International Journal of Photochemistry and Photobiology
2018; 2(1): 28-32
http://www.sciencepublishinggroup.com/j/ijpp
doi: 10.11648/j.ijpp.20180201.16

Pharmacological Properties of *Calophyllum inophyllum* – Updated Review

Win Min Oo

Department of Biochemistry, University of Medicine, Magway, Myanmar

Email address:
drwinminoo.ummg@gmail.com

To cite this article:
Win Min Oo. Pharmacological Properties of *Calophyllum inophyllum* – Updated Review. *International Journal of Photochemistry and Photobiology*. Vol. 2, No. 1, 2018, pp. 28-32. doi: 10.11648/j.ijpp.20180201.16

Received: July 30, 2018; **Accepted**: August 13, 2018; **Published**: September 12, 2018

Abstract: Natural products have been used as medicine since ancient times. With the advancement of research methods nowadays, the pharmacological properties of herbal plants have become an important role in the development and designation of drugs for different diseases. *Calophyllum inophyllum* is a large tree which grows well in different parts of the world. Various parts of *Calophyllum inophyllum* have been investigated for the pharmacological actions and some of the active constituents have been identified and isolated successfully. Furthermore, certain molecular mechanisms underlying the pharmacological effects have been revealed by different research groups across the world in recent years. This paper aims to review the different pharmacological actions of *Calophyllum inophyllum* together with recently discovered active constituents and mechanistic details. The published information on the pharmacological properties of *Calophyllum inophyllum* was gathered by using different database platforms including Google Scholar, PubMed, ScienceDirect, Scopus and SciFinder. The results show different pharmacological actions including anti-inflammatory, anticancer, antioxidant, wound healing, osteogenic, antimicrobial, lipid-lowering and antidiabetic effects of different parts of *Calophyllum inophyllum*. This review will provide the researchers with the background of the therapeutic potential of *Calophyllum inophyllum* and the extent of discovery that will lead to develop therapeutic agents for different pathological states in future.

Keywords: *Calophyllum inophyllum*, Clusiaceae, Pharmacology, Pharmacological Properties

1. Introduction

Calophyllum inophyllum is a large evergreen tree which belongs to the family Clusiaceae and grows to the height of 8 to 20 meters. The trunk produces whitish latex on bruising and the leaves have a characteristic features of opposite arrangements with thick shiny parallel vasculatures. The flowers appears in axillary cymes and are of moderate size and fragrant. *Calophyllum inophyllum* bears purple black ovoid fruits with a single seeds. The fruits and flowers are borne throughout the year. The plant is native to Africa, India and South East Asian countries [1].

Since late 1900s, research have been focused on the pharmacological properties of different parts of *Calophyllum inophyllum* and active constituents have been identified and isolated. Therapeutic potentials of *Calophyllum inophyllum* in certain diseases have proved by various in vivo and in vitro research across the world. Therefore, an updated review is needed regarding the pharmacological effects of different compounds present in *Calophyllum inophyllum* tree.

This article reviews the different pharmacological properties of *Calophyllum inophyllum* in important medical disorders in accordance with the evidence extracted from the diverse research groups. This review will aid researchers to realize how far the extent of understanding the treatment potential of *Calophyllum inophyllum* has gone and to construct further research towards the development of potent drugs in near future.

2. Method

The electronic database including Google Scholar, PubMed, ScienceDirect, Scopus and SciFinder were searched for pharmacological properties of *Calophyllum inophyllum* from 1950 to now to obtain the relevant data.

3. Results and Discussion

3.1. Osteogenic Property

Calophyllolide which is present only in the nuts of *Calophyllum inophyllum* processes osteogenic property. The dry nuts contain approximately 2mg/g of calophyllolide. Calophyllolide content declines in the nuts during maturity. In *in vitro* experiments, calophyllolide activated alkaline phosphate (ALP) activity in dose-dependent fashion in murine osteoblastic MC3T3-E1 cells but it was not cytotoxic significantly. The evidence of inducing osteoblast differentiation was explained by a rise in mineralization and ALP staining. Furthermore, it induced the expression of ALP and osteocalcin [2]. These supports the therapeutic potential of *Calophyllum inophyllum* in osteoporosis.

3.2. Anti-inflammatory Property

A number of experimental studies results in the evidence that different parts of *Calophyllum inophyllum* show anti-inflammatory property. Ethanol extracts of stem bark and seeds of *Calophyllum inophyllum* exhibited maximum inhibition at 250 µg/ml in proteinase inhibition and hemolysis assays. In Freund's adjuvant induced arthritis rats, treatment with bark and seeds extracts reduced paw edema volume by 28.57 and 36.36 % respectively as compared with Diclofenac administration that had 43.51 % inhibition. Biochemical and hematological parameters of arthritis rats returned to normal by treating with oral intake of 250 mg/kg of the bark and seeds extracts [3]. In in vitro studies, 50µg/ml of crude oil of the fruits of *Calophyllum inophyllum* inhibits lipooxygenase and cyclooxygenase at 88% and 77% respectively. At the gene expression level, *Calophyllum inophyllum* extract inhibits nitric oxide production and down-regulates inducible nitric oxide synthase (iNOS), cyclooxygenase (COX)-2 and nuclear factor-kappaB (NF-kB) genes [4].

The active constituents are Inophyllum A, C, E, calophyllolide, calophynic acid, 11,12-anhydroinophyllum A, potocatechuic acid, 1,7-dihydroxy-6-methoxyxanthone, beta-sitosterol, n nonacosane, gallic acid, and sitosterol-3-O-beta-D-glucophyranoside [5]. A new xanthone named inophinnin isolated from the stem bark of *Calophyllum inophyllum* has been recently shown to be anti-inflammatory [6]. Calophyllolide, a major constituents in *Calophyllum inophyllum* seeds, induces anti-inflammatory cytokine, interleukin-6, while it represses the expression of pro-inflammatory cytokines such as interleukin-1β, interleukin-6, tumor necrotic factor-α in experimental studies [7]. Among active constituents of the bark and leaves, amentoflavone processes an inhibitory effect on 15-lipooxygenase (LOX) [8].

3.3. Wound Healing Property

Topical application of Calophyllolide obtained from ethanolic extract of *Calophyllum inophyllum* seeds inhibited accelerated collagen formation and enhanced wound closure in animal models [7]. Irrigation with ionization marine solution with 10% *Calophyllum inophyllum* oil and 90% *Aleurites moluccana* induced regeneration of corneal epithelium and repress inflammation alkali burns in animal experiments [9]. In the scratch test assay on human keratinocyte cells, intubation in 0.1% of the oil extract of *Calophyllum inophyllum* accelerated wound closure with the healing factor 1.3 to 2.1 higher than control [10].

Regarding the mechanisms, the nut oil of *Calophyllum inophyllum* up-regulates the genes involved in cell adhesion, cell proliferation and O-glycan synthesis [11]. Calophyllolide of *Calophyllum inophyllum* seeds inhibits myeloperoxidase activity and induces M2-relation gene expression leading to M2 macrophage skewing [7].

3.4. Antibacterial and Antifungal Property

Bhat and colleagues first described the antimicrobial action of the oil of *Calophyllum inophyllum* against *gram-positive* bacteria in 1954 [12]. Later, Potti and Kurup reported a green yellow semi-solid compound, C32H46O6, isolated from the root bark inhibits the growth of *gram-positive* bacteria in 1970 [13].

According to experimental results, 20 µg/disc of caloxanthone A, calphynic acid, brasiliensic acid, inophylloidic acid, calophyllolide and inophyllum C and E isolated from root and nut of *Calophyllum inophyllum* inhibited *Staphylococcus aureus* but showed no effects on *Vibrio anguillarium*, *Escherichia coli* in agar well diffusions assays. However, the antibiotic action was lower than that of control, oxacillin [14].

Methanol extract of *Calophyllum inophyllum* stem bark has significant antibacterial action against *Pseudomonas aeurginosa, Staphylococcus aureus* and *Staphylococcus epidermidis* at 25 µg/ml concentration and against *Bacillus licheniformis*, *Bacillus subtilis, Escherichia coli* and *Klebsiella pneumoniae* at 50 µg/ml concentration [15].

The oil extract of *Calophyllum inophyllum* seeds exhibits two different antimicrobial actions. It directly inhibit mitosis of *gram-positive* bacteria while the extract accelerates the release of beta-defesin 2 peptide from macrophage to inhibit *gram-negative* bacteria [10].

Methanol and n-hexane extracts of discarded peel of *Calophyllum inophyllum* fruits exhibit significant antimicrobial activity against *Staphylococcus aureus* and *Mycobacterium smegmatis* [1].

Ethanol and chloroform extracts of *Calophyllum inophyllum* leaves are also active against gram-positive bacteria – *Staphylococcus aureus, Streptococcus pyrogenes* and *Corynebacterium diptheriae* but lack antimicrobial effect on *gram-negative* organisms. Butanol extract of the leaves exhibited antibacterial action on both gram-positive and -negative bacteria except *Escherichia*. Regarding active constituents of the leaves, canophyllic acid is active against *Proteus mirabillis* while canophyllol is much more potent against gram-positive strains. Friedelin is active against against *Staphylococcus aureus, Corynebacterium diptheriae, Salmonella typhi, Klebsiella pneumoniae* and *Proteus mirabillis*. Inophynone processes antibacterial action on *Staphylococcus aureus* [16].

Aqueous extract of Calophyllum inophyllum leaves exerts inhibitory effect on Microsporum canis, Trichophyton schoenleinii and Aspergillus nigar. Butanol extract of the leaves is active against Trichophyton simil and Trichophyton mentagrophytes while chloroform extract shows antifungal effect on Pseudallescheria boydii and Aspergillus nigar. Regarding active constituents, friedelin present in the leaves is active against Aspergillus niger, Pseudallescheria boydii and Trichophyton schoenleinii. Canophyllol and inophynone lack antifungal effect [16].

3.5. Anticancer Property

Caloxanthone N and gerontoxantone C isolated from ethanol extract of *Calophyllum inophyllum* have cytotoxic effect on chronic myelogenous leukemia cell line (K562) with IC50 of 7.2 and 6.3 µg/ml respectively [17]. 1/10,000 v/v of *Calophyllum inophyllum* oil can absorb UV rays (maximum 300nm) and has sun protection factor of 18-22. Similarly, 1% *Calophyllum inophyllum* oil is able to inhibit UV-induced DNA damage by 85% without significant irritation or cytotoxicity [18]. Furthermore, *Calophyllum inophyllum* contains 4-phenylcoumarins which inhibits Epstein-Barr virus early antigen (EBV-EA) activation caused by 12-O-tetradecanoylphorbol-13-acetate in Raji cells. Calocoumarin-A also protects mouse skin tumor formation in carcinogenesis experiments [19].

The stem bark of *Calophyllum inophyllum* contains different xanthones (inophinone, pyranojacareubin, rheediaxanthone A, macluraxanthone and 4-hydroxyxanthone). Among them, iophinone, rheediaxanthone A, macluraxanthone and 4-hydroxyxanthone exhibited anti-proliferative actions on 5 different cell lines – SNU-1, HeLa, NCI-H34, Hep G2 and K562. Pyranojacareubin lacks anticancer activity propably due to pyran ring fusion in its structure [20]. Ethanolic extract of the twigs of *Calophyllum inophyllum* contains a prenylated xanthone called caloxanthone O that is cytotoxic to human gastric cancer cell line (SGC-7901) with IC50 being 22.4 µg/ml [21]. 3β, 23-epoxy-friedelan-28-oic acid, canophyllol, canophyllic acid and 3-oxo-friedelan-28-oic acid and oleanolic acid isolated from the stems and leaves and isocalophyllic acid, 3-oxofriedelin-28-oic acid, canophyllic acid, amentoflavone, shikimic acid inophyllum C and inophyllum E present in the leaves of *Calophyllum inophyllum* inhibits cell growth in human leukemia HL-60 cells [22].

The fruit extract of *Calophyllum inophyllum* shows significant antitumor effect on MCR-7 cells with IC50 of 23.59 µg/ml by inducing cell cycle arrest at G0/G1 and G2/M phases and apoptosis. *Calophyllum inophyllum* represses Bcl-2 expression, anti-apoptostic protein, while inducing pro-apoptotic Bax, p53 and cytochrome C. The extract influences mitochondrial apoptotic pathway by enhancing intracellular reactive oxygen species (ROS), disturbing normal mitochondrial potential and activating caspase-3 [23].

Yellow and green pigments contained in seed oil of *Calophyllum inophyllum* are cytotoxic to DLD-1 human colon cancer cells as they inhibit cell cycle at check points – G1-S and G2-M. The pigments also induce cell death in A549 and H1975 human non-small cell lung cancer cell lines with IC50 being 0.1206 and 0.0676% respectively in 24 hour incubation. The green pigment has synergistic effect on gefitinib, a selective epidermal growth factor receptor blocker to potentiate the cell death in A549 and H1975 cells [24].

Calophyllolide, caloxanthone A, calophynic acid, brasiliensic acid and inophylloidic acid isolated from roots and nuts of *Calophyllum inophyllum* exhibited IC50 value of 3.5, 7.7, 10.5, 11.0 and 9.4 µg/ml respectively on human epidermoid carcinoma of the nasopharynx cell (KB). On another hand, calaustralin and inophyllum E lacked such cytotoxic effect [14]. Inophyllum A present in the root of *Calophyllum inophyllum* induces apoptosis in Jurkat T lymphoblastic leukemic cells via the generation of reactive oxygen species and mitochondrial membrane disruption with simultaneous activation of caspase 2, 9 and 3. This suggests the anticancer action of Inophyllum A in *Calophyllum inophyllum* roots is a potential inducer of intrinsic apoptosis pathway in chemotherapy [25].

3.6. Neuropharmacological Properties

According to the experiments in rodent models, the leaf extract of *Calophyllum inophyllum* sedative and anxiogenic effects on the nervous system. The administration of 100 and 200 mg/kg of the extract significantly reduced head dips frequency in the hole board test on the animals. It prolonged the duration spent in the dark arena in the light and dark box test. In open field test, the total locomotion was reduced by the extract intake, the rearing and the grooming frequencies were decreased and the duration spent in closed arm was prolonged significantly as compared with control [26].

Different xanthones of *Calophyllum inophyllum* – euxanthone, mesuaxanthone-A, B, 6-desoxy jacerubin, jacareubin, calophyllin-B, dehydroxycycloguanandin can exert CNS depressant property with ptosis, decline in motor activity, sedation, muscle tone loss, enhanced sleeping time and ether anesthesia in animal models. However, these compounds lack analgesic, anticonvulsant and antipyretic properties [27]. Yet, the methanol extract of *Calophyllum inophyllum* stem barks has analgesic action at the dose of 100mg/kg and 200mg/kg in mice [15].

3.7. Lipid-Lowering Property

Diastereomeric mixture calphyllic acid and isocalophyllic acid, 3-oxofriedelin-28-oic acid, canophyllic acid, amentoflavone, shikimic acid inophyllum C and inophyllum E present in the leaves of *Calophyllum inophyllum* have different lipid lowing activities on plasma cholesterol, triacylglycerol and phospholipids [28].

3.8. Antioxidant Property

The reducing power and DPPH (diphenyl picrylhydrazyl) free radical scavenging power of the methanol extract of the leaves are more potent than those of aqueous extract. Total phenol concentrations of methanol and aqueous extracts of the leaves are 140 ± 17 and 97 ± 9 mg/g respectively.

Methanol and aqueous extracts contains flavonoid contents of 177 ± 5 and 89 ± 3 mg/g respectively [29].

Calphyllic acid and isocalophyllic acid, canophyllic acid present in the leaves of *Calophyllum inophyllum* have antioxidant property at 200 µg/ml concentration. They are able to scavenge hydroxyl radicals and superoxide anions and suppress malondialdehyde production [28]. Delta-tocotrienol contributes to 236 mg/kg of kernel oil of *Calophyllum inophyllum* [30]. This may also prevents free radical chain reactions of lipid peroxidation preventing the generation of harmful peroxide radicals.

3.9. Antiviral Property

Dipyranocoumarins – calophyllolide, inophyllums B, C, G, and P present in the seeds and leaves of *Calophyllum inophyllum* have non-nucleoside reverse transcriptase inhibitory effect which may contribute to the development of new drugs for retroviral infections [31, 31]. Inophyllums B and P inhibit reverse transcriptase with IC50 being 38 and 130 nM respectively. HIV-1 grown in cultures also sensitive to these inophyllums [33-35].

3.10. Antidiabetic Property

The potential antidiabetic effects of *Calophyllum inophyllum* are of two mechanisms. The first one is inhibition of α-glucosidase enzyme required for intestinal absorption of dietary glucose and the second one, the reduction of insulin resistance in peripheral tissues particularly the skeletal muscles [8, 36-37]. The bark and leaves of *Calophyllum inophyllum* contain numerous flavonoids and coumarins – inophyllum D, H, calanone, isocordato-oblongic acid, amentoflavone, carpachromene and lupenone, all of which inhibit α-glucosidase enzyme [8].

The diastereomeric mixture of Calophyllic acid and isocalophyllic acid (F015) extracted from *Calophyllum inophyllum* leaves reduces insulin resistance by enhancing glucose uptake in skeletal muscle cells. The mechanism is via the activation of phosphatidylinositol-3-kinase (PI3K) and extracellular signal-regulated kinases 1 and 2 (ERK1/2) without the involvement of 5'AMP-activated kinase (AMPK) (Prasad et al, 2013). F015 also reduces palmitate-induced insulin resistance by reversal of insulin-stimulated phosphorylation of IRS-1, AKT and GSK-3β. FO15 inhibits the generation of reactive oxygen species and associated inflammation induced by fatty acid by downregulating JNK, ERK1/2 and p38 MAPK. F015 prevents against inflammation-stimulated IRS-1 serine phosphorylation and reverses insulin-stimulated IRS-1 tyrosine kinase leading to promoting insulin sensitivity [37].

4. Conclusion

Different parts of *Calophyllum inophyllum* tree have certain pharmacological properties – osteogenic, anti-inflammatory, wound healing, antibacterial, antifungal, anticancer, lipid-lowering, antioxidant, neuropharmacological and antidiabetic effects. The bioactive compounds have been identified, leading towards the development of new potent drugs for common diseases.

Conflict of Interest

The author declares there is no conflict of interest.

References

[1] Ha MH, Nguyen VT, Nguyen KQC, Cheah ELC, Heng PWS. Antimicrobial activity of *Calophyllum inophyllum* crude extracts obtained by pressurized liquid extraction. Asian Journal of Traditional Medicines. 2009; 4(4): 141-6.

[2] Liu WH, Liu YW, Chen ZF, Chiou WF, Tsai YC, Chen CC. Calophyllolide content in *Calophyllum inophyllum* at different stages of maturity and its osteogenic activity. Molecules. 2015 July; 20(7): 12314-27.

[3] Perumal SS, Ekambaram SP, Dhanam T. In vivo antiarthritic activity of the ethanol extracts of stem bark and seeds of *Calophyllum inophyllum* in Freund's complete adjuvant induced arthritis. Pharm. Biol. 2017 Dec; 55(1): 1330-1336.

[4] Tsai SC, Liang YH, Chiang JH, Liu FC, Lin WH, Chang SJ, Lin WY, Wu CH, Weng JR. Anti-inflammatory effects of *Calophyllum inophyllum* L. in RAW264.7 cells. Oncol Rep. 2012 Sep; 28(3): 1096-102.

[5] Zakaria MB, Vijayasekaran, Llham Z, Muhamad NA. Anti-inflammatory activity of *Calophyllum inophyllum* fruits extracts. Procedia Chemistry. 2014 Dec; 13: 218-220.

[6] Ee GC, Mah SH, Rahmani M, Taufiq-Yap YH, Teh SS, Lim YM. A new furanoxanthone from the stem bark of *Calophyllum inophyllum*. J Asian Nat Prod Res. 2011 Oct; 13(10): 956-60.

[7] Nguyen VL, Truong CT, Nguyen BCQ, Vo TV, Dao TT, Nguyen VD, Trinh DT, Huynh HK, Bui CB. Anti-inflammatory and wound healing activities of calophyllide isolated from *Calophyllum inophyllum* Linn. PLoS One. 2017 Oct; 12(10): e0185674.

[8] Aminudin NI, Ahmad F, Taher M, Zulkifli RM. α-glucosidase and 15-lipoxygenase inhibitory activities of phytochemicals from *Calophyllum inophyllum*. Nat Prod Commun, 2015 Sep; 10(9): 1585-7.

[9] Said T, Dutot M, Labbe A, Warnet JM, Rat P. Ocular burn: rinsing and healing with ionic marine solutions and vegetable oils. Ophthalmologica. 2009; 223(1): 52-9.

[10] Leguillier T, Lecso-Bornet M, Lemus C, Rousseau-Ralliard D, Lebouvier N, Hnawia E, Nour M, Aalbersberg W, Ghazi K, Raharivelomanana P, Rat P. The wound healing and antibacterial activity of five ethnomedical *Calophyllum inophyllum* oil: an alternative therapeutic strategy to treat infected wound. PLoS One. 2015 Sep; 10(9): e0138602.

[11] Ansel JL, Lupo E, Mijouin L, Guillot S, Butaud JF, Ho R, Lecellier G, Raharivelomanana P, Pichon C. Biological activity of Polynesian *Calophyllum inophyllum* oil extract on human skin cells. Planta Med. 2016 Jul; 82(11-12): 961-6.

[12] Bhat SG, Kane JG, Sreenivasan A. The in Bitro evaluation of the antibacterial activity of undil oil (*Calophyllum inophyllum* linn.). Journal of the American Pharmaceutical Associaiton. 1954 Sep; 43(9):

[13] Potti GR, Kurup PA. Anti-bacterial principle of the root bark of *Calophyllum inophyllum*: isolation and antibacterial activity. Indian Journal of Experimental Biology. 1970; 8(1): 39-40.

[14] Yimdjo MC, Azebaze AG, Nkengfack AE, Meyer AM, Bodo B, Fomum ZT. Antimicrobial and cytotoxic agents from *Calophyllum inophyllum*. Phytochemistry. 2004 Oct; 65(20): 2789-95.

[15] Mishra US, Murthy N, Choudhury PK, Panigrahi G, Mohapatra S, Pradha D. Antibacterial and analgesic effects of the stem barks of *Calophyllum inophyllum*. International journal of ChemTech Research. 2010 Apri-June; 2(2): 973-979.

[16] Ali M, Mahmud S, Perveen S, Rizwani GH, Ahmad VU. Screening for the antimicrobial properties of the leaves of *Calophyllum inophyllum* Linn. (Guttiferae). Jour. Chem. Soc. Pak. 1999; 21(2): 195-198.

[17] Xiao Q, Zeng YB, Mei WL, Zhao YX, Deng YY, Dai HF. Cytotoxic prenylated xanthones from *Calophyllum inophyllum*. J Asian Nat Prod Res. 2008 Sep-Oct; 10(9-10): 993-7.

[18] Said T, Dutot M, Martin C, Beaudeux JL, Boucher C, Enee E, Baudouin C, Warnet JM, Rat P. Cytoprotective effect against UV-induced DNA damage and oxidative stress: role of new biological UV filter. Eur J Pharm Sci. 2007 Mar; 30(3-4): 203-10.

[19] Itoigawa M, Ito C, Tan HT, Kuchide M, Tokuda H, Nishino H, Furukawa H. Cancer chemopreventive agents, 4-phenylcoumarins from *Calophyllum inophyllum*. Cancer Lett. 2001 Aug; 169(1): 15-9.

[20] Mah SH, Ee GC, The SS, Sukari MA. *Calophyllum inophyllum* and *Calophyllum soulattri* source of anti-proliferative xanthones and their structure-activity relationships. Nat Prod Res. 2015; 29(1): 98-101.

[21] Dai HF, Zeng YB, Xiao Q, Han Z, Zhao YX, Mei WL. Caloxanthones O and P: two new prenylated xanthones from *Calophyllum inophyllum*. Molecules. 2010 Jan; 15(2): 606-12.

[22] Li YZ, Li ZL, Yin SL, Shi G, Liu MS, Jing YK, Hua HM. Triterpenoids from *Calophyllum inophyllum* and their growth inhibitory effects on human leukemia HL-60 cells. Fitoterapia. 2010 Sepl 81(6): 586-9.

[23] Shanmugapriya, Chen Y, Kanwar JR, Sasidharan S. Anticancer activity and molecular mechanism of polyphenol rich *Calophyllum inophyllum* fruit extract in MCF-7 breast cancer cells. Nutr Cancer. 2017 Nov-Dec; 69(8): 1308-1324.

[24] Hsieh C, Lin YW, Chen CH, Ku W, Ma F, Yu H, Chu C. Yellow and green pigments from *Calophyllum inophyllum* L. seed oil induce cell death in colon and lung cancer cells. Oncol Lett. 2018 Apri; 15(4): 5915-5923.

[25] Chan KM, Hamzah R, Rahaman AA, Jong VY, Khong HY, Rajab NF, Ee GC, Inayat-Hussain SH. The pyranoxanthone Inophyllin A induces oxidative stress mediated apoptosis in Jurkat T lymphoblastic leukemia cells. Food Chem Toxicol. 2012 Aug; 50(8): 2916-22.

[26] Ibironke GF, Ugege OG. Neurobehavioural activities of the ethanol leaf extract of *Calophyllum inophyllum* in rodents.

[27] Gopalakrishnan C, Shandaranarayanan D, Nazimudeen SK, Viswanatha S, Kameswaran L. Anti-inflammatory and C. N. S. depressant activities of xanthones from *Calophyllum inophyllum* and Mesua ferrea. Indian Journal of Pharmacology. 1980; 12(3): 181-191.

[28] Prasad J, Shrivastava A, Khanna AK, Bhatia G, Awasthi SK, Narender T. Antidyslipidemic and antioxidant activity from the leaves of *Calophyllum inophyllum*. Phytomedicine. 2012 Nov; 15; 19(4): 1245-9.

[29] Dutta S, Ray S. Evaluation of antioxidant potentials of leaf aqueous and methanolic extracts of 140 ± 17 and 97 ± 9 mg/g respectively in relation to total phenol and flavonoid contents. Int J Pharm Bio Sci. 2014 July; 5(3): 411-450.

[30] Crane S, Aurore G, Joseph H, Mouloungui Z, Bourgeois P. Compostion of fatty acids triacylglycerols and unsaponifiable matter in *Calophyllum calaba* L. oil from Guadeloupe. Phytochemistry. 2005 Aug; 66(15): 1825-31.

[31] Laure F, Raharivelomanana P, Butaud JF, Bianchini JP, Gaydou EM. Screening of anti-HIV-1 inophyllums by HPLC-DAD of *Calophyllum inophyllum* leaf extracts from French Polynesia Islands. Anal Chim Acta. 2008 Aug; 624(1): 147-53.

[32] Pawar KD, Joshi SP, Bhide SR, Thengane SR. Pattern of anti-HIV dipyranocoumarin expression in callus cultures of *Calophyllum inophyllum* Linn. J Biotechnol. 2007 Jul; 130(4): 346-53.

[33] Patil AD, Freyer AJ, Eggleston DS, Haltiwanger RC, Bean MF, Taylor PB, Caranfa MJ, Breen AL, Bartus HR, Johnson RK, et al. The inophyllums, novel inhibitors of HIV-1 reverse transcriptase isolated from the Malaysian tree, *Calophyllum inophyllum* Linn. J Med Chem. 1993 Dec; 36(26): 4131-8.

[34] Spino C, Dodier M, Sotheeswaran S. Anti-HIC coumarins from Calophyllum seed oil. Bioorganic & Medicinal Chemistry Letters. 1998; 8: 3475-3478.

[35] Taylor PB, Culp JS, Debouck C, Johnson RK, Patil AD, Woolf DJ, Brooks I, Hertzberg RP. Kinetic and mutational analysis of human immunodeficiency virus type 1 reverse transcriptase inhibiton by inophyllums, a nobel class of non-nucleoside inhibitors. J Biol Chem. 1994 Mar; 269(9): 6325-31.

[36] Prasad J, Maurya CK, Pandey Jm Jaiswal N, Madhur G, Srivastava AK, Narender T, Tamrakar AK. Diastereomeric mixture of calophyllic acid and isocalophyllic acid stimulates glucose uptake in skeletal muscle cells: involvement of PI-3-kinase- and ERK1/2 dependent pathways. Mol Cell Endocrinol. 2013 May; 370(1-2): 11-9.

[37] Jaiswai N, Guanaganti N, Maurya CK, Narender T, Tamrakar AK. Free fatty acid induced impairment of insulin signaling is prevented by the diastereomeric mixture of calophyllic acid and isocalophyllic acid in skeletal muscle cells. Eur J Pharmacol. 2015 Jan; 746: 70-7.