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ANTI-CANCER ACTIVITY OF CYPERUS ROTUNDUS: A REVIEW

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ABSTRACT

Musta, popularly known as *nagarmotha* traditionally and commonly as coco-grass/java grass/nut grass/purple nut sedge/purple nutsedge/red nut sedge (Cyperus rotundus)(Family:Cyperaceae), is a herbal plant in traditional *ayurvedic* medicine, which has since long used for treating fevers; digestive system disorders(diarrhea, vomiting,indigestion); emenagogue; analgesic in dysmenorrhea and as diuretic combined with other diuretics in urinary disorders; aromatic; antioxidant; hypolipidemic and hypocholesterolemic. This plant is pharmacologically and clinically evaluated for various activities like analgesic, anti-bacterial, anti-cancer, anti-convulsant, anti-diarrhoeal, anti-spasmoodic, anti-emetic, anti-hyperglycemic, anti-inflammatory, anti-malarial, anti-microbial, anti-mutagenic, radical scavenger, antioxidant, anti-platelet, anti-pyretic, gastroprotective, hepatoprotective, hypolipidaemic, hypotensive and tranquilizer. It is promulgated to possess a wide range of many phytochemical constituents. The current review is presented to give a comprehensive account of all anti-cancer activity of Cyperus rotundus. It will be helpful to create interest towards *musta* and may be useful in developing new and economical anti-cancer formulations with more therapeutic value. The part used of the selected plant is rhizome. As per retrospective review essential oil, methanolic, ethanolic extract, etc. are found having anti-cancer activity against different cell lines of various origins and animal models. Also, it can be used as chemopreventive ingredient in the herbal anti-cancer formulation. Total 23 research articles, peer viewed research papers, abstracts and classical texts were reviewed and anti-cancer activity of *musta* was noted during this research review.

KEYWORDS: *Musta, nagarmotha,* Cyperus rotundus, anti-cancer activity.

INTRODUCTION

According to GLOBOCAN out of 14.1 million new cases diagnosed, 8.2 million mortalities occurred due to cancer in 2012. The burden of the cancer cases will increase to 24 million new cases each year by 2035. As per recent survey, more than 8,06,000 cases are diagnosed and more than 0.3 million deaths/year in India due to cancer. According to National Cancer Registry Programme of the Indian Council of Medical Research(ICMR), more than 1300 Indians die every day due to cancer. Between 2012 and 2014, the mortality rate due to cancer increased by approximately 6%. In 2012, there are 4,78,180 deaths out of 29,34,314 cases reported. In 2013 there are 4,65,169 deaths out of 30,16,628 cases. In 2014, 4,91,598 people died in 2014 out of 28,20,179 cases. This incidence rate has raised to 300% in past 4 decades and if the scenario remains same the burden of present incidence rate will increase from 0.232% to >1%.

The role of carcinogenic agents in diets necessitates the perpetual search for natural anti-mutagens of promising anticancer therapeutics. Historically, natural products have been regarded as providing the primary leading compounds.

ANTI-CANCER STUDIES.

The fresh Cyperus rotundus L. rhizomes collected from Riyadh city in Saudi Arabia were crushed; directly immersed in water and hydro-distilled for 6-7hours using Clevenger apparatus, yielding its total extract. The 0.2% of yellowish oil with a strong aromatic odour was obtained by extraction with diethyl ether from the aqueous distillate, dried over anhydrous Na_2SO_4, and the ethereal layer was finally evaporated at room temperature. Air dried tubers were powdered and extracted with 85% ethanol by cold maceration until exhaustion. The ethanol extract was evaporated using a rotary evaporator to give a dark residue.

19 compounds were identified by GC-FID and GC-MS analysis.

1. **Sesquiterpenes(41.2%):** α-cyperone(21.1%), 4-oxo-α-ylangene(12.8%), Caryophyllene oxide (3.5%).
2. **Monoterpene(13.8%):** trans-Pinocarveol(3.6%), Cyperene(0.3%), Pinocarvone(0.2%), Myrtenal (1.7%), trans-Verbenol(1.5%), α-Terpineol(0.8%), Verbenone(1.7%), Carvone(0.1%), Myrtenol (2.8%), trans-Carveol(0.5%), p-Cymen-8-ol(0.9%), epi-Cubebol(0.4%), Cubebol(0.5%), Humulene epoxide-II(2.6%).

The essential oil recovered with diethyl ether demonstrated potent cytotoxic activities against colon(HCT-116), hepatocellular(HepG-2) and breast MCF-7) human cancer cell lines with IC_{50} values of 1.06, 1.17 and 2.22µg/mL respectively, evaluated by crystal violet staining(CVS) method. The ethanolic extract showed moderate cytotoxic activity against HCT-116, Hep G-2 and MCF-7 human cancer cell lines with IC_{50} values of 38.3, 43 and 48.5µg/mL, respectively.[1]

Essential oil obtained from tubers of Cyperus rotundus(Cyperaceae) composed of 33 volatile compounds(cyperene, α-cyperone, isolongifolen-5-one, rotundene, and cyperorotundene) were determined by GC-MS, using both electron impact(EI) and chemical ionization(CI) detection modes on apolar and polar stationary phases. The oxidative effect of the essential oil was evaluated by 1,1-diphenyl-2-picrylhydrazyl(DPPH), xanthine/xanthine oxidase assays, and the scavenging of superoxide radical assay generated by photo-reduction of riboflavin; the anti-mutagenic activity by following the inhibition of H_2O_2 UV photolysis which induced strand-break formation in pBS plasmid DNA scission assay. It significantly increased apoptotic DNA fragmentation in L1210 leukaemia cells(in-vitro) indicated by MTT assay and exhibited antioxidant, cytotoxic, and apoptotic properties.[2]

A study investigated the in-vitro cytotoxicity(MTT assay) of ethanol extract of Cyperus rotundus L.(whole plant) with different concentration(500, 250 and 125ppm) in comparison to triton-x100(the reference control), verifying the safety of the examined extract and plant with an IC_{50} less 100 µg/ml against Vero(Normal, African green monkey kidney) cells.[3]

To find out toxic action of drug in comparison to Etoposide standard drug(LD_{50} =7.4625) a quick and low cost toxicity test(Brine shrimp bioassay-lethality observed in term of death of larvae) was performed for C.rotundus crude extract showing the presence of tannins, saponins, carbohydrate in colour reaction method. The drug showed non-toxic significant effects at 10, 100, 1000 µg/ml concentrations.[4]

6-Acetoxy cyperene, a patchoulane-type sesquiterpene isolated from Cyperus rotundus rhizomes induces caspase-dependent apoptosis in human ovarian cancer cells. The n-hexane fraction of an ethanol extract of C.rotundus-rhizomes was found to inhibit cell growth in ovarian (A2780, SKOV3 and OVCAR3) and endometrial (Hec1A and Ishikawa) cancer cells. Among the 13 sesquiterpene isolated from the n-hexane fraction, some patchoulane-type compounds showed moderate cytotoxic activity with 6-acetoxy cyperene showing most

potent cytotoxic activity in human ovarian cancer cells. But eudesmane-type compounds did not showed cytotoxic activity. To study cell cycle progression and apoptosis, propidium iodide/Annexin-V-staining and terminal deoxynucleotidyl transferase dUTP(deoxynucleotide triphosphate) nick end labeling assay were performed indicating 6-acetoxy cyperene induced apoptosis, shown by the accumulation of sub-G1 and apoptotic cells. 6-acetoxy cyperene treatment stimulated the activation of caspase-3, caspase-8 and caspase-9 and poly(ADP-ribose) polymerase in a dose-dependent manner. Pretreatment with caspase inhibitors neutralized the pro-apoptotic activity of 6-acetoxy cyperene.[5]

In a phytochemical study the antioxidant, cytotoxic and apoptotic activities of both methanol and aqueous extracts from C.rotundus aerial part were determined. Orientin was obtained as the major compound isolated from the butanol fraction of methanol extract determined by RMN spectroscopic analysis. The methanol and aqueous extracts: inhibited 88% and 19% of xanthine oxidase activity; inhibited lipid peroxidation by 61.5% and 42.0%; inhibited OH formation by 27.1% and 25.3%, respectively. Methanol extract induced DNA degradation. The methanol extract demonstrated higher cytotoxicity on K562 cells[IC_{50}=(175.0$\pm$1.2) µg/mL] compared to that observed on L1210 cells [IC_{50}=(400.0$\pm$1.3)µg/mL]. No significant cytotoxic activity was shown towards L1210 and K562 cells after treatment with up to 800µg/ mL aqueous extract. L1210 cells exposed to 400 and 800µg/mL of the methanol extract during 48 hours, showed a clearly fragmented DNA with DNA ladder formation characteristic of apoptosis, whereas the control cells did not provide this specific ladder DNA profile. Thus, methanol extract from Cyperus rotundus inhibited the proliferation of both murine and human leukemia cells and induced apoptosis in a concentration- dependent manner.[6]

The bioassay guided fractionation and isolation of active constituents of Cyperus scariosus R. Br and Cyperus rotundus was done by chromatographic techniques. The study evaluated their anti-oxidant activity by DPPH and ABTS. The activity guided isolation led to isolation of twelve compounds Which are: Stigmasterol, β-sitosterol, Lupeol, Gallic acid, Quercetin, β-amyrin, Oleanolic acid, β-amyrin acetate 4- hydroxyl butyl cinnamate, 4-hydroxyl cinnamic acid, Caffeic acid and Kaempferol. Among the isolates, the compounds Gallic acid and Quercetin displayed potent radical scavenging activity with an IC_{50} values of 0.43 and 0.067 µg/ml.[7]

Fulgidic acid, isolated from C.rotundus rhizomes reduced the production of nitric oxide(NO), prostaglandin E_2(PGE_2), tumour necrosis factor-α(TNF-α), and interleukin-6(IL-6) in lipopolysaccharide(LPS)-induced RAW264.7 macrophages. It suppressed the LPS-induced expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) at the protein level, as well as iNOS, COX-2, TNF-*α*, and IL-6 at mRNA levels. It suppressed the LPS-induced transcriptional activity of activator protein-1 (AP-1) as well as the phosphorylation of c-Fos and c-Jun. Contrary, fulgidic acid did not show any effect on LPS-induced nuclear factor κB(NF-κB) activity. Hence, fulgidic acid suppressed expression of iNOS, COX-2, TNF-*α*, and IL-6 through down-regulating AP-1 activation in LPS- induced RAW264.7 macrophages.[8]

In this study, the anti-oxidative potential of a hydro-alcoholic extract of C. rotundus(CRE) was evaluated by various antioxidant assays, including antioxidant capacity by the phosphomolybdenum method, total antioxidant activity in linoleic acid emulsion systems, 1,1-diphenyl-2-picrylhydrazyl(DPPH), superoxide, hydroxyl radicals and nitric oxide(NO) scavenging. CRE was further evaluated for its reducing potential as well as Fe(2+)/ascorbate induced lipid peroxidation in rat liver homogenate; comparing with standard antioxidants such as butylated hydroxytoluene, tocopherol, L-ascorbic acid and catechin. CRE exhibited high reduction capability and powerful free radical scavenging, especially against DPPH and superoxide anions as well as a moderate effect on NO. CRE inhibited lipid peroxidation in rat liver homogenate induced by Fe(2+)/ascorbate and prevented deoxyribose degradation in both non-site-specific and site-specific assays showing the hydroxyl radical scavenging and metal chelating activity of the hydro-alcoholic extract. CRE demonstrated peroxidation inhibiting activity in the linoleic acid emulsion system. Total phenolic and flavonoid content of CRE was determined by a colorimetric method.[9]

The tubers extract of .rotundus(Cyperaceae) were investigated for its in-vitro antibacterial, antioxidant, cytotoxic and apoptotic activities. The total oligomers flavonoids(TOFs) and ethyl acetate extracts showed a significant ability to inhibit nitroblue tetrazolium reduction by the superoxide radical in a non-enzymatic superoxide generating system. TOF and ethyl acetate extracts suppressed growth and proliferation of L1210 cells derived from murine lymphoblastic leukaemia. Morphological features of treated cells and characteristic DNA fragmentation revealed that the cytotoxicity was due to induction of apoptosis.[10]

Total Oligomers Flavonoids(TOFs) and ethyl acetate extracts of C.rotundus were analyzed, in-vitro, for their antioxidant activity using several biochemical assays: the xanthine(X)/xanthine oxidase(XO), the lipid peroxidation induced by H_2O_2 in K562 human chronic myelogenous leukemia cells and the DNA damage in pKS plasmid DNA assay induced by H_2O_2 /UV-photolysis and for their apoptotic effect.

C. rotundus inhibited enzyme xanthine oxidase(XO), the lipid peroxidation and exerted apoptotic effect. Total Oligomers Flavonoids(TOFs) and ethyl acetate extracts of C.rotundus were found to be efficient in inhibiting xanthine oxidase with IC_{50} values of 240 and 185µg/ml and superoxide anion with IC_{50} values of 150 and 215µg/ml respectively in K562 human chronic myelogenous leukemia cells. Also, the extracts were effective in reducing the production of thiobarbituric acid reactive substances(TBARS) and were able to protect against H_2O_2/UV-photolysis induced DNA damage. Only TOF enriched extract exerts growth inhibition on K562 cells through apoptosis induction. Therefore, these extracts were subjected to further separation by chromatographic methods. Three major compounds(catechin, afzelechin and galloyl quinic acid) from the TOF enriched extract and five major compounds(luteolin, ferulic acid, quercetin, 3-hydroxy, 4-methoxy- benzoic acid and 6,7-dimethoxycoumarin) from ethyl acetate extract were isolated and determined by spectroscopic data analysis. In addition, evaluated biological activities of catechin, ferulic acid and luteolin revealed that the luteolin was most active in reducing the production of TBARS(MDA=1.5nM), inhibiting significantly the proliferation of K562 cells(IC_{50}=25µg/ml) and protecting against H_2O_2/UV-photolysis induced DNA damage.[11]

Myrtenal, a natural monoterpene and anti-neoplastic agent against diethylnitrosamine induced phenobarbital promoted experimental hepatocellular carcinoma. Myrtenal treatment significantly reduced elevated level of microsomal lipid peroxidation in the liver. On the contrary, the Phase-I hepatic drug metabolizing enzymes(cytochrome-P_{450}, cytochrome-b_5, NADPH-cytochrome-c reductase, NADH-cytochrome-b_5 reductase) levels were decreased and the Phase-II enzymes(glutathione-S-transferase, uridine 5′-diphospho-glucuronyl transferase) were increased in carcinogen-administered animals, which were reverted to near normalcy upon myrtenal administration. Myrtenal restrained the liver cancer by preventing the DEN–PB induced up-regulation of TNF-α protein expression by immunoblot. Furthermore, transmission electron microscopic examination also indicated that myrtenal prevents the carcinogen-induced changes in the architecture of liver tissue and cell structure.

Thus, the study showed that myrtenal has the ability to suppress the hepatocellular carcinoma in rats.[12]

A study evaluated mutagenic and anti-mutagenic effects of aqueous, TOF, ethyl acetate and methanol extracts from aerial parts of C.rotundus with the Salmonella typhimurium assay system. The different extracts showed no mutagenicity when tested with Salmonella typhimurium strains TA98, TA100, TA1535 and TA1538 either with or without the S9 mix. All extracts have anti-mutagenic activity against Aflatoxin B1(AFB1) in TA100 and TA98 assay system, and against sodium azide in TA100 and TA1535 assay system. TOF, ethyl acetate and methanol extracts exhibited the highest inhibition level of the Ames response induced by the indirect mutagen AFB1. Whereas, ethyl acetate and methanol extracts exhibited the highest level of protection towards the direct mutagen, sodium azide, induced response. In addition to antimutagenic activity, these extracts showed an important free radical scavenging activity towards the 1,1-diphenyl-2-picrylhydrazyl(DPPH) free radical. TOF, ethyl acetate and methanol extracts showed IC_{50} value of 15, 14 and 2µg/ml, respectively. Taken together, finding showed that C. rotundus exhibited significant antioxidant and anti-mutagenic activities.[13]

Treatment of MDA-MB-231 cells with an ethanol extract of C.rotundus rhizomes(EECR) and a methanol extract of C.rotundus rhizomes(MECR), but not a water extract of C.rotundus rhizomes, resulted in potent anti-proliferative activity. EECR exhibited highest apoptosis induction associated with upregulation of death receptor -(DR4), DR5 and pro-apoptotic Bax, as well as downregulation of anti-apoptotic survivin and Bcl-2. EECR treatment also downregulated Bid expression and activated caspase-8 and -9, the respective initiator caspases of the extrinsic and intrinsic apoptotic pathways. The increase in mitochondrial membrane depolarization was correlated with activation of effector caspase-3 and cleavage of poly(ADP-ribose) polymerase. The pro-apoptotic activity of the EECR may be regulated by a caspase-dependent cascade through activation of both intrinsic and extrinsic signaling pathways that is not associated with ROS generation or the PI3K/Akt and MAPK pathways.[14]

C. rotundus ethanolic extract exhibited weak to moderate anticancer activity(LC_{50}=2.528-4.939 mg/ml calculated from dose-dependent cell death) against neuro-2a cells used for screening of plants with tumoricidal effects.[15]

Methanolic extract of C.rotundus rhizome(MRCr) exhibited highest antioxidant activity determined by DPPH assay. It was further investigated for: cytotoxicity by MTT assay; apoptosis by flow cytometry stained with annexin V-Fluorescein isothiocyanate conjugate(AF) and propidium iodide(PI); cellular and nuclear changes under light and fluorescent microscope using 4',6'diamino-2-phenylindole(DAPI) stain, dual stains of AF/PI and acridine orange/ethidium bromide(AO/EB) against different human cancer cell lines-breast(MCF-7), cervical(HeLa), liver(Hep-G2), prostate(PC-3), colorectal(HT-29) and normal cell line(MCF-12A) evaluated as 50% inhibition of growth (IC_{50}). The cytotoxic effects against tested cancer cell lines ranged from 4.52±0.57 to 9.85±0.68µg/ml. The MRCr showed significant anticancer activity against all the tested cancer cell lines and also protected the non-cancer cells.[16]

In-vitro anti-proliferative potential of ethanol extract of the rhizome of C.rotundus was assessed against KB oral cancer cell line by MTT, SRB and LDH assay. MTT and SRB assay showed significant cell death in dose dependent manner at LD_{50} concentration of 12.5µg/ml. Increased LDH leakage was an indicator of loss of membrane integrity. Acridine Orange/Ethidium Bromide(AO/EB) fluorescent staining confirmed apoptotic/dead cells in extract treated group. Flow cytometry analysis of cell cycle confirmed, significant increase in S phase attributing to S phase arrest of KB oral cancer cells.[17]

A study investigated in-vitro cytotoxicity of aqueous and ethanol extracts of Cyperus rotundus using SRB and Trypan blue assay against human colon(HCT- 116) and Ehrlich Ascites Carcinoma(EAC) cell lines. SRB assay on HCT-116 cells indicated an IC_{50} value of 517.828µg/ml for aqueous extract and that 72.06µg/ml for ethanol extract. In trypan blue assay, IC_{50} values of 2158.63µg/ml and 160.19µg/ml were obtained for aqueous and ethanol extracts respectively on EAC cells. Positive control Doxorubicin exhibited IC_{50} of 11.221µg/ml and 23.325µg/ml against HCT-116 and EAC cells respectively.[18]

CONCLUSION

The selected herb Cyperus rotundus was reviewed for its methanolic, ethanoic, aqueous and essential oil. It showed angiogenesis, antioxidant, superoxide radical scavenging, cytotoxicity, anti-mutagenic, anti-proliferative, pro-apoptotic and cell-growth inhibition against various cell lines or animal models including leukaemia; lung cancer(A-549), liver cancer(Hep-2), colon cancer (Colon 502713, Colon 205, neuroblastoma cell lines human promyelocytic leukemia cells (HL-60); KB (oral squamous carcinoma cells); ehrlich ascites

carcinoma (a spontaneous murine mammary adenocarcinoma); human cervical cancer (HeLa) and human MCF-7 breast cancer. The probable mode of these anti-cancer activities in above cell line or animal models may be due to inhibition of fos-jun-DNA complex formation; activation of aspartate specific cysteine proteases or caspase-3 substrates like DFF45, PARP and caspase-6 substrate lamin-A; blockage of cells at S-phase; downregulation of c-Myc, H-ras and Bcl2 expression along with upregulation of P53, Bax and active Caspase-3 expression; inhibition of ODC activity, iNOS, COX-2 expression, and on levels of proinflammatory cytokines (IL-6, TNF-alpha, and PGE-2) due to inhibition of NF-kappaB, the upstream signaling molecule which regulates the expression of these genes; reactive oxygen species (ROS); apoptosis by complete blockage of DNA fragmentation by pretreatment of antioxidant *N*-acetyl-L-cysteine(NAC); inhibitory effect on cell proliferation via NF-κB suppression; decreased Bcl_2 and Bcl-xL expression and increased the expression of Bax, Bid, Bad, Apaf-1, cytochrome c, caspase-9, -3 and PARP cleavage; inhibition of superoxide formation, lipid peroxidation, inducing increased detoxifying enzyme system glutathione S-transferase(GST) activity; modulatory effects on the hepatic levels of Cytochrome P- 450(Cyt. P-450), Cytochrome b5(Cyt. b5), Aryl Hydrocarbon Hydroxylase (AHH), Glutathione S-transferase(GST). Hence, Cyperus rotundus can be used as chemopreventive ingredient in the herbal anti-cancer formulation.

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