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Reaserch article

Cyperus Rotundus in the Management of Metabolic Syndrome Benefit in the Treatment of Metabolic Syndrome

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ABSTRACT

Cyperus rotundus, (Cyperaceae), commonly known as the Nagarmotha (H) and Nut grass (E). Its pharmacological claims are anti-inflammatory, anti-pyretic, diuretic, wound healing property, post-parturition use and other reproductive disorders in females. In Charak Samhita, it 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 key words 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 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 found to be effective in the management data

Conclusion: We found that Cyperus rotundus is found to be effective in the management of MetS in clinical studies and also in experimental models. Some papers have highlighted the mechanistic approach of its phytoconstituents with respect to various diseases of MetS, which is mainly through its anti- inflammatory and antioxidant potentials

Keywords: Metabolic Syndrome; Cyperus rotundus; AYUSH; phytoconstituents; signaling pathways; Food Supplement

INTRODUCTION

The Metabolic syndrome (MetS) is a collection of obesity, raised blood pressure (BP), blood sugar, then atherosclerosis. It is eminent by a pool of interrelated atherogenic based risk factors which includes oxidative stress (OS), dyslipidemia, hypertension, diabetes, obesity, insulin resistance (IR), and lifestyle factors such as dietary patterns and physical idleness. Hyperglycaemia and hyperlipidemia are the primary causes resulting to hypertension and atherosclerosis. Abnormal level of inflammatory cytokines, reactive oxygen species, dysregulated lipid metabolism and insulin resistances 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 ponder on five medical ailments as a diagnosis guideline which includes following key point:

- 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 then environmental factors are responsible for manifestation of MetS. It is considered as "life style related non communicable chronic diseases" (NCDs) so its prevention from early age is recommended. The basic cause behind the manifestation of all the diseases of MetS, appears to chronic inflammation, resistance of insulin, and the visceral based obesity. These outcomes create the irregular adipocyte

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with M-1 macrophage infiltration and abnormal secretion of the adipokines for an example adiponectin and leptin, increased discharge 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 poor compliance in patients[1].Thus several new researches 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, AYUSH system of health care includes Ayurveda, yoga, and Unani, Siddha and Homeopathy. They have their own Materia-medica with 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 counseling (Satwavajaya) and medicines (Youkti Vyapasharya). He has emphasized more to regulate the quality, amount and time of feeding, customized to a person, based on their body and mind constitution (Prakrati), season and age indicating towards personalized medication [2]. The goals of therapy are to treat the underlying cause of the syndrome, to reduce morbidity, and to 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 relationship to natural sources. Among 19 natural based drugs that have been approved for worldwide marketing between the years 2005–2010, the 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, 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 (CR) in the management of MetS by depicting the probable role of the plant as whole or the reported active phytoconstituents on the mechanistic pathway leading to 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.

MATERIALS AND METHODS

We have searched the literature using PubMed, and Web of Science's database with the key words 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 lists 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 the PubMed (250) and Web of Sciences (226) based on the mentioned keywords with (Fig 1). Further these were processed by using Mendley software to screen out duplications and total of 160 were screened out. After that from these 160 we included those papers where studies carried on 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, Hypolipidaemic 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).

Figure1: Study selection criteria.

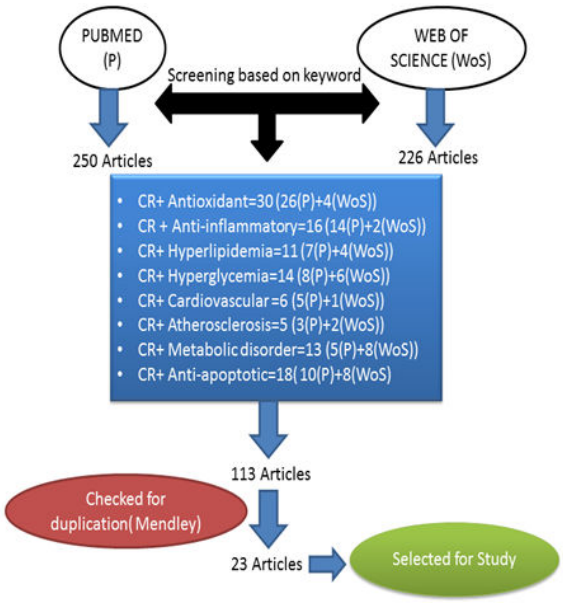
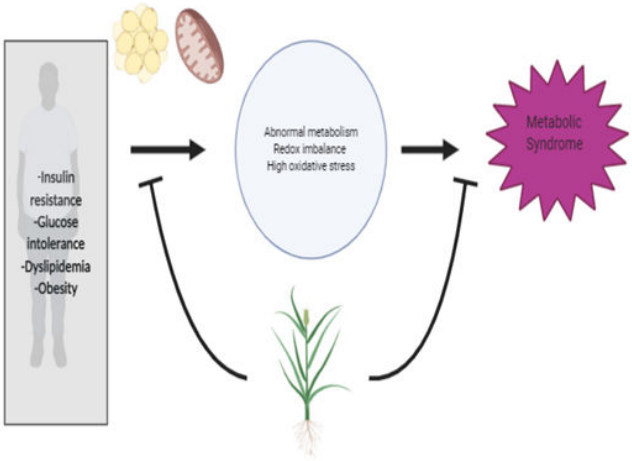


Figure2: Overall effect of Cyperus rotundus on metabolic syndrome



Overall effect of cyperus rotundus on metabolic syndrome

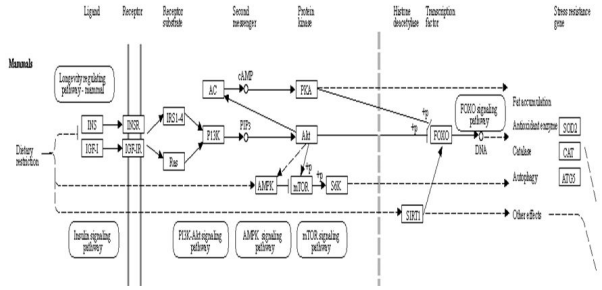
PLANT DESCRIPTION

- Kingdom: Plantae
- Subkingdom: Tracheophytes-Vascular plants
- Super division:Spermatophyta (seed plants)
- Division: Magnoliophyta-Flowering plants
- Class: Liliopsida (Monocotyledons)
- Subclass: Commelinids
- Order:Cyperales
- Family: Cyperaceae-Sedge family
- Genus:Cyperus L. Flat sedge
- Species: C. rotundus L.-nutgrass

BIOLOGICAL PROPERTIES IN THE CLASSICAL AYURVEDIC TEXTS ARE AS FOLLOW

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 to hypertension, cardio-vascular complications and other diabetic complications. MetS is linked to systemic based inflammatory progressions and increased the making of cytokines. That the oxygen centered free radicals further reduce NO bioavailability, resulting to vasoconstriction mediated hypertension and thrombus formation. Antioxidants may be divided in to enzymatic and non-enzymatic and the later 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 anti oxidant have been included in the table to shows the effect of dosage and its outcomes. (Table 1(a)). **Role of nutrient sensing pathway and its effect on oxidative stree**



FOXO is a trans-active gene concerned with the resistance to oxidative stress. The Nutrient sensing pathway such as the growth factor and TOR pathway can support longevity. In mammals these nutrient sensing pathway are down regulated through insulin like growth factor and TOR pathway deactivating the PI-3K-Akt-TOR intracellular signaling cascade and therefore initiating 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

Table1a: Effect of Cyperus rotundus on Reactive oxygen species (ROS).

S.No	MetS Factors	Dose	Parameters in %	GSH	SOD	CATALASE	ABTS	DPPH	FRAP	LPO(TBAR)	In vitro
1[9]	Anti-Oxidant	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 es sential oil on DPPH radicals			
	200 µg/ml				15%(0.15n m)		
	400 µg/mL						
					35%(0.35n m)		
	600 µg/mL				55%(0.55n m		
	800 µg/mL				65%(0.65n m)		
	1000 µg/ml				74%(0.74n m)		
3[11]	1mg/ml					15%	In vitro
	2mg/ml					60%	
	4mg/ml					70%	
4[12]	10ug/assay	5 ±3 %					In vitro
	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	32±1.5%
	30ug/assay	35.5±2%
	100ug/ assay	62.5±0.9%
	300ug/ assay	83.4±2.5%
	1000ug/ assay	89.8±4

ANTI-INFLAMMATORY

The anti-oxidant and the antiinflammation have an interlinking effects of anti-inflammation are interlinked with the anti-oxidant which reduce the reactive oxygen species (ROS) and nitric-oxide (NO) production, reduce the lipid peroxidation via the modulation in cell-signalling pathways and inflammation mediators [14]

Hence this cross talk was analysed by one of the studies where the rhizomes of Nutgrass were utilized as a typical traditional medicine for the management of inflammatory ailments. '(+)-Nootkatone and (+)-valencene derived from the rhizomes of Nutgrass increased the existence rates in septic mice because of "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 based enzyme mainly catalyzes the rate-limiting step in the Heme-degradation ,leading to the assembly of ferric ions, biliverdin, and this gets transformed into bilirubin by 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, HO-1 provides cytoprotective, anti-apoptotic, and immunomodulatory effects. This HO-1/CO complex can play a useful role in the change 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 appears the increase and finding of HO-1-inducible agents from Cyperus rotundus may have countless potential for beneficial intervention in such systemic inflammatory disorder.

In another study "α-Cyperone," one 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 stands to attribute vascular barrier integrity within the vascular disease and this takes part in systemic disease[17].(Since EPCR could even be the foremost member in 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 (PC) anticoagulant pathways play a vital role within the proper regulation in process of inflammation. Protein C is triggered on the surface of endothelial cells by the thrombin and thrombomodulin complex, is a process which may be additionally improved when PC binds to its membrane receptor, the endothelial-cell protein C receptor (EPCR)[17] . Also, there's an appearance of EPCR on the endothelium of big blood vessels which cause the increased concentration of PC 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 causes inhibition EPCR shedding, as shown via suppression PMA (Phorbol-12-Myristate-13-Acetate)-induced EPCR shedding through constraining 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 observation α-Cyperone constrains PMA-induced EPCR shedding via PKC pathway, this specify an experimental basis for further research on the 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 hydroalcoholic extract (70% alcohol) has shown anti-inflammatory action against the 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 edema 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 it has shown inhibition of NO and O2 production, induced by interferon-

gamma plus lipopolysaccharide, which is attributed to down regulation of iNOS, mRNA and protein expression. Its methanolic extract reduced the phorbol ester (PMA) induced production of O2. [21]. Another study published by Fernanda and coworkers in 2020, have demonstrated protection against inflammation by topical application of C. rotundus extract on a skin model, signifying that the extract might be a possible new therapeutic tool for the treatment of inflammatory disorders[22].

Systemic Inflammatory response: Inflammatory immune response necessitates the employment of leukocytes at the spot of inflammation upon foreign insult. Since the Chemokines are minor chemoattractant peptides that specify the directional signals for the cell operating and thus are vital for protective host response. In addition, it regulates the plethora of biological processes of hematopoietic cells to lead the cellular activation, differentiation and survival. The chemokine based signal is transduced by chemokine receptors (G-protein coupled receptors) expressed on the immune cells. After receptor activation, the alpha- and beta-gamma-subunits of G protein dissociate to activate diverse downstream pathways resulting in cellular polarization and actin reorganization. Various members of small GTPases are involved in this process. Induction of nitric oxide and production of reactive oxygen species are as well regulated by chemokine signal via calcium mobilization and diacylglycerol production. Source-KEGG Pathway.

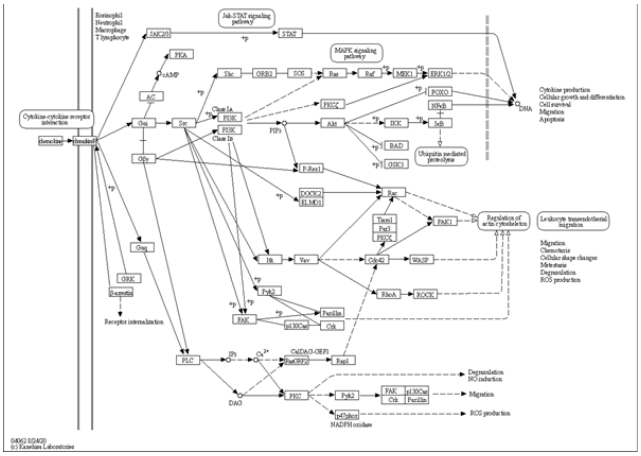


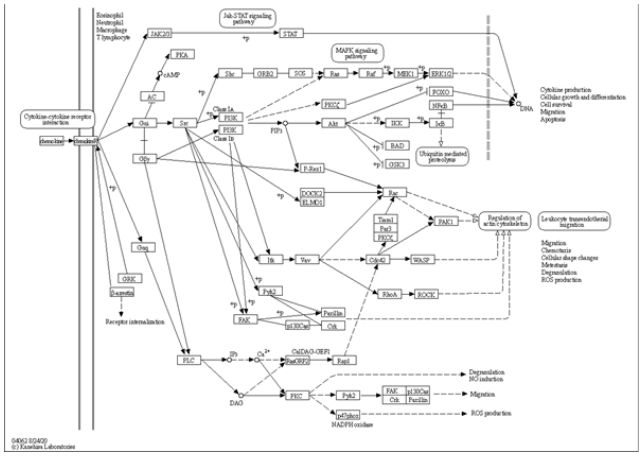
Table2: Effect of Cyperus rotundus on Anti-inflammatory.

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	

ANTI –APOPTOTIC

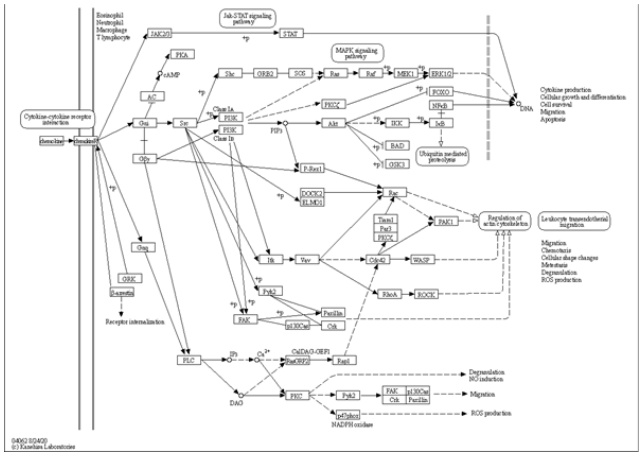
In one of the study CR rhizome's derived 6-acetoxy cyperene has shown the inhibitory effect on cell progression of ovarian based cancer (A2780, SKOV3 and OVCAR3) and endometrial cancer (Hec1A and Ishikawa) cells[23]. 13 -isolated sesquiterpenes from n-hexane some patchoulane-type compounds, but not eudesmane-type compounds, showed moderate cytotoxic activity. In precise, the patchoulane sesquiterpenes 6-acetoxy cyperene had the most powerful cytotoxicity and 6-acetoxy cyperene induced apoptosis, as observed by the accumulation of sub-G1 and apoptotic cells. Furthermore, the usage 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 ca spase dependentapoptosis 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 stimulated via the RAGE which in order participate in apoptosis.



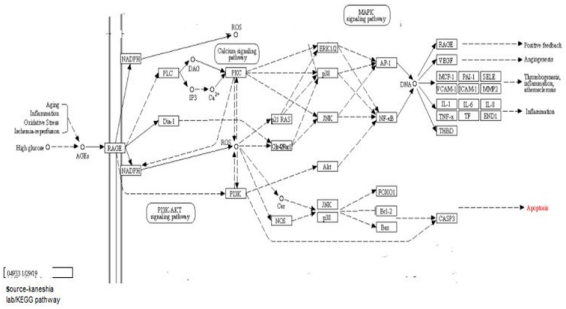
ANTI-OBESITY

A numeral of studies have confirmed that natural compound lik e epigallocatechingallate(EGCG)[24],quercetin[8],psynephrine, (27)genistein[25],esculetin,(29),berberine[26], resveratrol(31), guggulsterone(32) and capsaicin(33)(reference from 25-33 is not mentioned anywhere) 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) [27]



As this process further initiates the adipogenicity based transcription factors expression comprising CCAAT-enhancer-binding proteins (C/EBPα) and peroxisome proliferator-activated receptors (PPAR-γ). C/EBP and PPAR are the significant transcriptional regulators of adipogenesis and are required for the synthesis of numerous adipocyte associated functional proteins. C/EBP up-regulation intervenes the downstream up-regulation of PPAR and C/EBP expression [28]. Significant studies have demonstrated that Cyperus rotundus inhibits weight increase, exclusive of affecting food consumption or inducing any harmfulness. In the in-vitro study, 250 micro/mL of this extract was able to incite the lipolysis in 3T3-F442 adipocytes suggesting that this medicinal plant comprises of activators of beta-adrenoceptors (AR). It was established that administration of 45 or 220 mg/kg/day of C. rotundus tubers hexane extract for 60 days in Zucker rats induced a substantial reduction in weight gain without affecting food consumption or inducing toxicity [29]. Since pre-adipocytes lack the lipolytic activity until they are differentiated to a mature adipocytes.

Figure4: Flow diagram of PPAR family and its downstream process in presence of Cyperus rotundus.



Mechanism of the peroxisome proliferator activated receptor (PPAR) family and their regulation with respect to a plant phytoconstituents.The PPARs is the major 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.

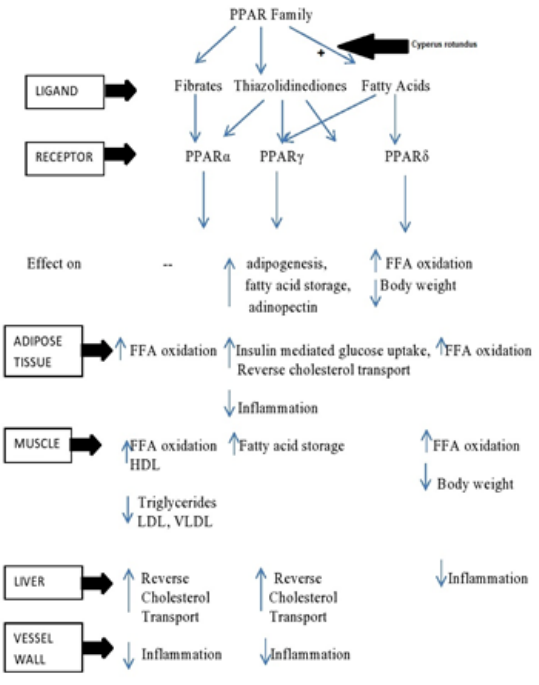


Table 3: Effect of CR on hyperlipidemia.

S.no	Hyperlipidemia	Treatment	Dose	Total Cholesterol		Triglyceride	HDL Cholesterol	LDL Cholesterol
				(0-140mg/dl) in %		(0-100mg/dl)	(0-60mg/dl)	(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)				
			45mg/kg	↑ 110%(1.14 ± 0.09)	↑ 101.46% (20mg/dl (1.14 ±0.09) NO CHANGE			
				No change				
			220mg/kg	↑ 112.22%	↑ 137.69%(			
				(1.16± 0.07)	11.25 ± 1.17			
				NO CHANGE	No change			
10[31]			Diabetic control	178+7.66	%	174.6±7.35	%	
			250mg/kg BW	128.34+3.32	72=5.22	115.12+ 14.43	65.9=14.40	
			500mg/Kg B.W	123.4+2.22	69+	106.6	61.03=7.5	
						7.35		

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) or type 2 (non insulin dependent). 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]. Daily oral administration of 500mg/kg of the extract considerably reduced the blood glucose levels in rats with alloxan induced diabetes [35]. The scientist established 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 250 and 500 mg/kg B.W of dose level body revealed a substantial antidiabetic activity, also improvement in body weight, and reduction in elevated biochemical parameters such as SGPT, SGOT, cholesterol, and triglyceride levels [30]

Fig7. Development of Type 2 diabetes is associated with insulin resistance. Factors like TNF alpha, FFA and cellular stress brings insulin resistance by inhibiting IRS-1 process .Stimulation of molecular mechanisms being represented by Serine/Threonine based phosphorylation, whereas interaction with SOCS regulates the expression, alteration of cellular localization. JNK,ERK,IKKbeta,PKCzeta, PKC-theta and mTOR are involved in this course. Due to hyperglycemia it has been proposed to lead the production of ROS in beta cells. With causing cellular components damage including PDX1- Loss of PDX-1, a serious regulator of insulin promoter activity, has also been proposed as an important mechanism leading to beta-cell dysfunction.

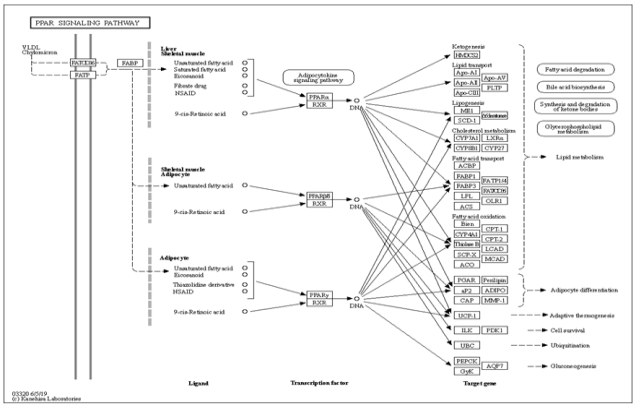


Table4: Effect of Cyperus rotundus on Hyperglycemia.

11	anti-hyperglycemic	Reference	Dose Studied	Glucose	Hypoglycemic percentage
		10[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%
		11[35]	Diabetic untreated	200mg/dl	
			200mg/kg	150 mg/dl	75%
			500mg/dl	120mg/dl	60%

CARDIOVASCULAR DISEASE

MetS atherosclerosis is the leading factor for CVD linked deaths. . It is characterized due to the high accumulation of lipids as well as leucocytes in the blood vessels which leads to the plaque formation . [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, this higher fructose diet is linked to activate cardiac linked Fas-dependent and mitochondria-dependent and mitochondria –dependent apoptotic pathways and hence suppressed the main survival pathway. This postulate 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 the narrowing of the arteries which hinders average flow of blood as well as causing it to rupture , leading to the thrombus (blood clot). This condition could foster the blockage of oxygen rich flow of blood to the 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 possibly lower down the level of ISO-induced cytosolic enzymes and maintained the cardio membrane by reestablishing level of antioxidant enzymes in heart tissue. At the higher concentration ,ISO was shown to bring disturbance in the cardiac muscles, leading to the 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 b.w. 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 of tuber based extract tuber extract of CR daily for 40 days along with a high-fat cafeteria diet .A new herbal supplement containing the tuber extract of C. rotundus was suggested for controlling obesity[46]

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).

Table 6: Effect of Cyperus rotundus on Cardioprotective.

CARDIOPROTECTIVE	12. http://nopr.niscair.res.in/		ALT	%	AST	%	CK	%	LDH	%	TROPONIN
		ISO	250		270		1.7		300		100 %

bitstream/1234567899/35695/1/IJEB%2054%282810%29%20670-675.pd	250 mg/kg	200	80	220	81	1.4	82	220	73	60%	500 mg/kg	180	72	180	66	1.25	73	160	53	40%

STUDIES AND DATA SPECIFIC TO THE ABOVE MENTIONED PARAMETERS

Antioxidant

- Mean value of SOD in two studies from range of 200ug to 250ug is 45±0.2
- Mean value of DPPH in range (Dose 25ug to 1000ug/ml) was found to be 60.92
- Mean value of FRAP from range (Dose 200ug/ml to 100ug/ml was found to be 49 % of inhibition
- Mean value from range of Dose from 1000ug to 400ug/ml was found to be 48.66% inhibition

Anti-Inflammation

- 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
- 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

Anti-Hyperglycemia

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

Cardio Protective

- Mean value for ALT in the range of 250mg/kg to 500mg/kg was found to be 60.8
- Mean value for AST in the range of 250mg/kg to 500mg/kg was found to be 73.5
- For CK the mean value for the range of 250mg/kg to 500mg/kg was 1.32
- For Troponin, the mean value for the dose range from 250mg/kg to 500mg/kg was found to be 50.0

CONCLUSION

Not much molecular biology and efforts for its understanding in the signaling pathway behind its several reported pharmacological actions has 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, antiinflammatory, hypolipidemic, properties, which are attributing to inhibition of NFkB, PKC, and capacity to direct neutralize the free radicals there by intrupting the free radical chain.

The major phytochemicals of oil of Cyperus rotundus includes- 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] and that of polar solvent extract includes - a sesquiterpenone characterized as 12-methyl cyprot-3-en-2-one-13-oic acid (1), two aliphatic ketone viz. n -dotriacontan-15-one (2) and n -tetracontan-7-one (8), fatty esters n -pentadecanyl octadec-9, 12- dienoate (n -pentadecanyl linoleate, 3) , n -hexadecanyl linoleate (4), n -hexadecanyl oleate (5) and n -pentacos-13′-enyl octadec-9-enoate (n -pentacos-13′-enyl oleate, 9), two steroidal esters s tigmast-5,22–dien-3 β –olyl n -dodecanoate (stigmasterol laurate, 6) and stigmast-5, 22-dien-3 β -olyl n -tetradecanoate (stigmasterol myristate, 7), β-sitosterol-3β-O-glucoside (10) and a triterpenic glycosidic ester lup-12, 20 (29)-dien-3β-ol-3-α-L-arabinopyranosyl-2'-oleate (lupenyl 3β-O-arabinpyranosyl 2′-oleate, 11).

The experimental and clinical studies support its claims described in the ayurvedic texts. However, based on the available data, its future studies could be focused to its anti-angeogenic potential and also in wound healing because both of these actiions are interlinked and it is also described in the ayurvedic texts.

Table A: List of Plants under lekhanya druv 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: lant'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]

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