ORIGINAL REVIEW PAPER

Pharmaceutical Science

KEY WORDS: Myricetin, Anticancer, anti-inflammatory, antioxidant, antihypertensive, platelet- aggregation, Central nervous system, antiphotoaging, bone disorder, antibacterial.

THERAPEUTIC POTENTIAL OF MYRICETIN

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ABSTRACT

The past of Myricetin increases more than 100 years. In the late eighteenth century it was first isolated from the bark of Myrica nagi Thunb (Myricaceae) harvested in India, like light yellow-coloured crystals. This compound is arising in nature is general amidst plants counting tea, berries, fruits, vegetables & medicinal herbs. Myricetin available in berries, vegetables & fruits is mainly in the form of glycosides other than free aglycones. Myricetin is usually plant derived flavonoid & for its nutraceutical cost. Studies of Modern pharmacological appear that Myricetin has a various biological activity anti-inflammatory (Treatment of inflammatory skin disorder), antitumor (Liver, Breast, Lung, Brain tumors), antioxidant activity (Free radical scavenging activity), bone disorder (Osteoporosis, Rheumatoid arthritis), Central nervous system (Alzheimer disease, Cerebral ischemia), dermatological activity (Photo-chemoprotective agent, Cosmetic application), antibacterial, antiviral & anti-obesity effects, apply cardiovascular protection, protects to neurological damage & protects the liver to potential injuries. Its main aim to enhance the solubility of compounds in the gastrointestinal tract & thus enhance the oral bioavailability & solubility of this compound because it has low solubility and low bioavailability, It includes various pathways of myrecitin like Nrf2-ARE pathway, Akt, mTOR & NF-κB pathways etc.

Myricetin (MYR) is a natural arising flavonols with hydroxyl substitutions at the 3, 5, 7, 3', 4' & 5' positions. Its arising in nature is general amidst plants counting tea, berries, fruits, vegetables & medicinal Herbs. Myricetin available in berries, vegetables & fruits & pleased in berries rises greatly as the berries mature. It is consumed in our regular edibles in vegetables, fruits & beverages like tea & wine. Liver is accountable for the metabolism & absorbed myricetin, with intestinal wall & kidney as the secondary sites [1]. Insoluble in water, that is 16.6 μg/mL. Therefore the degradation of myrecitin which is most stable at pH

2 was announced to be both temperature & pH dependent [2]. Studies of Modern pharmacological appear in Myricetin like a various biological activities (anti-inflammatory, antitumor, antibacterial, antiviral and anti-obesity effects, apply cardiovascular protection, protect to neurological damage & protect the liver to potential injuries [3]. Myrecitin has absolute oral bioavailability that is only 10%, acutely lower its effectiveness a therapeutic agent. It is important to raise the solubility & oral bioavailability of this compound for cardiovascular disease therapy applications. By dignity of nanosized, nanoformulations including nanocrystal, nanoemulsion, polymeric nanoparticles, den-drimers, carbon nanotubes, polymeric micelles & lipid nanocarriers ability to avoid the indigent oral bioavailability of insoluble drugs [4].

Indigent bioavailability & aqueous solubility of MYR control application for therapy of brain tumor. The polyphenolic compounds decay in factors of light, high temperature, microorganism, moisture & pH level; example, the degradation & very unstable at high pH or temperature. There are various customary methods, like auxiliary solvent & use of mixed solvents, prodrug formation by chemical modification, liposomal preparation, or use of cyclodextrin inclusion compounds, used to enhance the solubility of MYR. Although the only the improvement of the aqueous solubility & dissolution rate of MYR cannot prevent its quick degradation at high pH & temperature. Therefore, it would be appraise for formulation & development of MYR to both the solubility & prevention from its fast degradation as to apply its bioactivity [5]. Many health benefits assign to the myricetin such as reticent hyperglycemia, low hepatic triglyceride, reduced oxidative stress & cholesterol contents & protected liver injury the bioavailability of the myricetin by oral route was lower to the short absorption (9.62 & 9.74% at oral doses of 50& 100 mg/kg, respectively). Maximum concentrations (Cmax) & area under the curve (AUC) of myricetin risen after oral administration which contrast the amount which show myricetin which is absorbed by passive diffusion (In vivo). Prolong of getting maximum concentration (Tmax) (6.4 hr) shows less water solubility. Many pharmacokinetics properties like bioavailability of co-administered drugs with myricetin [6]. Myricetin is a flavonoid compounds that arepresent in large variety of fruits. Myricetin imitative to show anticancer activity that would lower pancreatic cancer growth to induction of cell apoptosis [7]. The various classes of polyphenols which shows potent anti-cancer property are catechins, favonols, favones, favonols, isofavones, anthocyanidins, etc. The present comprehensive reviews apply on myricetin, a favonol [8]. Myrecitin is best due to its antioxidant & free-radical scavenging potential. Its physicochemical instability critically impairs its quantity form design, evaluation & administration [9]. It includes all properties of drug like (pKa, logP, melting point etc) [10]. In the late 18 century it was first secluded from the bark of *Myrica nagi* Thunb (Myricaceae) harvested in India, like light yellow-coloured crystals. It often devour in our diet in vegetables, fruits & beverages such as tea & wine. Myricetin is found that the plant kingdom mostly found in Myricaceae, Anacardiaceae, Polygonaceae, Pinaceae & Primulacea families. Myricetin is usually plant derived flavonoid & for its nutraceutical cost. It can be accepted in many supplements including rose petals (Rosa damascene), blueberry leaves, sea buckthorn, chia seeds (Salvia hispanica), pistachio extract (Pistacia lentiscus), Japanese raisin tree (Hoveniadulcis), carob extract (Ceratoniasiliqua), grape seed extract & garlic [11].

Myricetin has two aromatic rings A & B in its structure they are merge by a 3-carbon chain forming a cyclic ring C & suggest that the existence of added hydroxyl groups in the basis of myricetin for being a strong antioxidant [12]. The structure of myricetin varies from quercetin having 1 extra hydroxyl at the 5'-OH of the phenyl moiety [13]. 2,3-double bond in the ring

crises the planarity of the molecule, has more rigidity & holds A & C rings in coplanar position permit 3-OH/4-O & 5-OH/4-O groups to be near. It is best hesitant with 6 hydroxyl groups, catechol group in the B ring, 3-hydroxyl group, 2, 3-double bond & 4-oxo group in the ring C which is important for lowering activities [14]. The existence of 3-hydroxyl group on ring C & the existence of 4-hydroxyl group on ring B affect the metabolism or absorption of myricetin [15].

Myricetin mostly present in nature like berries, vegetables & fruits, the form are glycosides other than free aglycones [1]. The 57.2 mg of Myr/g was taken out from the Lycium barbarum L. (fruits) [16], established in the Carménère grape's (skin) & has higher concentrations of myricetin (2.4 mg/kg) other than grape species [17], other like bambara groundnut (Vigna subterrania) have 1800 mg g-1 of myricetin [18]. Myricetin is found in some of the fruits & vegetables is carried out around 188 mg/kg of myricetin from the dryaerial parts of the plant Limonium sinense together with myricetin glycosides, myricetin 3-O- α-rhamnopyrano (309 mg/kg), myricetin 3-O-β-galactopyranoside (63 mg/kg) & myricetin 3- O-β-arabinopyranoside (18 mg/kg) [19]. 7 types of myricetin glycosides are present like myricetin 3'-methylether-3-O-glucoside, myricetin 3'-methylether-3-Ogalactoside, myricetin 4'-methylether-3-O-rhamnoside, myricetin 3',5'-dimethylether-3-O-glucoside, myricetin 3',5'-dimethylether-3-O-rhamnoside, myricetin 3',4'-dimethyl ether 3-O-β-D-glucopyranoside & myricetin 3-O-αL-(2''-O-α-L-rhamnopyranosyl)-rhamnopyranoside from the dried leaves of plant Licania densifora [20]. Various source of myrecitin are listed in table 1.

Table 1

SOURCE	BOTANICAL NAME	MYRECITIN (mg/kg)	REFERENCE
1-BERRY			
-Cranberry	Vaccinium oxycoccos (wild)	74,142	21,22,23,24,106
- Black current	Ribes nigrum Ojebyn	71	22,23,24,107
- Crow berry	Empetrum hermaphroditum (wild)	49	22,23,24
- Bog whortleberry	Vaccinium uliginosum (wild)	26	22,23,24
- Blueberry	Vaccinium corymbosum Northcountry	26	23,24,22,105
- Bilberry	Vaccinium myrtillus (wild)	14,21	22,23,24
2-VEGETABLES			
-French Peas	Pisum sativum	48.5(0.01ef)	22,23,24
-broccoli	Brassica oleracea	62.5(0.06ef)	22,23,24
-Carrot	Daucus carota	525.3g ± 10.5	22,23,24
-Cauliflower	Brassica oleracea	1586.9d ± 33.7	22,23,24
-Spinach	Spinacia oleracea	1660.9c ± 30.2	22,23,24
-Turnip	Brassica rapa	457.0h ± 18.3	22,23,24
3-FRUITS			
-Apple	Malus pumila	308.9± 12.4	22,23,24
-Apricot	Prunus armeniaca	406.9± 16.3	22,23,24
-Plum	Prunus domestica	564.1 ± 11.3	22,23,24
-Strawberry	Fragaria ananassa	3382.9 ± 101.5	22,23,24
4-MEDICINAL PLANTS			
-Desi kikar(bark)	Vachellia nilotica	188.9 ± 3.8	22,23,24
-Sohanjana (leaves)	Moringa oleifera	5804.4 ± 116.1	22,23,24
-Sohanjana(roots)	Moringa oleifera	170.2 ± 6.8	22,23,24
-Aloe vera(leaves)	Aloe barbadensis Miller	1283.5 ± 38.5	22,23,24
-Peepal(fruits)	Sacred fig	694.0 ± 13.9	22,23,24

Phytochemical, Pharmacological and Pharmaceutical Properties-

The plan like pharmaceutical approaches or delivery systems to enhance the solubility, absorption & therapeutic potential of myricetin that are most importance. Many formulationapproaches, like salt formation, particle size reduction (e.g., Nano suspensions or drug nanocrystal), amorphous solid dispersions, prodrugs & complexation (e.g., cyclodextrins), its main aim to enhance the solubility of compounds in the gastrointestinal tract & thus enhance the oral bioavailability [25]. In current years, pharmaceutical cocrystal have allure rising attention to improve physicochemical properties of APIs without converting their chemical structure, like the solubility, dissolution rate, melting point, stability & bioavailability [26]. Solubility of myricetin cocrystal, its kinetic solubility, thermodynamic solubility & intrinsic dissolution rate (IDR) [27]. Many phytochemicals studies taken out from the fruits, leaves & bark of M. Esculenta show the existence of many active phytoconstituents that show a various biological effect. It is a rich source of phenolic compounds, flavonoids & flavonols. The bioactive compounds shows in the plant are in the class of alkaloids, glycosides, diarylheptanoids, ionones, steroids, saponins, triterpenoids & volatile compounds [28]. It is plant based flavonoid known for its nutraceuticals value. It is lead ingredient in various foods & beverages. Myricetin is a hexahydroxy flavone that is flavone substituted by hydroxyl groups at positions 3, 3', 4', 5, 5' & 7. The relative molecular mass is 318.246 [29]. It is known mainly for its iron-chelating, anti-oxidant, anti-inflammatory & anticancer properties. Many findings have showed the activity of myricetin for a category of enzymes manage for alteration in structures & processes of Deoxy ribo nucleic acid (DNA) & Ribonucleic acid (RNA) [30]. In-vivo pharmacological activities (antioxidant & hepatoprotective) of formulated pro-liposomes were probe in CCl4 (carbon tetrachloride) induced hepatotoxicity mice. Notably better pharmacological effects mostly antioxidant & hepatoprotective activity of MRC, were gained via TPGS modified pro-liposome formulation other than the TPGS-free pro-liposome & unformulated MRC [31].

Pathways Used in Myricetin-

The human keratinocytes survey the effect of myricetin on the TNF-α stimulated manufacturing of inflammatory mediator's alliance to the Akt, mTOR & NF-κB pathways, which control the transcription genes required in immune & inflammatory responses. Myricetin & N-acetyl cysteine reduced the TNF-α-stimulated manufacturing of cytokines & chemokines & manufacturing of reactive oxygen variety in keratinocytes. The outcome of myricetin may reduce TNF-α-stimulated inflammatory mediator manufacturing in keratinocytes by conquer the arouse of the Akt, mTOR & NF-κB pathways [32]. Myricetin on gene expressions in genome-wide & basal of mechanisms. The total 44K gene inquiry, myricetin therapy upregulate the signals of 143 gene inquiry (0.33% of total inquiry) & downregulated signals of 476 gene inquiry (1.08% of total inquiry) by higher than or equal to 2- fold in HepG2 cells. The network pathway survey disclose that nuclear factor

(erythroid- derived 2)-like 2 (Nrf2)-mediated antioxidant response element (ARE) activation is involved in myricetin-induced genes expressions. All events are finally raising nuclear Nrf2 accumulation & ARE-binding activity to improve ARE-mediated genes expressions. The therapy with Nrf2 small interfering RNA decreases the myricetin-induced ARE activity & gene expression [33].

The unity of myricetin of a potential chemo preventive agent main matter of its reticence of tumor angiogenesis & reveal the anticancer effects of myricetin in vivo. Rat aortic ring assay discloses that myricetin also affect the growth of micro vessels & the organization of vascular networks. Further, an ELISA shows that myricetin lower the levels of vascular endothelial growth factor (VEGF) in vivo & in vitro. Western blot analysis show that myricetin down regulate VEGFR2 & p38MAPK. The myricetin could notable reticence tumor angiogenesis & having a potential as a chemo preventive agent because of reticence to angiogenesis [34].

Myricetin subdue the cell viability of the MCF-7 cells through the evocation of apoptosis as evaluate by MTT Assay & flow cytometry. The therapy of myricetin activated glycogen synthase kinase-3β (GSK3β) & Bax protein expression & inhibited β-catenin/cyclin D1/proliferating cell nuclear antigen (PCNA)/survivin & promoted caspase-3 activity in the MCF-7 cells. Results showed that myricetin subdue the cell viability of human breast cancer MCF-7 cells through PAK1/MEK/ERK/GSK3β/β-catenin/cyclin D1/PCNA/survivin/Bax-caspase-3 signalling [35]. MYR causes pancreatic cancer cell death in vitro & in vivo by evocation of apoptosis & mechanism of action is via the reticence of the PI-3 kinase pathway.

This compound is therapeutic potential agent to be used to prevent the progression & metastases of pancreatic cancer [36]. Myricetin exhibits a notably induction of differentiation in the human osteoblast-like cell line MG-63. The evaluation of MYR affects inflammatory cytokines-mediated apoptosis in osteoblast cells. TNF-a / IL-1h improves apoptotic DNA fragmentation in anti Fas IgM-treated MG-63 cells by rising Fas receptor expression. Therefore TNF-a/ IL-1h therapy does not induce apoptosis. Therapy of MG-63 cells with myricetin not only inhibited anti-Fas IgM-induced apoptosis, but also stop the synergetic effect of anti-Fas IgM with TNF-a/IL-1h on cell death. This specifies a potential use of MYR in avert osteoporosis by relicensing inflammatory cytokines-mediated apoptosis in osteoblast cells [37].

In A549 cells, TNF-α stimulation upregulate the manufacturing of interleukin-6 (IL-6) & interleukin-8 (Il8). The pre-treatment with myricetin notably reduced and notice the reaction triggered by TNF-α. The myricetin strongly rising the deacetylase pursuit through lower phosphorylation, but not expression, of sirtuin-1 (SIRT1) in TNFα-stimulated A549 cells. Myricetin-mediated SIRT1 pursuit was farther reveal by the lowered acetylation of NF-κB p65 & p53. All of these parallel changes were back by addition of salermide (SIRT1 inhibitor), illustrating the censorious role of SIRT1 in mediation of anti-inflammatory processes by myricetin [38].

Myr notably alleviated AB-induced cardiac hypertrophy, fibrosis & cardiac dysfunction in both WT & Nrf2-KD mice. Myr also inhibited phenylephrine- (PE-) induced neonatal rat cardiomyocyte (NRCM) hypertrophy & hypertrophic markers expression in vitro. The Myr markedly rising Nrf2 activity, lower NF- κB activity & inhibited TAK1/p38/JNK1/2 MAPK was signal in WT mouse hearts. It evaluate that Myr could impede TAK1/p38/JNK1/2 signal via reticence Traf6 ubiquitination & its interaction with TAK1 after Nrf2 knockdown in NRCM. Myr be a potential plan for therapy or adjuvant therapy for malignant cardiac hypertrophy [39].

Various Activities of Myrecitin

Figure 1 includes various biological activities with their properties.

Myricetin flavonoid is well-known for its antioxidant, anti-inflammatory & anti-tumor potential [40]. Table 2 includes all biological activities of myrecitin with in-vivo studies for preclinical application of myrecitin [104].

BIOLOGICAL ACTIVITIES	MODELS USED	DOSE OF CHEMICAL	PERIOD OF STUDIES	REFERENCES
ANTIOXIDANT	Rat models	100 mg/kg	2 weeks	41
ANTICANCER	Female wistar rats	50, 100, 200 mg.kg	16 weeks	42
	Adults in the Netherlands.	Consumption of food of Flavonoids among 5898 individuals	-	43
PLATELET AGGREGATION	Mice	0, 25, 50, 100 µmol/L	9 days, 48 h, 2h, 4h for each groups	44
ANALGESIC& ANTIINFLAMMATORY	Monkeys & Dogs	10 mL/kg and 5 mL/kg	7 days respectively	45
PROTECTIVE EFFECT AGAINSTALZHEIMER DISEASE.	Female Mice model	200, 100, 50 mg/kg	10 days	46
ANTIHYPERTENSIVE	Male Wistar Rats model	5 and10 mg/kg	21 days	47
	Male Wistar Rats model	100 and 300 mg/kg	6 weeks	48

Antioxidant Activity-

Myricetin show to hinder the tert-butylhydroperoxide (t-BOOH)-initiated chemi luminescence of mouse liver homogenates as return by the acquire IC50 value of 15 mM [49]. These announce counsel that MYR have probable to protect against lipid peroxidation & more free radical-mediated cell injuries. The MYR also reduce t-BOOH-induced raising levels of oxidative stress parameters plus malondialdehyde & the protein carbonyl group of erythrocytes from Type-2 diabetic patients in vitro [50]. There is various scavenging activity of myrecitin to numbers of radicals and ions are as shown in below table 3.

Table-3

TEST	OUTCOME	CONTROL	REFERENCE
SUPEROXIDE	Hinder by 24.6%, 79.5% & 96.4% when appeal concentrations of 0.001 mM (0.32 µg/mL), 0.01 mM (3.2 µg/mL) &0.1 mM (32 µg/mL), respectively, while IC50 calculated as 0.6 µM (0.2 µg/mL).	β-Actin as internal control.	51
	At 1.86 µg/mL, search superoxide radicals in nitroblue tetrazolium hypoxanthine/xanthine oxidase evaluation.	Ascorbic acid (IC50 5.8 µg/mL).	52
TEAC	Activity of 2.40 mM (764µg/mL) trolox/mg sample after 20 min. The IC50 value was found to 22 µg/mL.	Trolox (0.2 mg/mL)	53
FRAP	590 µmol Fe2+/L at 10 µM (0.32 µg/mL).	Gallic acid	54
Ascorbic acid-induced lipid peroxidation	Reticence in rat brain by 92%, 95% & 95% at 0.1, 1.0 & 4.0 mM myricetin, singly (concentrations correspond to 32, 320 µg/mL & 1.3 mg/mL, respectively).	Ascorbic acid (0.1 or 1.0 mM).	55
Ferrous sulfate induced lipid peroxidation	Reticence in rat brain by 28%, 71% & 91% at 0.1, 1.0 & 4.0 mM myricetin, singly (concentrations correspond to 32, 320 µg/mL and 1.3 mg/mL, respectively).	Ferrous sulfate (1.0 mM).	55
Collagenase in human dermal fibroblasts	Reticence by 12.7% & 29.6%.at myricetin concentration of 0.1 (32 µg/mL) & 0.2 mM (64µg/mL), individually.	1,10-phenanthroline (39.4%and 75.1%, respectively).	51

Anticancer Activity-

Different formulations for the treatment of various cancers along with their aim are listed in Table 4. Vast analysis of the anticancer activities of myricetin has specified that the compound is cytotoxic towards a number of human cancer cell lines, including hepatic, skin, pancreatic and colon cancer cells (Table 5).

Table-4

FORMULATION	TYPE OF CANCER	AIM	REFERENCE
Biocompatible lipid nanoparticles	Against breast cancer	Sensitization of MDA- MBA231 mammary cancer to Docetaxel by MYR loaded into biocompatible lipid nanoparticles by means ofsub-G1 cell cycle arrest mechanism	56
Gold nanoparticles	against breast cancer	Utilization of plant- derived Myricetin molecule coupled with ultrasound for the synthesis of gold nanoparticles against breast cancer	57
Silica nanoparticles	Against non-small Cell lung cancer (NSCLC)	Folic acid (FA)- conjugated mesoporous silica nanoparticles combined with MRP-1 siRNA improves the suppressive effects of myricetin on non-small cell lung cancer (NSCLC)	58
Lipid-based nanocarriers	Against lung cancer	Pulmonary conveyance of anticancer drugs by mean of lipid-based nanocarriers for the	59
		treatment of lung cancer	
Solid lipid nanoparticles	Against human lung adenocarcinoma	MYR loaded solid lipid nanoparticles helicases MLKL & RIPK3 in human lung adenocarcinoma	60
Nanoencapsulated phospholipid complex	Against lung Carcinoma	Promoted antitumor activity of myricetin against lung carcinoma via nanoencapsulated phospholipid complex in respirable microparticles	40
Protein nanoparticles	Against hepatocellular cancer	A target-specific oral formulation of doxorubicin protein nanoparticles: efficacy and safety in hepatocellular cancer	61
Nano liposomes	Against glioblastoma	Myricetin nanoliposomes induced SIRT3-mediated glycolytic metabolism leading to glioblastoma cell death	62

Table-5

CELL LINE/ENZYMES	EFFECTS ON MYRECITIN	REFERENCE
BRAIN		
U251, NCH89 & LN229	No effect when alone, the	63
cells	IC50 value for each cell line was begin to be >200 µM. A merger of myricetin (150 µM) & TRAIL (50 ng/mL) yielded a synergistic activity & risen cell death in U251, NCH89 & LN229 by 59%, 65% and 52%, singly.	
BREAST		
MCF-7	IC50 2.70 µg/mL contrast to vinblastine (IC50 45.6 µg/mL). Risen GSH pleased of cells & also risen the EROD reaction 2-fold at a conc of 25 µM.	64,65
CERVIX		
HeLa cells	Cytotoxic with IC50 18.9 µg/Ml	66
COLON		

Epithelial adenocarcinoma cells	Growth of cells specify at 50 μM by decreasing COX-2 & cyclin D1 expression	67
HCT116	Specify the growth of human colon carcinoma cells by halting the cell cycle in G2/M phase & convince apoptosis; LD50 28.2 μM.	68
LEUKEMIA		
HL-60	Alone in merger with	69
	piceatannol, induced apoptotic cell death through a ROS-independent cell death pathway. The outcome was higher with the merger therapy.	
PROSTATE		
22Rv1	Inspire of TCDD-induced EROD pursuit in cancer cells;IC50 value 3.0 μM	70
UTERUS		
RL95-2 endometrial cancer cells	Inspire of CYP1 activity of cancer cells; IC50 values 3 μM and decreased.	71

Anti inflammatory Activity-

Myricetin (62.5–125 μg/mL) appear activity opposed to the Porphyromonas gingivalis- induced inflammatory response in host cells & avert NF-κB activation in a monocyte model. The molecule persuades the secretion of IL-6, IL-8 & MMP-3 by P. gingivalis-stimulated gingival fibroblasts. Myricetin act as a therapeutic agent for the therapy of periodontitis, a serious gum infection that damages the soft tissue & demolish the bone that supports your teeth [72]. Myricetin exhibit anti-inflammatory activity by inhibiting the production of LPS-induced prostaglandins [73]. The composite was found to inspire the production of LPS- stimulated NO, pro-inflammatory cytokines, PGE2 production & COX-2 in RAW 264.7 macrophages [74]. MYR does not have any effect on cell viability. Mixture of all hinders the RANKL-stimulated activation of p-38, ERK & cSrc signaling & the RANKL-tonic shame of IkB in RAW264.7 cells. However the secretion of LPS-induced TNF-α & IL-1β in RAW264.7 cells was notably reticent by myricetin [75].

Antihypertensive Activity-

The antihypertensive activity of myricetin has been shown in vivo. Hypertension &oxidative stress started by deoxycorticosterone acetate (DOCA) was reduced after therapy with oral doses of 100 & 300 mg myricetin/kg body weight in rats [76]. Depletion in systolic blood pressure & a reversal of DOCA-induced rising in heart rate was clear. It reversed rising levels of thiobarbituric acid-reactive substance & lowering levels of SOD & CAT & also depletion glutathione concentrations in the heart tissue of rats after exposure to DOCA [77].

Platelet-Aggregation Activity-

A land experiment specifies that myricetin has the potential to hinder thrombin & that the composite could therefore be helpful in the therapy of thrombotic disease [78]. A prostacyclin-stimulated rise in quantity of platelet adenosine 3151-cyclic monophosphate (cyclic-AMP) was restoring by myricetin. The mechanism of anti-aggregating activity release modify the platelet cyclic-AMP metabolism happen via reserve of phosphodiesterase activity [79]. Exposure to 150 μM myricetin caused 14%, 26%, 5% & 49% reticence of rabbit platelet aggregation, induced by ADP, arachidonic acid, collagen & PAF singly [80].

Central Nervous System Activity-

Protective effects of myricetin stem from the effect of the composite against specific proteins, known as tau proteins, which are liberal in the distal portions of axons &serve to provide flexibility & stability to microtubules [81]. Pathologies of the nervous system, like AD & PD can evolve when tau proteins flatter defective & are later unable to sufficiently stabilize microtubules. The tau proteins impart steadiness to the microtubules through isoforms & phosphorylation [82]. Myricetin make an anti-tau effect at a conc of 50 μM in HeLa-C3 cells. A second-mode of action that can be probe generally is the ability of myricetin to block Alzheimer associated β-amyloid fibril formation [83].

Antiphotoaging Activity-

A mechanism-based showed that myricetin reduced UVB-induced keratinocytes death & reduces malondialdehyde levels, which are rising retinue exposure to UVB rays. The capacity of myricetin to impede UVB-induced generation of H2O2 in keratinocytes can be joint to itsanti-oxidant potential, which assists the scavenging of free radicals. The compound also impedes the UVB-induced activation of c-jun-NH2 terminal kinase (JNK) in keratinocytes [84]. Myricetin is able to defeat UVB-induced COX-2 expression in mouse skin epidermalJB6 P+ cells. It hinders UVB-induced initiation of activator protein-1 and NF-κβ, as well as Fyn kinase activity. The activity was found to be same to that of 4-amino-5-(4-chloro- phenyl)-7-(t-butyl)-pyrazolo [3,4-d] pyrimidine, a prominent Fyn inhibitor. The compound hinders MEK1 kinase activity & transformation of JB6 P+ mouse epidermal cells in vitro [85]. Myricetin can lower Akt activity &stimulate apoptosis in UVB-irradiated keratinocytes HaCaT cells by lowering phosphorylation of Akt and Bad (a pro-apoptotic protein) at a concentration of 20 μM [86].

Bone-Disorder Activity-

It also averted a PTH-induced lower in diaphyseal calcium content at a concentration of 10´6 M [87]. Hsu & coworkers that myricetin rising BMP-2 synthesis, ensue in the subsequent activation of SMAD1/5/8 & p38 MAPK. The venture maybe related to the beginning of osteoblast maturation &differentiation, followed by rising in bone mass. To tonic osteoblast contrast at many levels, from maturation to ending contrast. Starting of contrast by MYR begin to related with rising bone morphogenetic protein-2 (BMP-2) production & rising activation of SMAD1/5/8 & p38 MAPK [88].

Analgesic Activity-

Myricetin (0.1–10 mg/kg i.p.) produce analgesic effect in a neuropathic pain model in rats, by lower spinal nerve ligation-induced mechanical allodynia & thermal hyperalgesia lasting for several hours [89]. The composite lower voltage-activated calcium channel currents (ICa(V)) in vitro by 10%–56% at lower concentrations (0.1–5 μM), the higher concentrations (10–100 μM), it reviving a 20%–40% rising in ICa(V). The MOA divulge that the analgesic activity of myricetin can be related to its PKC-induced lower of ICa (V) in rat dorsal root ganglia neurons. Hagenacker & coworkers the composite also reduced voltage-activated potassium channel currents (IK(V)) in vitro by 18%–78% at concentrations of 1–75 μM, they were independent of the voltage applied. This depletion of IK (V) in rat sensory neurons found to be p38 dependent. MYR appeal a notable analgesic effect, through back the acetic acid- induced squirm result & defeat time in the late phase of the formalin test [90].

Antimicrobial Activity-

The composite show poor inhibitory activity against E. coli primase; the pursuit was 60-fold weaker against DNA-B helicases. It reticent the growth of methicillin-resistant Staphylococcus aureus, multidrug-resistant Burkholderia cepacia & vancomycin-resistantEnterococci [91]. It show a potent activity opposed to recombinant sortase A & B obtained from S. aureus with IC50 values of 44.03 & 36.89 μM, singly & a corresponding MIC value more than 300 μM [92]. At a conc of 0.5 mg/mL, myricetin produced notable zones of reserve, ranging from 13.4 mm to 19.2 mm, against B. subtilis, Corynebacterium diphtheria, C. diphtheriticum, Micrococcus lysodiecticus, S. aureus, S. epidermidis, S. saprophyticus, Enterococcus faecalis, E. faecium, Streptococcus pneumonia, S. pyogenes, E. coli, K. pneumonia, P. mirabilis, P. aeruginosa, S. typhi, S. paratyphi, S. dysenteriae, S. sonneie & S. flexneriae,

but the potency was more against Gram-positive bacteria [93]. Antitubercular activity shown (MIC 50 µg/mL) after reveal Mycobacterium tuberculosis to MYR [94].

Miscellaneous Activity-

The concentration of 100 µM, it reserve ATP-dependent Ca2+ uptake by rat liver plasma membrane vesicles higher than 20%. The same concentration, it reticent K+-dependent p-nitro phenyl phosphatase by 83%, it may not exert any effect on 51-nucleotidase, alkaline phosphatase&Ca2+-activated ATPase. Myricetin (52 µM) decreased the starting rate of 45Ca uptake by 50% after pre-incubating for 10 min. The MOA suggested that lipid solubility &hydroxylation at positions 5, 7, 31, 41 in the structure enhanced the ability to reticent Ca2+ uptake [95].Myricetin (0.03 mM) was reticent to lipoxygenase activity by 91% in liver cytosol of rat fed oxidized palm oil [96]. It lowered the production of oxygen-glucose deprivation-induced free radical, responsible for swelling of C6 glial cells. MYR start to depletion rising levels of intracellular calcium, typical of ischemic injury to cells, at many concentrations, i.e. 100 pM, 1 nM &10 nM [97]. Estrogens is the main female sex hormones, play a main role in twain menstrual &estrous reproductive cycles. Myricetin taken by mouth at 100 mg/kg/day, produced estrogenic activity by rising the uterus weight & height in immature Wistar albino rats when contrast to that of controls (ethiny l67 estradiol, ethinyl estradiol + tamoxifen and genistein) [98].

Toxicity Studies on Myrecitin-

Myricetin mostly studied In vitro & In vivo. Many studies raising concerns with poor effects. Intraperitoneal administration of this compound at amount of 1000 mg per kg b.w. to mice they do not show any harmful effects or fatalities [99]. Myrecitin not shown any harmful at amount above 100 mg/kg (LD50 value) in zebra fish larvae induced by UVB-generated ROS [100]. Kim & coworkers [101] showed myricetin is not cytotoxic towards human umbilical vein endothelial cells (HUVECs). The hydroxyl groups on the B-ring are joint to theprotective effect. An LD50 value of 100 µM was accepted for MYR. At 50 µM, it suppressed HUVEC tubular structure formation stimulated by vascular endothelial growth factor (VEGF) by 47%. It would be toxic towards biological source. Canada & coworker [102] showed myrecitin at 450 µM basis a cellular damage to isolated guinea pigenterocytes. The cellular viability was reduced by as much as 60% & lactic dehydrogenase leakage was rising by 41%. Superoxide is produced by autoxidation that would be managed for harmful of the compound; the radical may produce intestinal injury. Myricetin exert pro-oxidant effects at high concentrations in ascorbic acid-free systems with the formation of the Fe-EDTA complex [103].

Conclusion & Future Prospective

Myrecitin was first isolated from the bark of *Myrica nagi* Thunb. (Myricaceae) harvested in India, like light yellow-coloured crystals. Myricetin is present in berries, vegetables & fruits mainly in the form of glycosides other than free aglycones. Myricetin is a natural arising flavonols with hydroxyl substitutions at the 3, 5, 7, 3', 4' & 5' positions. Myricetin show a various biological activities anti-inflammatory (treatment of inflammatory skin disorder) antitumor (liver, breast, lung, brain tumors), antioxidant activity (free radical scavenging activity), bone disorder (osteoporosis, rheumatoid arthritis), central nervous system (alzheimer disease, cerebral ischemia), dermatological activity (photo-chemoprotective agent, cosmetic application), antibacterial, antiviral and anti-obesity effect applies cardiovascular protection, protects to neurological damage & protects the liver to potential injuries.

Myricetin is usual flavonoid is known for its nutraceuticals value. It is soluble in organic solvent like ethanol etc. and insoluble in aqueous medium. MYR is lipophilic in nature. It includes various pathways of myricetin like Nrf2-ARE pathway, Akt, mTOR & NF-κB pathways etc. In further studies work on effect of myricetin liver cancer. Nanocarriers can significantly increase the drug bioavailability and increase solubility. Nanocarriers are one of the best ways to overcome from many limitations in present time. It is shown from various in vivo studies; myricetin can be developed as an anti-inflammatory & analgesic agent in near future.

Acknowledgement

Authors are very thankful to Research and Development department, Integral University Lucknow for providing the necessary facilities required for successful completion of this review work.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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