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A review on the Phytochemistry and Pharmacology of *Psidium guajava* L. (Myrtaceae) and Future direction

Koto-te-Nyiwa Ngbolua,[1,3*] Lufuluabo G. Lufuluabo,[2] Lengbiye E. Moke,[1] Gédéon Ngiala Bongo,[1] Clément Inkoto Liyongo,[1] Colette Masengo Ashande,[3] Bienvenu Songowe Sapo,[1] Benjamin Gbolo Zoawe,[3] Pius T. Mpiana[2]

ABSTRACT

The aim of the present review is to provide information on the ethnomedical use and scientific knowledge on *Psidium guajava* to researchers in the field of biology, chemistry and pharmacognosy. A literature search was conducted to obtain information about the phytochemistry and pharmacology of *Psidium guajava* from the electronic databases like PubMed, PubMed Central, Science Direct and Google scholar. Scientific name of this plant species was used as keyword for the search, along with the terms phytochemistry and pharmacology. The chemical structure of the *P. guajava* naturally occurring compounds was drawn using ChemBioDraw Ultra 12.0 software package. An extensive survey of literature (Multidisciplinary advanced bibliographic surveys) revealed that *Psidium guajava* L. is a good source of health promoting secondary metabolites like Flavonoids, Tannins, glycosides, terpenoids, etc. The medicinal plant *Psidium guajava* is reported to possess various pharmacological properties like anti-oxidant, anti-inflammatory, antibacterial, anticough, antidiarrheal, antidiabetic, antihyperlipidemic, cardioprotective, antimutagenic, hepatoprotective and larvicidal effects. These properties are due to the presence of various phytochemicals like tannins, alkaloids, phenols, glycosides, flavonoids and steroids.

The present review can therefore help inform future scientific research towards the development of novel drugs against Sickle cell Anemia because of the presence of naturally occurring triterpenoids acids like Guavacoumaric, Ursolic, 2α-hydroxyursolic, Maslinic, Asiatic, Jacoumaric, Isoneriucoumaric, Guajavanoic and Guavenoic acids.

Keywords: *Psidium guajava,* primary health care, phyto-constituents, pharmacology, electronic databases

*Corresponding Author:
Prof. Koto-te-Nyiwa Ngbolua, PhD, Département de l'Environnement, Faculté des Sciences, Université de Gbadolite, B.P. 111 Gbadolite, Province du Nord-Ubangi, République Démocratique du Congo
jpngbolua@unikin.ac.cd

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INTRODUCTION

Tropical medicinal plant species are known for their richness in biologically active secondary metabolites and essential oils of therapeutic relevance. The principal advantages claimed for therapeutic uses of botanicals against various ailments are their safety besides being economical, effective and their easy availability. Because of these advantages the medicinal plants are widely used by the traditional healers in their day to day practice.[1] The World Health Organization (WHO) reported that about 80% of the population living in developing countries relies on traditional medicine for their primary health care needs.[2] This is the case of Democratic Republic of the Congo (DRC) where medicinal plants represent the key product for both urban and rural populations for their health care needs because the costs of conventional drugs are often unaffordable. These plants have found to have great therapeutic relevance for fighting major health problems.[3-10] The present review was conducted in order to obtain updated information about the phytochemistry and pharmacology of *P. guajava* L., a useful medicinal plant species of pharmaceutical relevance which could be developped as medicine for managing various ailments including Sickle cell anemia.

BOTANY

The plant *Psidium guajava* L. (figure 1) belongs to the family of Myrtaceae which is native from tropical America. This family contains dicotyledonous plant widely distributed in warm regions of the world and it contains approximately 3000 species divided into 130 genera. Guava is an exotic fruit and its shape ranges from round, ovoid, to pear-shaped, and with an average diameter and weight ranging from 4-10cm and 100-400 g respectively. Classified as a berry, this plant species is composed of a fleshy mesocarp of varying thickness and a softer endocarp with numerous small, hard yellowish-cream seeds embedded throughout it.[11-13]

[1]Département de Biologie, Faculté des Sciences, Université de Kinshasa, B.P. 190 Kinshasa XI, République Démocratique du Congo
[2]Département de Chimie, Faculté des Sciences, Université de Kinshasa, B.P. 190 Kinshasa XI, République Démocratique du Congo
[3]Département de l'Environnement, Faculté des Sciences, Université de Gbadolite, B.P. 111 Gbadolite, Province du Nord-Ubangi, République Démocratique du Congo

PHYTOCHEMISTRY

The fruit of *P. guajava* contains vitamins A and C, some minerals like iron, calcium and phosphorus. Manganese exists in this plant in combination with phosphoric, oxalic and malic acids. The fruit is also rich phytochemicals such as saponins (combined with oleanolic acid, morin-3-O-α-L-lyxopyranoside and morin-3-O-α-L arabopyranoside), flavonoids (guaijavarin and quercetin).[14,15] In the headspace, the reported major constituents were: hexanal, (E)-2-hexenal, (E,E)-2,4-hexadienal, (Z)-3-hexenal, (Z)-2-hexenal, (Z)-3-hexenyl acetate and phenol, while β-caryophyllene, nerolidol, 3-phenylpropyl acetate and caryophyllene oxide were the major volatile constituents present in the hydro-distilled essential oil.[16] The fruit also contains pentane-2-thiol.[17] The leaves of *P. guajava* contain an essential oil rich in cineol, tannins, triterpenes and flavonoids.[18] Quercetin and its glycosides were isolated from this plant species (table 1) along with other flavonoids like morin-3-O-α-L-lyxopyranosidemorin-3-O-α-L-arabinopyranoside,[19] kæmpferol and luteolin-7-O-glucoside and apigenin-7-O-glucoside.[20]

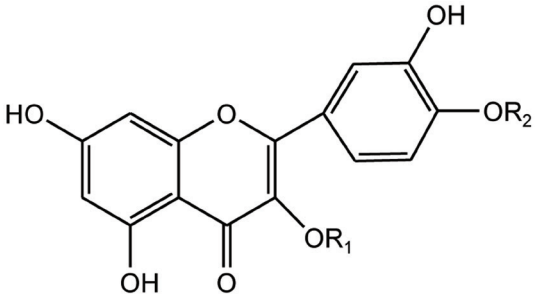
Phytochemicals of pharmacological relevance for human health and wellbeing like Guavin B, Guavin A, Isostrictinin, Strictinin (figure 2), Amritoside or ellagic acid 4-gentiobioside, Pedunculagin and (+)-gallocatechin were also isolated from the leaves of *P. guajava*.[21,22]

Matsuo et *al.*[22] isolated in leaves of the medicinal plant *P. guajava*the following compounds namely menthol, α-pinene, β-bisabolene, β-pinene, β-copanene, limonene, terpenyl acetate, isopropyl alcohol, caryophyllene, longicyclene, cineol, caryophyllene oxide, humulene, farnesene, selinene, curcumene and cardinene.[23]

They contain as well phytofluene, (all-E)-, (9Z)-, (13Z)-, and (15Z)-beta-carotene, (all-E)-gamma-carotene, (all-E)-, (9Z)-, (13Z)-, 8 and (15Z)-lycopene, (all-E, 3R)-beta-cryptoxanthin, (all-E, 3R)- rubixanthin, (all-E,3S,5R,8S)-cryptoflavin, (all-E, 3R, 3'R, 6'R) lutein, (all-E, 3S, 5R, 6R, 3'S, 5'R, 8'R)-, and (all-E, 3S, 5R, 6R, 3'S, 5'R,8'S) neochrome.[24] Secondary metabolites like Guavanoic acid, guavacoumaric acid, 2α-hydroxyursolic acid, isoneriucoumaric acid, jacoumaric acid, asiatic acid, ilelatifol D and β-sitosterol-3-O-β-D-glucopyranoside were also isolated from the leaves of *P. guajava* (table 2).[25]

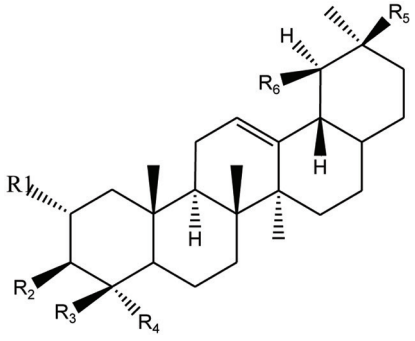
The triterpenoids isolated from the leaves of *P. guajava* are guavanoic acid (20β-acetoxy-2α,

Table 1 **Quercetin and its glycosides isolated from *P. guajava* leaves**



Flavonoid	R_1	R_2
Quercetin	H	H
Quercetin 3-O-L-arabinofuranoside	L-arabinofuranoside	H
Quercetin 3-O-a-L-arabinopyranoside	L-arabinopyranoside	H
Quercetin 3-O-ß-D-glucoside.	-D-glucoside	H
Quercetin 3-O-ß-D-galactoside	D-galactoside	H
Quercetin 3-O-ß-L-rhamnoside.	-L-rhamnoside.	H
Quercetin 3-O-ß-D arabinopyranoside	D arabinopyranoside	H
Quercetin 3-O-gentiobioside	gentiobioside	H
Quercetin 4'-glucuronoide	H	Glucuronic acid

Table 2 **List of Triterpenic acids isolated from *P. guajava* leaves**



	R_1	R_2	R_3	R_4	R_5	R_6
Guavanoic acid	OH	OH	CH_3	CH_3	-OAc	CH_3
Guavacoumaric acid	OH	OH	R	CH_3	H	CH_3
Guajanoic acid	OMe	R	CH_3	CH_3	H	CH_3
Ursolic acid	H	OH	CH_3	CH_3	H	CH_3
2a-hydroxyursolic acid	OH	OH	CH_3	CH_3	H	CH_3
Maslinic acid	OH	OH	CH_3	CH_3	CH_3	H
Asiatic acid	OH	OH	CH_3	CH_2OH	H	CH_3
Jacoumaric acid	OH	R	CH_3	CH_3	H	CH_3
Isoneriucoumaric acid	R	OH	CH_3	CH_3	H	CH_3

Figure 1 Photography of the plant ***Psidium guajava*** L.

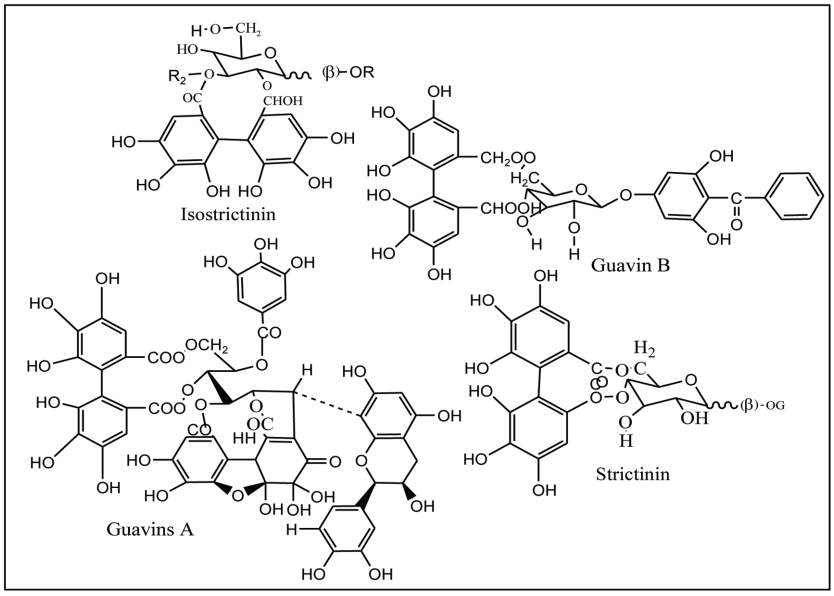


Figure 2 Structures of tannins isolated from ***P. guajava*** leaves

3β-dihydroxyurs12-en-28-oic acid), and guavacoumaric acid (2α, 3βdihydroxy-24-p-zcoumaroyloxyurs-12-en-28-oic acid), along with six known compounds asiatic acid, jacoumaric acid, 2α-hydroxyursolic acid, isoneriucoumaric acid, β-sitosterol-3-O-β-D-glucopyranoside, and ilelatifol D.[26] The structures of guajavolide (2a-, 3β-6β-, 23-tetrahydroxyurs-12-en-28, 20β-olide, guavenoic acid (2 alpha, 3 beta, 6 beta, 23-tetrahydroxyurs-12,20 (30)-dien28-oic acid) and guajavanoic acid isolated from fresh leaves of *P. guajava* are given in figure 3.

Many compounds were isolated from the leaves of *P. guajava*. This include: obtusinin, goreishic acid I Guajanoic acid, beta-sitosterol, uvaol, oleanolic acid, ursolic acid, psidiumoic acid, obtusol, Guajadialbetulinic acid, lupeolellagic acid-4-O-beta-D-glucopyranoside, quercetin-3-O-(6"-galloyl) beta-D-galactopyranoside, 1-O-(1, 2-propanediol)-6-O-galloyl-beta-D-glucopyranoside, quercetin, quercetin-3-O-α-L-arabinofuranoside, quercetin-3-O-β-D-arabinopyranoside, quercetin-3-O-β-D-glucoside and quercetin-3-O-β-D-galactoside and (±)-Guajadial B.[27,28]

Ryu et *al.*[29] identified 60 compounds in a hexane fraction of *P. guajava*, including β-eudesmol, α-copaene, phytol, α-patchoulene, β-caryophyllene oxide, caryophylla-3(15), 7(14)-dien-6-ol, (E)-methyl isoeugenol, α-terpineol, and octadecane. Shao et *al.*[30] isolated and identified clovane-2 beta, 9 alpha-diol, 2 beta-acetoxyclovan-9 alpha-ol, 9 beta-diol, ent-T-muurolol, clov-2-ene-9 alpha-ol, (+)-globulol, (+)-caryolane-1, isophytol, gossypetin, tamarixetin, kaempferol, guajaverin, quercetin, avicularin, chrysin 6-C-glucoside, guavinoside A, guavinoside B 3'-Omethyl-3, 4-methylenedioxyellagic acid 4'-O-beta-D-glucopyranoside and p-hydroxy-benzoic acid.

The seed of *P. guajava* contain oil, proteins and starch.[31] Quercetin-3-O-β-D-(2"-O-galloyl glucoside)-4'-O-vinylpropionate was isolated from the leaves of this medicinal plant species.[32] The twigs of *P. guajava* contain calcium, magnesium, phosphorous, potassium and sodium. Guava has been reported to be the second fruit with the highest concentration of ascorbic acid (ranging from 60-1000 mg/100 g) of all fruits.[33]

PHARMACOLOGY

Antioxidant activity

Recent findings revealed that *P. guajava* is an excellent source of antioxidant phytochemicals.[34] The methanolic extract of leaves revealed high antioxidant activity. The active principles are quercetin, quercetin-3-O-glucopyranoside, morin, ascorbic acid, carotenoids, and polyphenolics.[35]

Antibacterial activity

The aqueous and organic extracts of *P. guajava* leaves revealed antibacterial activity against *Staphylococcus aureus, Proteus spp., and Shigella spp*. While no activity *against Citrobacter spp*, *Alcaligenes fecalis*, and *Aspergillus spp* was observed.[36,37] The aqueous extracts of *P. guajava* leaves, roots and stem bark were active against the gram-positive bacteria *Bacillus subtilis* and virtually inactive against the gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*. The aqueous, alcohol and chloroform extracts of leaves were effective against *Aeromonas hydrophila, Shigella spp* and *Vibrio spp*, *Staphylococcus aureus, Sarcina lutea* and

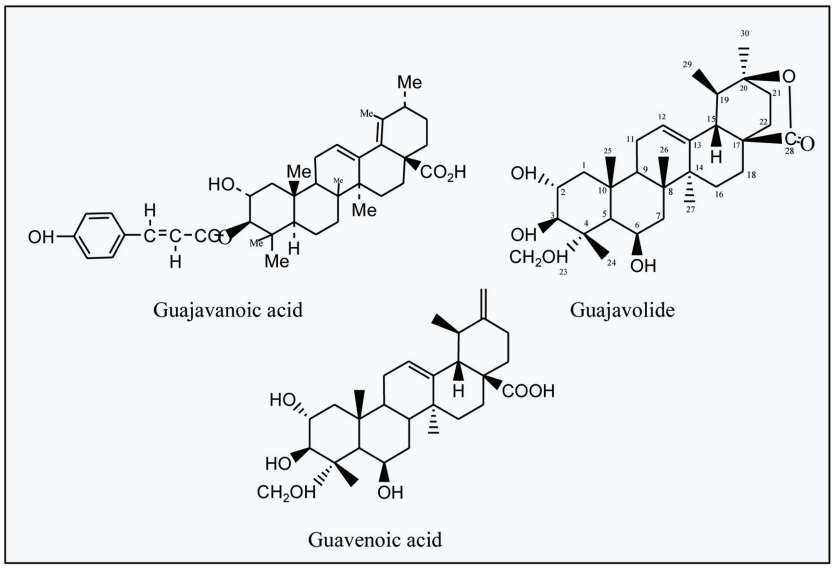


Figure 3 Structures of Guajavolide, Guajavanoic acid and Guavenoic acid isolated from the leaves of ***P. guajava***

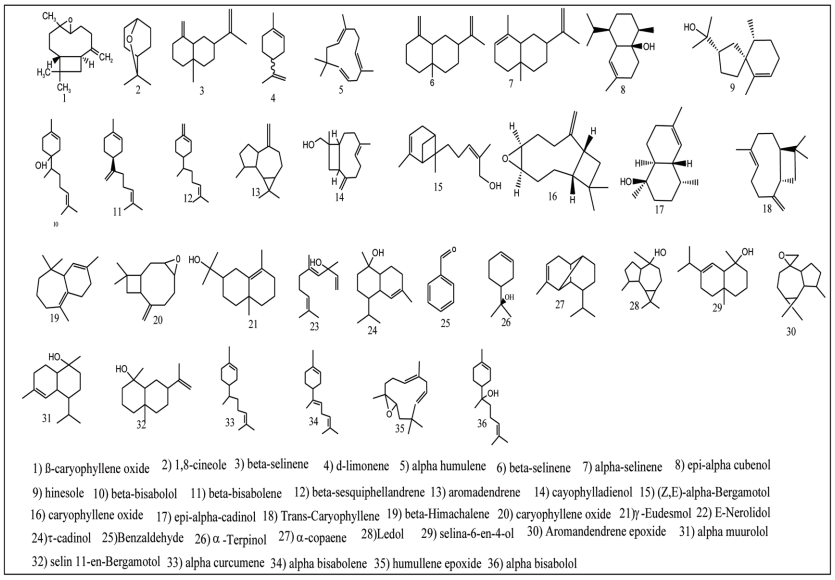


Figure 4 Chemical structure of the major compounds of essential oil from ***Psidium guajava***[13]

Mycobacterium phlei.[18] The antimicrobial activity of *P. guajava* is attributed to guajaverine,psydiolic acid and the flavonoid compound guaijaverin.[38] The essential oil γ–terpinene and γ–pinene displayed antimicrobial activity against *Propionibacterium acnes*.[39]

Anti-diarrheal activity

The leaves of *P. guajava L.* is traditionally used as an antidiarrheal medicine.[40,41] This activity is explained through spasmolytic, antibacterial and antiamoebic effects and phytochemicals such as flavonoids and tannins have been reported to exhibit the antidiarrheal activity through denaturing protein hence forming interaction protein-tannates which reduce the intestinal mucosa permeability.[42,43] Additionally, the calcium-antagonist properties of the biologically active compound namely quercetin explain the spasmolytic effect of this popular herbal remedy.[44]

Anti-diabetic and anti-hyperlipidemic activities

P. guajava is used in folk medicine for the treatment of diabetes mellitus.[45] The leaves aqueous extract, was reported to possess inhibitory effect against carbohydrate-degrading enzymes and also possess the ability to suppress the postprandial blood glucose level in human.[46] The leaf extract is also claimed as inhibitor of lipase.

This extract inhibits carbohydrate absorption and prevents obesity, heart disease and atherosclerosis.[46] The medically active principles in the ethanolic and n-butanol extracts were identified as the tannins isostrictinin, strictinin, and pedunculagin.[47]

Gallic acid, catechin and quercetin inhibit the formation of α-dicarbonyl compounds and AGEs formation in BSA glycation systems.[48] Quercetin, kaempferol, myricetin displayed inhibitory effects against sucrose, maltase, and α-amylase.[49]

Cardioprotective effects

P. Guajava L. was reported to possess cardioprotective effects against myocardial ischemia-reperfusion injury in isolated rat hearts with quercetin and gallic acid as the biologically active compounds.[50] The alcoholic, aqueous and ethyl acetate soluble fractions and essential oil of the leaves of *P. guajava* inhibit the ventricular contraction of isolated rabbit heart.[51] Aqueous leaves extract of *Psidium guajava* possess contractile effect on rat aorta rings.[52] Acute intravenous administration of the aqueous extract of *P. guajava* leaf was reported to cause reduction in systemic arterial blood pressure and heart rates of hypertensive rats. Secondary metabolites such as polyphenolic compounds, flavonoids, pentacyclic triterpenoids, quercetin, guiajaverin, tannins present in this plant are considered as responsible for the observed hypotensive bioactivity.[53]

Antimutageni cand anticancer activities

P. guajava L. leaves were reported to possess antimutagenic activity, flavonoids were claimed to be responsible for this activity.[51,52-54] The plant was also reported to possess anticancer effects against selected cancerous cell lines like cervical cancer (HeLa), breast cancer (MDA-MB-231) and osteosarcoma (MG-63), colorectal carcinoma (RKO-AS45-1), and lung fibroblast (Wi-26VA4).[55,56] The compound β-caryophyllene oxide isolated from

the essential oil of *P. guajava* was reported to kill myeloma, prostate and breast cancer cell lines.[57]

Hepatoprotective activity

The aqueous extract of leaves of *P. guajava* possesses an interesting hepatoprotective activity.[58] Indeed, injury induction of healthy clone 9 liver cells using 5% alcohol concentration for 30 minutes revealed the hepatoprotective properties of *Psidium guajava* extracts. Hot water extracts showed high hepatoprotective and lower cytotoxic effects than other extracts.[59-60]

Larvicidal effect of essential oils

The essential oil obtained from leaves of *Psidium guajava* has displayed promising larvicidal activity against *A. aegypti* with LC_{50} ranging from 39.48 to 64.25 µg mL^{-1}.[59]

Others pharmacological actions of *Psidium Guajava* L. and toxicity

The leaves of the plant *P. guajava* were reported to possess also interesting pharmaceutical properties such as retroviral reverse transcriptase inhibitor activity, depressant activity on central nervous system, antinociceptive/analgesic activity, anticestodal activity, spasmolytic activity, Anticough action, antifungal activity and anti-ulcer activity. The water extract of the leaves of this medicinal plant species has no short term harmful effect and was found to be non toxic toward animal model systems like rats and mice at 5000 mg/Kg.[61]

CONCLUSION AND SUGGESTIONS

The literature survey revealed that *Psidium guajava* L. is a pharmacologically and chemically much studied plant species, although the diversity of secondary metabolites present in the plant species especially triterpenoids derived acids (Guavacoumaric, Ursolic, 2α-hydroxyursolic, Maslinic, Asiatic, Jacoumaric, Isoneriucoumaric, Guajavanoic and Guavenoic acids) make *P. guajava* a good candidate for the development of new lead compounds against Sickle cell Anemia.

REFERENCES

1. Chavan SS, Shamkuwar PB, Damale MG, Pawar DP. A comprehensive review on *Annona reticulata*. International Journal of Pharmaceutical Sciences and Research 2014; 5(1): 45-50.
2. Ngbolua KN, Mihigo SO, Mpiana PT, Inkoto CL, Masengo CA, Tshibangu DST, Gbolo BZ, Baholy R, Fatiany PR. Ethno-pharmacological survey and Ecological studies of some plants used in traditional medicine in Kinshasa city (Democratic Republic of the Congo). Tropical Plant Research 2016 ; 3(2) : 413-427.
3. Bongo GN, Ngbolua KN, Masengo CA, Karume KL, Mukiza J, Tshilanda DD, Tshibangu DST, Ngombe NK, Mbemba TF, Mpiana PT. Pharmacological screening of *Gymnanthemum coloratum* (Willd.) H. Rob. & B. Kahn (Compositae) and *Terminalia ivorensis* A. Chev. (Combretaceae) from DR Congo: Spotlight on the antisickling, antibacterial and anti-diabetic activities. Tropical PlantResearch, 2017 ; 4(3): 441–448.
4. Ngbolua KN, Lengbiye EM, Likolo JB, Djolu RD, Masengo CA, Mpiana PT. A Mini-review on the Pharmacognosy and Phytochemistry of the Tropical Medicinal Plant *Annona senegalensis* Persoon (Annonaceae). Tropical Plant Research 2017; 4 (1): 168-175
5. Ngbolua KN, Rafatro H, Rakotoarimanana H, Ratsimamanga US, Mudogo V, Mpiana PT, Tshibangu DST. Pharmacological screening of some traditionally-used antimalarial plants from the Democratic Republic of Congo compared to its ecological taxonomic equivalence in Madagascar. International Journal of Biological & Chemical Sciences 2011a; 5 (5): 1797-1804.
6. Ngbolua KN, Rakotoarimanana H, Rafatro H, Ratsimamanga US, Mudogo V, Mpiana PT, Tshibangu DST. Comparative antimalarial and cytotoxic activities of two Vernonia species: *V. amygdalina* from the Democratic Republic of Congo and *V. cinerea* subsp *vialis* endemic to Madagascar. International Journal of Biological & Chemical Sciences 2011b; 5 (1): 345-353.
7. Bongo GN, Inkoto C, Masengo CA, Tshiama C, Lengbiye E, Djolu R, Mutwale K, Ngombe K, Mbemba T, Tshilanda D, Mpiana PT, Ngbolua KN. Antisickling, antioxidant and antibacterial activities of *Afromomum alboviolaceum* (Ridley) K. Schum, *Annona senegalensis* Pers. and *Mondia whitei* (Hook. f.) Skeels. American Journal of Laboratory Medicine, 2017; 2(4): 52-59.
8. Ngbolua KN, Mandjo BL, Munsebi JM, Masengo CA, Lengbiye EM, Asamboa LS, Konda RK, Dianzuangani DL, Ilumbe M, Nzudjom AB, Kadimanche M, Mpiana PT. Etudes ethnobotanique et écologique des plantes utilisées en médecine traditionnelle dans le District de la Lukunga à Kinshasa (RD du Congo). International Journal of Innovation and Scientific Research, 2016 ; 26(2) : 612-633.
9. Ngbolua KN, Tshibangu DST, Mpiana PT, Mihigo OS, Mavakala BK, Masengo CA, Muanyishay LC. Anti-sickling and antibacterial activities of Some Extracts from *Gardenia ternifolia* subsp. *jovis-tonantis* (Welw.) Verdc. (Rubiaceae) and *Uapaca heudelotii* Baill. (Phyllanthaceae). Journal of Advances in Medical and Pharmaceutical Sciences, 2015; 2 (1): 10-19.
10. Ngbolua KN, Bishola TT, Mpiana PT, Mudogo V, Tshibangu DST, Ngombe KN, Ekutsu EG, Gbolo BZ, Kabena NO. Ethno-pharmacological survey, in vitro antisickling and free radical scavenging activities of *Carapa procera* DC. stem bark (Meliaceae). Nova Journal of Medical and Biological Sciences 2 (2): 01-14, 2014.
11. Flor de Maria NR. Guava (*Psidium guajava* L.) fruit phytochemicals, Antioxidant Properties and Overall Quality as Influenced by Postharvest Treatments. MSc Thesis: The University Of Florida, 2005.
12. A. Vikrant A, T. Narender T, C.P Kashyap CP. Preliminary Phytochemical Analysis of the Extracts of *Psidium* Leaves. Journal of Pharmacognosy and Phytochemistry 2012; 1(1): 1-5.
13. Tércioda SS, Marcia FS and Luciano. Essential oil of *Psidium guajava*: Influence of genotpes and environment. Scientia Horticulturae 2017; 38-44).
14. Hernandez DF. Plants of the Philippines. 2nd Edition: 1980.
15. Arima H, Danno G. Isolation of antimicrobial compounds from guava (*Psidium guajava* L.) and their structural elucidation. Bioscience, Biotechnology and Biochemistry 2012; 66 (8): 1727-1730.
16. Paniandy JC, Chane-Ming J, Pieribattesti JC. Chemical composition of the essential oil and headspace solid-phase micro-extraction of the guava fruit (*Psidium guajava* L.). Journal of Essential Oil Research 2000; 12(2): 153-158.

17. Bassols F, Demole EP. The occurrence of pentane-2-thiol in guava fruit. Journal of Essential Oil Research 1994; 6(5): 481-483.
18. Neviton RS, Diógenes AGC, Michelle SS, Celso VN, Benedito PDF. An Evaluation of Antibacterial Activities of *Psidium guajava* L.). 2005; Brazilian Archives of Biology and Technology 48 (3): 429-436.
19. Arima H and Danno G. Isolation of antimicrobial compounds from Guava (*Psidium guajava* L.) and their structural elucidation. Bioscience Biotechnology Biochemistry 2002; 66(8):1727-30.
20. Abdel WSM, Hifawy MS, El GoharyandM HM. Isak. Study of Carbohydrates, Lipids, Protein, Flavonoids, Vitamine C and Biological Activity of Psidiumguayava L. Growing in Egypt. Egypt J. Biomed Sci. 2004; 16: 35-52.
21. Seshadri T, Vasishta K. Polyphenols of the leaves of Psidium guava L; quercetin, guaijaverin, leucocyanidin, amritoside. Phytochemistry 1965; 4: 989–92..
22. Matsuo T, Hanamure N, Shimoi K, Nakamura Y, Tomita I. Identification of (+)-gallochatechin as a bio-antimutagenic compound in *Psidium guava* leaves. Phytochemistry 1994; 36(4):1027-9.
23. Li J, Chen F, Luo J. GC/MS analysis of essential oil from the leaves of *P. guajava*. Zhong Yao Cai 1999; 22(2):78-80.
24. Mercadante AZ, Steck A, Pfander H. Carotenoids from guava (*Psidium guajava* L.): isolation and structure elucidation. J Agric Food Chem. 1999; 47(1):145-51.
25. Begum S, Hassan SI, Siddiqui BS, Shaheen F, Ghayur MN, Gilani AH. Triterpenoids from the leaves of *Psidium guajava*. Phytochemistry 2002; 61(4):399-403.
26. Begum S, Siddiui BS and Hassan SI. Triterpenoids from Psidium guajava leaves. Nat Prod Letters 2002; 16(3):173-7.
27. Begum S, Hassan SI, Siddiqui BS. Two new triterpenoids from the fresh leaves of *Psidium guajava*. Planta Medica 2002; 68(12):1149-52.
28. Metwally AM, Omar AA, Harrazand FM, El Sohafy SM. Phytochemical investigation and antimicrobial activity of *Psidium guajava* L. leaves. Pharmacogn Mag. 2010; 6(23):212-8.
29. Gao Y, Wang GQ, Wei K, Hai P, Wang F, Liu JK. Isolation and biomimetic synthesis of (±)–guajadial B, a novel meroterpenoid from *Psidium guajava*. Org Lett. 2012; 14(23):5936-9.
30. Ryu NH, Park KR, Kim SM, Yun HM, Nam D, Lee SG, Jang HJ, Ahn KS, Kim SH, Shim BS, Choi SH, Mosaddik A, Cho SK, Ahn KS.. A hexane fraction of guava Leaves (*Psidium guajava* L.) induces anticancer activity by suppressing AKT/mammalian target of rapamycin/ribosomal p70 S6 kinase in human prostate cancer cells. Journal of Medicinal Food 2012; 15(3):231-41.
31. Burkill HM. The useful plants of West Tropical Africa. Edition 2. Vol. 4. Families M-R. Royal Botanic Gardens Kew: 1997.
32. Shao M, Wang Y, Jian YQ, Sun XG, Huang XJ, Zhang XQ, Ye WC.. Chemical constituents of leaves of *Psidium guajava*. Zhongguo Zhong Yao Za Zhi 2014; 39(6):1024-9.
33. Michael HN, Salib JY, Ishak MS. Acylated flavonol glycoside from *Psidium guajava* L. seeds. Pharmazie 2002; 57(12): 859-60.
34. Okwu DE, Ekeke O. Phytochemical screening and mineral composition of chewing sticks in South Eastern Nigeria. Global Journal of Pure and Applied Sciences 2003; 9(2): 235-238.
35. Jimenez-Escrig A, Rincon M, Pulido R, Saura-Calixto F. Guava Fruit (*Psidium guajava* L.) as a New Source of Antioxidant Dietary Fiber. Journal of Agricultural and Food Chemistry 2001; 49(11): 5489-93.
36. Suganya T, Fumio I, Siriporn O. Antioxidant Active Principles Isolated from *Psidium guajava* Grown in Thailand. Scientia Pharmaceutica 2007; 75: 179-193.
37. Chah KF, Eze CA, Emuelosi CE, Esimone CO. Antibacterial and wound healing properties of methanolic extracts of some Nigerian medicinal plants. Journal Ethnopharmacology 2006; 104: 164–167.
38. Limsong J, Benjavongkulchaiand E, Kuvatanasuchati J. Inhibitory effects of some herbal extracts on adherence of *Streptococcus* mutans. Journal Ethnopharmacology 2004; 92(2-3): 281-9.
39. Athikomkulchai S, Watthanachaiyingcharoen R, Tunvichuen S, Vagamhasuwan P, Karnsomkiet P, Jong PS, Nijsiri R. The development of anti–acne products from *Eucalyptus globules* and *Psidium guajava* oil. Journal of Health Research 2008; 22(3):109-13.
40. Ross IA. Medicinal plants of the world: Chemical constituents, traditional and modern medicinal uses. New Jersey; Humana press, 1999.
41. Lozoya X, Meckes M, Abou-Zaid M, Tortoriello J, Nozzolillo C, Arnason JT. Quercetin glycosides in *Psidium guajava* L. leaves and determination of a spasmolytic principle. Arch med res. 1994; Archives of Medical Research 25(1): 11-5.
42. Shakeera BM, Sujatha K, Sridharan G, Manikandan R. Antihyperglycemic and antihyperlipidemic potentials of *Psidium guajava* in alloxan-induced diabetic rats. Asian Journal of Pharmaceutical and Clinical Research 2013; 6 (2): 88-89.
43. Ezekwesili JO, Nkemdilim UU, Okeke UU. Mechanism of antidiarrhoeal effect of ethanolic extract of *Psidium guajava* leaves. Biokemistri 2010; 22(2): 85-90.
44. Morales MA, Tortoriello J, Meckes M, Paz D, Lozoya X. Calcium–antagonist effect of quercetin and its relation with the spasmolytic properties of *Psidium guajava* L. Archives of Medical Research 1994; 25(1):17-21.
45. Sunagawa M, Shimada S, Zhang Z, Oonishi A, Nakamura M, Kosugi T. Plasma insulin concentration was increased by long-term ingestion of Guava Juice in Spontaneous Non-Insulin-Dependent Diabetes Mellitus (NIDDM) Rats. Journal of Health Science 2004; 50(6): 674-8.
46. Yamanobe Y, Hattori F, Shimomura K. Extracts from *Uncaria gambier, Psidium guajava, Filipendula* as lipase inhibitors. Patency number JP 2000103741, Kind A2, Date 20000411, Application number JP 1998-277896, 1998.
47. Maruyama Y, Matsuda H, Matsuda R, Kubo M, Hatano T, Okuda T. Study on *Psidium guajava* L. Antidiabetic effect and effective components of the leaf of *Psidium guajava* L. (Part 1). Shoyakugaku Zasshi (Japan) 1985; 39(4): 261-9.
48. Wu JW, Hsieh CL, Wang HY, Chen HY. Inhibitory effects of guava (*Psidium guajava* L.) leaf extracts and its active compounds on the glycation process of protein. Food Chemistry 2009; 113: 78–84.
49. Wang H, DuYJ, Song HC. Alpha-Glucosidase and α-amylase inhibitory activities of guava leaves. Food Chemistry 2010; 123: 6–13.
50. Yamashiro S, Noguchi S, Matsuzaki T, Miyagi K, Nakasone J, Sakanashi M et al. Cardioprotective Effects of Extracts from *Psidium guajava* L. and *Limonium wrightii*, Okinawan Medicinal Plants, against Ischemia reperfusion injury in Perfused Rat Hearts. Pharmacology 2003; 67(3):128-35.
51. Conde Garcia EA, Nascimento VT. Santiago Santos AB. Inotropic effects of extracts of Psidium guajava L. (Guava) leaves on the Guinea pig atrium. Brazilian Journal of Medical and Biological Research 2003; 36(5): 661-8.
52. Olatunji-Bello I, Odusanya AJ, Raji I, Ladipo CO. Contractile effect of the aqueous extract of *Psidium guajava* leaves on aortic rings in rat. Fitoterapia 2007; 78(3): 241-3.
53. Ojewole JA. Hypoglycemic and hypotensive effects of *Psidium guajava* Linn. (Myrtaceae) leaf aqueous extract. Methods and Findings in Experimental and Clinical Pharmacology 2005; 27(10):689-95.
54. Teixeira R, Camparoto M, Mantovaniand M, Vicentini V. Assessment of two medicinal plants *Psidium guajava* L. and *Achilleamille folium* L. in: *in vitro* and *in vivo* assays. Genetics and Molecular Biology 2003; 26(4): 551-5.
55. Sul´ain MD, Zazaliand KE, Ahmad N. Screening on anti-proliferative activity of *Psidium guajava* leaves extract towards selected cancer cell lines. Journal of US China Medical Science 2012; 9: 30–37.

56. Vieira Braga T, Gonçalves, das Dores R, Soncin RC, Gontijo EFC, Márcia da Silva TL, de Pilla VF, Carvalho MDG, de Paula SA. Antioxidant, antibacterial and antitumor activity of ethanolic extract of the *Psidium guajava* leaves. American Journal of Plant Sciences 2014; 5: 3492–3500.
57. Kim C, Cho SK, Kapoor S, Kumar A, Vali S, Abbasi T et al. (2014). β–Caryophyllene oxide inhibits constitutive and inducible STAT3 signaling pathway through induction of the SHP–1 protein tyrosine phosphatase. Molecular Carcinogenesis 2014; 53(10):793-806.
58. Roy CK, Kamath JV, Asad M. Hepatoprotective activity of *Psidium guajava* Linn. leaf extract. Indian J Exp Biol. 2006; 44(4):305-11.
59. Hung-Hui C, Po-Hua W, Diana L, Yun-Chiehand P, Ming-Chang W. Hepatoprotective Effect of Guava (*Psidium guajava* L.) Leaf Extracts on Ethanol-Induced Injury on Clone 9 Rat Liver Cells. Food and Nutrition Sciences 2011; 2: 983-988.
60. Luiza AM, Gustavo F. Larvicidal extract of essential oils from Brazilian cultivars of guava on *Aedes aegypti* L. Industrial Crops & Products 2017; 108: 684-689.
61. Metwally AM, Omar AA, Ghazy NM, Harraz FM, El Sohafy SM. Monograph of *Psidium guajava* L. leaves. Pharmacognosy Journal 3(21): 89-104.