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DIOSPYROS MELANOXYLON ROXB IN CANCER PREVENTION: PHARMACOLOGICAL SCREENING, PHARMACOKINETICS AND CLINICAL STUDIES

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ABSTRACT: Plants contain a galaxy of phytoconstituents which accounts for their remedial worth. This plant has been used expansively for its medicinal value all over the world. Different plant parts have been used for its different pharmacological screening, including cancer therapy and leaves can be wrapped to create the "beedi" filled with tobacco which has outsold conventional cigarettes in India. Extraction of plant material with organic solvent and elucidation of pure compounds using a different technique with the different solvent system are an extremely imperative limitation. Elucidation of pentacyclic triterpenoid, ursolic acid from *D. melanoxylon* and molecular mechanisms has vast chances for the development of enhanced therapy for different diseases, including cancer, and clinical studies. Our extensive intention of this study is to give a general delineate on the thyme *D. melanoxylon* and its cancer prevention potential, diverse pharmacological action, ethnomedicinal uses, and chemical compounds. We also focus the extraction methodology, elucidation, pharmacokinetic and various clinical trials of ursolic acid chiefly obtained from *D. melanoxylon*.

INTRODUCTION: *Diospyros melanoxylon* Roxb. is numerically and economically the most important genus of Ebenaceae. Concerning 500 species are prevalent primarily of the family Ebenaceae in tropics and subtropics. *D. melanoxylon* is flowering tree known as Coromandel Ebony or East Indian Ebony. It is an inhabitant of India and Sri Lanka that has a hard, and dry bark.

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In the vicinity, it is identified as temburini or tendu in Hindi. In Odisha, West Bengal and Jharkhand it is well-known as kendu. Kendu is a middle-sized tree, height up to 10 -15 feet, branchlets, and young leaves, inflorescence clothed with a soft grey or tawny tomentum. Leaves are mostly sub-opposite, coriaceous, 3 - 6 inches long but sometimes much longer up to 12 inches, when fully grown glabrous above, tomentose or pubescent beneath [1].

It is very famous for making 'beedi' which has considered conformist cigarettes in India [2]. It is very well known as medicinal herbs which have been widespread in the world for diverse diseases having the less adverse effect and extra beneficial consequence [3-7]. It is anticipated for 184 countries of the world exposed that there were 14.1 million

fresh cancer cases, 8.2 million cancer deaths, and 32.6 million people existing with cancer (within 5 years of analysis) in 2012 globally according to The International Agency for Research on Cancer [8]. Next, to 2030, it is expected that in attendance will be 26 million new cancer cases and 17 million cancer deaths per year [9].

At present, in spite of substantial labors, unmoving cancer ruins as a violent murderer globally. Furthermore, throughout the previous decade, new synthetic chemotherapeutic substances at present to utilizing clinically have not thrived in satisfying prospects in spite of the substantial price of their progress. Thus there is a stable insist on expanding novel, efficient, and reasonable anticancer medicines [10]. Beginning the prehistoric drug, human diseases can be treated using chemical compounds obtained from plants. Herbal medicines have established rising awareness over the past 30 years for their possible as a new cancer preventive and healing mediators [11, 12]. At the same time, there is rising proof for the possibility of plant-derived compounds as inhibitors of different phases of cancer and connected inflammatory progressions, underscoring the significance of these goods in cancer prevention and treatment.

About 60% of isolated drugs from herbal medicines presently utilized for cancer treatment and the plant kingdom are the mainly momentous foundation [13]. Recently, 16 novel compounds from the plant being investigated in clinical trials. Out of them, 13 compounds are in phase I or II, and 3 compounds are in phase III. Out of these, one is *flavopiridol*, obtained from the Indian herb *Dysoxylum binectariferum*, and *meiso indigo*, obtained from the Chinese plant *Indigofera tinctoria*, have been revealed to demonstrate anticancer effects with minor toxicity compared to conventional drugs [14]. 3000 herbs have been investigated for anticancer properties and its constitute a common alternative for cancer management in several countries globally [15, 16]. In the world, about 10% to 40% of plant derived products for cancer treatment is utilizing recently and in Asiatic patients reaching about 50 % [17–19].

Kendu leaves contain valuable flavones and pentacyclic triterpene possessing antimicrobial properties [20]. The kendu bark shows antihyper-glycemic activity [21] and has important anti-plasmodial property against *Plasmodium falciparum*, which causes malaria in human beings [22]. The leaves contain ursolic acid having a beneficial effect in diverse diseases including cancer therapy. Preclinical studies of ursolic acid have plenty of proof that is naturally and synthetically occurring and having chemopreventive and therapeutic properties [23].

Our broad objective of this review is to give a general delineate on the thyme *Diospyros melanoxylon* Roxb. and their anticancer activity, ethnomedicinal uses, diverse pharmacological screening, and chemical compounds. We also converse the facts of extraction, elucidation and diverse mechanism of ursolic acid obtained from *D. melanoxylon* and its various preclinical and clinical studies.

Chemical Compounds: A chemical compound is one type of chemical substance having a distinctive chemical structure existing of two or more different chemical elements [24-26] that can be separated into simpler substances by chemical reactions [27]. Fruits of *D. melanoxylon* contain flavonoids, saponins, tannins, terpenoids, and alkaloids. Kendu leaves contain valuable flavones and pentacyclic triterpenes *viz.*, ursolic acid, lupeol, betulin, betulinic acid, α, and β amyrin, oleonic acid, and β-sitosterol. It is also posses ceryl alcohol, lupeol, betulin, sitosterol, triterpene alcohol, triterpene carboxylic acid, *i.e.* diospyric acid [1].

Extraction and Elucidation of Ursolic Acid: The main active compound of *D. melanoxylon* is ursolic acid, a pentacyclic triterpenoid, accomplished by a diversity of methods [28]. Generally, the plant material is extracted with different solvents according to increasing the polarity using a suitable extraction method. N-hexane and petroleum ether mainly used for removing waxy and fatty materials that are not required for pharmacological activity. The solvent extract is concentrated using the vacuum dryer and kept in a flask with properly sealed and stored in the refrigerator. The common method of elucidation is with organic solvent using either column chromatography, partition chromatography, solid phase extraction method, high-pressure liquid chromatography (HPLC), or high-performance thin layer chromatography

(HPTLC) after iodine derivatization [29]. For elucidation and analysis of ursolic acid, some particular methods are used like gas chromatography including the essential silylation or methylation step, liquid chromatography coupled with UV and MS spectrometry [30-33]. Then the bioactive fraction was taken for further fractionation, purification followed by elucidation. Pure ursolic acid appears in the forms of hair like needles having 284 °C melting point.

Another study was carried out with chloroform extract and subjected to column chromatography with chloroform fraction and increasing the solvent methanol. 18-20 fractions contained major compound out of 25 fractions and combined 18-20 fractions. The combined fractions were subjected for column chromatography with the solvent system ethyl acetate: chloroform (10:90) and collect fractions 4-7 (total 30 ml) having 45 mg compound which is a pale yellow powder and melting is 271-274 °C [34].

Mechanism of Action of Ursolic Acid: Formerly the compound ursolic acid has been revealed to stifle the proliferation of several tumor cells, encourage apoptosis[35] and reduce tumor promotion, metastasis, and angiogenesis [36]. It has been demonstrated to inhibit NF-κB activation induced by carcinogenic agents, like tumor necrosis factor (TNF), phorbol ester, okadaic acid, hydrogen peroxide, and cigarette smoke, through the suppression of IkBa kinase and p65/RelA phosphorylation. Besides, it suppresses constitutive and TNF-α- induced activation of NF-κB in DU145 and LNCaP cells in dose-dependent manner [37]. It downregulates the expression of various NF-κB and STAT regulated gene products involved in proliferation, survival, and angiogenesis and induced apoptosis in both cell lines [38].

It has been demonstrated to prevent the development of lung cancer by suppressing cigarette smoke extract-induced human bronchial epithelial cell injury. It suppresses constitutive NF-κB activation and down-regulation of cell survival, proliferative, and metastatic (MMP-9) proteins and induce apoptosis in colorectal cancer cells. It also has been revealed to suppress growth and induce apoptosis in gemcitabine-resistant human pancreatic cancer cells (MIA PaCa-2, PAN-1, and Capan-1) *via* modulation of the JNK and PI3K/AK/ NF-κB pathway [39]. At last, an enormous mainstream of these studies designates that ursolic acid can hinder tumor initiation, progression, and metastasis in an extensive assortment of preclinical cancer replicas.

Ethnomedicinal Uses: Day by day the demand of ethnomedicine is rising exponentially all over the world [40]. Traditionally in India, leaves of *D. melanoxylon* have been extensively used as a diuretic, styptic, laxative, carminative and ophthalmic agent asan astringent lotion. Ethnically, the bark is used as urinary discharge. Flower of *D. melanoxylon* is used in skin disease, inflammation of spleen and enrichment of blood. The seed of *D. melanoxylon* is used as a germicide and in the treatment of dysentery [41-43].

Pharmacological Screening:

Analgesic Activity: Nonsteroidal anti-inflammatory drugs (NSAIDs) trim down pain with repressing the formation of prostaglandins, by hindering the action of the enzyme Cyclo-oxygenase (COX). So, containment of fusion of prostaglandins (PGs) by NSAIDs truly lessens the fight of the mucosa to damage as well as snooping with restore developments. Selective COX-2 inhibitors were thought to be the result of this puzzle as it is obligatory that NSAIDs repress prostaglandin synthesis at sites of inflammation. It has been reported that extracts of stems bark and root bark screening for their analgesic activity by an acetic acid-induced writhing method and hot plate method, albino mice were divided into four different groups (six animals each) [44, 45]. Leaf of *D. melanoxylon* contains flavonoids having analgesic activity [46].

Anti-inflammatory Activity: Kendu leaves have valuable flavones, and pentacyclic triterpenes and flavonoids have anti-inflammatory activity [47]. Flavonoids are incredibly imperative secondary metabolite mainly inhibit the enzyme prostaglandin synthetase, additional purposely the endo-peroxidase and accounted to produce anti-inflammatory property [48]. This investigation observed that the flavonoids and pentacyclic triterpenoids of *D. melanoxylon* illustrated important anti-inflammatory activity in a dose-dependent way. This recommends that the further

experiment is carried out on this plant and their lead compounds with the vision of characterizing the potential activities.

Antiulcer Activity: Inequity among aggressive and protective factors causing gastric ulcer which is the most prevalent disease [49]. Medicine, healing of ulcers is embattled at either neutralizing aggressive factors (acid, pepsin, active oxidants, platelet aggravating factor "PAF", leukotrienes, endothelins, bile or exogenous factors including NSAIDs) or motivating the mucosal defences (mucus, bicarbonate, normal blood flow, prostaglandins (PG), nitric oxide) [50]. Pyloric ligation is one type of method mostly used for the evaluation of anti-ulcer drugs and increased the acid secretion, which in turn causes an increase in gastric volume, low pH, increased free and total acidity ensuing into an increase in ulcer index [51].

A recent investigation has been demonstrated that the anti-ulcer activity against pylorus ligation induced gastric ulcer model using a methanolic leaf extract of *D. melanoxylon*. The methanolic extract 200 mg/kg body weight reduces the ulcer index significantly ($p<0.05$) compared to control group [52]. It also lessens the total Acidity, Acidity free, and pH of the gastric content and viewing protection index 32% and 58% at the dose of 100 mg/kg and 200 mg/kg. Correspondingly, the standard drug ranitidine (50 mg/kg) proved 85% of ulcer protection.

Antihyperglycemic Activity: It has been demonstrated that the extracts are showing significant anti-hyperglycemic activity as compared to the standard drug. Ethanolic extract (200 mg/kg) show beneficial effects on blood glucose and hyperlipidemia associated with diabetes, which might be due to the presence of steroids, tannins, alkaloids and triterpenoids in the extract. Ethanolic extract could serve as a good adjuvant to other oral hypoglycemic agents and seems to be promising for the development of phytomedicines for diabetes mellitus [53]. Petroleum ether extract of *D. melanoxylon* leaves showed the antidiabetic effect at doses of 250 and 500 mg/kg in 1% v/v of Tween 80 (1 ml/kg p.o.) for 28 days to different groups of animals. It is proved that *D. melanoxylon* leaves effective for the treatment of both types of diabetes, *i.e.,* Insulin Dependent Diabetes Mellitus (IDDM) and Non-insulin Dependent Diabetes Mellitus (NIDDM) with a hypolipidemic property when compared to other diabetic drugs available in the market [54]. An additional study reported that the anti-hyperglycemic activity is *D. melanoxylon* Roxb. which was selected based on its abundant availability in Maharashtra state and based on ethnomedicinal information that the tribe of the Chotta Nagpur region (Orissa) use it extensively as antidiabetic [55].

Antimicrobial Activity: For the period of the previous few years, antimicrobial activities of plant extracts and natural products have been severely observed as they require for safe drugs which have augmented due to the abuse of antibiotics and an increase in immuno-deficiency disease [56].

The leaves of *D. melanoxylon* were explored for its antimicrobial activity and estimated by determining the zone of inhibition of *S. areas* (gram positive) and *E. coli* (gram negative) in different extracts like ethanolic and petroleum ether. Standard Ciprofloxacin was viewing zone of inhibition (mm) 24 and 30 for *S. aureus* and *E. coli* in that order. In the ethanolic extract, it was found 25 and 24 while in petroleum ether extract zone of inhibition was found with a value of 18 and 14 respectively. This revision demonstrated that the possibility of different extracts above microbes for the progress of novel antimicrobial mediator [57].

Anticancer Activity: It has been revealed that *D. melanoxylon* leaves contain ursolic acid (0.56%). Ursolic acid is a pentacyclic triterpenoid acts as a chemopreventive and chemotherapeutic agent in various types of cancer by inhibiting the initiation, promotion, and metastasis of cancer [20]. Ursolic acid inhibits the cell proliferation of Hep G2 human liver cancer cells [58]. It has been demonstrated the *in-vitro* anti-tumor activity in 2001 of ursolic acid [59]. Ursolic acid lessens the cell proliferation of many tumor cell lines and mechanisms of action have been tackled. It has been showed an early G1cytostatic effect for ursolic acid in B16 cells and MCF-7 breast carcinoma cells [60, 61].

Clinical Studies of Ursolic Acid: Clinical studies of ursolic acid mainly determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and pharmacokinetics in healthy adult

volunteers and patients with sophisticated tumors. It has been demonstrated that single dose ursolic acid liposomes (11, 22, 37, 56, 74, 98, and 130 mg/m^2) were administered as 4 hours intravenous infusion in 63 subjects (4 patients, 35 healthy volunteers, and 24 adults). It has been revealed that liposomal ursolic acid had convenient toxicities with MTD of 98 mg/m^2 for the first time. Mostly, the DLT was hepatotoxicity and diarrhea. Temporarily it has been demonstrated a linear pharmacokinetic profile of ursolic acid liposomal formulation [62].

Another study was carried out for 3 days of human subjects in the skin with incorporation of ursolic acid into the liposome and increased the ceramide content, with increases in hydroxyl ceramide. And also it has been revealed that increased the ceramide content in human skin after incorporation of ursolic acid into liposomes for 11 days [63]. From these reviews, we can say that ursolic acid has fabulous perspective into a powerful anticancer drug.

CONCLUSION: Our present assessments of *D. melanoxylon* have been contributed to tremendous positive roles in various diseases. It is documented for the use of many important chemical constituents in various health problems including cancer. Although, this plant has been used for a long time and so many research works have been done. The pentacyclic triterpenoid ursolic acid chiefly obtained from *D. melanoxylon* revealed chemopreventive and therapeutic potential in different cancer replicas and countless research works had been done as it is ubiquitous. Clinical trials are imperative parameters to develop it's reported worth for the prevention and treatment of assorted diseases. Still, there are opportunities to explore the different extract of the plant in the field of nano-technology mainly for cancer therapy [64], so that it can serve more effectively to the mankind.

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REFERENCES:

1. Mallavadhani UV, Panda AK and Rao YR: Anti-nociceptive, antiinflammatory of bioflavonoids. Pharmaceutical Biology 2001; 39: 20-4.
2. Lal P: "Bidi-A short history", Current Science (Bangalore, India: Current Science Association) 2009; 96: 1335-7.
3. Banerjee A, Rashid MHA, Rahman A and Pal TK: *In-vivo* screening of ethanolic extract of Biophytum sensitivum DC leaves on peptic ulcer induced by Aspirin in Wistar albino rats. International Journal of Pharmaceutical and Phytopharmacological Research 2014; 3: 414-2.
4. Harun Md. AR, Banerjee A and Maiti NJ: The queen of herb with a potent therapeutic constituent in various therapeutic disease states: A reappraisal. International Journal of Phytomedicine 2013; 5: 125-0.
5. Gopal V, Mandal V, Tangjang S and Mandal SC: Serum Biochemical, Histopathology and SEM Analyses of the Effects of the Indian Traditional Herb Wattakaka Volubilis Leaf Extract on Wistar Male Rats. Journal of Pharmacopunture 2014; 17: 13-9.
6. Ghosh N, Ghosh R, Bhat ZA, Mandal V, Bachar SC, Nima ND, Sunday OO and Mandal SC: Advances in Herbal Medicine for Treatment of Ischemic Brain Injury. Natural Product Communications 2014; 9: 1045-55.
7. Majumder S, Harun MAR, Chowdhury S, Gupta BK and Mandal SC: Ayurvedic Perspective of Human Metabolic Activities. The Pharma Review 2014; 12: 119-4.
8. GLOBOCAN 2012, http://globocan.iarc.fr/Default.aspx.
9. Thun MJ, DeLancey JO, Center MM, Jemal A, and Ward EM: The global burden of cancer: priorities for prevention. Carcinogenesis 2009; 31(1): 100-110.
10. Coseri S: Natural products and their analogs as efficient anticancer drugs. Mini-Reviews in Medicinal Chemistry 2009; 9(5): 560-571.
11. Newman DJ: Natural products as leads to potential drugs: an old process or the new hope for drug discovery? Journal of Medicinal Chemistry 2008; 51(9): 2589-2599.
12. Newman DJ, Cragg GM and Snader KM: Natural products as sources of new drugs over the period 1981–2002. Journal of Natural Products 2003; 66(7): 1022-1037.
13. Gordaliza M: Natural products as leads to anticancer drugs. Clinical and Translational Oncology 2007; 9(12): 767-776.
14. Saklani A and Kutty SK: Plant-derived compounds in clinical trials. Drug Discovery Today 2008; 13(3-4): 161-171.
15. Gerson-Cwillich R, Serrano-Olvera A and Villalobos-Prieto A: Complementary and alternative medicine (CAM) in Mexican patients with cancer. Clinical and Translational Oncology 2006; 8(3): 200-207.
16. Tascilar M, De Jong FA, Verweij J and Mathijssen RHJ: Complementary and alternative medicine during cancer treatment: beyond innocence. Oncologist 2006; 11(7): 732-741.
17. Cassileth BR and Deng G: Complementary and alternative therapies for cancer. Oncologist 2004; 9(1): 80-89.
18. Molassiotis A, Browall M, Milovics L, Panteli V, Patiraki E and Fernandez-Ortega P: Complementary and alternative medicine use in patients with gynecological cancers in Europe. International Journal of Gynecological Cancer 2006; 16(1): 219-224.
19. Mallavadhani UV, Mahapatra A, Jamil K and Reddy PS: Antimicrobial Activity of Some Pentacyclic Triterpenes

and Their Synthesized 3-O-Lipophilic Chains. Biol Pharm Bull 2004; 27: 1576-9.
20. Jadhav JK, Masirkar VJ and Deshmukh VN: Antihyperglycemic effect of *Diospyros melanoxylon* (Roxb.) bark against Alloxan-induced diabetic rats. International Journal of Pharm Tech Research 2009; 1: 196-200.
21. Kantamreddi VS and Colin WW: Investigation of Indian Diospyros Species for Antiplasmodial Properties. Evid Based Complement Alternat Med 2008; 5: 187-190.
22. Laszczyk MN: Pentacyclic triterpenes of the lupane, oleanane and ursane group as tools in cancer therapy. Planta Med 2009; 75: 1549-60.
23. Brown TL, LeMay HE, Bursten BE, Murphy CJ and Woodward P: Chemistry: The Central Science. Upper Saddle River, NJ: Pearson/Prentice Hall. AP Edition, 11th Ed, 2009: 5-6.
24. Hill JW, Petrucci RH, McCreary TW and Perry SS: General Chemistry. 4th Ed, Upper Saddle River, NJ: Pearson/Prentice Hall 2005: 6.
25. Whitten KW, Davis RE and Peck ML: General Chemistry. Saunders College Publishing/Harcourt College Publishers. 6th Ed, Fort Worth, TX, 2000: 15.
26. Wilbraham A, Matta M, Staley D and Waterman E: Chemistry. Upper Saddle River, NJ: Pearson/Prentice Hall. 1st Ed, 2002: 36.
27. Kowalski R: Studies of selected plant raw materials as alternative sources of triterpenes of oleanolic and ursolic acid types. J Agric Food Chem 2007; 55: 656-2.
28. Wojciak-Kosior M: Separation and determination of closely related triterpenic acids by high-performance thin-layer chromatography after iodine derivatization. J Pharm Biomed Anal. 2007; 45: 337-340.
29. Avila NS, Capote FP and de Castro MDL: Ultrasound-assisted extraction and silylation before gas chromatography-mass spectrometry for the characterization of the triterpenic fraction in olive leaves. J Chromatogr 2007; 1165: 158-5.
30. Gu JQ, Wang Y, Franzblau SG, Montenegro G and Timmermann BN: Dereplication of pentacyclic triterpenoids in plants by GC-EI/MS. Phytochem Anal 2006; 17: 102-6.
31. Cui T, Li JZ, Kayahara H, Ma L, Wu LX and Nakamura K: Quantification of the polyphenols and triterpene acids in Chinese hawthorn fruit by high-performance liquid chromatography. J Agric Food Chem 2006; 54: 4574-81.
32. Kontogianni VG, Exarchou V, Troganis A and Gerothanassis IP: Rapid and novel discrimination and quantification of oleanolic and ursolic acids in complex plant extracts using two-dimensional nuclear magnetic resonance spectroscopy-Comparison with HPLC methods. Anal Chim Acta 2009; 635: 188-5.
33. Takagi S, Masaki M, Matsuda K, Inoue K and Kase Y: Studies on the Purgative Drugs. (V). On the Constituents of the Fruits of *Prunes japonica* Thunb. Yakugaku Zasshi 1979; 99: 439-42.
34. Shanmugam MK, Manu KA, Ong TH, Ramachandran L, Surana R, Bist P: Inhibition of CXCR4/CXCL12 signaling axis by ursolic acid leads to suppression of metastasis in transgenic adenocarcinoma of mouse prostate model. Int J Cancer 2011; 129: 1552-63.
35. Kiran MS, Viji RI, Kumar VBS and Sudhakaran PR: Modulation of angiogenic factors by ursolic acid. Biochem Biophys Res Commun 2008; 371: 556-0.
36. Shanmugam MK, Rajendran P, Li F, Nema T, Vali S and Abbasi T: Ursolic acid inhibits multiple cell survival pathways leading to suppression of growth of prostate cancer xenograft in nude mice. J Mol Med (Berl) 2011; 89: 713-27.
37. Liu W, Tan X, Shu L, Sun H, Song J and Jin P: Ursolic acid inhibits cigarette smoke extract-induced human bronchial epithelial cell injury and prevents the development of lung cancer, Molecules 2012; 17: 9104-15.
38. Shishodia S, Majumdar S, Banerjee S and Aggarwal BB: Ursolic acid inhibits nuclear factor-kappa B activation induced by carcinogenic agents through suppression of I kappa B alpha kinase and p65 phosphorylation: correlation with down-regulation of cyclooxygenase 2, matrix metalloproteinase 9, and cyclin D1. Cancer Res 2003; 63: 4375-3.
39. Li J, Liang X and Yang X: Ursolic acid inhibits growth and induces apoptosis in gemcitabine-resistant human pancreatic cancer *via* the JNK and PI3K/Akt/NF-kappaB pathways. Oncol Rep 2012; 28: 501-0.
40. Mallavadhani UV, Panda AK and Rao YR: Phytochemistry 1998; 49: 901-51.
41. Hazra B: Journal of Indian Chemical Society 1981; LVIII: 627-8.
42. Gautam MP and Purohit RM: Indian Journal of Pharmacology 1973; 55.
43. Jackson C, Mbagwu H, Jackson I, Ekpe G and Etienam F: Analgesic activities of ethanolic extract of the root of *Carpolobia lutea*. African Journal of Pharmacy and Pharmacology 2011; 5: 367-0.
44. Bachhav RS, Gulecha VS and Upasani CD: Analgesic and anti-inflammatory activity of *Argyreia speciosa* root. Indian J Pharmacol 2009; 41: 158-1.
45. Pillai NPR, Parmar NSG and Ghosh MN: Analgesic effect of O-(beta-hydroxyethyl) rutoside in mice. Ind J Expt Biology 1985; 23: 219-6.
46. Hossinzadeh H, Ramezani M, fedishei M and Mahmoudi M: Anti-nociceptive, anti-inflammatory and antitoxicity effects of *Zhumeria majdae* extracts in mice and rats. Phytomedicine 2002; 9: 135-1.
47. Dirosa M: Biological properties of carrageenan. J Pharma Pharmacol 1972; 24: 89-102.
48. Agrawal RA, Garg C, Garg UB and Singh SK: Anti-ulcer activity of *Smithia conferta* in various animals. Journal of Saudi Chemical Society 2010; 14: 307-0.
49. AlKofahi A and Atta AH: Pharmacological screening of the antiulcerogenic effects of some Jordanian Medicinal Plants in rats. J Ethnopharmacol 1999; 65: 341-5.
50. Borelli F and Izzo AA: The plant kingdom as a source of anti-ulcer remedies. Phytother Res 2000; 14: 581-91.
51. Shree KMS: Anti-ulcer Activity of an aqueous suspension of *Saraca indica* flower against gastric ulcers in albino rats. Journal of Pharmacy Research 2010; 3: 17-20.
52. Gupta V, Jadhav JK, Masirkar VJ and Deshmukh VN: Antihyperglycemic effect of *Diospyros melanoxylon* (Roxb.) bark against Alloxan-induced diabetic rats. International Journal of Pharm Tech Research 2009; 1: 196-0.
53. Topno KK: Plants used by tribals of Chotta Nagpur against diabetes. Botanica Topno 1997; 47: 99-1.
54. Rathore K, Singh VK, Parag Jain Rao SP, Ahmed Z and Singh VD: *In-vitro* and *in-vivo* antiadipogenic, hypolipidemic and antidiabetic activity of *Diospyros melanoxylon* (Roxb). Journal of Ethnopharmacology 2014; 155: 1171-1176.
55. Ashutosh B, Khan MR, Jain NK, Dhariwa A, Jain S and Jain P: Study of antimicrobial activity in leaf extract of *Diospyros melanoxylon*. International Journal of Drug Discovery and Medical research 2013; 2: 129-0.

56. Grayer RJ and Harborne JB: Survey of antifungal compounds from higher plants. Phytochemistry 1994; 37: 19-42.
57. He X and Liu RH: Cranberry phytochemicals: isolation, structure elucidation and their anti-Proliferative and antioxidant activities. J Agric Food Chem 2006; 54: 7069-4.
58. Novotny L, Vachalkova A and Biggs D: Ursolic acid: an anti-tumorigenic and chemopreventive activity mini review. Neoplasm 2001; 48: 241-6.
59. Es-saady D, Simon A, Jayat-Vignoles C, Chulia AJ and Delage C: MCF-7cell cycle arrested at G1 through ursolic acid and increased reduction of tetrazolium salts. Anticancer Res 1996; 16: 481-6.
60. Es-saady D, Simon A, Ollier M, Maurizis JC, Chulia AJ and Delage C: Inhibitory effect of ursolic acid on B16 proliferation through cell cycle arrest. Cancer Lett 1996; 106: 193-7.
61. Wang XH, Zhou SY, Qian ZZ, Zhang HL, Qiu LH and Song Z: Evaluation of toxicity and single-dose pharmacokinetics of intravenous ursolic acid liposomes in healthy adult volunteers and patients with advanced solid tumors. Expert Opin Drug Metab Toxico 2013; 9: 117-5.
62. Both DM, Goodtzova K, Yarosh DB and Brown DA: Liposome-encapsulated ursolic acid increases ceramides and collagen in human skin cells. Arch Dermatol Res 2002; 293: 569-5.
63. Yarosh DB, Both D and Brown D: Liposomal ursolic acid (merotaine) increase ceramides and collagen in human skin. Horm Res 2000; 54: 318-1.
64. Harun MAR, Mandal V, Roy SC and Mandal SC: Herbal nanotechnology: an emerging tool in cancer therapy, In Choudhury H (ed) Biology, Biotechnology, and Sustainable Development. Delhi: Research India Publications (RIP) 2015: 86-108.

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