Life Science Informatics Publications

Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences

Journal Home page http://www.rjlbpcs.com/

RJLBPCS

ISSN 2454-6348

Original Review Article **DOI: 10.26479/2021.0703.03**

CYPERUS ROTUNDUS IN THE MANAGEMENT OF METABOLIC SYNDROME – BENEFIT IN THE TREATMENT OF METABOLIC SYNDROME

Nikhil Pandey, Priyanka Mishra, Yamini Bhusan Tripathi*

Department of Medicinal Chemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, India.

ABSTRACT: *Cyperus rotundus*, (Cyperaceae), commonly known as Nagarmotha (H) and Nutgrass (E). Its pharmacological claims are anti-inflammatory, anti-pyretic, diuretic, wound healing property, post-parturition use and other reproductive disorders in females. Charak Samhita is grouped under "lekhniya dravya", a group of medicinal plants acclaimed to clean the channels, by removing fat deposits and body weight-reducing effects. Here, we have reviewed its pharmacological and phytochemical properties by using keywords like metabolic syndrome (MetS), Hyperglycemia, Hyperlipidemia, Anti-oxidant, Anti-inflammation, Type II diabetes, Obesity, Blood pressure, Fatty liver and Atherosclerosis in the PubMed and Web of sciences. Result- We found 250 articles in PubMed and 226 in the web of sciences. The duplicates were excluded by using Mendeley software, and finally 23 papers were reviewed for experimental data. Conclusion- We found that Cyperus rotundus is effective in the management of MetS in clinical studies and experimental models. Some papers have highlighted the mechanistic approach of its phytoconstituents concerning various diseases of MetS, which is mainly through its anti-inflammatory and antioxidant potentials.

Keywords: Metabolic Syndrome, Cyperus rotundus, Phytoconstituents, Signaling pathways, Food Supplement.

Article History: Received: May 14, 2021; Revised: June 08, 2021; Accepted: June 22, 2021.

Corresponding Author: Dr. Yamini Bhusan Tripathi* Ph.D.

Department of Medicinal Chemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, India. Email Address: yaminimedchem.bhu@gmail.com

1.INTRODUCTION

Metabolic syndrome (MetS) is a cluster of obesity, elevated blood pressure (BP), blood sugar, and atherosclerosis. It is distinguished by a collection of interconnected atherogenic risk factors including oxidative stress (OS), dyslipidemia, hypertension, diabetes, obesity, insulin resistance (IR), and lifestyle factors such as dietary patterns and physical inactivity. Hyperglycemia and hyperlipidemia are the primary causes resulting in hypertension and atherosclerosis. Abnormal level of inflammatory cytokines, reactive oxygen species, dysregulated lipid metabolism and insulin resistance are interconnected to the syndrome. Various medical agencies such as International Diabetes Federation, National Cholesterol Education Program's Adult Treatment Panel III, and the WHO have suggested definition for metabolic syndrome but all concentrate on five medical conditions as a diagnosis guideline which includes following key point:

Box 1-Key criteria that constitutes MetS

- Waist Circumference- >35 inches or 88.9 cm (F)/ >40 inches or 101.6 cm (M)
- Fasting glucose =/> 100 mg/dL
- Triglycerides =/> 150 mg/dL
- High density lipoproteins (HDL) < 50mg/dL (F)/ <40mg/dL (M)
- Systolic blood pressure =/> 130 mmHg
- Diastolic blood pressure =/> 85 mmHg

Genetic predisposition, lifestyle and environmental factors are responsible for the manifestation of MetS. It is considered as "lifestyle-related non-communicable chronic diseases" (NCDs) so its prevention from an early age is recommended. The basic cause behind the manifestation of all the diseases of MetS appears to chronic inflammation, insulin resistance, and visceral obesity. These results in the creation of abnormal adipocyte with M-1 macrophage infiltration and abnormal secretion of adipokines e.g., adiponectin and leptin enhanced release of inflammatory cytokines including IL-1, IL-6, TNF-α, excess free radical generation associated with mitochondrial dysfunction and endoplasmic reticulum (ER) stress. The treatment strategies for MetS focus on lifestyle modification along with pharmacological interventions, but they are not enough. Most of the time they are also associated with several adverse effects, resulting in poor compliance in patients [1]. Thus, several new types of research are going on to develop specific food supplements and herbal medicines for its management with better compliance and acceptability. Efforts are also being made to understand the molecular mechanism behind the recommendations for changing the lifestyle and food habits in scientific terms for their acceptance by the educated and well-informed consumers.

Here recommendations of complementary medicine of different countries are being explored. In India,

the AYUSH system of health care includes Ayurveda, yoga, and Unani, Siddha and Homeopathy. They have their own Materia-medica with a specific way of diagnosis and treatments. In addition, 'Swaripa' a Tibetan medicine and naturopathy are also in practice. These systems include medicines, derived from plants, minerals and biological products, but in Ayurveda, Maharishi Charak has described three approaches of treatments. These are spiritual healing (Devavyapasharya), Psychological counselling (Satwavajaya) and medicines (Youkti Vyapasharya). He has emphasized more regulate the quality, amount and time of feeding, customized to a person, based on their body and mind constitution (Prakriti), season and age indicating towards personalized medication [2]. The goals of therapy are to treat the underlying cause of the syndrome, reduce morbidity, and prevent complications, including premature death. Many efforts have been made over the last decade to employ natural products in drug development. More than two-thirds of the active agents of drugs have a relationship to natural sources. Among 19 natural-based drugs that have been approved for worldwide marketing between the years 2005–2010, 7 have been classified as natural products, 10 as semi-synthetic natural products, and 2 as natural product-derived drugs [3]. Some examples include Veregen ™ as a mixture of catechins derived from green tea against genital warts, Sativex® derived from Cannabis plant for pain relief, and Exenatide (Byetta®) isolated from Heloderma suspectum as adjunctive therapy in type 2 diabetes [4]. In this review, the application of Cyperus rotundus (Indian nagarmotha) on reported pathways relating to MetS has been briefly discussed. It is one of the 10 plants of lekhan Dravya. All plants of this group are listed (Table-A) The Cyperus rotundus L. (Nut Grass), is a common perennial weed having a long list of pharmacological claims, (Table- B) This review attempts to sum up the application of Indian nagarmotha or Cyperus Rotundus (CR) in the management of MetS by depicting the probable role of the plant as a whole or the reported active phytoconstituents on the mechanistic pathway leading to the development of this syndrome. Their mechanism of action can either be by blocking the key receptor or manipulating the key signaling molecule in the pathways of pathogenesis. We have searched the literature using PubMed, and Web of Science's database with the keywords Cyperus rotundus, metabolic syndrome (MetS) Anti-inflammation Anti-oxidant, Hyperlipidemia, hyperglycemia, atherosclerosis, Blood pressure, Type II diabetes, Obesity, and their mode of action on metabolic pathways, for the inclusion of papers in order to prepare this review article. The references list of all the articles were searched manually to obtain relevant and additional information and analysis of experimental data and common parameters about the experiments.

Results: For our studies, we selected 23 papers out of 476 results with PubMed (250) and Web of Sciences (226) based on the mentioned keywords with (Fig 1). Further, these were processed by using Mendeley software to screen out duplications and a total of 160 were screened out. After that from these 160, we included those papers where studies carried on the animal model (i.e., Rats and Mice) and in vivo. Next, we considered only those studies which had "Cyperus rotundus" and not in combination with any other plant. Based on various studies (in-vivo and in vitro), reported earlier, we concluded that CR in any form, be it an extract or isolated phytoconstituents has shown its efficacy on animal models, as well as in cell cultures significant in terms of, anti-oxidant anti-inflammatory effect, Hypolipidemic activity, Anti-obesity, Type II diabetes and also in Cardiovascular Disorders such as atherogenesis. Therefore, from analysis of experimental data from above-selected papers, it could be suggested that CR is showing significant changes in anti-oxidant, anti-inflammatory, Hyperlipidemia /Obesity/ Hypoglycemia, anti-diabetic and cardio-protective (Table1, 2,3,4,6).

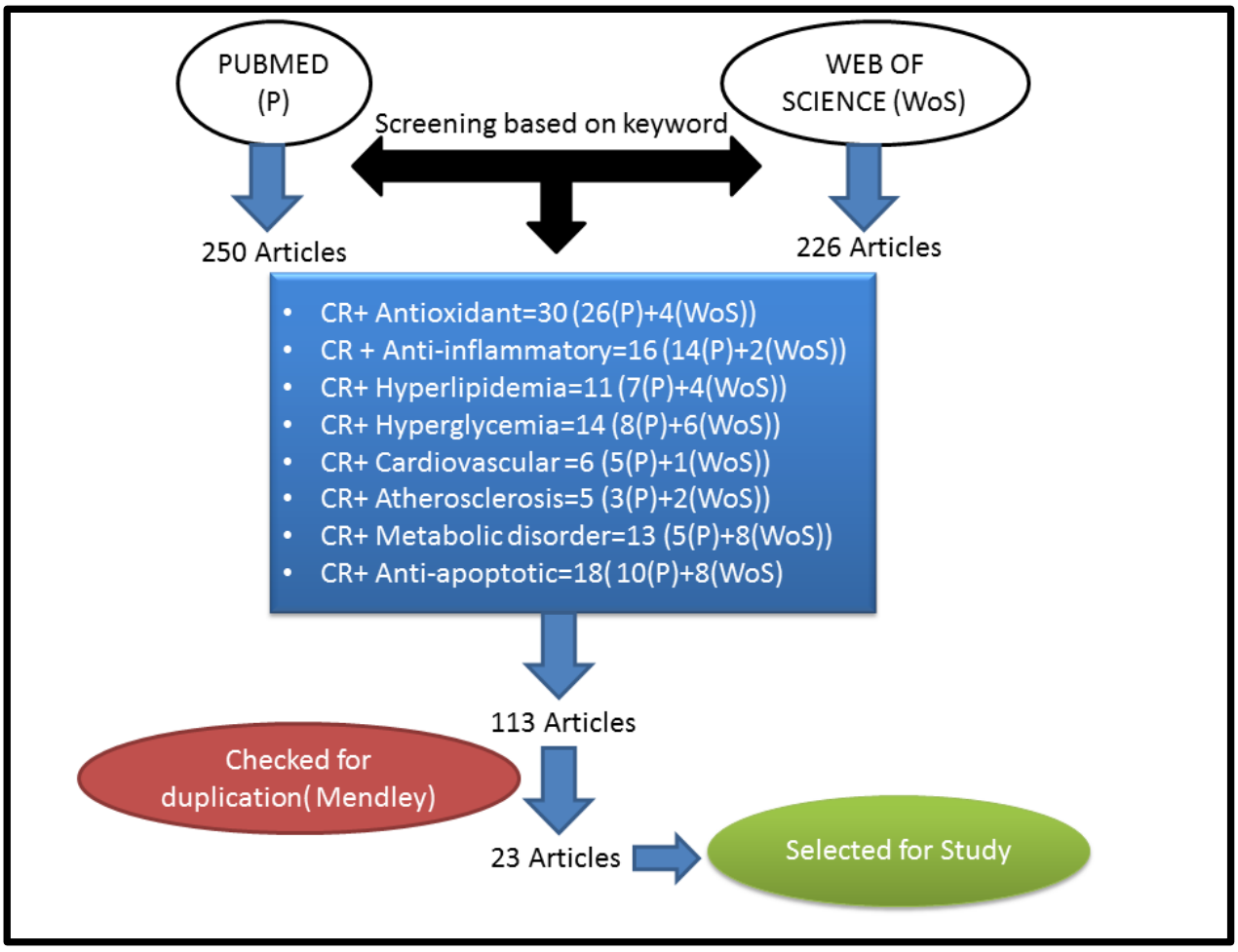

Fig.1 Study selection criteria

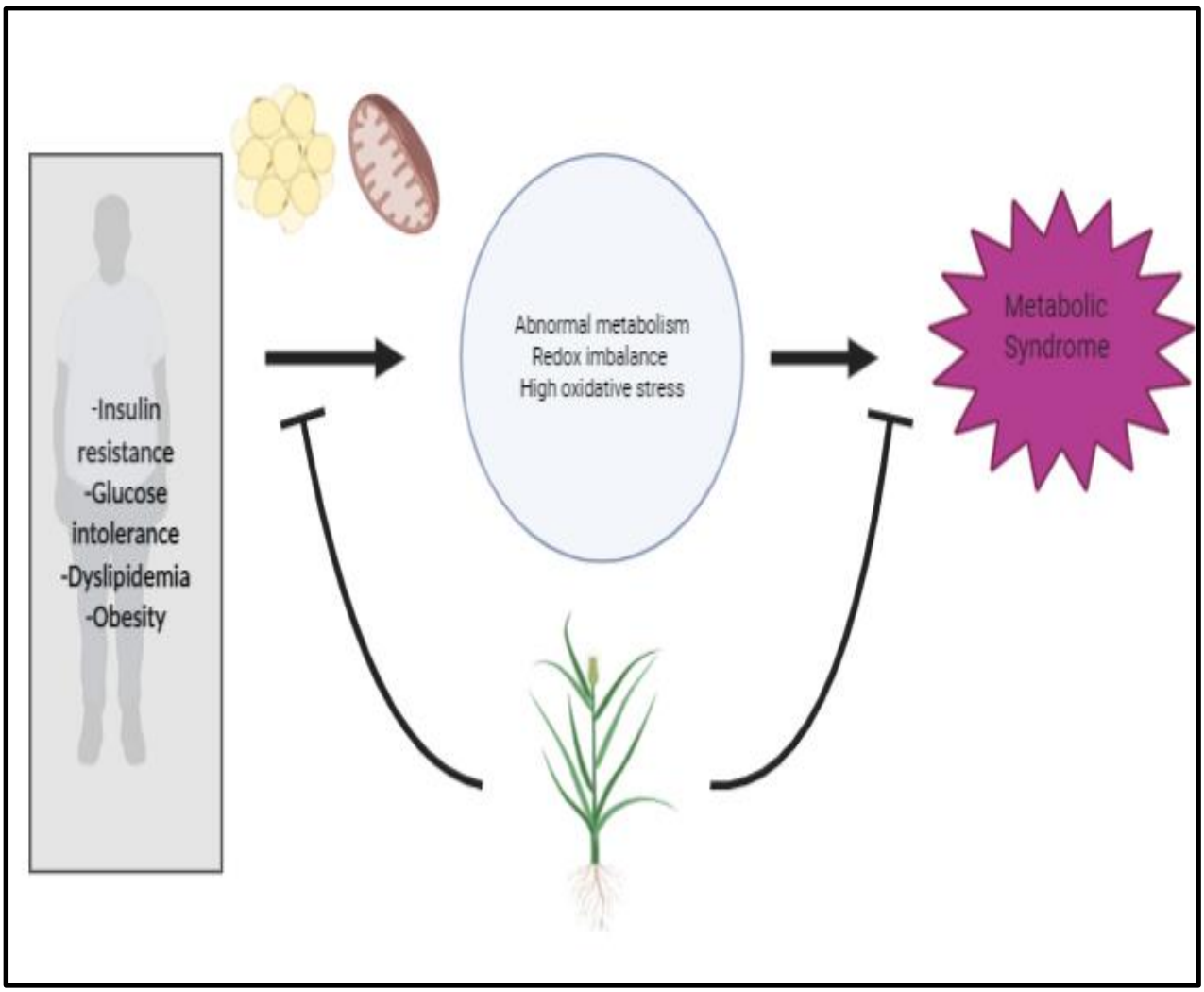

Fig.2 Overall effect of Cyperus rotundus on metabolic syndrome

a) Plant description-
b) Kingdom: Plantae
c) Subkingdom: Tracheophytes-Vascular plants
d) Super division:Spermatophyta (seed plants)
e) Division: Magnoliophyta-Flowering plants
f) Class: Liliopsida (Monocotyledons)
g) Subclass: Commelinids
h) Order: Cyperales
i) Family: Cyperaceae-Sedge family
j) Genus: Cyperus L. Flat sedge
k) Species: C. rotundus L.-nutgrass

Biological properties in the classical Ayurvedic texts are as follow

1. Anti-oxidant activity-

The clustering of metabolic abnormality is linked to oxidative stress and inflammation, which also leads to the progression of atherosclerosis. Since antioxidants are reducing agents which inhibit the oxidation of other bio-molecules, attributing to abnormal function and diseased physiology. The high production of ROS is attributed to low antioxidant enzymes, low reduced glutathione and mitochondrial dysfunction. It induces vascular disorders resulting in hypertension, cardiovascular complications and other diabetic complications. Mets are linked to systemic inflammatory processes and increased production of cytokines. That the oxygen centered free radicals further reduce NO bioavailability, resulting in vasoconstriction mediated hypertension and thrombus formation. Antioxidants may be divided into enzymatic and non-enzymatic and the latter one may be endogenous or exogenous, which includes normal diet and dietary supplements. The CR extract and its essential oil have shown substantial antioxidant potential [5] It scavenges the superoxide radicals, hydroxyl radicles, gas radicle peroxide, additionally to the property of metal chelating and reducing power [6]. It also reduces the lipid peroxidation, as measured by reduced thiobarbituric acid–reactive substances (TBARS) in several tissues including in rat-brain-mitochondria, induced by FeSO4 [7]. The high flavonoids and polyphenols contents in the polar and non-polar extracts of Nutgrass are attributed to this property [8]. Some of the studies done on CR w.r.t to antioxidant have been included in the table to shows the effect of dosage and its outcomes. (Table 1(a))

Table 1(a) - Effect of Cyperus rotundus on Reactive oxygen species (ROS)

S.No(Ref)	Dose	SOD	ABTS	DPPH	FRAP	LPO(TBAR)
1[9]	25ug/ml	2.28 ±1.23*		24.96 ±1.82*		
	50ug/ml	21.45 ±0.91*		47.27 ±2.12*		
	100ug/ml	43.13 ±2.14**		76.10 ± 1.52**		
	250ug/ml	55.12 ± 1.32**		81.27 ± 1.56**		

2[10]	0.1 mg/mL		36.1 ± 2 .4 (EC50 value)	57.6% 75.0 ± 4.1 at 0.1 mg/mL of C. rotundus esse ntial oil on DPPH radicals		
	200 µg/ml				15%(0.15 nm)	
	400 µg/mL				35%(0.35 nm)	
	600 µg/mL				55%(0.55 nm	
	800 µg/mL				65%(0.65 nm)	
	1000 µg/ml				74%(0.74 nm)	
3[11]	1mg/ml					15%
	2mg/ml					60%
	4mg/ml					70%
4[12]	10ug/assay	5 ±3 %				
	30ug/assay	25.7±1.5%				
	100ug/assay	29.9±7.2%				
	300ug/assay	47±0.9%				
	1000ug/assay	53±7.1%				
5[13]	Xanthine Oxidase by oil					
	50ug/ml	5				
	150ug/ml	15				

	300ug/ml	30				
6.[14]	total oligomers flavonoids (TOFs)					
	10ug/assay					
	30ug/assay					
	100ug/assay					
	300ug/assay					
	1000ug/assay					

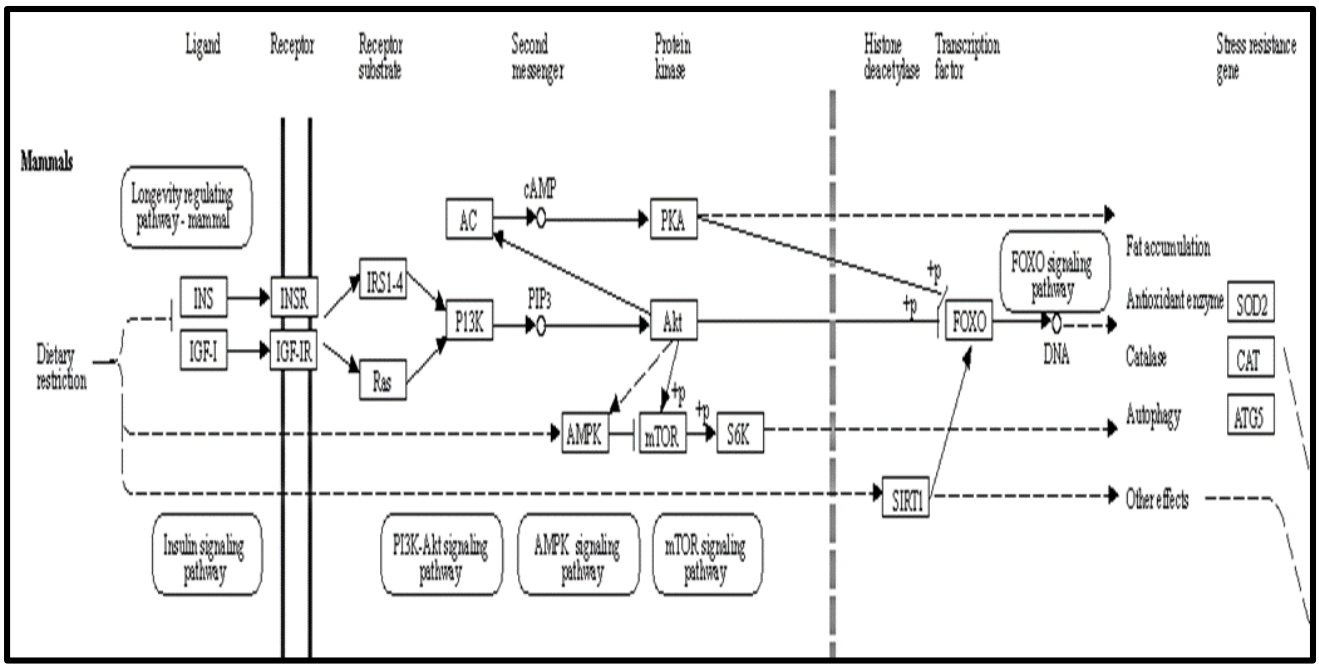

Fig1. Role of nutrient sensing pathway and its effect on oxidative stree. FOXO is a transactive gene involved in resistance to oxidative stress. Nutrient sensing pathway namely like growth factor and TOR pathway can sustain longevity. In mammals these nutrient sensing pathways are down regulated through insulin like growth factor and TOR pathway deactivating the PI-3K/Akt/TOR intracellular signaling cascade and consequently activating the FOXO pathway transcription pathway which are involved in stress gene i.e., SOD2 and CAT. CR shows scavenging potential as in showed in various above-mentioned studies. **Source-KEGCC pathway**

2. Anti-inflammatory– The anti-oxidant and the anti-inflammation have interlinking effects which reduce the reactive oxygen species (ROS) and nitric oxide (NO) production, reduced the lipid peroxidation via the modulation in cell-signaling pathways and inflammation mediators [14] Hence this cross-talk was analyzed by one of the studies where the rhizomes of Nutgrass were used as a typical folk medicine for the treatment of inflammatory diseases. A compound like "(+)-Nootkatone "and "(+)-valencene" from the rhizomes of Nutgrass increased the survival rates in septic mice because of the Heme oxygenase-1 induction [15]. Similarly in one of the studies by Ryter et al,.2006 [16], Heme oxygenase-1 (HO-1) which is an inducible enzyme mainly catalyzes the rate-limiting step in the degradation of Heme, leading to the production of ferric ions, biliverdin, and this gets converted into bilirubin by an enzyme called biliverdin reductase and also carbon monoxide(CO), which is highly up-regulated in mammalian tissues in response to a wide variety of pathophysiological stimuli, including vascular injury, ischemia, oxidative stress, and immune response. In this way, this inducible enzyme HO-1 shown to provide cytoprotective, anti-apoptotic, and immunomodulatory effects. This HO-1/CO can play a beneficial role in the modulation of such proinflammatory stimulators as inducible nitric oxide synthase (iNOS), tumor necrosis factor-alpha (TNF-), and high mobility group box1 (HMGB1) RAW264.7. Thus, it seems plausible that the development and discovery of HO-1-inducible agents from Cyperus rotundus may have great potential for therapeutic intervention in such systemic inflammatory disorder. In another study one of the important compounds "α-Cyperone," is among the sesquiterpenes compound (25.23% of the entire oil) is the foremost compound in Nutgrass oil [17] has shown anti-inflammation potential. Its mechanism of action has been reported through modulation of Endothelial cell protein C receptor (EPCR), which is attributed to vascular barrier integrity within the vascular disease and this takes part in systemic disease [17]. Since EPCR could even be the foremost member in the protein -C (PC) anti-coagulation system. The EPCR might be dismantled from the cell surface, and it'd be mediated by tumor necrosis factor-α converting enzyme (TACE) (14). The protein C anticoagulant pathways play a vital role within the proper regulation in process of inflammation. Protein C is activated on the surface of endothelial cells by the thrombin-thrombomodulin complex, a process which may be further enhanced when protein C binds to its membrane receptor, the endothelial-cell protein C receptor (EPCR) [17]. Also, there's an expression of EPCR on the endothelium of giant blood vessels which cause the increased concentration of protein C to avoid the low concentration of thrombomodulin within the vessels by providing an efficient activation of protein C [17]. Hence the studies show that α-Cyperone inhibits EPCR shedding, as shown by suppress PMA (Phorbol-12-Myristate-13-Acetate)-induced EPCR shedding through

inhibiting the expression and activity of TACE. Besides that, α-Cyperone also inhibits the effect on PKC translocation, but do not have an impact on phosphorylation of c-Jun N-terminal kinase (JNK), p38 and extracellular regulated protein kinases (ERK) 1/2. Provided these observations, it is worth noticing the α-Cyperone inhibition effect on PMA-induced EPCR shedding through the PKC pathway, which can provide an experimental basis for further research on α-Cyperone [18] The pathogenesis of inflammatory diseases features a selection of important mediators like gas (NO) and superoxide (O2-). The alcoholic extract of C. rotundus has shown anti-inflammatory property in-vivo and in-vitro studies. In one experiment with albino rats, its alcoholic extract (70% alcohol) has shown anti-inflammatory activity against a carrageenan-induced model of oedema and against formaldehyde induced arthritis [19] and analgesic potential in formalin-induced writhing, in the dose-dependent manner ranging from 300mg/kg to 500mg/kg) [20]. In the model of carrageenan-induced paw oedema model, it reduced the edema; within the acetic acid-induced peritonitis, decreased the protein content of the peritoneal exudates. In the murine macrophage cell line, RAW 264.7 culture has shown inhibition of NO and O2 production, induced by interferon-gamma plus lipopolysaccharide, which is attributed to downregulation of iNOS, mRNA and protein expression. Its methanolic extract reduced the phorbol ester (PMA) induced production of $O_{2.}$ [21]. Another study published by Fernanda and coworkers in 2020 has demonstrated protection against inflammation by topical application of C. rotundus extract on a skin model, suggesting that the extract might be a possible new therapeutic tool for the treatment of inflammatory disorders [22].

Table 2 - Effect of Cyperus rotundus on Anti-inflammation

Anti-inflammation	**Treatment**	**Dose**	**Xylene induced ear edema (mg)**	**Inhibition (%)**	**Model**
[11]**.**	Control	-	61,12 ± 7,44		In vivo
	Dexamethasone	50	49,46 ± 1,95*	19,08	
		150	37,9 ± 2,57*	38,48	
		300	19,06 ± 1,61*	68,81	
	Aqueous Extract	50	42,52 ± 2,72*	30,43	
		150	28,9 ± 2,01*	52,71	
		300	15,66 ± 1,05*	74,38	

3. Anti –Apoptotic- CR role in apoptosis was shown by one of the studies where CR rhizome's derived 6-acetoxy cyperene has shown the inhibitory effect on cell growth of ovarian cancer like A2780, SKOV3 and OVCAR3 and endometrial cancer (Hec1A and Ishikawa) cells [23]. Further there were thirteen isolated sesquiterpenes from the n-hexane some like patchoulane-type compounds, but not eudesmane-type compounds, showed moderate cytotoxic activity. In particular, the patchoulane sesquiterpenes 6-acetoxy cyperene had the most potent cytotoxicity 6-acetoxy cyperene induced apoptosis, as observed by the accumulation of sub-G1 and apoptotic cells. Furthermore, the treatment with 6-acetoxy cyperene stimulated the activation of caspase-3, caspase-8 and caspase-9 and poly (ADP-ribose) polymerase in a dose-dependent manner. Furthermore, treatment with 6-acetoxy cyperene 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. Taken together, these data suggest that 6-acetoxy cyperene, a patchoulane-type sesquiterpenes isolated from C. rotundus rhizomes, is an anti-tumor compound that causes caspase-dependent.

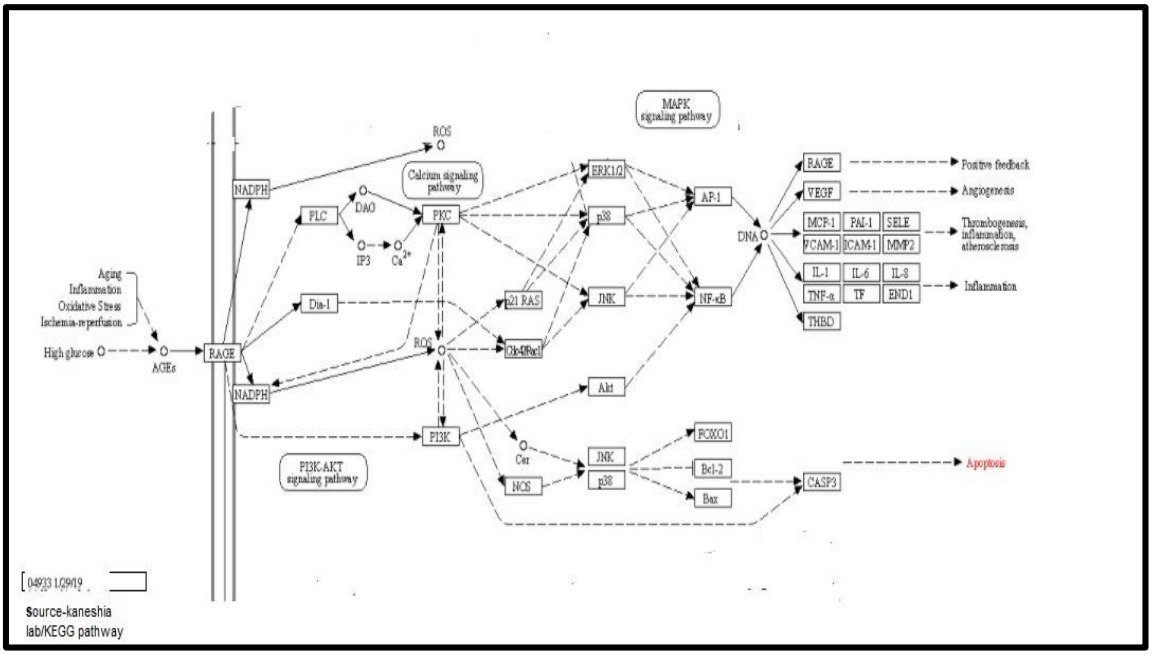

Fig3.Apoptotic Signaling Pathway: In MetS, factors like aging/high glucose/inflammation causes formation of AGE's and bind to its receptor RAGE. This activates multiple intracellular pathways. Here PI3K-Akt pathway is induced via RAGE which in turn participate in apoptosis

Source KEGG Pathway

4. Anti-obesity- A number of studies have demonstrated that natural compounds

likeepigallocatechingallate(EGCG),quercetin,psynephrine,[27]genistein,esculetin,[29],berberine,res veratrol[31], guggulsterone[32] and capsaicin[33] inhibited adipogenesis. Since the metabolic syndrome describes a cluster of metabolic abnormalities where abdominal obesity in one of the factors especially the population of high cardiovascular risk. With respect to abdominal obesity adipose tissue is a highly active endocrine organ that produce and secrete numerous inflammatory mediators along with immune mediators called as adipokines [34]. Induction of adipogenesis starts with the change in cell shape along with the alteration in levels of cytoskeletal components and extracellular components. [35] As this process further initiates the adipogenicity transcription factors expression including C/EBPα (CCAAT-enhancer-binding proteins) and PPAR-γ (peroxisome proliferator-activated receptors.) C/EBP and PPAR are the central transcriptional regulators of adipogenesis and are required for the synthesis of many adipocytes associated functional proteins. C/EBP up-regulation facilitates the downstream Up-regulation of PPAR and C/EBP expression. Significant numbers of studies have demonstrated that CR inhibits weight gain, without affecting food consumption or inducing any toxicity. Like in one the study where In vitro, 250 micro/mL of this extract was able to stimulate lipolysis in 3T3-F442 adipocytes suggesting that this medicinal plant contains activators of beta-adrenoceptors (AR). It was demonstrated that administration of 45 or 220 mg/kg/day of C. rotundus tubers hexane extract for 60 days in Zucker rats induced a significant reduction in weight gain without affecting food consumption or inducing toxicity. Since pre-adipocytes lack the lipolytic activity until they are differentiated to a mature adipocyte.

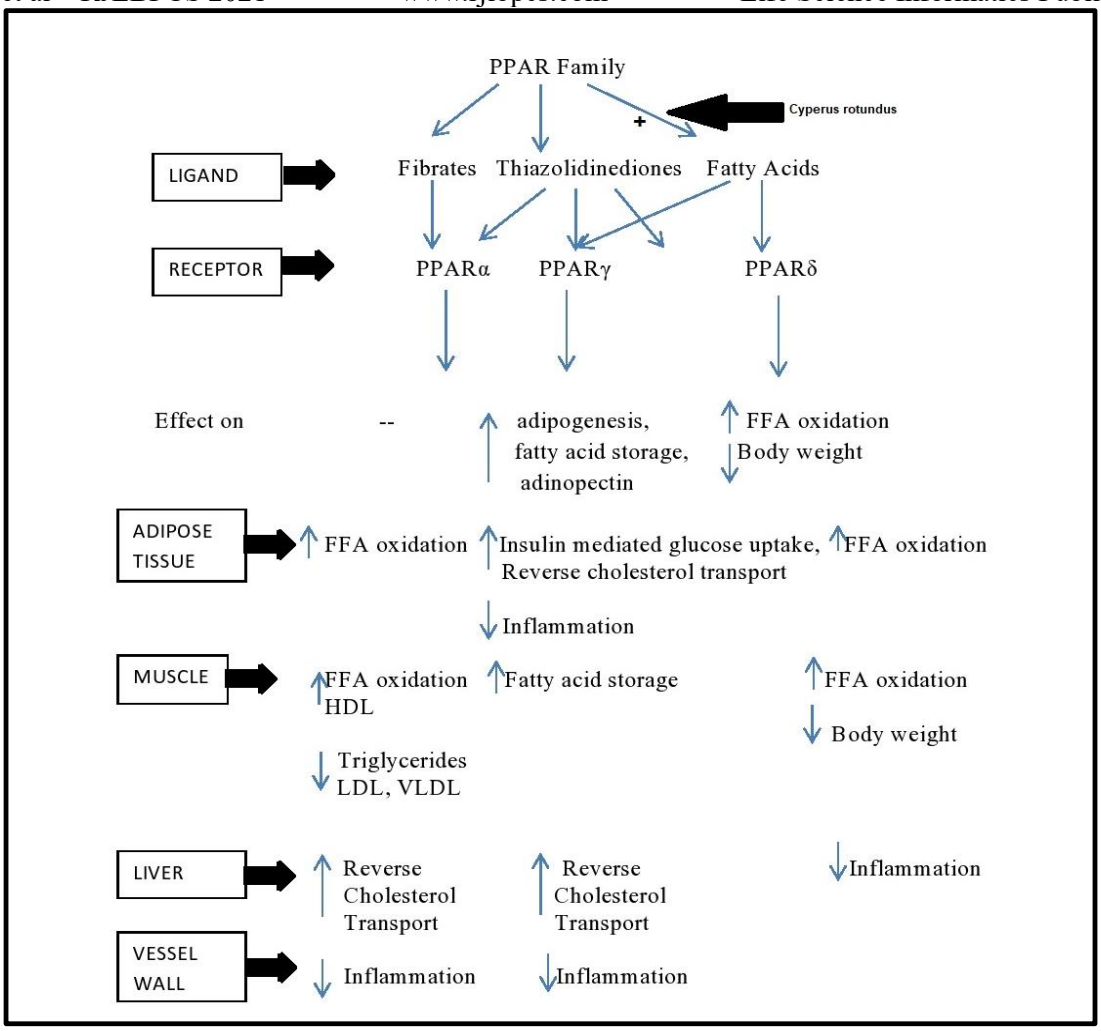

Fig 4- Flow diagram of PPAR family and its downstream process in presence of *Cyperus rotundus*

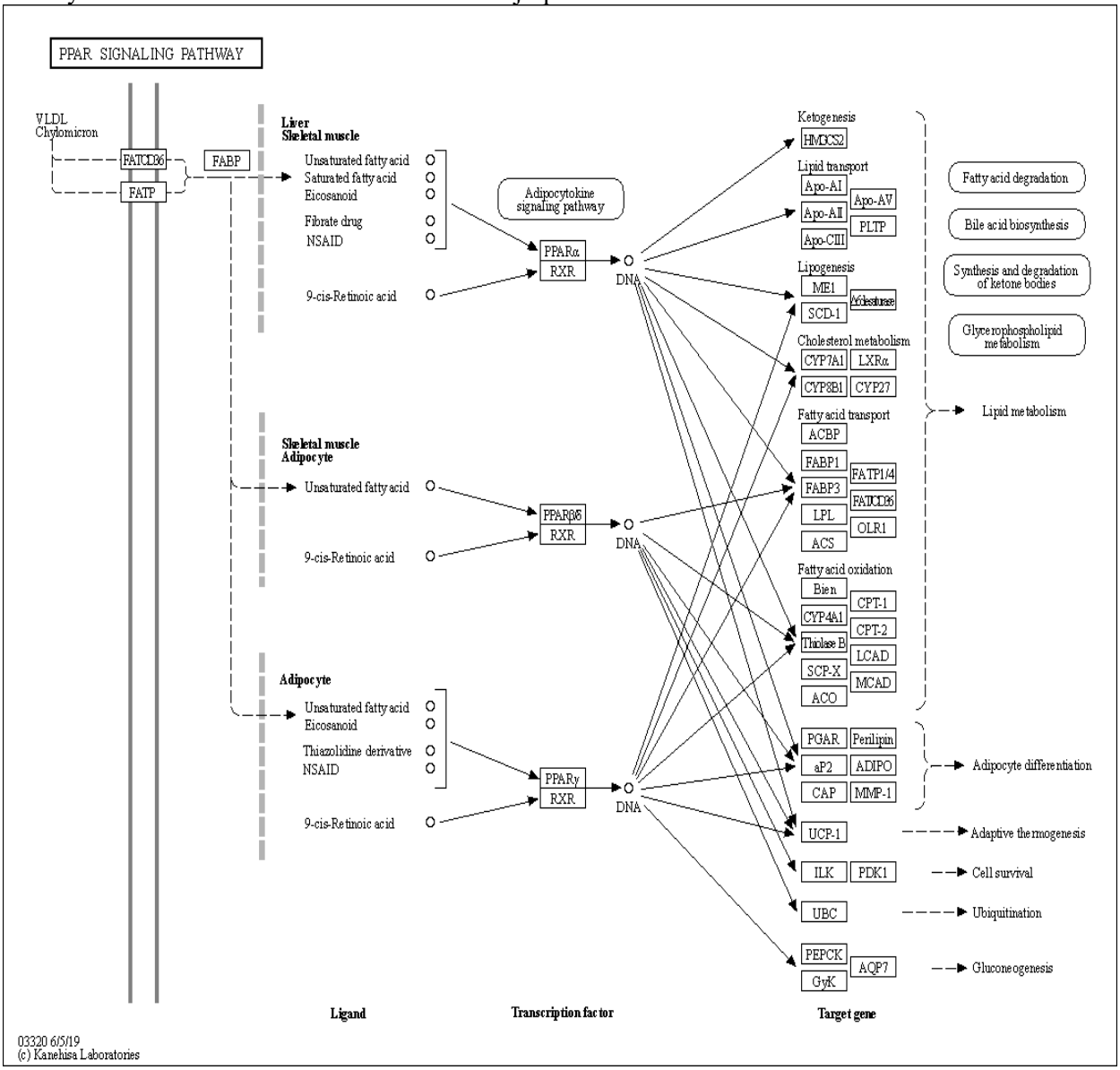

Fig. 5&6-Mechanism of the peroxisome proliferator activated receptor (PPAR) family- Here the possible regulation with respect to the plant phytoconstituents. The PPARs are the ligand induced or activated nuclear receptors for the all three isoforms of PPAR i.e. α, δ and γ, which get activated by a number of fatty acids and its derivative, besides they function as regulators in the biosynthesis, storage and metabolism of fats. Hence PPAR ligands have shown the importance of these receptors in terms of regulation of lipids and glucose equilibrium. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5813859/)

Source-KEGG Pathway

Table 4- Effect of CR on hyperlipidemia

Ref.	Hyperlipidemia	Treatment	Dose	Total Cholesterol (0-140mg/dl) in %	Triglyceride (0-100mg/dl)	HDL Cholesterol (0-60mg/dl)	LDL Cholesterol (0-60mg/dl)
8[30]		Ethanol Extract	Control				
			250mg/kg	105mg/dl =75%	75mg/dl=75%	42mg/dl=70%	45mg/dl= 75%
			500mg/kg	100mg/dl =71%	65mg/dl=65%	45mg/dl=75%	40mg/dl=66 %
9[29]		Ethanol Extract	control	20mg/dl (1.03±0.07)			
10[31]			45mg/kg	↑ 110%(1.14 ± 0.09) No change	↑ 101.46% (20mg/dl (1.14 ±0.09) NO CHANGE		
			220mg/kg	↑ 112.22% (1.16±0.07) NO CHANGE	↑ 137.69%(11.25 ± 1.17) NO CHANGE		
				178+7.66	174.6±7.35		
				128.34+3.32	115.12+ 14.43		
				123.4+2.22	106.6 +7.35		

5. Anti-diabetic-

Both overweight and obesity are linked to chronic low-grade inflammation by releasing pro-inflammatory cytokines from macrophage imbedded adipocytes [32]. These cytokines are thought to be at the core of the complications associated with diabetes, malfunction of metabolism of lipids, carbohydrate and proteins/ all these changes are collectively linked to increased risk of complication from the vascular diseases [33]. Clinically most patients can be categorized under type 1 (insulin dependent by diabetes) or type 2 (noninsulin dependent diabetes). For the treatment of type 2 diabetes many oral hypoglycemic drugs are administered like sulfonyl urea or biguanides, but they are associated with numerous side effects. This marks the major advantages for herbal medicine for its low incidence of serious side effects [34]. Oral daily administration of 500mg/kg of the extract significantly lowered down the blood glucose levels in rats with alloxan induced diabetes [35]. The scientist concluded that this anti-hyperglycemic activity can be attributed to its anti –oxidant activity of CR showed a strong DPPH radical scavenging action in-vitro. These results are converged with CR potential to suppress AGE formation and protein oxidation in a model of fructose mediated protein glycoxidation [36]. researchers have concluded that since this non-enzymatic glycation shown to correlate with severity of diabetes and its complication CR could be a candidate for targeting diabetic complication. Similarly, the ethanolic extract of CR rhizomes was evaluated for its antidiabetic activity in streptozotocin (STZ)-induced diabetic Swiss mice at dose levels of 250 and 500 mg/kg body weight revealing a significant antidiabetic activity, improvement in body weight, and reduction in elevated biochemical parameters such as SGPT, SGOT, cholesterol, and triglyceride levels [30]

Table 5- Effect of Cyperus rotundus on Hyperglycemia

Referenc	Dose Studied	Glucose	Hypoglycemic
[30]	Diabetic control	364.5±22.46	
	250mg/kg BW	181.95±14.50	49.91%
	500mg/Kg B. W	170.54±15.66	46.78%
[35]	Diabetic untreated	200mg/dl	
	200mg/kg	150 mg/dl	75%
	500mg/dl	120mg/dl	60%

6. Cardiovascular Disease

MetS atherosclerosis is the leading factor for CVD linked deaths. It is characterized by the high accumulation of lipids and leucocytes in blood vessels which leads to the formation of plaque. [37][38]. Development of metabolic syndrome is also pushed further by the regular consumption of fructose. Regular intake of high fructose diet elevates the blood pressure and glucose level, moreover this high fructose diet is linked to activate cardiac Fas-dependent and mitochondria-dependent and mitochondria –dependent apoptotic pathways and hence suppressed the main survival pathway. This provide the insights for one possible mechanism for increasing the cause of heart failure in metabolic syndrome's affected patient[39]. Gradually this accumulation causes the plaques to harden, causing narrowing of the arteries which hinders the flow of blood and causing it to rupture, and formation of a thrombus (blood clot). This can further block the oxygen-rich blood flow to various organs[40][41].Systemic inflammatory process is associated with promotion of plaque formation diagnosed as atherosclerosis[42][43]. A study conducted by Jahan et al.[44] on isoproterenol (ISO), a synthetic catecholamine, to find out the hypo-lipid emic activity of C. rotundus. In this study, observation was made that 200mg/kg b.w extract can potentially lower down the level of ISO-induced cytosolic enzymes and maintained the cardio membrane by reestablishing level of antioxidant enzymes in heart tissue. At high concentrations, ISO was shown to disturb the cardiac muscles, leading to oxidative stress induced cardio toxicity disturb cardiac muscles, leading to oxidative stress-induced cardiotoxicity[45]. In turn, cytosolic enzymes are released, leading to cell necrosis, contractile failure, and finally myocardial infarction. The tuber extract of C. rotundus contains activators of β-adrenoceptors (AR) that reduce obesity by stimulating thermogenesis of brown adipose tissue (3T3-F442 adipocytes). The body weight gain, organ weight (liver, kidney, and spleen), serum triglyceride level, and the total cholesterol level in obese rats can be significantly. reduced by orally administering 300 mg/kg of aqueous tuber extract of C. rotundus daily for 40 days along with a high-fat cafeteria diet (HFCD). A new herbal supplement containing the tuber extract of C. rotundus was suggested for controlling obesity[46]

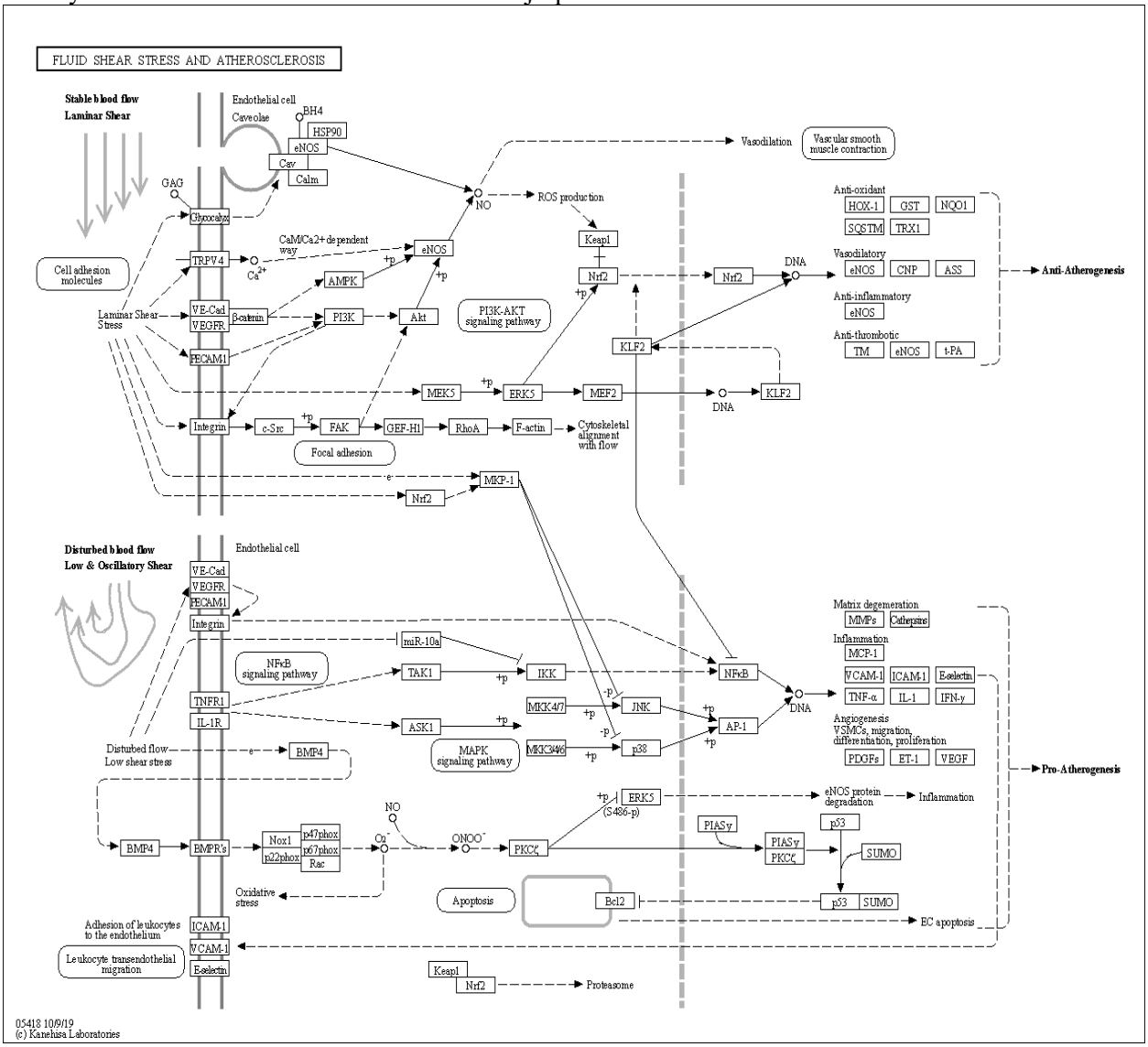

Fig8-Atherosclerosis signaling pathway Shear stress represents the frictional and resistance force of blood, which then exerts the pressure at the endothelial surface of the vessel wall and plays a key role in vascular biology. Therefore, it leads to progression of atherosclerosis. Continuous maintained laminar flow with increase in the shear stress start to up regulates the expressions of endothelial cell (EC) genes and proteins that are key protective factors against the atherosclerosis. The vital shear stress-induced transcription factors that mostly control the expression of these genes are- Kruppel-like factor 2 (KLF2) and nuclear factor erythroid 2-like 2 (Nrf2). Similarly On the other hand, low shear stress and disturbed flow with associated reciprocating, mostly causes the upregulates of the EC genes and proteins that create oxidative and inflammatory states in the artery wall, as result progression of atherogenesis. Important transcriptional events that reflect this condition of ECs in disturbed flow include the activation of activator protein 1 (AP-1) and nuclear factor kappaB (NF-kappaB).

Source -KEGG PATHWAY

Table 6- Effect of Cyperus rotundus on Cardioprotective

[76]		**ALT**	**%**	**AST**	**%**	**CK**	**%**	**LDH**	**%**	**TROPONIN**
	ISO	250		270		1.7		300		100%
	250mg/	200	80	220	81	1.4	82	220	73	60%
	500mg/	180	72	180	66	1.25	73	160	53	40%

Box 2- Studies and data specific to the above mentioned parameters in all the tables

1) Antioxidant –

1.1) Mean value of SOD in two studies from range of 200ug to 250ug is 45±0.2

1.2) Mean value of DPPH in range (Dose 25ug to 1000ug/ml) was found to be 60.92

1.3) Mean value of FRAP from range (Dose 200ug/ml to 100ug/ml was found to be 49 % of inhibition

1.4) Mean value from range of Dose from 1000ug to 400ug/ml was found to be 48.66% inhibition

2) **Anti-Inflammation** –

2.1) Mean value for anti- inflammation from xylene based edema in dose range of 5000ug/ml to 30000ug/ml was found to be 52.5% inhibition

3) **Hyperlipidemia** –

Mean value for hyperlipidemia from the range of 45mg/ml to 500mg/ml is observed to be 71.75 ±7.0 (Total Cholesterol),and 66.73±6.6(Triglyceride) level

4) Anti-Hyperglycemia

4.1) Mean values for glucose value in two studies were found to be 57.92 in dose range of 200mg/kg to 500mg/kg BW

5) **Cardio protective** –

5.1) Mean value for ALT in the range of 250mg/kg to 500mg/kg was found to be 60.8

5.2) Mean value for AST in the range of 250mg/kg to 500mg/kg was found to be 73.5

5.3) For CK the mean value for the range of 250mg/kg to 500mg/kg was 1.32

5.4) For Troponin, the mean value for the dose range from 250mg/kg to 500mg/kg was found to be 50.0

Table A. List of Plants under lekhanya dravya

Plants in dravya guna as per Ayurveda. These 10 plants are described as lekhanyia (Hypolipidemic or anti-obesity)

Name of drug	Latin name	Part used	Common name
Musta	*Cyprus rotundus*	Rhizome	Nutgrass
Kutha	*Saussurea lappa*	Root	Costus, Kuth, or Putchuk
Haridra	*Curcuma longa*	Rhizome	Turmeric
Daruharidra	*BerberisAristata*	Stem / Root	Indian Barberry
Vacha	*Acorus calamus*	Rhizome	Sweet flag
Ativisha	*Aconitum heterophyllum*	Tuber	Indian Atees
Katurohini	*Picrorrhiza kurroa*	Root	Kutki
Chitrak	*Plumbago Zeylanica*	Root bark	Ceylon leadwort, doctorbush or wild leadwort
Chirbilva	*Holoptelea integrifolia*	Bark	Indian elm or jungle cork tree
Hemvati	*Iris ensata*	Rhizome	Japanese iris or Japanese water iris

Table B

Plant's pharmacological activities .

S.No	plant part used	Solvent used for extraction	Pharmacological activity	References
1	Rhizomes	Ethanol,Acetone	Anti-oxidant property	[47] [48]
2	Rhizomes	Ethanol	wound healing	[49]
3	Rhizomes	Ethanol	anti-pyretic	[50]
4	Rhizomes	Methanol/petroleum ether/ethyl acetate	anti-diarrheal	[51]
5	Rhizomes	Hydro-ethanol	anti-hyperglycemic	[35][52]
6	Rhizomes	Ethanol	anti-microbial	[53]

7	Rhizomes	Ethanol	anti-convulsant	[54]
8	Rhizomes	Ethanol	anti-ulcer	[55]
9	Rhizomes	methanol	gastroprotective	[56]
10	Rhizomes	Ethanol	anti-histamine	[57]
11	Rhizomes	ethyl acetate	hepatoprotective	[58]
12	Rhizomes	Ethanol	anti-allergic	[59]
13	Rhizomes	methanol,hydro alcohol	cardioprotective and anti hyperlipidemic	[60]
14	rhizomes	ethanol	cytoprotective effect	[61]
15	Rhizomes	Ethanol	neuroprotective	[62]
16	Rhizomes	hexane	inhibition of brain Na+ K+ ATPase activity	[63]
17	Rhizomes	methanol	cytotoxic effect	[14] [64]
18	Rhizomes	hydroalchol	antiviral	[65]
19	Tubers	ethanol/ether /distilled water	anti-inflammatory	[66]
20	Tubers	water	anti-diarrheal	[67]
21	Tubers	water	anti-obesity	[46]
22	Tubers essential oil	N.A	ovicidal and larvicidal	[68]
23	Tubers	methanol	anti-malaria	[69][70]
25	Tubers	ethanol	Hypotensive	[71]
26	Tubers	water	anti-emetic	[72]
27	Tubers	NA	anti-cariogenic	[73]
28	Tubers	ethanol	anti-platelet	[74]
29	Essential oil	NA	Analgesic activity	[66]
30	Essential oil	NA	Anti-arthritic activity	[66]
31	Rhizome-essential oil	Ethanol	Anti-candida activity	[75]

2. CONCLUSION

Not much molecular biology and efforts for its understanding in the signaling pathway behind its several reported pharmacological actions have been reported and needs further studies. however, all these studies showed its protective response against all the diseases of MetS. The existing knowledge indicates its mechanism of action through its antioxidant, anti-inflammatory, hypolipidemic, properties, which are attributing to inhibition of NFkB, PKC, and capacity to direct the neutralization the free radicals thereby interrupting the free radical chain. Since its major phytochemical of oil of Cyperus rotundus include- α-copaene (11.4-12.1%), cyperene (8.411.7%), valerenal (8.7-9.8%), caryophyllene oxide (7.8-9.7%) and trans-pinocarveol (5.2-7.4%) [10] [12] which validates its medicinal properties. The experimental and clinical studies support its claims described in the Ayurvedic texts. However, based on the available data, future studies could be focused on its anti-angiogenic potential and also in wound healing as these two factors are important to combat the overall complication arising in Diabetes and other MetS based complication.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

FUNDING

None.

ACKNOWLEDGEMENT

NP and PM are thankful to their respective agencies ICMR AND UGC BHU for providing research fellowship**.**

CONFLICT OF INTEREST

Authors have no conflict of interest.

REFERENCES

1. National heart L and BI. Metabolic Syndrome | NHLBI, NIH. U.S Department of Health and Human Services.
2. Banerjee S, Debnath P, Debnath PK. Ayurnutrigenomics: Ayurveda-inspired personalized nutrition from inception to evidence. Vol. 5, Journal of Traditional and Complementary Medicine. National Taiwan University; 2015. p. 228–33.

3. Harvey AL. Natural products in drug discovery. Vol. 13, Drug Discovery Today. Elsevier Current Trends; 2008. p. 894–901.
4. Tabatabaei-Malazy O, Larijani B, Abdollahi M. Targeting metabolic disorders by natural products.Vol. 14, Journal of Diabetes and Metabolic Disorders. BioMed Central Ltd.; 2015 p. 1–21.
5. Hu QP, Cao XM, Hao DL, Zhang LL. Chemical Composition, Antioxidant, DNA Damage Protective, Cytotoxic and Antibacterial Activities of Cyperus rotundus Rhizomes Essential Oil against Foodborne Pathogens. Sci Rep. 2017 Mar 24 ;7.
6. Kakarla L, Katragadda SB, Tiwari AK, Kotamraju KS, Madhusudana K, Kumar AD, et al. Free radical scavenging, α-glucosidase inhibitory and anti-inflammatory constituents from Indian sedges, Cyperus scariosus R. Br and Cyperus rotundus L. Pharmacogn Mag .2016;12(47):S488–96.
7. Fraga CG, Leibovitz BE, Tappel AL. Lipid peroxidation measured as thiobarbituric acid-reactive substances in tissue slices: characterization and comparison with homogenates and microsomes. Free Radic Biol Med ;1988 4(3):155–61.
8. Ibrahim SRM, Mohamed GA, Alshali KZ, Al Haidari RA, El-Kholy AA, Zayed MF, et al. Lipoxygenase inhibitors flavonoids from Cyperus rotundus aerial parts. Rev Bras Farmacogn .2018 ;28:320–4.
9. Yazdanparast R, Ardestani A. In vitro antioxidant and free radical scavenging activity of Cyperus rotundus. J Med Food. 2007 Dec 1 ;10(4):667–74.
10. Hu QP, Cao XM, Hao DL, Zhang LL. Chemical Composition, Antioxidant, DNA Damage Protective, Cytotoxic and Antibacterial Activities of Cyperus rotundus Rhizomes Essential Oil against Foodborne Pathogens. Sci Rep 2017 Mar 24 7(1):1–9.
11. Soumaya KJ, Dhekra M, Fadwa C, Zied G, Ilef L, Kamel G, et al. Pharmacological, antioxidant, genotoxic studies and modulation of rat splenocyte functions by Cyperus rotundus extracts. BMC Complement Altern Med [Internet]. 2013 Feb 6 ;13(1):28.
12. Kilani-Jaziri S, Bhouri W, Skandrani I, Limem I, Chekir-Ghedira L, Ghedira K. Phytochemical, antimicrobial, antioxidant and antigenotoxic potentials of Cyperus rotundus extracts. South African J Bot. 2011 Aug 1;77(3):767–76.
13. Kilani S, Ledauphin J, Bouhlel I, Sghaier M Ben, Boubaker J, Skandrani I, et al. Comparative study of Cyperus rotundus essential oil by a modified GC/MS analysis method. Evaluation of its antioxidant, cytotoxic, and apoptotic effects. Chem Biodivers. 2008;5(5):729–42.
14. Kilani S, Ben Sghaier M, Limem I, Bouhlel I, Boubaker J, Bhouri W, et al. In vitro evaluation of antibacterial, antioxidant, cytotoxic and apoptotic activities of the tubers infusion and extracts of Cyperus rotundus. Bioresour Technol .2008 Dec;99(18):9004–8.

15. Tsoyi K, Jang HJ, Lee YS, Kim YM, Kim HJ, Seo HG, et al. (+)-Nootkatone and (+)-valencene from rhizomes of Cyperus rotundus increase survival rates in septic mice due to heme oxygenase-1 induction. J Ethnopharmacol .2011 Oct 11;137(3):1311–7.
16. Ryter SW, Alam J, Choi AMK. Heme oxygenase-1/carbon monoxide: From basic science to therapeutic applications. Vol. 86, Physiological Reviews. 2006. p. 583–650.
17. Huang B, He D, Chen G, Ran X, Guo W, Kan X, et al. α-Cyperone inhibits LPS-induced inflammation in BV-2 cells through activation of Akt/Nrf2/HO-1 and suppression of the NF-κB pathway. Food Funct .2018 May 1;9(5):2735–43.
18. Ma Y, Zhao Y, Zhang R, Liang X, Yin Z, Geng Y, et al. α-Cyperone Inhibits PMA-Induced EPCR Shedding through PKC Pathway. Biol Pharm Bull. 2017 ;40(10):1678–85.
19. Sivapalan SR. Medicinal uses and Pharmacological activities of Cyperus rotundus Linn-A Review. Int J Sci Res Pub . 2013;3(5).
20. Dang GK, Parekar RR, Kamat SK, Scindia AM, Rege NN. Antiinflammatory activity of Phyllanthus emblica, Plumbago zeylanica and Cyperus rotundus in acute models of inflammation. Phyther Res ;2011 Jun 25(6):904–8.
21. Seo WG, Pae HO, Oh GS, Chai KY, Kwon TO, Yun YG, et al. Inhibitory effects of methanol extract of Cyperus rotundus rhizomes on nitric oxide and superoxide productions by murine macrophage cell line, RAW 264.7 cells. J Ethnopharmacol. 2001 Jun ;76(1):59–64.
22. Rocha FG, de Mello Brandenburg M, Pawloski PL, da Silva Soley B, Angelim Costa SC, Meinerz CC, et al. Preclinical study of the topical anti-inflammatory activity of Cyperus rotundus L. extract (Cyperaceae) in models of skin inflammation. J Ethnopharmacol. 2020 Feb 23 ;254:112709.
23. Ahn JH, Lee TW, Kim KH, Byun H, Ryu B, Lee KT, et al. 6-Acetoxy Cyperene, a Patchoulane-type Sesquiterpene Isolated from Cyperus rotundus Rhizomes Induces Caspase-dependent Apoptosis in Human Ovarian Cancer Cells. Phyther Res. 2015 Sep 1 ;29(9):1330–8.
24. Favarin DC, Robison De Oliveira J, Freire De Oliveira CJ, De A, Rogerio P. Potential Effects of Medicinal Plants and Secondary Metabolites on Acute Lung Injury. Biomed Res Int .2013 2013:12.
25. Kim HK, Nelson-Dooley C, Della-Fera MA, Yang JY, Zhang W, Duan J, et al. Genistein decreases food intake, body weight, and fat pad weight and causes adipose tissue apoptosis in ovariectomized female mice. J Nutr [Internet]. 2006 Feb 1 [cited 2021 Mar 30];136(2):409–14.
26. Imtiyaj Khan M, Sri Harsha PSC, Giridhar P, Ravishankar GA. Pigment identification, antioxidant activity, and nutrient composition of Tinospora cordifolia (willd.) Miers ex Hook. f & Thoms fruit. Int J Food Sci Nutr. 2011 May;62(3):239–49.
27. Spalletta S, Flati V, Toniato E, Di Gregorio J, Marino A, Pierdomenico L, et al. Carvacrol reduces

adipogenic differentiation by modulating autophagy and ChREBP expression. PLoS One [Internet]. 2018 Nov 1 ;13(11).

28. Farmer SR. Transcriptional control of adipocyte formation [Internet]. Vol. 4, Cell Metabolism. NIH Public Access; 2006; p. 263–73.
29. Lemaure B, Touché A, Zbinden I, Moulin J, Courtois D, Macé K, et al. Administration of Cyperus rotundus tubers extract prevents weight gain in obese Zucker rats. Phyther Res ;2007 Aug 21(8):724–30.
30. Singh P, Khosa RL, Mishra G, Jha KK. Antidiabetic activity of ethanolic extract of Cyperus rotundus rhizomes in streptozotocin-induced diabetic mice. In: Journal of Pharmacy and Bioallied Sciences. Medknow Publications; 2015 . p. 289–92.
31. Fayaz P. Pharmacological screening of aqueous extracts of cyperus rotundus linn., for anti-obesity and cardio vascular properties (Doctoral dissertation, RGUHS).
32. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity & inflammation: The linking mechanism & the complications. Arch Med Sci 2017;13(4):851–63
33. Shi J, Fan J, Su Q, Yang Z. Cytokines and Abnormal Glucose and Lipid Metabolism Vol. 10, Frontiers in Endocrinology. Frontiers Media S.A.; 2019. p. 703.
34. Luna B, Feinglos MN. Oral Agents in the Management of Type 2 Diabetes Mellitus. Vol.63, American Family Physician. 2001 May. Available from: www.aafp.org/afpAMERICANFAMILYPHYSICIAN1747
35. Raut NA, Gaikwad NJ. Antidiabetic activity of hydro-ethanolic extract of Cyperus rotundus in alloxan induced diabetes in rats. Fitoterapia. 2006 Dec;77(7–8):585–8.
36. Ardestani A, Yazdanparast R. Cyperus rotundus suppresses AGE formation and protein oxidation in a model of fructose-mediated protein glycoxidation. Int J Biol Macromol 2007 Dec 1;41(5):572–8
37. Eckel RH, Barouch WW, Ershow AG. Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases working group on the pathophysiology of obesity-associated cardiovascular disease Vol. 105, Circulation. Circulation; 2002 p. 2923–8.
38. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: Process, indicators, risk factors and new hopes. Vol. 5, International Journal of Preventive Medicine. Isfahan University of Medical Sciences (IUMS); 2014 p. 927–46. Available from: /pmc/articles/PMC4258672/
39. Bantle JP. Dietary fructose and metabolic syndrome and diabetes Vol. 139, Journal of Nutrition. American Society for Nutrition; 2009 p. 1263S. Available from: /pmc/articles/PMC2714385/
40. Zaman AG, Helft G, Worthley SG, Badimon JJ. The role of plaque rupture and thrombosis in

coronary artery disease. Vol. 149, Atherosclerosis. Atherosclerosis; 2000. p. 251–66.

41. Bui QT, Prempeh M, Wilensky RL. Atherosclerotic plaque development. Vol. 41, International Journal of Biochemistry and Cell Biology. Int J Biochem Cell Biol; 2009. p. 2109–13.
42. Arida A, Protogerou AD, Kitas GD, Sfikakis PP. Systemic inflammatory response and atherosclerosis: The paradigm of chronic inflammatory rheumatic diseases . Vol. 19, International Journal of Molecular Sciences. MDPI AG; 2018
43. Manduteanu I, Simionescu M. Inflammation in atherosclerosis: A cause or a result of vascular disorders? . Vol. 16, Journal of Cellular and Molecular Medicine. Wiley-Blackwell; 2012 p. 1978–90.
44. Majid A, Sayer SA. Protective effect of phenolic extract of Cyperus rotundus rhizomes on myocardial infarction induced by isoproterenol in female rats. InIOP Conference Series: Materials Science and Engineering 2018 Dec 1 (Vol. 454, No. 1, p. 012005).
45. Upaganlawar A, Gandhi H, Balaraman R. Isoproterenol induced myocardial infarction: Protective role of natural products. J Pharmacol Toxicol. 2011;6(1):1–17.
46. K, A., D. M, and B. P. “Anti-obesity potential of Cyperus rotundus l. Aqueous tuber extract in rats fed on high fat cafeteria diet”. Asian Journal of Pharmaceutical and Clinical Research, Apr. 2014;Vol. 7, No.2: pp. 88-92,
47. Pal D, Dutta S. Evaluation of the antioxidant activity of the roots and rhizomes of Cyperus rotundus L. Indian J Pharm Sci. 2006 ;68(2):256–8.
48. Kamala A, Middha SK, Gopinath C, Sindhura HS, Karigar C. In vitro antioxidant potentials of Cyperus rotundus L. rhizome extracts and their phytochemical analysis. Pharmacogn Mag. 2018 Apr 1;14(54):261–7.
49. Puratchikody A, Devi C, Nagalakshmi G. Wound healing activity of Cyperus rotundus Linn. Indian J Pharm Sci. 2006;68(1):97–101.
50. Gupta MB, Palit TK, Singh N, Bhargava KP. Pharmacological studies to isolate the active constituents from Cyperus rotundus possessing anti-inflammatory, anti-pyretic and analgesic activities. Vol. 59, The Indian journal of medical research. 1971 .p. 76–82. Available from: https://pubmed.ncbi.nlm.nih.gov/5574385/
51. Uddin SJ, Mondal K, Shilpi JA, Rahman MT. Antidiarrhoeal activity of Cyperus rotundus. Fitoterapia. 2006 Feb;77(2):134–6.
52. Tran HHT, Nguyen MC, Le HT, Nguyen TL, Pham TB, Chau VM, et al. Inhibitors of α -glucosidase and α -amylase from Cyperus rotundus. Pharm Biol 2014 Jan 18;52(1):74–7. Available from: http://www.tandfonline.com/doi/full/10.3109/13880209.2013.814692
53. Sharma SK, Singh AP. Antimicrobial investigations on rhizomes of Cyperus rotundus Linn [Internet]. Vol. 3, Der Pharmacia Lettre. 2011;Pg 427–31. Available from:

https://www.researchgate.net/publication/279558303_Antimicrobial_investigations_on_rhizomes_of_Cyperus_rotundus_Linn

54. Rawal SK. ANALGESIC AND ANTI-CONVULSANT ACTIVITIES OF CYPERUS ROTUNDUS (LINN.). Int J Pharm Educ Res. 2019 Apr 8;1(1):10–3.
55. Ahmad M, Bin Rehman A, Muhammad N, Younus M, Wazir A. Assessment of anti-inflammatory, anti-ulcer and neuro-pharmacological activities of Cyperus rotundus Linn. Vol. 27, Pak. J. Pharm. Sci. 2014.
56. Güldür ME, Ozgönül A, Kilic IH, Sögüt O, Ozaslan M, Bitiren M, et al. Gastroprotective effect of Cyperus rotundus extract against gastric mucosal injury induced by ischemia and reperfusion in rats. Int J Pharmacol. 2010;6(2):104–10.
57. Sangeetha DP, Banumathi V, Ganthimathi S, Shameem FR. ANTI-HISTAMINE ACTIVITY OF AMIRTHA SANJEEVI KULIGAI (PILL). Int J Ayurveda Pharma Res .2015 Dec 15 :2(5). Available from: https://ijapr.in/index.php/ijapr/article/view/212
58. (13) (PDF) Hepatoprotective activity of rhizomes of Cyperus rotundus linn against carbon tetrachloride-induced hepatotoxicity [Internet]. [cited 2021 Mar 30]. Available from: https://www.researchgate.net/publication/287900849_Hepatoprotective_activity_of_rhizomes_of_Cyperus_rotundus_linn_against_carbon_tetrachloride-induced_hepatotoxicity
59. Jin JH, Lee DU, Kim YS, Kim HP. Anti-allergic activity of sesquiterpenes from the rhizomes of Cyperus rotundus. Arch Pharm Res. 2011 Feb ;34(2):223–8.
60. Jahan N, And K-U-R, Ali S. Cardioprotective and Antilipidemic Potential of Cyperus rotundus in Chemically Induced Cardiotoxicity. Int J Agric Biol [Internet]. 2012 [cited 2021 Mar 30]; Available from: http://www.fspublishers.org
61. Zhu M, Luk HH, Fung HS, Luk CT. Cytoprotective effects of Cyperus rotundus against ethanol induced gastric ulceration in rats. Phyther Res. 1997 Aug 1;11(5):392–4.
62. Kumar w, Khanum F. Hydroalcoholic extract of cyperus rotundus ameliorates H2O 2-induced human neuronal cell damage via its anti-oxidative and anti-apoptotic machinery. Cell Mol Neurobiol. 2013 Jan;33(1):5–17.
63. Ngamrojanavanich N, Manakit S, Pornpakakul S, Petsom A. Inhibitory effects of selected Thai medicinal plants on Na+,K+-ATPase. Fitoterapia 2006 Sep;77(6):481–3.
64. Mannarreddy P, Denis M, Munireddy D, Pandurangan R, Thangavelu KP, Venkatesan K. Cytotoxic effect of Cyperus rotundus rhizome extract on human cancer cell lines. Biomed Pharmacother . 2017 Nov 1 ; 95:1375–87.
65. Soltan MM, Zaki AK. Antiviral screening of forty-two Egyptian medicinal plants. J Ethnopharmacol. 2009 Oct 29 126(1):102–7.
66. Biradar S, Kangralkar VA, Mandavkar Y, Thakur M, Chougule N. Antiinflammatory,

antiarthritic, analgesic and anticonvulsant activity of cyperus essential oils. Vol. 2, International Journal of Pharmacy and Pharmaceutical Sciences. 2010.

67. Daswani P, Brijesh S, Tetali P, Birdi T. Studies on the activity of Cyperus rotundus Linn. tubers against infectious diarrhea. Indian J Pharmacol 2011 June ;43(3):340–4.
68. NOPR: Ovicidal and larvicidal activities of Cyperus giganteus Vahl and Cyperus rotundus Linn. essential oils against Aedes albopictus (Skuse) .
69. Weenen H, Nkunya MHH, Bray DH, Mwasumbi Kinabo LBLS, Kilimali VAEB. Antimalarial activity of Tanzanian medicinal plants. Planta Med . 1990;56(4):368–70.
70. Thebtaranonth C, Thebtaranonth Y, Wanauppathamkul S, Yuthavong Y. Antimalarial sesquiterpenes from tubers of Cyperus rotundus: structure of 10,12-Peroxycalamenene, a sesquiterpene endoperoxide. Phytochemistry . 1995 ; 40(1):125–8.
71. Ahmad M, Mahayrookh, Mehjabeen, Rehman A, Jahan N, Ahmad S. HYPOTENSIVE, SPASMOLYTIC AND SPASMOGENIC EFFECT OF CYPERUS ROTUNDUS CRUDE EXTRACT AND ITS FRACTIONS. undefined. 2013;
72. Shinde S, Phadke S, Bhagwat AW. Effect of Nagarmotha (Cyperus rotundus linn) on reserpine-induced emesis in pigeons . Vol. 32, Indian Journal of Physiology and Pharmacology. 1988. p. 229–30.
73. Yu HH, Lee DH, Seo SJ, You YO. Anticariogenic properties of the extract of Cyperus rotundus. Am J Chin Med [Internet]. 2007;35(3):497–505.
74. Seo EJ, Lee DU, Kwak JH, Lee SM, Kim YS, Jung YS. Antiplatelet effects of Cyperus rotundus and its component (+)-nootkatone. J Ethnopharmacol [Internet]. 2011 Apr 26 ;135(1):48–54.
75. Duarte MCT, Figueira GM, Sartoratto A, Rehder VLG, Delarmelina C. Anti-Candida activity of Brazilian medicinal plants. J Ethnopharmacol 2005 Feb 28; 97(2):305–11.
76. Khwaja S, Mahmood T, Siddiqui HH. Effect of ethanolic extract of Cyperus rotundus L. against isoprenaline induced cardiotoxicity.Indian Journal Of Experimental Biology.2016 Oct,Vol.54:670-675