	*Proteus mirabilis* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Antibacterial	Leaf	Essential oil	*Salmonella enterica* serovar *Typhi* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Antibacterial	Leaf	Essential oil	*Staphylococcus aureus* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Antibacterial	Leaf	Essential oil	*Streptococcus pyogenes* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Antibacterial	Leaf	Essential oil	*Vibrio cholerae* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Anticancer	Fruit	Methanol	Breast cancer cell line (MDA-MB435)	30.6 µg/ml (ED_{50})	(Pradhan et al., 2012)
In vitro	Anticancer	Fruit	Methanol	Breast cancer cell line (SKBR3)	56.1 µg/ml (ED_{50})	(Pradhan et al., 2012)
In vitro	Antifungal	Fruit	Chloroform	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Adikaram et al., 1989)
In vitro	Antifungal	Fruit shell	Chloroform	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Adikaram et al., 1989)
In vitro	Antifungal	Fruit shell	Chloroform	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Fruit, stem bark, root bark	2,6-dimethoxybenzoquinone	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Adikaram et al., 1989)
In vitro	Antifungal	Fruit, stem bark, root bark	Psoralene	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Adikaram et al., 1989)
In vitro	Antifungal	Fruit, stem bark, root bark	Xanthotoxin	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Adikaram et al., 1989)
In vitro	Antifungal	Leaf	Essential oil	*Candida albicans* assay	10 µl	(Chintaluri et al., 2015)
In vitro	Antifungal	Root bark	Chloroform	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Adikaram et al., 1989)
In vitro	Antifungal	Root bark	Dichloromethane	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Root bark	Ethyl acetate	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Root bark	Petroleum ether	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Stem bark	Dichloromethane	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Stem bark	Ethyl acetate	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Bandara et al., 1988)

	Activity	Part used	Compound	Bioassay / model	Dose	Reference
In vitro	Antifungal	Stem bark	Petroleum ether	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Stem bark	2,6-Dimethoxybenzoquinone	*Aspergillus niger* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Stem bark	2,6-Dimethoxybenzoquinone	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Stem bark	Chloroform	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Adikaram et al., 1989)
In vitro	Antifungal	Stem bark	Osthenol	*Aspergillus niger* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Stem bark	Osthenol	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Bandara et al., 1988)
In vitro	Antifungal	Stem bark, root bark	Osthenol	Thin Layer Chromatography-*Cladosporium cladosporioides* assay	100 µl	(Adikaram et al., 1989)
In vitro	Antioxidant	Stem bark	Methanol	1,1-diphenyl2-picrylhydrazyl free radical scavenging assay	18.8 µg/ml (IC50)	(Shermin et al., 2012)
In vitro	Cardioprotective	Bark	(2'R)-7-hydroxy-8-(2',3'-dihydroxy-3'-methylbutyl)-2H-1-benzopyran-2-one	Nitric oxide production inhibition in LPS-activated BV-2 cell assay	21.6 µM	(K. H. Kim et al., 2009)
In vitro	Cardioprotective	Bark	Columbianetin	Nitric oxide production inhibition in LPS-activated BV-2 cell assay	33.5 µM	(K. H. Kim et al., 2009)
In vitro	Cardioprotective	Bark	Osthenol	Nitric oxide production inhibition in LPS-activated BV-2 cell assay	22.3 µM	(K. H. Kim et al., 2009)
In vitro	Cardioprotective	Bark	Seselin	Nitric oxide production inhibition in LPS-activated BV-2 cell assay	23.1 µM	(K. H. Kim et al., 2009)
In vitro	Immunomodulatory	Fruit	Methanol	Cellular lysosomal enzyme activity assay	0.38 mg/ml (EC_{50})	(Tripathy and Pradhan, 2014)
In vitro	Immunomodulatory	Fruit	Methanol	Phagocytic assay	0.04 mg/ml (EC_{50})	(Tripathy and Pradhan, 2014)
In vivo	Anticancer	Fruit	Methanol	Dalton's ascitic lymphoma mouse	570 mg/kg	(Eluru et al., 2015)
In vivo	Anticancer	Root	Methanol	MCF-7 tumor bearing rat	200 mg/kg	(Gitanjali and Debasish, 2015)
In vivo	Anticatatonic	Bark	Ethanol	Chlorpromazine-induced catatonic rat	200 mg/kg	(Srivastava et al., 2014)
In vivo	Antidiabetic	Fruit	NA	Fluoride-exposed rat	2.5 g	(Vasant and Narasimhacharya, 2013)
In vivo	Antidiarrheal	Bark	Alcohol	Rat	200 mg/kg	(Senthilkumar et al., 2010)
In vivo	Antidiarrheal	Bark	Aqueous	Rat	200 mg/kg	(Senthilkumar et al., 2010)
In vivo	Anthelminthic	Fruit shell	Acetone	*Paramphistomum cervi* assay	150 mg/ml	(Islam et al., 2019)
In vivo	Anthelminthic	Fruit shell	Methanol	*Paramphistomum cervi* assay	150 mg/ml	(Islam et al., 2019)
In vivo	Antilipidemic	Fruit	NA	Fluoride-exposed rat	2.5 g	(Vasant and Narasimhacharya, 2013)
In vivo	Antioxidant	Fruit	Methanol	Carbon tetrachloride-induced liver damaged rat	200 mg/kg	(Chitra, 2009)
In vivo	Antioxidant	Fruit	NA	Fluoride-induced hepatic oxidative stress in rat	2.5 g	(Vasant and Narasimhacharya, 2011)
In vivo	Antioxidant	Fruit	NA	Fluoride-induced renal oxidative stress in rat	2.5 g	(Vasant and Narasimhacharya, 2011)
In vivo	Cardioprotective	Fruit	Ethanol	Isoproterenol-induced myocardial infarction in rat	200 mg/kg	(Manohar et al., 2016)
In vivo	Diuretic	Leaf	Methanol	Rat	200 mg/kg	(Parial et al., 2009)
In vivo	Hepatoprotective	Fruit	Methanol	Carbon tetrachloride-induced liver damaged rat	200 mg/kg	(Chitra, 2009)
In vivo	Immunomodulatory	Fruit	Methanol	Mouse	400 mg/kg	(Sunitha and Mohan, 2013)
In vivo	Immunomodulatory	Fruit	Methanol	Rat	400 mg/kg	(Sunitha and Mohan, 2013)
In vivo	Wound healing	Fruit	Methanol	Dead-space wounded rat	400 mg/kg	(Ilango and Chitra, 2010)
In vivo	Wound healing	Fruit	Methanol	Excision wounded rat	400 mg/kg	(Ilango and Chitra, 2010)
In vivo	Wound healing	Fruit	Methanol	Incision wounded rat	400 mg/kg	(Ilango and Chitra, 2010)

ED= effective dose, NS= not stated, NA= not applicable

5. Conclusion

T This comprehensive review of bioactivities of *L. acidissima* shows that this plant species has a wide range of ethnomedicinal uses and there is more scientific evidence for its ethnomedicinal applications. Therefore, other bioactivities and phytochemical studies should be

carried out to produce more scientific evidence confirming the ethnomedicinal uses for standardization, safety, and efficacy purposes in future. In addition, more bioactive compounds should be discovered from this plant species, and they could be the candidates as a major compound in future research to fight diseases such as cancer. Then, these useful bioactive compounds could be synthesized in the lab to produce on a large scale without decreasing the population of this plant species. To date, a huge number of bioactive compounds have been isolated from various plant species. However, not all compounds or extracts have *in vivo* and clinical trial evidence and mechanisms of action for their bioactivities. Therefore, there is an urgent need to conduct these studies in order to find more effective drugs with little or no side effects compared to the drugs currently used. This study analyzed, documented, and summarized the reported bioactivities of *L. acidissima*. In addition, this work will be very useful to researchers who are interested in studying further bioactivities and phytochemical studies using this plant species.

Author Contributions

Both authors contributed equally to this work (initiated the research idea, developed, organized, analyzed and interpreted the data, wrote the manuscript, suggested the research methods, structured the paper, and edited the manuscript).

Conflict of Interest

The authors declare that there is no conflict of interest.

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Ethical Approval/Informed Consent

Ethics committee approval is not required for this study and was not provided.

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