ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 7, Suppl 1, 2014

ISSN - 0974-2441

Review Article

Pupalia Lappacea Juss [L]: A REVIEW OF PHYTOCHEMISTRY AND THERAPEUTIC APPLICATION

PRASAD. P. NAIDU, Dr. M. MADAKKA*, BANDI RAJESH

Department of Biotechnology and Bioinformatics, Yogi Vemana University, Kadapa-516003, Andhra Pradesh, India.
Email: madakka@gmail.com

Received: 7November 2013, Revised and Accepted: 5 December 2013

ABSTRACT

Pupalia lappacea containing diverse group of phytochemicals, namely; 1- docosa-nol, stearic acid, stigamasterol, β-sitosterol, saropeptate (N-benzoyl-L-Phyenylalaninol acetate), β-sitosterol-3-0-D–glucopyranoside, Stigmasterol-3-0-β-D-glucopyra-noside and 20 – hydroxylecdysone are known to have potential therapeutic application. In folklore and ayurvedic medicine, it has been used to treat wounds, bone fractures, boils, cough, toothache, fever and malaria, diarrhea, urethra pain, leucorrhoea and many other disorders. Invivo Clinical studies showed that ethanolic extracts of *Pupalia lappacea* have anticioceptive, antipyretic, anti-inflammatory properties. Invitro experimental studies had revealed that *Pupalia lappacea* exhibits antioxidant and anticancer properties. Clinical studies should be initiated to generate novel drugs and to prove its immense therapeutic efficacy as a potent phytomedicine.

Keywords: *Pupalia lappacea,* Anticancer, Anticioceptive, Phytomedicine.

INTRODUCTION

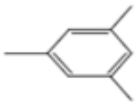
A member of Amaranthaceae family, *Pupalia lappacea* is also known as forest burr or creeping cock's comb. It is a perennial herb, erect or prostrate and sprawling, 60-90cm tall. It is found in the hedges of fields, fruit orchard, dry scrub forests and waste places of Kashmir to kaunanat an altitude of 300-1050m and in all states of India [1].

Taxonomy
Kingdom: Plantae
Phylum: Magnoliophyta
Class: Magnoliopsida
Order: Caryophyllales
Family: Amaranthaceae
Genus: Pupalia
Species: lappaceae

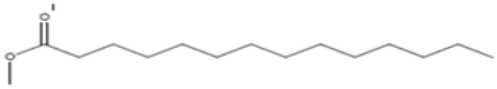
In folklore and ayurvedic medicine, *Pupalia lappacea* is one of the earliest documented examples of plants employed for treatment of disease and maintenance of health. Decotion of *Pupalia lappacea* in water is used by the people of Nigeria republic in the treatment of urethra pain, endometritis, cystitis and leucorrhoea [2] and as laxative, purgative in Tanzania [3]. The people of the northern region of Kenya used the whole plant in the treatment of skin diseases in human goat and as a tonic, restorative, stimulant and in performance improvement [4]. The leaf paste of *Pupalia lappacea* with seasamum or carthamus oil is an effective and inexpensive treatment of bone fracture for human being as well as cattle [5] and inflammatory condition. Stem is used as tooth brush for treating toothache [6]. A decotion of the black powder of plant is drunk to cure piles and for enema, fever and malaria [7]. The dried leaves and fruit are powdered and dusted on sores as a medicine. Roots boiled in water and the infusion is drunk three times a day for Syphilis [8]. For instance, it is used as anti vomitory, anti emetic and antalgic in the south western part of Nigeria and the republic of Benin [2] and as antisterility plant for promoting reproduction in bukjina fasa [9]. Phytochemical investigations revealed the presence of sterols, alkaloids, saponins, glycosides and ecdysterone from different parts of the plant. Recent in vitro and in vivo experimental studies reported the wide range of therapeutic applications of *Pupalia lappacea.* Advances in science tends to confirm many of the therapeutic applications of *Pupalia lappacea* reported in folklore medicine by defining mechanisms of action and exploring its potential for disease prevention and treatment. Hence, the main objective of present review is to examine the phytochemistry and therapeutic applications of *Pupalia lappacea* and its role in disease treatment.

PHYTOCHEMISTRY

Plants are a natural source of biologically active compounds known as phytoconstituents [10, 11]. Preliminary analysis of *Pupalia lappacea* for chemical constituents showed the presence of alkaloids, amino acids, glycosides, flavanoids, glycosides, saponins, tannins, starch, steroids, terpenoids and coumarins. GC-MS Analysis of ethanolic extracts of *Pupalia lappacea* reported the presence of various phytochemicals [12] (Figure 1). Phytochemical analysis of foliage of *Pupalia lappacea* by TLC and NMR Spectroscopy afforded 8 compounds, namely; 1- docosa-nol, stearic acid, stigamasterol, β-sitosterol, saropep-tate (N-benzoyl-L-Phyenylalaninol acetate), β-sitosterol-3-0-D–glucopyranoside, Stigmasterol-3-0-β-D-glucopyra-noside and 20 – hydroxylecdysone [13].



Benzene, 1,3,5- trimethyl-
(Synonyms: Mesitylene)



Methyl tetradecanoate

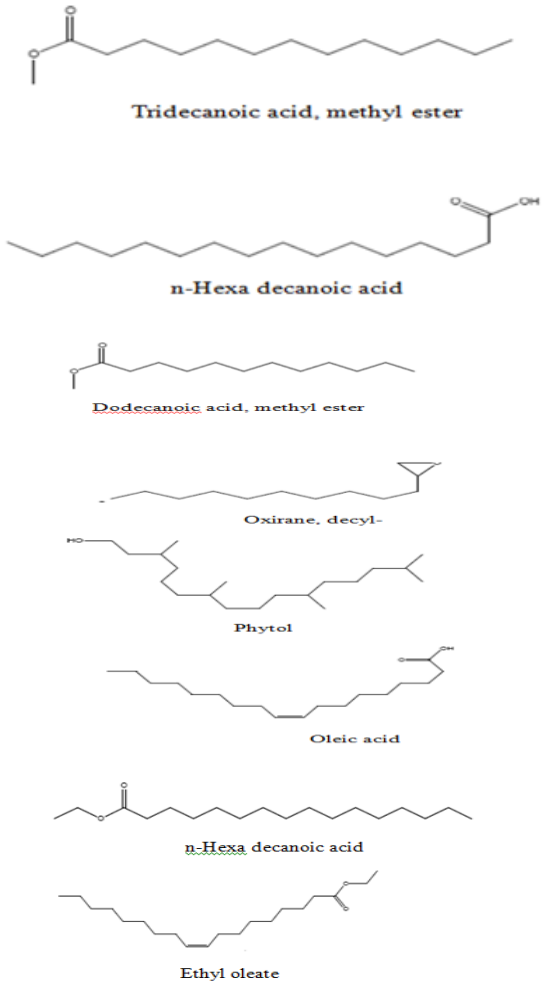


Figure 1: GC-MS Analysis on EEPL-Chemical Compounds [12].

THERAPEUTIC APPLICATIONS

Antinociceptive activity

Nociception is defined as "the neural processes of encoding and processing noxious stimuli" [14]. It is the afferent activity produced in the peripheral and central nervous systems by stimuli that have the potential to damage tissue [15]. The receptors involved in pain detection are aptly enough referred to as nociceptors - receptors for noxious stimuli. These nociceptors are free nerve endings that terminate just below the skin as to detect cutaneous pain. Nociceptors are also located in tendons and joints, for detection of somatic pain and in body organs to detect visceral pain. Common examples of nociceptive pain include brain fractures, burns, bumps, inflammation, bruises, obstructions, myofascial pain.

Aqueous ethanolic extracts of aerial parts of *P. lappacea* were evaluated for their central and peripheral antinociceptive activity in male Swiss albino mice by using hot plate test and acetic acid induced writhing test respectively. Aqueous ethanolic extracts were administered orally at the dosage levels of 200, 300, 400 mg/kg of body weight in mice. The effect produced was in dose dependent manner. The extract has significantly reduced number of writhes at an oral dose of 600 mg/kg with percentage of inhibition of 64.75 which comparable with aspirin standard with percentage of inhibition of 75.0. Hot plate method showed an increase the latency period and has produced maximum latency time at 90 min which is not comparable with morphine standard because it has maximum latency at 120min after treatment. Involvement of opioid receptors in antinociception were analyzed by pretreatment with non-selective opioid receptor antagonist naloxone and it has not antagonized the analgesic effect of the extract but reduced the latency period suggesting that analgesic effect of the extract of *P. lappacea* might involve opioid receptors [16].

Anti-oxidant activity

Reactive oxygen species (ROS) like hydrogen peroxide, superoxide anions, hydroxyl radicals, nitric oxide and peroxynitrite radicals, play an important role in oxidative stress related to the pathogenesis of various types of diseases [17] including cancer, aging, heart disease, arthritis, Alzheimer's, Parkinson's disease. They cause cell mutations, damage immune cells and wipe out cytokine pathways, wrinkles by oxidative damage of DNA, proteins, Lipids. Free radicals contain an unpaired electron that desperately wants to pair with another electron by sharing from neighboring molecule. This can set off a chain reaction that wrecks havoc on cells. The antidote to free radicals is the antioxidant.

The antioxidant potential of n-hexane and dichloromethane extracts of *P. lappacea* was evaluated by using in vitro DPPH scavenging assay. All concentrations studied showed free radical scavenging activity, with dichloromethane exhibiting significant antioxidant activity (IC_{50}-0.029mg/ml) comparable to BHT (IC_{50}-0.018mg/ml), a synthetic antioxidant [12].

Anti inflammatory activity

Anti-inflammatory drugs are used to reduce inflammation and to ease pain in various conditions including joint pains, muscle pains, period pains, and pains after operations etc. They work by blocking the effect of cyclooxgenase (COX), a key enzyme in prostaglandins synthesis. Current evidence indicates that selective COX inhibitors have important adverse cardiovascular effects that include increased risks for myocardial infarction, stroke, heart failure and hypertension. These side effects can be minimized by using ayurvedic drugs which are available in the naturals.

Anti-inflammatory activity of ethanolic extract of leaves of *Pupalia lappaceae* were evaluated in Wistar strain rats by using different methods such as carrageenan, cotton pellet, croton oil, histamine and serotonin induced oedema. Different doses (100 and 300 mg/kg/i.p.) of Ethanolic Extracts of P. lappaceae (EEPL) was injected to rats and the results compared with standard drug indomethacin (10 mg/kg). Paw volume was measured using digital plethysmometer. The EEPL showed the maximum inhibitory activity at 300 mg/kg/i.p. in a dose dependent manner. These inhibitions were statistically significant ($p<0.01$-0.001). These results indicated that EEPL is a bioactive agent and having significant results in anti-inflammatory action by inhibition of the exudation, and leukocytes recruitment into the inflamed tissues [13].

Anticancer Activity

Cancer is the result of abnormal proliferation of cells without differentiation and apoptosis. To increase the use of bioactive supplements as chemoprevention or adjuvant drug in cancer treatment, it is necessary to verify their biological effect and correlative mechanisms. The antitumor activity of medicinal plant derived compounds may result from a number of mechanisms, including perturbations in cell cycle progression, induction of G2/M phase arrest and induction of apoptosis. Cell cycle consists of a series of events involving growth stimulus, replication and division of a eukaryotic cell. Cellular stresses may activate signal transduction pathways referred to as checkpoints which lead to cell cycle arrest. The cell cycle checkpoints ensure completion of phase specific events and protect against genomic stability or in cases where the damage is too severe, switch the cell fate to programmed cell death [18, 19]. Many anticancer treatments initially cause perturbations in the cell cycle progression and the interrupted phase depends on the genetic background of the cell as well as the mode of action of given treatment.

Apoptosis is a tightly controlled and evolutionary conserved process of cellular suicide critical to normal embryonic development and maintenance of tissue homeostasis. Dysregulation of apoptosis underlies various pathological conditions including cancer and therefore programmed cell death is a valid target in cancer therapy

and prevention [20]. The demise of cells by apoptosis is marked by a well defined sequences of morphological and biochemical changes. Morphologically, Apoptotic cells become more compact, blebbing occurs at the membrane, chromatin become condensed and DNA is fragmented. Redistribution of phosphatidyl serine to the external side of the membrane occurs due to perturbation in the cellular membrane is one of the biochemical feature of apoptosis [21]. Early stages of apoptosis are associated with loss of mitochondrial membrane potential leading to release of cytochrome in to cytosol. Cytochrome interacts with Apaf-1, dATP/ATP and procaspase-9 to a form a complex known as apoptosome which in turn activates caspase-3 and caspases-7. Caspases-3 inactivates PARP by cleaving it in to 85KDa and 24KDa fragment and thereby preserves ATP resources of the cell for apoptosis [22]. Apoptotic regulatory proteins comprise both anti-apoptotic (Bcl-2, Bcl-x) and Pro-apoptotic members (Bad, Bax, Bik). Both Bax and Bcl2 are transcriptional targets of p53 [23], which specifically inhibit Proliferating cell nuclear antigen (PCNA), the marker of dividing cell [24, 25]. Dichloromethane extracts of aerial parts of *Pupalia lappaceae* has shown cytotoxic effects on J774 and W138 cells with an IC_{50} value of 66.5±13.3 and 68.3±4.9 respectively [26]. Whole plant extracted in ethanol was found to have low cytotoxic activity on HeLa Cervical cancer cells [27]. More recent studies have revealed that aqueous ethanolic extracts of *Pupalia lappaceae* (EAPL) have anticancer activity with an IC_{50} value of 40±0.01µg/ml and are capable of inducing apoptosis in chronic myeloid leukemia (K562) cells. EAPL also demonstrated the molecular mechanisms underlying apoptosis like morphological and biochemical changes, activation of p53, cell cycle arrest at s phase, increase in annexin V (recombinant phosphatidylserine binding protein) positive cells, increase Bax/Bcl2 ratio, decrease in mitochondrial membrane potential, increase in cytochrome release from mitochondria, increase in caspase activity, cleavage of PARP and inhibition of PCNA in a dose dependent manner [28].

MISCELLANEOUS

The plant has been reported to have antiplasmodial & antipyretic activity. Dichloromethane extracts of *P. lappaceae* has shown moderate antiplasmodic activity (IC_{50}-50.29 µg/ml) against *P. falciparum* [26]. Ethanolic extracts of *P. lappaceae* was found to reduce the yeast elevated rectal temperature in a dose dependent manner and the effect was comparable to that of standard paracetmol [16].

CONCLUSION

Photochemical and pharmacological investigations carried over past few years on *P. lappaceae* reveals its multidisciplinary usage as phytomedicine. Phytochemical screening of *P. lappaceae* revealed the presence of steroids, terpenoids, flavanoids and phenolic compounds which may be responsible for its potential therapeutic application. Documented evidences in folklore and ayurvedic medicine have reported its use in pain relief. Chemotherapeutic agents used to treat various malignancies particularly anthracycline group exhibit cardiotoxicity. Massive stimulation of reactive oxygen species is responsible for it. Hence, *P. lappaceae* with antioxidant potential, then administered with antitumour drugs, could reduce the side effects of chemotherapy, and lower the risk of cardiotoxicity. Recent studies has revealed that ethanolic extracts of *p. lappaceace* target multiple pathways to inhibit growth of cancer cells which includes cell cycle arrest and induction of apoptosis.

Future research should focus on (a) Next level investigations involving modern techniques like HPTLC, GC, NMR must be carried out in order to isolate and elucidate the active principles present in different fractions. (b) Preclinical and clinical assessment of these compounds for prevention and treatment for cancers. (C) Pharmacokinetics and pharmacodynamics in humans. This might prove helpful to use its immense therapeutic efficacy as a potent phytomedicine.

REFERENCES

1. Anonymous. The Wealth of India: A Dictionary of Indian raw materials and industrial products. Council of Scientific and Industrial Research, New Delhi, India 1950; 3, p. 324.
2. Adjanohoun EJ, Adjakidje V, Ahyi MRA. Contribution aux etudes ethnobotaniques et floristiques en République Populaire du Bénin. Médecine traditionnelle et pharmacopée. Agence de Coopération culturelle et technique, Cotonou 1989; p.695.
3. Kokwaro JO. Medicinal plants of east Africa. East African literature bureau, Kampala, Nairobi. Da Es Salaam 1976; p.175.
4. Timberlake JR. Ethnobotany of the pokot of northern Kenya. Unpublished report, East African Herbarium Nairobi Multigraphite 1987; p.96.
5. Rao PP and Reddy RP. A note on folklore treatment of bone fracture from Ranga Reddy District, Andhra Pradesh. Ethnobotany 1999; 11:107-108.
6. Reddy SC, Reddy KN, Murthy EN and Raju US. Traditional Medicinal plants in Seshachalam Hills, Andhra Pradesh, India. Journal of medicinal plants research 2009; 3: 408-412.
7. Ndjonka D, Agyare C, Luersen K, Hensel A, and Liebau E. In-vitro Antileishmanial activity of traditional medicinal plants from Cameroon and Ghana. International Journal of Pharmacology 2010; 6:863-871.
8. Kokwaro JO. 2009. Plant species and diseases treated: Medicinal plants of east Africa. 3rd ed. 2009; p: 37.
9. Fernandez de la Pradilla C. Des Plantes qui nousont gueris. Japanese d' Afrique. Ouagadougous, Bukina Faso, Tome 1989; 1:208.
10. Shrivastav S, Sindhu R, Kumar S, Kumar P. Anti-psoriatic and phytochemical evaluation of Thespesia populnea bark extract, Int. J. Pharm. Pharm. Sci 2009; 1: 176-185
11. Rakesh K Sindhu, Sandeep Arora. Free radical scavenging and antioxidant potential of *ficus lacor* buch. Hum, Asian J Pharm Clin Res, 2013; 6 : 184-186
12. Rajesh Pandiyan, Latha Subbiah, Selvamani Palaniswamy, Saraswathy Ariyamuthu, Thambidurai Muthuswamy, Rajesh kannan Velu. A wide array on anti-inflammatory study in an ethanolic extracts of Pupalia lappaceae juss. (Amaranthaceae) by using wistar rats, Scholars Research Library. Archives of Applied Science Research 2009; 1(2): 150-158.
13. Felix AA and Domingo O. Antioxidant activity and chemical constituents of *P. lappacea* (L) Juss. Research Journal of Biological Sciences 2008; 3:783-785.
14. Loeser JD, Treede RD. The Kyoto protocol of IASP Basic Pain Terminology. Pain 2008; 137(3): 473-7.
15. Portenoy Russell K, Brennan Michael J. Chronic Pain Management. In Good, David C, Couch, James R. *Handbook of Neurorehabilitation*. Informa Healthcare 1994.
16. Vajrala Neeharika, Humaira Fatima, Bommineni Madhava Reddy. Evaluation of antinociceptive and antipyretic effect of Pupalia lappacea Juss, International Current Pharmaceutical Journal, January 2013; 2(2): 23-28
17. Abirami MS, Muthuswamy. Antioxidant potential, total phenolic and total flavonoids content of various extracts from whole plant of *Polycarpaea corymbosa* lam. Asian J Pharm Clin Res 2013; 6: 121-124.
18. Molinari M. Cell cycle checkpoints and their inactivation in human cancer. Cell Prolif 2000; 33: 261–74.
19. Murray AW. Recycling the cell cycle: cyclins revisited. Cell 2004; 116: 221–34
20. Kaufmann SH, Gores GJ. Apoptosis in cancer: cause and cure. Bioessays 2000; 22: 1007–17.
21. Bratton DL, Fadok VA, Richter DA, Kailey JM, Guthrie LA, Henson PM: Appearance of phosphatidylserine on apoptotic cells requires calcium-mediated nonspecific flip-flop and is enhanced by loss of the aminophospholipid translocase. J Biol Chem1997; 272: 26159–26165.
22. Saraste A, Pulkki K. Morphologic and biochemical hallmarks of apoptosis. Cardiovasc Res2000; 45:528–537.

23. Chipuk JE, Green DR. Cytoplasmic p53: bax and forward.Cell Cycle2004, 3:429–431.
24. Mercer WE, Shields MT, Lin D, Appella E, Ullrich SJ:Growth suppression induced by wild-type p53 protein is accompanied by selective down-regulation of proliferating-cell nuclear antigen expression. Proc Natl Acad Sci USA 1991, 88:1958–1962.
25. Jackson P, Ridgway P, Rayner J, Noble J, Braithwaite A. Transcriptional regulation of the PCNA promoter by p53.Biochem Biophys Res Commun 1994; 203:133–140.
26. Joanne Bero, Habib Ganfon, Marie-Caroline Jonville, Michel Frédérich, Fernand Gbaguidi, Patrick DeMol, Mansourou Moudachirou, Joelle Quetin-Leclercq. In vitro antiplasmodial activity of plants used in Benin in traditional medicine to treat malaria, Journal of Ethnopharmacology 2009; 122:439–444.
27. A Sowemimo, M van de Venter, L Baatjies, T Koekemoer. 2009. Cytotoxic activity of selected Nigerian plants. Afr. J. Trad. CAM 2009; 6 (4): 526 – 528.
28. Alvala Ravi, Mallika Alvala, Venkatesh Sama, Arunasree M Kalle, Vamshi K Irlapati, B Madhava Reddy. Anticancer activity of Pupalia lappacea on chronic myeloid leukemia K562 cells, DARU Journal of Pharmaceutical Sciences 2012; 20: 86-96.